David E. Wazer
Douglas W. Arthur
Frank A. Vicini *Editors*

Accelerated Partial Breast Irradiation

Techniques and Clinical Implementation

Second Edition

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Accelerated Partial Breast Irradiation: History, Rationale, and Controversies

1

Thomas A. Buchholz and Eric A. Strom

1.1 Introduction

Radiation therapy plays a very important role in the management of early-stage and non-invasive breast cancer treated with breast conservation. Long-term outcome data from randomized prospective trials that compared a breast-conserving surgical procedure alone or in combination with whole breast irradiation have conclusively demonstrated that radiation improves outcome (Fisher et al. 2002a; Veronesi et al. 2001; Vinh-Hung and Verschraegen 2004; Early Breast Cancer Trialists' Collaborative Group 2005). The Early Breast Cancer Collaborative Trialists' Group has performed a meta-analysis of the raw data from these trials. Their most recent update included data from over 9,000 patients treated in 14 trials, and had a median follow-up for the populations of ten years. For the 7,575 patients with lymph node-negative disease, the use of radiation reduced the 15-year isolated local recurrence rate from 28.3% to 10.4%. For the 1,513 patients with lymph node-positive disease, the 15-year isolated local recurrence was reduced from 39.9% to 10.9%. Importantly, these improvements also led to a statistically significant reduced 15-year breast cancer mortality rate for patients with lymph node-negative disease and those with lymph node-positive disease (Early Breast Cancer Trialists' Collaborative Group 2005).

Radiation therapy also plays an important role in reducing breast recurrences in patients with ductal carcinoma in situ treated with breast conservation. To date, four randomized prospective trials have demonstrated that the addition of whole breast irradiation after lumpectomy reduces the probability of noninvasive and invasive breast recurrence when compared with lumpectomy alone.

Based on these results, whole breast irradiation should be considered a standard component of breast-conservation therapy for most patients with early-stage invasive disease

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and most patients with ductal carcinoma in situ. In addition to whole breast treatment, two randomized trials investigated whether the addition of a tumor-bed boost following whole breast irradiation offered further benefit for patients with invasive disease (Bartelink et al. 2002; Romestaing et al. 1997). Both of these studies demonstrated a small but statistically significant reduction in ipsilateral breast tumor recurrence. Correspondingly, the highest level of medical evidence available to date suggests that the optimal radiation treatment schedule should include five weeks of daily therapy directed to the ipsilateral breast followed by 1–1.5 weeks of additional daily therapy directed to the tumor-bed region.

The studies investigating radiation and breast conservation therapy proved to be one of the more significant advances in the local–regional management of breast cancer. Advances in imaging, pathological assessment of surgical specimens, surgical techniques and radiation treatment delivery, as well as an increasing use of systemic therapies, have continued to improve the outcomes of patients treated with breast conservative surgery and whole breast irradiation. For example, investigators from The University of Texas M. D. Anderson Cancer Center reported their 27 years of experience in treating 1,355 patients with breast-conservation therapy for invasive disease and found that the five-year rate of in-breast recurrence was significantly lower in the patients treated between 1994 and 1996 compared to the subgroup treated before 1994 (1.3% vs. 5.7%, $p = 0.0001$) (Cabioglu et al. 2005). In part, this was due to the fact that the more recent patient cohort was less likely to have positive or unknown margin status and more likely to receive systemic treatments in addition to surgery and radiation. The five-year recurrence risk of 1.3% is equivalent to that achieved with mastectomy.

An equally positive finding of recent studies is that the radiation component of breast-conservation therapy is associated with a very low rate of normal-tissue toxicity rate. A large study that analyzed the national Surveillance, Epidemiology, and End Results (SEER) database found that there was no evidence for an increase in cardiac death rate in the patients treated for a left sided vs. a right sided breast cancer since 1980 (Giordano et al. 2005). Similarly, a study that evaluated the SEER-Medicare database found no increase in cardiac events in patients over the age of 65 who were treated with radiation for a left-sided breast cancer (Patt et al. 2005). Newer methods of three-dimensional dose compensation using multiple subfields (sometimes referred to as intensity-modulated radiation or IMRT) also reduce the acute and late effects of radiation on the breast (Pignol et al. 2008; Donovan et al. 2007). For example, Pignol et al. reported on a randomized trial that found that IMRT had lower rates of moist desquamation for patients receiving whole breast irradiation compared to wedge compensation (Pignol et al. 2008). Donovan et al. published a similar randomized trial in which IMRT dose compensation minimized the risk of a radiation-induced long-term cosmetic consequence, such as change in the photographic appearance of the breast (Donovan et al. 2007). The newer IMRT techniques also have the additional benefit of decreasing the dose to the contralateral breast by 65–82% (Borghero et al. 2007). Accordingly, whole breast treatment should be considered to be relatively safe, with a low probability of long-term normal tissue injury.

However, despite its many positive benefits, radiation therapy is also associated with some disadvantages, the foremost of which is perhaps is the fact that it is a relatively complex and expensive treatment. Radiation treatments require physical resources, such as linear accelerators, simulators, and treatment planning systems, in addition to significant personnel resources, such as specialty-trained physicians, physicists, dosimetrists, and therapists.

This level of expertise is not available in every city in the United States, and the deficiency is even more pronounced in other countries. A second major downside of radiation therapy is that the treatments are inconvenient. As mentioned, standard whole breast irradiation in the United States is typically administered over 6–7 weeks and treatments are preceded by 2–3 days of treatment planning. The five-day-a-week treatment schedule may require patients to miss work and can lead to other significant lifestyle disruptions. These factors are particularly relevant for patients who do not live in close proximity to a radiation treatment facility. Standard whole breast treatment may require such individuals to temporarily relocate, which might cause financial burdens such as temporary lodging expenses and the costs of missing work. Furthermore, such relocation may mean separating patients from their families, friends, and other supporters.

These downsides of radiation have been shown to have consequences. First, some women elect to forgo breast-conservation therapy and be treated with mastectomy in order to avoid the need for radiation treatments. In fact, a number of studies have found an inverse relationship between the use of breast-conservation therapy and the distance from a patient's home to the nearest radiation facility (Athas et al. 2000). Furthermore, the regions of the country with the lowest density of radiation treatment facilities have the lowest rates of breast-conserving treatment (Farrow et al. 1992). An even more serious consequence that can result from the inconvenience of the radiation treatment schedule is that some patients treated with breast-conservation therapy elect to forgo the radiation component of their treatment. Recent pattern-of-care studies have indicated that approximately 20% of patients with early-stage invasive breast cancer treated in the United States do not receive radiation as a component of breast-conservation therapy (Nattinger et al. 2000). This option has been proven to place these patients at a higher risk for tumor recurrence, and possibly a higher risk of death.

The magnitude of the problem posed by the time required to administer radiation treatments is much greater outside the United States. There is a shortage of radiation treatment facilities in many countries that makes the traditional scheduling of breast treatments impractical. In these countries, there can be extended delays in starting radiation therapy due to patient backlogs, and in other countries the scheduling of radiation and the shortage of facilities have hindered the use of breast-conservation therapy.

One strategy for overcoming some of these issues is to accelerate the course of radiation treatments. Although this may seem like an intuitive solution, there are biological reasons why the five- to six-week treatment course for whole breast irradiation was originally developed. In short, this schedule was thought to optimize the therapeutic ratio (defined as the probability of achieving tumor control vs. the probability of causing a normal-tissue injury). Decreasing the radiation treatment schedule to less than five weeks would require an increase in the daily dose per fraction, and this increase, unfortunately, has a greater effect on the probability of normal-tissue injury than tumor control.

Despite these theoretical concerns, the early work investigating hypofractionated whole breast treatment has provided encouraging results. In a randomized prospective clinical trial, Whelan et al. (2002) compared a 16-fraction course of whole breast irradiation (42.5 Gy given over 22 days) to a 25-fraction course (50 Gy given over 35 days). This study was limited to patients with favorable disease; all patients had negative lymph nodes, 80% had T1N0 disease, and 75% were over the age of 50. A 2007 update of this trial with

ten-year results continued to show equivalent local control and breast cosmesis between the two arms. A similar prospective trial performed in the United Kingdom compared 50 Gy in 25 fractions (five weeks) to 40 Gy in 15 fractions (three weeks) and again reported favorable results with the shortened schedule, with a five-year in-breast recurrence rate of 2.8% and a similar outcome with respect to the photographed appearance of the breast (Dewar et al. 2007).

The volume of normal tissue included in the treatment volume is also an important determinant of normal tissue toxicity after radiation. It was hypothesized that the treatment course could be further shortened to a one- to five-day duration without increasing the risk of a normal-tissue injury by reducing the volume of normal tissue included in the radiation field. This rationale led to the investigation of accelerated partial breast irradiation (APBI). In this strategy, radiation is delivered only to the tumor-bed region of the breast plus an arbitrarily defined margin. To date, APBI has been delivered with a variety of techniques, including single-fraction intraoperative brachytherapy, electron or orthovoltage treatment, low dose rate interstitial brachytherapy (temporary implantation of radioactive sources), high dose rate interstitial brachytherapy, high dose rate brachytherapy delivered with a balloon-catheter system, and three-dimensional conformal external-beam radiation treatment. Although these strategies differ in many key variables, such as the dose of radiation delivered and the volume of breast tissue treated, they all share the common characteristic of attempting to shorten the treatment schedule from 6–7 weeks to a course that lasts a week or less.

1.2 History of APBI

Over the past eight years, APBI has generated a great degree of enthusiasm among both cancer care providers and breast cancer patients. However, the first investigations of APBI as an alternative to conventional whole breast irradiation began some time ago and were abandoned due to a lack of efficacy. The first two trials investigating APBI were conducted in the United Kingdom in the early 1990s. Investigators at Guy's Hospital conducted a relatively small Phase I/II trial in which a low dose rate brachytherapy implant directed to the tumor-bed region was used as the sole radiation component of breast-conservation therapy (Fentiman et al. 1996). After a median follow-up of six years, a local in-breast relapse developed in 10 patients (37%). This rate is similar to that predicted for treatment with lumpectomy without any radiation. A much larger Phase III clinical trial comparing whole breast external-beam irradiation to APBI was conducted at the Christie Hospital during this same period of time (Magee et al. 1998). The APBI approach used in this trial was a fractionated external-beam approach that utilized a single electron field. It should be recognized that the targeting of the APBI to the region at greatest risk in this trial was relatively crude by today's standards. Since this study was conducted, a number of improvements in imaging and treatment planning have been developed. In the Christie trial, APBI proved to be an inferior treatment than whole breast irradiation. The eight-year actuarial local recurrence rate was 25% for those treated with partial-breast therapy, as opposed to a 13% rate for those receiving whole breast treatment (Magee et al. 1998).

These discouraging results led to a reluctance to pursue the concept of APBI any further for a period of time.

In the late 1990s, interest in APBI was renewed. Investigators hoped that the high local recurrence rates noted in the early studies could be avoided with more stringent patient selection criteria, more uniform definitions of target volumes, a greater ability to define the target due to improved imaging and treatment planning, and more uniform dose prescriptions. In addition, in the first APBI trials, many important pathologic factors that were subsequently found to be associated with local–regional recurrence were not evaluated systematically. Specifically, these studies included patients with unassessed or positive surgical margins and patients who did not undergo axillary lymph node evaluation. Finally, the presence or absence of lymphovascular-space invasion and/or an extensive intraductal component was not analyzed.

In the United States, the first studies of APBI investigated treatment delivered with an interstitial implant (usually a double-plane implant), with the targeted region typically being the tumor bed plus a 2.0–2.5 cm margin. Eligibility was limited to patients with tumors less than 4 cm in size with 0–3 positive lymph nodes who were treated with a breast-conserving surgery that achieved negative surgical margins. Unlike previous experiences, these initial studies reported 3–5 year breast recurrence rates ranging from 1% to 5%, with recent ten-year updates continuing to demonstrate excellent results (King et al. 2000; Vicini et al. 2003a, 2007). The efficacy of the interstitial implant approach was also confirmed in many European centers. One of the leading European centers investigating APBI has been the National Institute of Oncology in Hungry. Investigators from this institution completed a Phase I/II trial with encouraging results and have begun a follow-up Phase III trial (Polgar et al. 2004). On the basis of the initial favorable data in approaches utilizing multicatheter implants, the Radiation Therapy Oncology Group (RTOG) conducted a multicenter Phase II trial investigating a double-plane brachytherapy approach to APBI. After a relatively short median follow-up period, the in-breast recurrence rate and the normal-tissue toxicity rate were both excellent (Arthur et al. 2008).

The double-plane interstitial breast brachytherapy approach to APBI, however, has not been widely adopted in the United States. The treatment technique requires a specialized skill set, and the procedure and its planning require a significant amount of time. Technological advances, such as the use of template-guided approaches, have improved the reproducibility and convenience of interstitial brachytherapy, but even with these improvements, brachytherapy remains a less popular option for APBI in the United States.

The initial therapeutic success of interstitial brachytherapy, coupled with its lack of widespread adoption, led to the development of a number of other methods of delivering APBI. In Italy and the United Kingdom, single-fraction intraoperative electron-beam or orthovoltage treatments have been studied in Phase II trials, and now both of these approaches are now being tested in Phase III studies (Veronesi et al. 2003; Vaidya et al. 2004). In the United States, alternatives to double-plane interstitial implants have also been developed. William Beaumont University (Vicini et al. 2003b) and New York University (Formenti et al. 2004) have studied a conformal three-dimensional external-beam approach to APBI in pilot trials that were followed by a Phase II RTOG study, which proved the feasibility of this approach in a multicenter setting. Another approach developed in the United States that has proven to be the most popular method of APBI has been

to use a catheter balloon-based brachytherapy device that is inflated within the tumor bed and after-loaded with a high dose rate iridium source to deliver fractionated brachytherapy. The first balloon-based device approved by the Federal Drug Administration as a treatment-delivery device was the MammoSite (Cytec Corporation, Marlborough, MA, USA). Despite a lack of long-term safety and efficacy data, it has been estimated that over 40,000 of these devices have been sold for the purpose of APBI.

Arguably, the use of APBI has outpaced clinical data that prove that it is an appropriate alternative to whole breast treatment. The most mature data concerning the safety and efficacy of APBI to date were derived from studies investigating the double-plane brachytherapy approach; however, as mentioned, this approach represents a relatively small percentage of the current APBI practice pattern. Brachytherapy treatment using the MammoSite and other more recently developed balloon-based devices is fundamentally different from that of a double-plane interstitial implant in many ways, and although the early results of a registry trial tracking outcomes of patients treated with MammoSite ABPI appear promising, five-year data available on the safety and efficacy of treatments with this approach are still not available.

Currently, one major controversy is whether APBI should be considered an investigational treatment or be an accepted as an alternative to whole breast irradiation. Table 1.1 lists some reasons in favor of and against considering APBI to be an accepted standard of care. In 2003, the American Brachytherapy Society issued a report suggesting that APBI could be considered an appropriate treatment option for selected patients provided there was an adequate quality-assurance program in place (Arthur et al. 2003). In addition, the American Society of Breast Surgeons has also accepted APBI as a standard-of-care treatment option for appropriately selected candidates (American Society of Breast Surgeons 2008). More recently, the American Society of Therapeutic Radiology and Oncology has formed a partial breast radiation task group to develop a consensus statement regarding this issue.

Table 1.1 Should APBI be considered investigational or an accepted standard of care?

Reasons to consider APBI as an investigational treatment:
1. There have been no completed Phase III trials comparing more recent APBI approaches to whole breast treatment. The only APBI Phase III study completed to date showed this approach to be inferior.
2. The long-term efficacy of APBI with modern techniques remains unknown.
3. The appropriate patient-selection criteria for APBI treatment are unknown.
4. The late normal-tissue effects of APBI are unknown. The majority of long-term quality-of-life complications associated with hypofractionated radiation treatments develop years after completion of the treatment and are not necessarily related to the absence of short-term side effects.
Reasons to consider APBI an acceptable standard of care for selected patients:
1. Mature results from a comparative Phase III trial will likely not be available for a decade.
2. Whole breast irradiation is not an option for some breast cancer patients because of its protracted treatment schedule.
3. Initial institutional and Phase II multicenter trials investigating APBI have shown excellent local control rates and low rates of serious normal-tissue injury.

Many have contended that whole breast irradiation should continue to be the standard of care until longer-term safety and efficacy data are available from well-designed clinical trials of APBI (Buchholz 2003; McCormick 2003). This is particularly true of patients who are able to undergo whole breast treatment with only minor inconvenience. For those with favorable characteristics who are unable to receive a three- to four-week course of whole breast irradiation, APBI is a reasonable alternative that is likely be better than complete omission of radiation therapy, and is an appropriate consideration if the alternative is undergoing mastectomy to avoid the need for a course of whole breast treatment.

1.3 Controversies Regarding the Use of APBI

The major question concerning the use of APBI as an alternative to whole breast irradiation is whether APBI will prove to be as safe and effective. As previously highlighted, the benefits derived from radiation therapy as a component of breast-conservation are very significant. A meta-analysis of trials investigating whole breast irradiation after breast conservation surgery indicated has shown that radiation not only reduces the recurrence rate but also improves overall survival (Early Breast Cancer Trialists' Collaborative Group 2005). These considerations are particularly important in that other studies have indicated that the majority of patients are willing to accept the toxicity and inconvenience of the treatment if they perceive there to be decrease in the risk of recurrence—even if that decrease is just 1% (Ravdin et al. 1998). The success of whole breast treatment in women with favorable disease characteristics that may be considered appropriate for APBI is outstanding. For example, investigators from our institution reported only a 1.3% five-year breast recurrence risk for patients treated with breast-conserving surgery and whole breast irradiation between 1994 and 1996 (Cabioglu et al. 2005). Others have also reported annual risks of breast recurrences of approximately 0.5% (Fisher et al. 2002b). It is highly unlikely that APBI will improve upon such excellent results. However, when the risk for recurrence is so low, it may be appropriate to consider accepting a slightly higher risk due to the convenience benefits of ABPI. It will also require long-term outcome data from very large randomized trials to demonstrate whether APBI achieves an equivalent outcome to whole breast treatment.

The hypothesized degree of difference in outcome between the whole breast irradiation and APBI is highly dependent on patient-selection criteria. Factors such as patient age, margin status, pathological primary and lymph node stage, lymphovascular space invasion, grade, molecular features of the disease, presence of an extensive intraductal component of the disease, and use of systemic therapies all likely affect the volume of breast tissue that needs to be included within the radiation field in order to achieve optimal success.

1.3.1 What Volume of Breast Tissue Is at Risk for Residual Disease After Breast-Conserving Surgery?

The enthusiasm for considering less than whole breast treatment arose after considering the patterns of breast tumor recurrence in patients treated with breast-conservation without

adjuvant radiation therapy. Data from clinical trials suggest that, of the 30% of patients who experience recurrences when radiation therapy is not delivered, the vast majority (approximately 80%) will have the breast tumor recurrence develop at the site of the original disease (Veronesi et al. 2001; Clark et al. 1992; Liljegren et al. 1999). In addition, the absolute percentage of recurrences that develop at a location far from the tumor bed is low, ranging from 3% to 5% (Veronesi et al. 2001; Clark et al. 1992; Liljegren et al. 1999). From these data, many researchers have hypothesized that treatment directed solely to the site of the primary tumor may be adequate.

While it is clear that the tissue approximating the tumor bed is at greatest risk for residual disease, the appropriate volume around the tumor bed that would encompass the entire extent of residual disease is less clear. For patients with residual disease, it is likely that the greatest disease burden will be located next to the tumor-bed cavity and that the density will diminish as a function of distance from the cavity. Unfortunately, modern diagnostic tools do not permit clinicians to map out three-dimensional volumes containing residual cancer cells that act as the source of breast recurrences. Therefore, the target volumes included with APBI treatment tend to treat the tumor bed with a circumferential 1–2 cm additional margin. One concern about this empiric approach is that some studies that suggest that residual disease may also extend beyond the volumes included within APBI-targeted regions. Figure 1.1 shows a pictorial representation of this important concept. If a patient with a distribution of residual disease such as that shown in the figure does not receive any additional treatment, the regions closest to the tumor bed would be identified as the first sites of tumor recurrence. As effective treatment was given to an

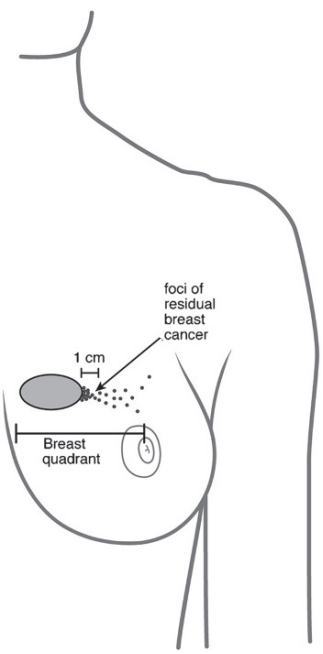

Fig. 1.1 Illustration of a medial tumor bed with residual disease extending from the tumor bed into upper lateral quadrant. If no radiation is given in this situation, it is likely that the tumor would recur first at the tumor bed site. However, it is clear that only giving radiation to a volume 1 cm in radius around the tumor site would also be an ineffective strategy (reprinted with permission from Buchholz et al. 2005)

extended volume around the tumor bed, recurrences within that treatment volume may be avoided, but there would continue to be a risk that some volume of disease would be left untreated. In such a scenario, the first site of recurrence would again be at the margin of the treatment. If the margin was extended, the most common site of first recurrence would then be at the new margin of treatment.

The concept described above is supported by studies of the distribution of disease in mastectomy specimens, which suggest that residual disease may extend beyond a 1–2.5 cm margin around the tumor excision cavity. One of the first pieces of evidence of this came from Roland Holland's work in 1985, in which mastectomy specimens from 282 women with localized T1 and T2 tumors were carefully examined (Holland et al. 1985). In this study, 28% of the cases of index tumors measuring 2 cm or smaller were found to have a focus of residual in situ or invasive carcinoma that was more than 2 cm from the primary tumor. Later, Faverly et al. (2001) mapped the disease extent in 135 patients with tumors smaller than 4 cm and again found that a large percentage of cases had a disease that extended beyond the margins around the primary tumor that are typically included in APBI treatment. Finally, Vaidya et al. (1996) also performed a careful three-dimensional pathologic analysis of whole-mount mastectomy specimens and reconstructed the residual tumor volume present after an initial lumpectomy. Residual disease was detected in 63% of the cases, and in 79% of these cases the disease extended beyond 25% of the breast volume surrounding the lumpectomy cavity. It is important to recognize that if such cases were treated with breast-conserving surgery without radiation, the most common site of recurrence would be the primary tumor site. However, these data indicate that this pattern of failure does not provide scientific rationale for directing therapies to a 1–2 cm margin of tissue around the tumor bed.

A more recent study explored the distribution of noninvasive components of disease as a function of patient age in patients with an invasive carcinoma. In this study, the radial distribution of noninvasive cancer was much greater for patients that were less than 40 years old compared to older patients. The one subgroup for whom the noninvasive component of disease remained within 5 mm of the invasive disease was patients who were 65 years or older and had a noninvasive component of low or intermediate grade (Imamura et al. 2000).

Data from studies investigating the value of magnetic resonance imaging (MRI) in patients with early-stage breast cancer also raise questions as to whether APBI treatment covers the appropriate volume of tissue at risk for residual disease. For example, a study reporting the results of MRI scans in 267 patients who were undergoing breast-conservation surgery found that 18% of patients had foci of disease outside the index tumor bed (Bedrosian et al. 2003). Furthermore, an international collaborative study that examined MRI scanning in 417 patients with early-stage breast cancer reported that 24% had incidental lesions detected away from their index site of disease (Bluemke et al. 2004). Seventy-one percent of these lesions were histologically confirmed to be cancer, and only 8% of these incidental lesions were detected by mammography. As MRI scans are not routinely performed prior to APBI, these studies suggest that a significant percentage of the patients treated with APBI will have a disease that extends beyond the treatment volume.

In addition to the pathologic and radiologic rationale for the use of whole breast treatment, the clinical data available to date suggest that APBI approaches may not include all areas at risk of residual disease. Attempts have been made to avoid whole breast irradiation

by treating the tumor bed plus a wider margin with surgery, but these approaches were unsuccessful. Specifically, the Milan III trial compared results using very wide excision (quadrantectomy) with and without whole breast irradiation (Veronesi et al. 2001). The ten-year rate of breast tumor recurrence rate in the quadrantectomy-only group was 24% vs. 6% in the surgery plus whole breast irradiation arm. The trial was not powered to analyze effects in particular subgroups, but a particularly high recurrence rate was noted in younger patients, and those with tumors had an extensive intraductal component in the surgery-only arm. Another important finding was that patients with positive lymph nodes who were randomized to not receive radiation therapy had a poorer survival ($p = 0.038$), again suggesting that the prevention of local recurrences by radiation is of paramount importance.

These data suggest that the volume of breast irradiated and the patient-selection criteria will in part determine the success of APBI. It should be recognized that the volume of breast treatment is determined both by the extent of surgical resection and by the type of APBI approach used. Ideally, the surgical resection should provide widely negative margins, and the APBI approach should treat as large a volume of tissue around the surgical cavity as possible. Indeed, some of the early data concerning outcomes after APBI treatments suggest that larger volumes are associated with lower rates of recurrence. For example, Vicini et al. (2007) at William Beaumont Hospital reported excellent ten-year tumor control rates in a single-institution experience that treated highly selected patients with a large-volume implant that included the tumor bed with 2 cm margins. However, Perera et al. (2003) at the London (Ontario) Regional Cancer Center performed implants that treated only the tumor bed as delineated by surgical clips, and reported a five-year breast tumor recurrence rate of 16%. Two-thirds of these recurrences developed outside of the implanted volume.

As these data indicate, one of the limitations on current APBI approaches is the uncertainty over what constitutes the most appropriate target volume. APBI is often considered to be a single therapeutic strategy, but it is important to recognize that different APBI approaches target different volumes of peritumoral tissue. In addition, the volume of tissue that must be included in APBI treatments is also dependent on the completeness of the surgical procedure. Currently there are neither good data nor a clear consensus on the optimal volume of breast tissue that should be treated with APBI, and the language used to describe treatment volumes is inconsistent. These factors make comparisons between institutional experiences difficult. There continues to be a need to standardize APBI treatments in order to provide a better understanding of benefits and shortcomings. A major advance in this area has been in the development of standards for Phase III APBI trials that are ongoing in the United States, Canada, and Europe.

1.3.2 Which Patients May Be the Most Appropriate for APBI?

Patient selection is a critical determinant of whether APBI treatments will likely include the region at risk of residual disease. Randomized trials that have investigated radiation omission have helped define the factors that are associated with a lower risk of having residual disease after surgery. These factors include older age (particularly over 70 years),

Table 1.2 Patient selection criteria for APBI

	ASBC (Holland et al. 1985)	ABS (Vicini et al. 2007)	NSABP/RTOG
Age	>50	≥45	>45
Histology	IDC, DCIS	Unifocal IDC	DCIS or any histology
Size	≤2 cm	≤3 cm	≤3 cm
Margins	≥2 mm	No tumor on ink	No tumor on ink
LN	Negative	Negative	<4 + LN

ASBC, American Society of Breast Surgeons; *ABS*, American Brachytherapy Society; *NSABP*, National Surgical Adjuvant Breast and Bowel Project; *RTOG*, Radiation Therapy Oncology Group; *DCIS*, ductal carcinoma in situ; *IDC*, infiltrating ductal carcinoma; *LN*, lymph node(s)

wide negative surgical margins, T1 primary disease, lack of an extensive intraductal component, lack of lobular histology, estrogen receptor-positive disease, treatment with systemic therapy, and pathologic N0 disease (Veronesi et al. 2001). These factors are all associated with a lower risk of recurrence when patients are treated with surgery alone, so it is likely that those with residual disease after surgery will have a lower disease burden that is more often localized near the tumor bed. There is no uniform consensus on the patient and disease characteristics that are appropriate for considering APBI. Table 1.2 provides details about statements concerning patient selection that have been issued by the American Society of Breast Surgeons and the American Brachytherapy Society (Arthur et al. 2003; American Society of Breast Surgeons 2008). Also included are the eligibility criteria for an ongoing National Surgical Adjuvant Breast and Bowel Project (NSABP)/RTOG Phase III trial that is comparing APBI to whole breast treatment.

1.3.3 Does APBI Deliver an Adequate Radiation Dose?

A final issue of importance when considering whether APBI will prove to be as effective as whole breast treatment concerns the dose of radiation. In general, whole breast irradiation plus a tumor-bed boost provides a significantly higher biologically effective dose to the volume of the breast included in APBI treatments. Although a variety of dose schedules have been used in APBI treatments, the most common prescription dose (and the dose selected for the planned American Phase III clinical trial) is 34 Gy delivered in ten fractions, with fractions given twice daily over a period of five days. Rosenstein et al. (2004) recently estimated the biological equivalent dose (BED) of this schedule for tumors and late-responding normal tissues compared to standard whole breast treatment plus a tumor-bed boost. The BED for the tumor was 1.7 times higher for the whole breast plus boost schedule compared to the 34 Gy in ten fractions APBI schedule (assuming an alpha/beta ratio for tumor of 10 Gy). These data indicate that the dose to the area at greatest risk of disease is less with APBI. This is an important consideration given that trials investigating use vs. omission of a tumor-bed boost after whole breast treatment suggest that dose escalation minimizes the risk of recurrence (Bartelink et al. 2002; Romestaing et al. 1997).

Estimating the success of APBI through calculations of BED significantly oversimplifies a very complex process. Most APBI techniques, particularly MammoSite, have significant dose inhomogeneity within the treated volume. For example, the treatment dose with a MammoSite is almost twice as high at the surface of the balloon as it is at the prescription dose point located 1 cm from the balloon. Therefore, regions within the target volume may receive significantly higher BEDs if they are close to the applicator surface. In addition, the effectiveness of radiation is also dependent on the treatment time, and the shortened treatment course associated with APBI may reduce the risk of tumor-cell repopulation during treatment. Finally, the biological properties of breast cancers vary; correspondingly, the alpha/beta ratios and proliferation rates are also likely to vary from case to case. Therefore, dose comparisons between the two treatment schedules are difficult to estimate. The fractionation schedule and total dose used for APBI may prove appropriate for estrogen-receptor, low-grade, "luminal" cancers, but less optimal for triple negative disease or "basal-like" cancers.

1.3.4 Can APBI Increase Rates of Normal Tissue Injury?

Data from Phase II trials and institutional reports suggest that APBI approaches are associated with low rates of acute normal-tissue injuries (Vicini et al. 2003a,b, 2007, 2008; Veronesi et al. 2003; Vaidya et al. 2004; Formenti et al. 2004). However, the more important question that is yet to be fully answered is whether late normal-tissue complications may be increased. As highlighted above, dosages of 34 Gy in ten fractions provide a lower BED to late-responding normal tissues compared to 66 Gy in 33 fractions and would thus be predicted to carry less of a risk for injury (Rosenstein et al. 2004). Furthermore, the decreased volume of irradiated tissue will also be an important factor in decreasing the risk of injury with APBI, and this component is not considered in BED calculations. One possible concern, however, is that (as previously noted) many APBI techniques have significant dose inhomogeneity within the treatment volume. For example, a brachytherapy catheter placed against a rib or the chest wall may give a significantly higher BED to this important normal tissue than conventional therapy. Therefore, it is important that these promising APBI techniques be investigated in protocols that carefully track and report late radiation injuries. Late normal-tissue injuries resulting from radiation are difficult to study in that they may occur many years after treatment. For example, in a study of breast cancer patients who were treated with a hypofractionated radiation regimen, Bentzen et al. (1990) found that it took 15 years of follow-up after treatment to detect 90% of the ultimate incidence of late grade 3 complications.

1.3.5 Convenience Benefits of APBI

It is clear that APBI offers a convenience advantage over whole breast irradiation. Five-day APBI treatment approaches are potentially 85% shorter than conventional whole breast

plus tumor-bed boost therapy. However, for patients treated with surgery and chemotherapy, the shortened course of radiation would have only a 10–15% decrease in the length of the overall breast cancer treatment. In addition, it should be recognized that for elderly patients with stage I disease, two Phase III trials indicated equivalent five-year control and toxicity with a three-week hypofractionated whole breast irradiation schedule compared to a five-week irradiation schedule (Whelan et al. 2002; Dewar et al. 2007). When compared to this whole breast treatment approach, most APBI schedules require only six fewer treatment visits, making the convenience benefits of APBI less relevant. Finally, some patients may find the twice-daily treatment required by most APBI schemes to cause a greater disruption of their lives than once-daily treatment.

1.3.6 Will APBI Increase Access to Medical Facilities and Reduce Costs?

One potential advantage of APBI would be to improve access to radiation therapy facilities. However, unlike in other countries, few patients in the United States endure long delays before starting radiation therapy because of limited access to treatment machines. In addition, most APBI approaches require significantly greater treatment planning time and time for quality assurance than conventional external-beam whole breast treatments. Therefore, the total impact of APBI in improving access to care may not be significant in the United States.

With respect to treatment cost, there is currently no evidence that treatment with either MammoSite or a double-plane interstitial implant costs less than conventional whole breast irradiation followed by a boost. Suh et al. (2003) calculated direct medical costs and Medicare fee schedules, and modeled the treatment costs of various breast irradiation approaches to the patients and society, and found that APBI using either double-plane implants or balloon-based brachytherapy techniques was significantly more expensive than conventional whole breast plus tumor-bed boost therapy. Due to the complexity of the treatment and special equipment required, it is possible that APBI would have been less likely to have been favorably received by the medical community without the enhanced reimbursements charged for these treatments.

1.4 Conclusions

APBI has the potential to be an exciting improvement in radiation treatment for patients with early-stage breast cancer. However, new advances in breast cancer treatment should be carefully evaluated in clinical trials that are appropriately designed to assess safety and efficacy end points. Premature adoption of initially promising therapies can lead to long-term setbacks. A perfect example of this in breast cancer was the premature adoption of high-dose chemotherapy with bone-marrow transplant. Widespread adoption of this approach after favorable short-term Phase II trials impaired the completion of Phase III studies. As most of the Phase III trials were eventually negative, it became apparent that thousands of patients received a treatment that was later proven to be less than optimal.

Studying APBI as an alternative to whole breast treatment is difficult because it requires long-term follow-up. Furthermore, depending on the patient-selection criteria used, differences between these two approaches may be subtle, and detecting such a difference in comparative trials will require thousands of patients. To date, such trials have not been completed. The only relatively mature studies available concerning the efficacy and safety of APBI have been from institutional studies using double-plane interstitial brachytherapy as the APBI technique. No long-term outcome data are available for the external-beam or MammoSite APBI approaches.

It is imperative to recognize that short-term success may not translate into satisfactory long-term results with respect to both efficacy and toxicity. As previously indicated, the complications of a hypofractionated APBI scheme may not appear for many years. An example of the necessity of long-term follow-up is found in the unsuccessful Phase II trial at Guy's Hospital, which investigated APBI with an interstitial brachytherapy technique. The original publication of the Guy's Hospital experience reported "encouraging" results in 1991 (Fentiman et al. 1991); however, in 1996, as the data matured, the authors concluded that this approach was inadequate (Fentiman et al. 1996).

Modern conventional whole breast irradiation provides excellent outcomes for patients treated with breast conservation, providing a high benchmark against which new treatments must be compared. It is highly unlikely that APBI will improve upon these excellent results, because it is a less intensive approach with respect to both volume of treatment and the dose delivered to the targeted treatment volume. Whereas some patients may accept a small increase in the probability of recurrence for the added convenience of APBI, most breast cancer patients report that they wish to do everything possible to minimize this risk.

Fortunately, Phase III randomized trials in the United States, Europe, and Canada are being successfully conducted to help define the efficacy and potential limitations of APBI compared to whole breast treatment. It is hoped that these studies will refine our understanding of APBI and determine its appropriate role as a component of breast-conserving therapy.

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Who Is a Candidate for APBI?

2

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2.1 Introduction

There are many aspects to consider when determining whether a woman is an appropriate candidate for accelerated partial breast irradiation (APBI). First, however, it is necessary to have a full appreciation of the challenge that this new approach presents to the conventional treatment paradigm for early-stage breast cancer. Until recently, the accepted local management of breast cancer has always stressed the importance of treatment directed to the entire breast. Over the past three decades, the management of early breast cancer has evolved from radical en bloc regional resection to breast-conserving surgery followed by radiotherapy, but the minimal target tissue requirement has always included the entire breast. Prior to screening mammograms, breast cancer went undetected until clinically evident, and often presented in a locally advanced stage. However, as public awareness has increased regarding the role of mammographic screening, breast cancer is increasingly detected earlier in the disease process and frequently presents as a small nonpalpable tumor. In view of this changed clinical presentation, it is appropriate to ask whether there should be a parallel reduction in the extent of local treatment.

The concept that the extent of treatment to the breast could be safely reduced was first tested by moving from mastectomy to lumpectomy. When introduced, the concept of breast preservation was initially considered to be extreme and dangerous. Many felt that to compromise the radical extent of the surgical resection would result in a diminished ability to cure the cancer. It was the carefully measured steps of a handful of pioneering surgeons and radiation oncologists that ultimately led to the widespread acceptance that breast conservation was both safe and practical. This profound shift in treatment paradigm nonetheless held fast to the philosophy of treating the entire breast with the addition of adjuvant

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radiotherapy—a practice that was ultimately embraced with remarkable speed, as the requisite radiation therapy technology was widely available and easily applied.

Despite initial controversy, many years of rigorous investigation led to breast conservation becoming established as an appropriate alternative to mastectomy in properly selected early-stage breast cancer. In 1990, based upon early but compelling clinical trial results, the National Institutes of Health published a consensus statement on early-stage breast cancer supporting breast-conservation surgery followed by radiotherapy as an appropriate method of primary therapy for women with stage I–II breast cancer (NIH 1990). More recently, survival data after a twenty-year follow-up of large prospectively randomized studies have become available that definitively establish the equivalence of lumpectomy followed by whole breast radiotherapy as compared to mastectomy (Fisher et al. 2002; Veronesi et al. 2002). However, despite this overwhelming evidence, many women who are eligible for breast-conservation therapy continue to lose their breasts to mastectomy (Athas et al. 2000; Hebert-Croteau et al. 1999; Hahn et al. 2003; Du et al. 1999). This phenomenon is likely due to many factors, but the logistical barriers of treatment duration and travel distance encountered with the standard 5–7 weeks of daily whole breast radiotherapy can be a hardship for many women and play a role in treatment decisions. These factors may push a number of women towards mastectomy (when they would rather preserve the breast) or towards lumpectomy only (where they face an increased risk of in-breast failure). The desire to avoid conventional whole breast radiotherapy, as a result of either patient preference or physician bias, has been documented through data from the National Cancer Institute Surveillance, Epidemiology, and End Results registry, which finds a steady increase in the rate of breast-conserving surgery without radiotherapy in patients diagnosed with either invasive or noninvasive disease (Nattinger et al. 2000; Baxter et al. 2004).

Local treatment options for breast cancer depend upon the definition of the tissue at risk. If the target tissue following lumpectomy is indeed the whole breast, then the constraints of normal tissue tolerance dictate that radiation treatment be delivered daily over several weeks to achieve the dose necessary to eradicate microscopic residual disease. However, if the volume of the target can be substantially reduced to include only a portion of the breast, then dose–volume relationships strongly suggest that the radiation treatment course can be safely accelerated and completed in a matter of days. As such, APBI could potentially overcome the barriers presented by conventional whole breast irradiation, and provide more patients with the option of breast-conservation treatment. Additionally, APBI may provide the option of breast preservation for patients who are not currently considered as candidates; for example in patients who have experienced a local recurrence following breast conservation with whole breast irradiation, and in those diagnosed with breast cancer after having previously received mantle irradiation for Hodgkin's disease (Kuerer et al. 2004; Chadha et al. 2008).

As previously noted, the change in focus from a treatment target that encompasses the entire breast to one that encompasses only part of the breast represents a profound shift of the treatment paradigm, and one that is likely as controversial as the step from mastectomy to breast conservation. For a new treatment paradigm of this nature to be broadly accepted, four components are necessary: (1) supporting data with respect to both the pathologic anatomy of breast cancer and in-breast failure patterns; (2) appropriate patient selection

criteria; (3) partial breast treatment techniques that can be safely and widely performed, and; (4) solid clinical data that demonstrate that APBI can offer equivalent local control, complication rates, and cosmetic outcomes to those achieved with conventional whole breast radiotherapy. The importance of achieving all four of these components is further highlighted when considering the recent meta-analysis data, which clearly demonstrate the importance of optimal local control on survival (Clarke and Darby 2005). This chapter will focus on a review of the supporting background data and appropriate patient selection criteria. Subsequent chapters will review treatment techniques and outcome data.

2.2 Pathologic Data

There are no data that unequivocally demonstrate that radiotherapy to the *entire* breast is required to achieve local control in patients with early-stage breast cancer. In fact, the literature regarding the pathologic anatomy of breast cancer offers limited guidance. Prior to 1990, most papers on this subject suggested that breast cancer was a diffuse, multicentric process that extended well beyond the confines of the clinically obvious tumor mass (Holland et al. 1985). Extrapolation of the findings of these older, methodologically limited studies to contemporary early-stage breast cancer patients is of questionable utility. Patients in these early studies presented with clinically advanced, palpable cancers that were subjected to mastectomy. These mastectomy specimens were then histologically examined for residual tumor after a "simulated" gross tumor excision that was meant to estimate the "lumpectomy" that would have been performed were breast conservation pursued. While of historical interest, such studies have little or no relevance to current breast cancer management. In this era of meticulous mammographic, surgical, and pathologic assessment techniques, patients present more commonly with small, nonpalpable tumors that are completely resected with carefully evaluated microscopically negative margins. In contemporary studies of patients managed in accordance with such modern practice, limited pathologic data are available that detail the extent of microscopic residual disease within the breast after "lumpectomy"—information that would be directly relevant for defining the remaining target tissue. The contemporary studies that have addressed this question applied extensive microscopic evaluations of both mastectomy and quadrantectomy specimens and have consistently found that residual disease beyond the clinically evident primary tumor mass is most likely ductal carcinoma in situ (DCIS) (Faverly et al. 1992, 1994; Imamura et al. 2000; Ohtake et al. 1995). These studies have consistently presented evidence that suggests that the extension of tumor for most patients is limited to less than 1 cm from the primary lesion. However, until Vicini et al. (2004), estimates of residual microscopic disease extent beyond a surgically obtained negative microscopic margin have not been possible. In this study, lumpectomy re-excision specimens were examined to determine the perpendicular extent of any residual microscopic extent. It was found that, in >90% of cases where the lumpectomy achieved a negative microscopic margin as defined by the National Surgical Breast and Bowel Project (no tumor on ink), any component of residual microscopic disease was limited to within 1 cm.

2.3 Anatomic Patterns of In-Breast Failure After Breast-Conserving Treatment

The strongest support for partial breast treatment as an appropriate option for early-stage breast cancer is the anatomic location of in-breast failures following lumpectomy. Three prospective randomized studies of lumpectomy only vs. lumpectomy plus whole breast radiotherapy have documented the specific location in the breast of local recurrences (Uppsala-Oreboro Breast Cancer Study Group 1990; Veronesi et al. 2001a; Clark et al. 1992). The location of in-breast failure was categorized as either adjacent to the lumpectomy cavity (true recurrence) or far removed from the lumpectomy cavity ("elsewhere failure") (Uppsala-Oreboro Breast Cancer Study Group 1990; Veronesi et al. 2001a; Clark et al. 1992). Each of these studies found that the primary location of treatment failure is at the site of lumpectomy, and "elsewhere failures" occur at a rate of less than four percent. Of particular note, "elsewhere failures" occurred with equal frequency in both the group of patients receiving whole breast radiotherapy and the group treated with lumpectomy alone (Table 2.1). The conclusion drawn from these data is that "elsewhere failures" likely represent a new primary tumor, and that the primary benefit of whole breast radiotherapy is to prevent breast cancer recurrence in the lumpectomy bed (Morrow 2002). This is compelling evidence to support the view that equivalent rates of local control may be achieved if radiotherapy is directed to the lumpectomy cavity plus a 1–2 cm margin.

If a partial breast target can be appropriately defined, a direct follow-on question would ask if comparable local control could be achieved with a wider local excision and no radiotherapy. The answer to this is complex but, under most circumstances, appears to be "no," as prospective clinical trials of partial mastectomy alone have been associated with high rates of local recurrence. For example, in a study reported by Veronesi et al. (2001a),

Table 2.1 Location of in-breast failure reported in prospective randomized trials investigating breast conservation therapy (reproduced with permission from Arthur 2003)

Author	Pt no.	Median f/u mo's	In-breast failures (%)		True recurrence[b] (%)		Elsewhere failures[c] (%)	
			No WBI[a]	WBI	No WBI	WBI	No WBI	WBI
Veronesi et al. (2001a)	579	109	20.5	5.4	17.6	3.7	2.9	0.7
Clark et al. (1992)	837	43	25.7	5.5	22.1	4.5	3.5	1.0
Uppsala-Oreboro (1990)	381	33	5.7	2.2	4.1	1.6	1.5	0.5

[a]Postlumpectomy whole breast radiotherapy
[b]Recurrence at the site of lumpectomy
[c]Recurrence beyond the site of lumpectomy

quadrantectomy was compared to quadrantectomy plus whole breast radiotherapy, and local failure was observed in 23.5% vs. 5.8%, respectively. The local failure rate was found to be independent of the extent of partial breast resection, which indicates that radiotherapy is required in addition to conservative surgery. The inability to remove all microscopic disease is not necessarily due to an inadequacy of surgery, but rather to unrecognized multifocality, unrecognized microscopic disease extent, and/or the inadequacy of microscopic margin assessment (Fisher et al. 1999).

2.4 Proper Selection Criteria

The importance of proper patient selection for APBI cannot be overstated. A comprehensive evaluation must be performed to include patient and tumor characteristics as well as technical feasibility. Further, patients must be informed participants in the treatment decision process, with a balanced educational approach employed when obtaining informed consent.

The formation of selection criteria for APBI has to date been a careful exercise of choosing specific patient and tumor characteristics to minimize the risk of tumor recurrence or complications. The goal of current criteria are to identify patients where the tissue at risk postlumpectomy is most likely to be in immediate proximity to the excision cavity, and the risk of harboring residual microscopic disease at remote locations "elsewhere" within the breast is limited (Recht and Houlihan 1995).

All selection criteria must include patients who, first and foremost, are appropriate candidates for breast conservation therapy. Patients with documented multicentric tumor and who are at increased risk for complications (pregnancy, connective tissue disorders) are excluded. Small primary tumor size, older age, no evidence of axillary nodal metastases, histology limited to invasive ductal carcinoma, and negative microscopic margins of excision are the primary criteria currently applied. However, a comparison of different institutional experiences shows that, despite their common cautious theme, there is some variability in the criteria chosen (Table 2.2). The presence of an extensive intraductal component (EIC), up to three positive axillary nodes, infiltrating lobular histology, pure DCIS, and young age have been allowed in some series (Vicini et al. 2002, 2003b, 2007a; Arthur et al. 2003, 2008; King et al. 2000; Wazer et al. 2001; 2002; Kaufman et al. 2007; Lawenda et al. 2003; Krishnan et al. 2001; Kuske and Bolton 1995; Kuske et al. 2002, 2004; Polgar et al. 2002, 2005; Strnad et al. 2004; Ott et al. 2007). Most authors currently advocate the position that the presence of any of these features should exclude patients from consideration for APBI (Arthur et al. 2002; American Brachytherapy Society 2007; American Society of Breast Surgeons 2008; Vicini et al. 2003a). This advocacy was further exemplified through review of the details of patient and tumor characteristics of those who were actually treated in the experiences with greater than five-year follow-up and reporting excellent in-breast control. In these successful treatment experiences, the majority of patients treated represent conservative selection criteria; see Table 2.3 (Vicini et al. 2003b, 2007a; Wazer et al. 2002; Kaufman et al. 2007; Arthur et al. 2008; Polgar et al. 2004, 2007). It should be noted that the median age in the majority of these experiences was >60, tumor size was <1.5 cm, and they were estrogen receptor positive and axillary lymph node negative.

Table 2.2 Selection criteria and quality assurance methods in successful partial breast irradiation experiences

Series	# Pts	Median tumor size (range) (mm)	EIC±	IDC only	N±	Age limit (years)	Negative margins required	Quality assurance technique[a]
William Beaumont Hospital (Vicini et al. 2003b, 2007a)	199	11	No	Yes	Yes[b] (13%)	>45	Yes (≥2 mm)	Postimplant CT
Virginia Commonwealth University (Arthur et al. 2003)	44	11 (3–40)	No	No (9%)	Yes (18%)	>45[c]	Yes	Postimplant CT
Oschner Clinic (King et al. 2000)	51	14 (mean)	Yes (14%)	No	Yes (18%)	>45	Yes	Postimplant CT
Tufts/Brown Universities (Wazer et al. 2001, 2002; Kaufman et al. 2007)	33	1.3 (0.5–2.0)	Yes (55%)	Yes	Yes (9%)	None	Yes	Direct visualization or orthogonal pair
Massachusetts General Hospital (Lawenda et al. 2003)	48	? (<20)	No	?	No	None	Yes	Direct visualization or orthogonal pair
University of Kansas (Krishnan et al. 2001)	25	10 (mean)	No	No (12% ILC)	No	>45	No[d]	Orthogonal pair
RTOG 95-17 (Kuske and Bolton 1995; Kuske and Arthur 2002, 2004; Arthur et al. 2008)	99	? (<3 cm)	No	Yes	Yes	None	Yes	Orthogonal pair
Budapest, Hungary (Polgar et al. 2002, 2005; Vicini et al. 2002)	81	13 (1–20)	No	Yes	Yes (micro-mets)	No	Yes (≥2 mm)	Variable angle orthogonal pair
German–Austrian Phase II trial (Strnad et al. 2004; Ott et al. 2007)	251	12.1 (mean)	No	?	Micro only	<35	Yes	Postimplant CT

EIC± included patients whose tumors contained an extensive intraductal component and the proportion of patients in the study with such findings (in parentheses); *IDC* is the patients with infiltrating ductal carcinomas only; if *no* then in the proportion of patients in the study that are non-IDC is given in parentheses; *N*± included patients with histologically positive axillary lymph nodes and the proportion of patients in the study with such findings (in parentheses); *?* refers to unknown/not reported

[a]Methods of assuring that the target received the prescription dose

[b]Patients with positive axillary nodes were excluded, beginning in 1995

[c]Early experience allowed four patients <45 years old

[d]Having a focus of microscopic disease at the margin allowed

Table 2.3 Published guidance on selection criteria—successful experiences with >5-year follow up

Institution		No. cases	Age (median)	Size (median)	Margin	ER+ (%)	LN− (%)
William Beaumont Hospital (Vicini et al. 2003b, 2007a)		199	65	11 mm	Neg	86	88
Tufts/Brown Universities (Wazer et al. 2002; Kaufman et al. 2007)		33	63 (mean)	13 mm (mean)	Neg	79	91
RTOG 95-17 (Arthur et al. 2008)	HDR	66	62	88% T1	Neg	80	80
	LDR	34	62	88% T1		64	79
Budapest, Hungary (Polgar et al. 2004) Phase I/II Trial		45	56	12 mm	Neg	84	80 (17% cNO)
Budapest, Hungary (Polgar et al. 2007) Phase III Trial		127	58	14 mm	Neg	91	90 (5% cNO)

ER+, estrogen receptor positive; *LN–*, negative axillary node dissection; *cN0*, clinically node negative, no dissection performed

In addition to clinical patient selection criteria, the one additional aspect that is crucial to the implementation of APBI is a quality assurance program that ensures that a treatment target is appropriately defined and dosimetrically covered within the intended prescription dose.

Examples of improper patient selection criteria and inadequate quality assurance methods for partial breast irradiation are described in Table 2.4. These trials represent early partial breast irradiation studies from Europe and convincingly demonstrate that poor selection and poor technique will lead to poor results (Fentiman et al. 1996; Magee et al. 1996; Ribeiro et al. 1993). Microscopic margin assessment was not employed in two of the studies, and it is unclear as to how many of the accrued patients would have been eligible for breast conservation treatment by modern standards. Further, the authors acknowledge problems in the quality assurance of the treatments, including poorly defined methods for target delineation and the inability to confirm dosimetric coverage of the target.

An additional treatment experience with a high rate of local failure that used interstitial brachytherapy for APBI has been reported from Canada (Perera et al. 2003). The patient cohort in this trial was comprised of 39 patients with T1 or T2 breast cancers and treated to 37.2 Gy in ten fractions (given twice daily) over one week. The five-year actuarial rate of ipsilateral breast recurrence was 16%, comprising six ipsilateral recurrences, of which two occurred within the lumpectomy site and four were categorized as new primaries located at a distance from the initial lesion. The local failure rate was higher then most institutional APBI experiences reported to date, and prompted a careful evaluation of the selection criteria and treatment technique employed. Nineteen percent of patients had infiltrating lobular carcinomas, and the minimum tumor-free margin width was 2 mm or smaller in 31% of patients. Of particular note, the median implant volume in this study was 30 cc (range: 10–111 cc), which is significantly smaller than the implant volumes reported in any other single-institution study (60–215 cc) (Vicini et al. 2003a). The high rate of local failure observed in this study is most likely due to an inadequately defined target volume which included only tissue encompassed within the confines of surgical clips. As surgical clips are

Table 2.4 Selection criteria and quality assurance methods in unsuccessful partial breast irradiation experiences: >15% in-breast failure rate

Author/institution	No. cases	Tumor size	EIC±	IDC only	N±	Age limit (years)	Negative margins required	Quality assurance technique[a]
Guy's Hospital, London, England (Fentiman et al. 1996)	27	<4 cm clinically (#3 were >4 cm)	Yes (30%)	No (16%)	Yes (32%)	<70	No Gross resection only	No
Christie Hospital Manchester, England (Magee et al. 1996)	353	<4 cm (75% were 2–4 cm)	Yes (3%)	No (15%)	? No dissection	<70	No Gross resection only	No
London Regional Cancer Center (Ribeiro et al. 1993; Perera et al. 2003)	39	Mean 15.6 cm; range (0.4–45 cm)	Yes (8%)	No	Yes[b] (21%)	None	Yes	Orthogonal pair, clip coverage

EIC± included patients whose tumors contained an extensive intraductal component and the proportion of patients in the study with such findings (in parentheses); *ILC* included patients with infiltrating lobular carcinomas and the proportion of patients in the study with such findings (in parentheses); *N*± included patients with histologically positive axillary lymph nodes and the proportion of patients in the study with such findings (in parentheses); *?* indicates unknown/not reported

[a]Methods of assuring that the target received the prescription dose

[b]Includes two patients with unknown nodal status

placed to define just the lumpectomy cavity, this would exclude immediately adjacent tissue-at-risk from the prescribed radiation dose.

Physician and patient interest in APBI has continued to increase. In response to this interest, two professional societies have issued recommendations regarding patient selection criteria. Both societies seek to incorporate the lessons learned from accumulated clinical experience and to provide the broader medical community with guidance in the selection of potentially eligible patients. The American Brachytherapy Society (ABS) and the American Society of Breast Surgeons (ASBS) have independently developed patient selection criteria that are generally viewed as both cautious and reasonable (Arthur et al. 2002; American Brachytherapy Society 2007; American Society of Breast Surgeons 2008). Both societies based their criteria recommendations on previously published data and focused on five characteristics felt to best define risk: patient age, tumor size, histologic type, axillary nodal status and microscopic margin assessment. These criteria are detailed in Table 2.5. The 2007 revised ABS criteria (American Brachytherapy Society 2007) include: patients ≥50 years of age (a noted change from the original age criteria of ≥45 years), invasive ductal carcinoma only, tumor size of ≤3 cm, negative resection margins (defined as "no tumor on ink"), and a negative axillary nodal status. Similar in concept to those promulgated by the ABS, the revised 2005 ASBS (American Society of Breast Surgeons 2008) patient selection criteria include: patients ≥45 years of age; invasive ductal carcinoma or DCIS; tumor size of ≤3 cm; negative resection margins (defined as at least 2 mm in all directions); and a negative axillary nodal status.

Interestingly, there is a notable discrepancy in the two sets of criteria in that the ASBS includes the treatment of DCIS, whereas the ABS does not. This difference of opinion reflects a surgical perspective largely influenced by research work on the conservative management of DCIS by Silverstein et al. (Silverstein 2000, 2003; Silverstein and Lagios 2007; American Society of Breast Surgeons 2008). These authors have claimed that when unifocal DCIS is resected with a pathologically confirmed circumferentially clear margin of >1 cm, then the addition of postoperative whole breast irradiation is of no benefit. These findings are neither universally accepted nor supported by prospective clinical trial data, but they are nonetheless embraced by many in the surgical community and have lead some

Table 2.5 Patient selection criteria

	American Brachytherapy Society (Arthur et al. 2002; American Brachytherapy Society; Arthur 2003)	American Society of Breast Surgeons (American Society of Breast Surgeons 2008; Arthur 2003)
Age (years)	≥50	≥45
Diagnosis	Invasive ductal carcinoma	Invasive ductal carcinoma or ductal carcinoma in situ
Size (cm)	≤3	≤3
Margin status	Negative: no tumor involving inked margin	Negative: at least 2 mm in all directions
Nodal status	Negative axillary lymph node dissection or sentinel lymph node evaluation	Negative axillary lymph node dissection or sentinel lymph node evaluation

to manage select cases of DCIS with wide resection only. Therefore, there has been a greater willingness amongst surgeons to include DCIS as candidates for APBI.

Currently, there are four principal methods of APBI: (1) multicatheter brachytherapy; (2) balloon-based brachytherapy (MammoSite Radiation Therapy System, RTS); (3) external beam three-dimensional conformal radiotherapy (3D-CRT), and; (4) intraoperative radiotherapy with electrons or 50 kV photons. The experience with intraoperative treatment has centered on Milan, Italy (electrons) and London, England (50 kV photons) (Veronesi et al. 2001b, 2003; Vaidya et al. 2001a,b, 2004). Most long-term clinical experience with APBI has been accumulated with multicatheter brachytherapy, MammoSite RTS, and 3D-CRT. The first technique employed for APBI was multicatheter interstitial brachytherapy, and this method is currently being tested in Phase III trials in both Europe and North America. The newer techniques of MammoSite RTS and 3D-CRT are being tested as part of a Phase III trial in North America.

Each APBI technique offers a unique treatment approach with advantages and disadvantages depending upon the individual patient and treatment anatomy. As such, a technical feasibility assessment for each technique must be included as part of each patient evaluation. An important technical requirement is the ability to definitively identify the target. This is followed by an evaluation of which technique will best optimize target coverage and limit the risk of toxicity. If APBI is to be performed intraoperatively such that lumpectomy is immediately followed by the placement of brachytherapy catheters or the MammoSite RTS, then the target geometry at the time of wound closure will need to be anticipated. However, there is an increasing preference to perform APBI only in the postoperative setting when pathologic review is complete and patient eligibility can be fully assessed. In the postlumpectomy setting, CT or ultrasound imaging is necessary to define the excision cavity as well to evaluate for technical feasibility. Both imaging information and physical examination are essential to determine APBI feasibility and to guide the choice of the method of delivery. Often, more than one approach can be successfully employed, at which point patient preference can be considered.

Multicatheter interstitial brachytherapy was the APBI technique originally employed, and as a consequence has generated clinical experiences with the longest follow-up duration. This APBI technique requires the highest level of skill but it also offers the most flexible and adaptable technique of the three now commonly used. With this approach, an implant can be constructed to encompass each individual target regardless of size, location, or proximity to skin and/or chest wall. Multicatheter brachytherapy allows the physician to be less concerned with whether or not one can cover the target, and to focus instead on how to optimize the construction of the implant. Factors such as catheter number and the direction and location of catheter exit and entrance sites need to be considered, as they may affect the degree of patient discomfort and the ultimate cosmetic result (punctate scarring) (Kuske 1999; Cuttino et al. 2005). Many treatment centers have mastered the ability to deliver multicatheter brachytherapy; however, an integral part of proper patient selection for this technique is the anticipation of a patient's ability to tolerate additional breast trauma, and whether the size of the implant and number of catheters needed to cover the target is excessive.

The MammoSite RTS is a treatment device designed to simplify brachytherapy treatment delivery for both the physician and the patient (Keisch et al. 2003a,b; Arthur and Vicini 2004).

Although its design goals have largely been achieved, additional technical aspects need to be considered in its clinical implementation. In contrast to a multicatheter implant, where the catheters are placed to conform to the target, the MammoSite RTS is placed so that the target conforms to the balloon surface. Appropriate patient selection is critically dependent upon the geometry and location of the lumpectomy cavity, and these are dependent upon the characteristics of the breast, the size of the tumor, and the communication between the surgeon and the radiation oncologist. When selecting a patient for MammoSite RTS, additional technical factors to consider include the achievable volume after balloon inflation, balloon symmetry, cavity conformance to the applicator, and balloon-to-skin distance. Preplacement assessment must anticipate whether the balloon can be inflated properly and the treatment dose delivered successfully. The size and shape of the cavity and the anticipated distance from the balloon surface and skin need to be carefully evaluated by either intraoperative visual inspection or postoperative imaging. Currently there are three different balloon designs: small and large spherical shapes and a single-sized ellipsoid shape. In order to minimize the risk of wasted unused catheters, complete cavity imaging and geometry assessment will help to determine whether the patient is an appropriate candidate for balloon brachytherapy, whether a balloon can be successfully placed, which balloon size/shape is optimal, and where on the surface of the breast would be the best entry point for the catheter. As a result of both the success of the MammoSite device as a single-entry, intracavitary treatment approach and its inability to be used to treat all patients, many new single-entry intracavitary devices have been developed and have only recently been introduced onto the market. These new devices include both intracavitary multicatheter devices such as the Strut-Adjusted Volume Implant or SAVI (Cianna Medical, Aliso Viejo, CA, USA) and the ClearPath APBI System (North American Scientific, Chatsworth, CA, USA), as well as balloon-based devices that include the Contura Multi-Lumen Radiation Balloon (MLB) (Senorx, Aliso Viejo, CA, USA) and the Axxent Electronic Brachytherapy System (Xoft, Inc. Fremont, CA, USA), which relies on a balloon-based catheter for treatment delivery.

The use of 3D-CRT has added a noninvasive option to techniques for APBI (Formenti et al. 2002, 2004; Vicini et al. 2003c, 2005, 2007b; Baglan et al. 2003; Taghian et al. 2006). With external beam treatment, beam configurations can be adjusted to achieve dosimetric goals set by the treating physicians. However, as with other APBI techniques, proper patient selection for 3D-CRT is critical. In contrast to brachytherapy, 3D-CRT results in a markedly increased integral dose, the degree of which is dependent upon the field arrangement. Because of the need to account for both beam entry and exit, dose limits to surrounding normal tissues need to be carefully considered. To accomplish this, patient selection for this technique must include a thorough assessment of the size, shape and location of the target with respect to patient anatomy. Two characteristics of the excision cavity have been identified that make 3D-CRT APBI difficult to apply. The first relates to the size of the defined target, as breathing motion and patient set-up error must be compensated for by further increasing the field size. This results in an increased dose to the surrounding structures such that normal tissues receive doses that exceed currently proscribed limits. In general, it appears that when the excision cavity volume exceeds 20% of the ipsilateral breast volume, 3D-CRT will exceed acceptable normal tissue dose–volume constraints. The second limiting factor for 3D-CRT APBI is the location of the excision cavity within

the breast. When the cavity is located in the lower, inner aspect of the left breast, the resultant dose to the heart may exceed acceptable constraints. In the upper portions of the breast, cavity location may limit the choice of beam arrangements that result in excessive radiation doses to normal ipsilateral breast tissue. Finally, more subjective limiting factors are the reproducibility of the patient set-up position, the position of the breast, and the positional reproducibility of the partial breast target. A fidgety patient and/or a patient with large, pendulous breasts represent examples of poor patient selection for this technique.

The appeal of completing postoperative radiation treatment in a short time period must not overshadow the need for the eligible patient to thoroughly understand the risks and benefits of this new adjuvant treatment approach. A central part of the patient selection process for APBI, just as for any treatment, must be a thorough informed consent. As physician and patient enthusiasm for APBI expands, we must remember—and our patients should know—that there is a marked difference in the scope and follow-up of clinical trial data support between standard breast conservation treatment with whole breast irradiation and APBI. Conventional whole breast irradiation is supported by large robust randomized trials and decades of common clinical practice. In comparison, there are less than a thousand women treated with APBI that have been followed for more than five years, and this necessitates combining results from several single institutional trials. This underscores the need to support Phase III clinical trials that compare APBI to whole breast irradiation. In the interim, though, if APBI is to be offered to patients, the clinician must carefully acknowledge the controversy over the role of APBI in the management of early breast cancer, and thoroughly educate the patient as to the justification for treating a partial breast target and the extent of clinical trial data currently available to support such an approach.

In summary, patient selection for APBI incorporates patient and tumor characteristics, technical considerations and a thorough informed consent. A cautious and highly selective approach is recommended, with the goal of maintaining in-breast control rates that approach 95–100% and acceptable cosmetic results, as achieved with whole breast irradiation. Ongoing studies will not only help further define the potential of APBI, but will also better define appropriate selection criteria so that as many women as possible will have the opportunity to pursue this innovative treatment approach.

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Pathologic Anatomy of Early-Stage Breast Cancer and Its Relevance to APBI: Defining the Target

3

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3.1 Determining the Extent of Disease Beyond the Lumpectomy Cavity

While several recent studies have demonstrated excellent five-year results using accelerated partial breast irradiation (APBI), the optimal clinical target volume (CTV) to be used in these patients has not been clearly defined (Vicini et al. 2003; Wallner et al. 2004). The CTV, which refers to the volume of breast tissue around the lumpectomy cavity requiring radiotherapy (RT), is crucial in determining the efficacy of adjuvant PBI in comparison to whole breast RT. It is important to consider whether PBI treats the appropriate volume of breast tissue at risk of harboring residual disease.

There are three bodies of data that can be used to help define the optimal CTV for APBI. These data include (1) mastectomy studies in which the distribution of cancer in the breast is correlated with the site of the initial tumor, (2) re-excision studies in which the presence, amount, and distance of residual disease is correlated with the initial tumor, and (3) published results with APBI in which the actual CTV used is correlated with the local recurrence rates.

3.1.1 Mastectomy Studies

The classic pathologic evaluation of mastectomy specimens performed by Holland et al. suggested that microscopic disease was present in a multicentric pattern with relatively high frequency. Breast cancer multifocality was studied in mastectomy specimens by correlated specimen radiography and histological techniques. It was found that up to 40% of patients undergoing breast-conserving therapy (BCT) might have residual tumor within the breast (Fig. 3.1). This analysis justified the concept that whole breast treatment, either

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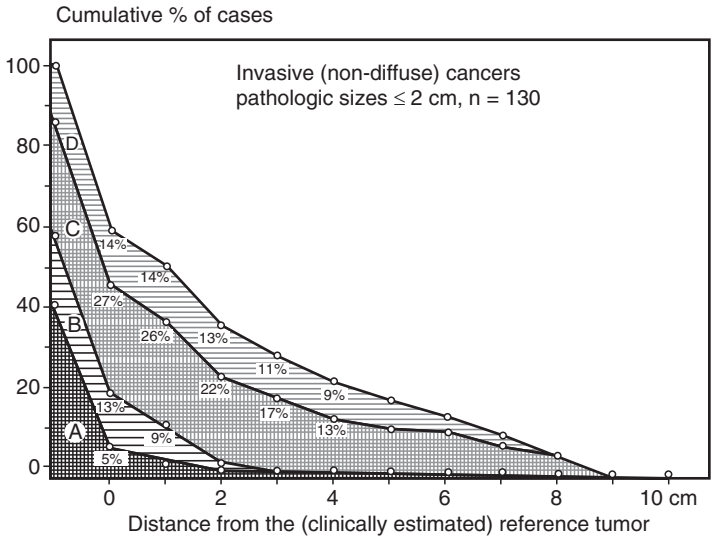

Fig. 3.1 Results from Holland et al.

with surgery or RT, was necessary to achieve local control. It was also one of the main sources of pathologic information that supported the use of whole breast RT as a component of standard BCT in the 1980s (Faverly et al. 1992; Holland et al. 1985).

However, since the publication of these data, there have been significant advances in the detection, selection, and management process of patients treated with BCT, and it is uncertain how many of the cases included in Holland's study would have been eligible for BCT by modern standards. In addition, this study suggested that residual disease could be found in the breast after simulated gross excisions >2 cm from the primary tumor in >29% of patients (with no extensive intraductal component). However, a review of the study details finds that the majority of cases were clinically detected (>80%) with a median tumor size of almost 4 cm. Additionally, the extensive mapping procedure used in the study was described as having an error of "less than 15 mm," which is significant when considering the possibility of performing PBI. The most important aspect to consider is that it is impossible to extrapolate the data generated from the "gross simulated excision" used in this study to a lumpectomy with negative microscopic margins routinely achieved in the clinic today. For example, in the analysis from William Beaumont Hospital, disease extended greater than 10 mm into the breast in approximately 26% of patients after an initial lumpectomy with positive margins vs. only 10% in patients with initial negative margins (Goldstein et al. 2003). As a result, it is difficult to know whether the findings of Holland's study can be applied to patients selected for BCT with modern mammographic evaluation and rigorous pathologic evaluation.

Contrary to Holland's data, recent publications applying thorough pathologic processing of quadrantectomy and mastectomy specimens from women considered appropriate for BCT by modern standards reveal that the microscopic extension of malignant cells is much less likely to be beyond 1 cm. For example, Ohtake et al. used a subgross and

stereomicroscopic technique to examine the extent of residual DCIS remaining in the breast after *actual* quadrantectomies in 20 patients with invasive cancer. Using a computer graphic, three-dimensional reconstruction of the mammary duct–lobular system, the average *maximum* distance of extension was 11.9 mm. Patients >50 years of age had a maximum extension of <8 mm. In contrast to Holland's study, the mean tumor size in this contemporary study was 1.7 cm (Ohtake et al. 1995). In a related study, Imamura et al. measured the maximal DCIS extension in 253 mastectomy specimens in women with invasive breast cancer. The authors found that the median DCIS extension was only 9 mm and was related to patient age. The maximum disease extension was measured in relation to the edge of the invasive tumor. In patients ≥40 years of age, the maximum extension was <9 mm in all cases (Imamura et al. 2000). The results of these studies point out two key issues. First, it is unlikely that the distribution of cancer in a breast in contemporary cases detected through screening mammography is similar to the findings in clinically detected cases from the early 1980s reported by Holland. Second, selection criteria for PBI clearly identify patients with smaller tumors and negative margins whose patterns of disease distribution in the breast are more likely to mirror those described in the Imamura, Ohtake and current studies. Hopefully, additional pathologic analyses using contemporary patients will help to further clarify these issues.

3.1.2 Re-excision Pathologic Studies

One primary re-excision study of patients treated at William Beaumont Hospital was conducted to help define the CTV for APBI. The study population originated with 441 patients derived from a dataset of 607 consecutive patients (reviewed by one pathologist) who underwent re-excision before RT (as part of their standard BCT). The surgical treatment in all patients included an initial excisional resection with a rim of normal breast parenchyma around the clinically apparent tumor or the tissue around the tip of the needle localization wire. Patients underwent a re-excision of the primary tumor site for inadequate margin distances or questionable postsurgical mammography results at the discretion of the surgeon or radiation oncologist (Goldstein et al. 2003; Vicini et al. 2004). The re-excision specimens were reviewed for presence, type, amount, and linear (radial) extension of cancer cells from the edge of the original margin. An example of the detailed pathologic analyses is shown in Fig. 3.2.

In 333 of these 441 cases, it was possible to measure the greatest perpendicular extension of any residual disease (DCIS or invasive cancer) from the edge of the original lumpectomy specimen. Because no PBI protocols allow patients with positive margins to be enrolled, only 134 cases with initial negative margins (per NSABP criteria) were studied (199 patients had initial positive margins). In more than 90% of these 134 patients, when any residual disease was present (38% of cases), it was limited to <10 mm from the edge of the original lumpectomy margin. When more restrictive criteria were used (e.g., initial excision specimens with margins that were negative, near:least amount, or near:intermediate amount with invasive carcinoma to specimen maximum dimension ratios of <0.3, or margins that are negative or near:least amount with invasive carcinoma to specimen maximum dimension

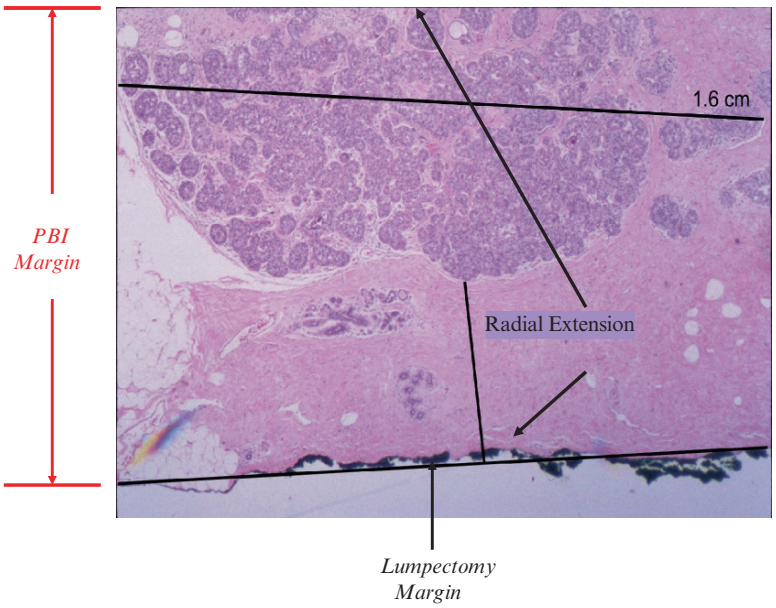

Fig. 3.2 Example of radial extension from re-excision analysis data from William Beaumont Hospital

Table 3.1 Factors in initial excision specimens and the presence of ≥1 cm extension of carcinoma in re-excision specimens (combining margin status with invasive carcinoma/specimen dimension ratio)

Initial excision specimen margin group	Percentage of re-excision specimens with ≥1 cm maximum extension (no. cases)			
	Initial excision specimen invasive carcinoma: specimen dimension ratio			
	<0.3	0.3–0.6	≥0.6	Total
Negative	0 (0/13)	0 (0/3)	100 (2/2)	28 (2/18)
Near:least amount	0 (0/40)	0 (0/13)	40 (2/5)	3 (2/58)
Near:intermediate amount	0 (0/10)	5 (1/20)	0 (0/4)	3 (1/34)
Near:greatest amount	36 (4/11)	57 (4/7)	0 (0/5)	35 (8/23)
Total (>1.0 cm extension)	5 (4/74)	12 (5/43)	25 (4/16)	9.7 (13/133)

ratios of <0.6), it was possible to accurately identify all 13 patients (9.7%) with disease extending ≥10 mm from the edge of the margin (Table 3.1).

These results suggest that, using NSABP criteria for negative margins (no tumor on ink), a margin of 10 mm beyond the tumor bed will be adequate to cover any residual disease remaining in the breast in >90% of patients treated with PBI. In addition, it is possible to accurately identify all patients with disease extending beyond 10 mm using more restrictive pathologic criteria.

3.1.2.1 Concerns Regarding Re-excision Analysis

Although the results in the current re-excision analysis suggest that a 1.0 cm margin beyond the lumpectomy cavity provides an adequate CTV for PBI (with negative margins per NSABP criteria), they are by no means conclusive. Clearly, it is not certain if the assumption that the maximal, perpendicular extension distance of invasive carcinoma or DCIS measured from the inner edge of the granulation tissue reaction in the re-excision specimen provides an accurate representation of residual cancer distribution in the breast. Because a variable amount of breast tissue is removed (or destroyed) around the lumpectomy edges through electrocautery or tissue processing, the actual extension of disease in some patients may be underestimated. However, the results obtained were from numerous surgeons with variable surgical techniques. Despite obvious inconsistencies, the range and standard deviation of maximal extension in all 333 cases were very small. Combined with the clinical results obtained with PBI, this pathologic analysis does provide some assurance that a 1.0 cm margin beyond the lumpectomy cavity may be sufficient for most patients treated with PBI. Additional similar pathologic studies and long-term clinical PBI data are needed to help clarify this issue.

3.1.3 Recurrence Patterns in PBI

A multitude of clinical studies utilizing APBI that can correlate the volume of tissue irradiated (i.e., CTV) with local recurrences have been published for patients treated with multicatheter interstitial brachytherapy, and more recently intracavitary breast brachytherapy and three-dimensional external beam radiation therapy techniques (Kestin et al. 2000; Vicini et al. 1999, 2008a) (Table 3.2).

Table 3.2 Prospective randomized trials of lumpectomy with/without RT

Trial	No. patients	Tumor size (cm)	Surgery	% Patients with recurrence		% Reduction in recurrence
				CS alone	CS + RT	(CS vs. CS + RT)
NSABP B06 (Fisher et al. 2002)	1,265	<4.0	WE	36	12	67
Milan III (Veronesi et al. 1993)	601	<2.5	Q	24	6	75
Scottish (Forrest et al. 1996)	584	<4.0	WE	5	6	75
Sweden (Liljegren et al. 1994)	381	<2.0	Q	24	9	63
Ontario (Clark et al. 1996)	837	<4.0	WE	35	11	69
British (Renton et al. 1996)	399	<5.0	WE	35	13	63

3.1.3.1 Multicatheter Interstitial Brachytherapy

Multicatheter interstitial brachytherapy (MIB) is the APBI technique with the longest follow-up. It entails the placement of numerous catheters (typically 10–20) in the breast at the time of initial lumpectomy or shortly thereafter. The catheters are positioned to encompass the lumpectomy cavity in appropriate planes to allow a homogeneous dose to be delivered to the tumor bed with a defined margin (typically 10–15 mm). The catheters are then after-loaded with either low dose rate (LDR) or high dose rate (HDR) sources to deliver the prescribed dose to the targeted breast tissue.

Several Phase II and III studies have been reported using MIB. The group at the Oschner clinic was among the first to evaluate MIB. Eighty-four patients with invasive tumors of less than 4 cm, negative surgical margins, and 0–3 positive lymph nodes were implanted and treated with either HDR or LDR brachytherapy. A 2.5% rate of ipsilateral breast tumor recurrence (IBTR) was reported with a median follow-up of 84 months. Compared to a case-controlled cohort treated with whole breast RT, no significant difference in IBTR or local–regional failures was noted with MIB (Vicini et al. 2003; King et al. 2000). Vicini et al. (2003) reported on 199 patients older than 40 years of age (most with tumors of less than 3 cm, excision margins of greater than 2 mm, and negative axillary lymph node sampling) treated with MIB using either HDR or LDR brachytherapy. At five years, matched pair analysis of these MIB patients showed equivalent local control of 1% as compared with patients treated with whole breast RT. Furthermore, the Radiation Therapy Oncology Group (RTOG) 95–17 conducted a Phase I/II trial to evaluate MIB. This study included patients with small tumors (<3 cm), negative margins, 0–3 axillary lymph nodes without extracapsular extension, treated with either HDR or LDR brachytherapy. After a median follow-up of 74 months, the HDR brachytherapy group revealed an in-breast recurrence rate of 3%, and the LDR brachytherapy group had a 6% in-breast recurrence rate (Arthur et al. 2008; Kuske et al. 2006).

3.1.3.2 Intracavitary Brachytherapy

Given the technical challenges of MIB, intracavitary brachytherapy has become the most widely used APBI technique. The most common device, MammoSite (Cytyc Corporation, Marlborough, MA, USA) is a single-lumen breast brachytherapy catheter that is temporarily inserted through a single puncture site on the skin of the breast and positioned centrally within the lumpectomy cavity. The inflated balloon allows a single radioactive source to be temporarily positioned in the center of the balloon to deliver targeted RT dose to tissues immediately surrounding the balloon surface (i.e., lumpectomy cavity). A total of 34 Gy (3.4 Gy per fraction, twice daily) is prescribed to 1 cm from the balloon surface.

Keisch et al. (2003) reported the initial experience with the MammoSite brachytherapy device in a prospective multi-institutional study. Eligible patients included those older than 45 years of age, a tumor less than 2 cm in size, negative surgical margins, and no axillary disease. At a median follow-up of five years, there were no recurrences. Recently, the American

Society of Breast Surgeons (ASBS) has reported on the largest experience of patients treated with MammoSite (Vicini et al. 2008a). After a median follow-up of 37.5 months, of the 1,440 patients with early -tage breast cancer, only 23 (1.6%) developed an IBTR.

3.1.3.3 Three-Dimensional Conformal External-Beam Radiation Therapy

The most recent technique developed for the delivery of APBI is that of three-dimensional conformal external-beam radiation therapy (3D-CRT). As opposed to brachytherapy, this noninvasive technique uses external-beam radiation to deliver APBI to the lumpectomy cavity and a margin of 10–15 mm (with an extra margin of 10 mm added for setup error). 3D-CRT has the least number of patients treated and limited follow-up. The RTOG has conducted a Phase I/II trial to evaluate the feasibility and reproducibility of 3D-CRT in delivering APBI. There have been very few variances, indicating that this technique is reproducible at a multi-institutional level (Vicini et al. 2005). However, since this is the most recent technique of APBI, the rates of recurrence using 3D-CRT are yet to be reported. Unpublished data with a short-term follow-up seem to indicate similar low recurrence rates to those obtained with other techniques.

In the above clinical studies, most have included the lumpectomy cavity with 10–15 mm margin for the CTV, and the local recurrences observed have remained low.

3.1.4 Composite Disease Extension

Using the above studies to delineate the target volume for partial breast irradiation, the composite maximum intraductal extension can be estimated. The series by Imamura and Ohtake concluded that the average maximum intraductal extension was 9 mm and 11.9 mm, respectively. The William Beaumont Hospital data using re-excision analysis revealed a maximum radial extension of <10 mm in 90% of patients. Therefore, if a radiation dose of PBI is prescribed to 1 cm around the lumpectomy cavity, the pathologic area of risk should be covered.

3.2 Impact of Radiation on Local Recurrences

The rationale for giving adjuvant whole breast RT after lumpectomy in patients treated with BCT is that even after tumor excision with negative margins, many patients may harbor significant areas of occult, residual microscopic disease in the breast. Therefore, whole breast radiation therapy must be delivered to the lumpectomy cavity and the entire breast in an effort to “sterilize” any residual foci of cancer. There are multiple randomized trials comparing breast-conserving surgery alone versus breast-conserving surgery plus RT (see Table 3.3). The percentage of patients with elsewhere failures is not impacted by

Table 3.3 The impact of whole breast radiation therapy on "elsewhere" failures

	% Elsewhere failures	
Trial	CS alone	CS + RT
NSABP B06 (Fisher et al. 2002)	2.7 (17/636)	3.8 (24/629)
Ontario (Clark et al. 1992)	3.5 (15/421)	0.9 (4/416)
Milan (Veronesi et al. 2002)	2.8 (8/280)	0.6 (2/299)
Finland	5.5 (4/72)	5.0 (4/80)
Sweden (Liljegren et al. 1994)	1.5 (3/194)	0.5 (1/187)
Range	1.5–5.5	0.5–5.0

the addition of radiation therapy. In the study by Veronesi et al. (2002) with 20 years of follow-up, the overall rate of ipsilateral breast recurrence was nearly identical to the rate of contralateral carcinoma in women who received postoperative whole breast RT, suggesting that elective treatment with RT beyond the quadrantectomy (i.e., surgical) bed provided minimal additional benefit. Patterns of failure after standard BCT and after excision alone (without adjuvant radiation) show that the large majority of recurrences are in the immediate vicinity of the tumor bed. This suggests that the major value of postlumpectomy RT is to eradicate residual disease in the region of the tumor bed, and that areas of occult disease in the remainder of the breast maybe of little practical significance in many patients.

As discussed above, regardless of technique, clinical results of APBI continue to show that the risk of IBTRs is quite low. The three- to five-year rate of IBTR has ranged from 0% to 6% (Vicini et al. 2003, 2008b). Despite the small number of recurrences with APBI, much effort has been expended to correctly classify these into either "true recurrences" or "elsewhere" failures (Smith et al. 2000; Krauss et al. 2004). Unfortunately, the parameters that have been used in the past to distinguish the type of IBTR (e.g., recurrence location within the breast, tumor histology, flow cytometry, and time to IBTR) do not provide a definitive, reproducible characterization of a newly identified, malignant lesion in a previously treated breast, and the application of variable parameters can have a significant impact on the reported rates and patterns of recurrence. The rates of elsewhere failures vs. true recurrences vary depending on the classification scheme employed. Since clinical estimates can be inaccurate in defining the type of IBTR, recent evidence indicates that molecular clonality loss of heterozygosity (LOH) assays provide additional, more accurate information. Comparison of the LOH mutation pattern using markers of frequently deleted tumor suppressor genes is a well-established method for determining the clonality of two breast carcinomas (Tse et al. 2003; Regitnig et al. 2002, 2004; Lininger et al. 1998; Kung et al. 2002; Kollias et al. 2000; Leong et al. 1998; Mead et al. 1997).

The reason why it is important to accurately establish the type of IBTR is that it can help to define useful criteria for optimizing local control after BCT and to establish the efficacy of APBI. Because the rate of IBTR is generally quite low after any form of BCT, the incorrect classification of even a small number of these recurrences may lead to less valid assumptions of treatment efficacy. This is critically important for the accurate interpretation of data that will be generated in clinical trials, such as in the recently opened National Surgical and Adjuvant Bowel and Breast Project B-39/Radiation Oncology

Group 0413 Phase III trial that is comparing WBI with APBI. The incorrect classification of IBTRs in this particular trial could potentially result in an invalid conclusion about the role of WBI in eradicating and/or preventing the development of other cancers in areas in the breast unrelated to the index lesion that is being treated.

In a recent study, the clonality of IBTRs relative to the initial carcinoma was analyzed using a PCR-based assay in 57 patients treated with BCT. It was found that 34 IBTRs (60%) were clonally related to the initial carcinoma and that 23 (40%) were clonally different. Clinical IBTR classification and molecular clonality assay results differed in 44% of all cases (McGrath et al. 2007).

Likewise, molecular clonality assays should be considered when attempting to determine risk factors for local recurrence after standard WBI. In the past, there have been inconsistent conclusions generated from treatment data exploring the association of several variables (margin status, radiation dose, extent of surgical resection, etc.) with the risk of local recurrence after BCT. Some of these inconsistencies may easily be attributed to the incorrect classification of even a small number of IBTRs. In the future, with the use of the molecular clonality assays, there is likely to be more accurate reporting of these results.

3.3 Conclusions

The optimal margin of tissue requiring RT after lumpectomy in patients treated with PBI remains controversial. However, recent radiographic and pathologic data suggest that a margin of 10 mm around the tumor bed appears adequate to cover any disease remaining in the breast after lumpectomy in most (>90%) patients treated with PBI, provided the final negative margins are negative using the NSABP criteria. More restrictive pathologic criteria can be used to identify patients with disease beyond 10 mm. Additional pathologic analysis as well as long-term clinical data on patients treated with PBI are required to provide stricter guidelines in establishing the optimal CTV for PBI.

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The Radiobiology of Accelerated Partial Breast Irradiation

4

Alexandra Stewart and Roger Dale

Breast-conserving surgery has been shown to be a viable alternative to mastectomy in selected breast cancers (Fisher et al. 2002a; Veronesi et al. 2002; Clark et al. 2005). A meta-analysis performed by the EBCTCG has shown that the addition of whole breast radiotherapy (WBRT) to breast-conserving surgery results in a decrease in the five-year rate of local recurrence from 26% to 7% (Early Breast Cancer Trialists' Collaborative Group 2000). For every four local recurrences prevented, one death from breast cancer was avoided. When breast-conserving treatment is combined with systemic therapy such as tamoxifen, the risk of both local and distant disease recurrence is further reduced (Fisher et al. 2002b). However, overall survival is not altered by the addition of radiotherapy, possibly due to late toxicity from radiotherapy (Fisher et al. 2002a; Clark et al. 2005).

Therefore, treatment strategies that avoid or diminish the irradiation of normal tissue have been explored. In patients with early breast cancer, pathological examination of mastectomy specimens has shown that invasive tumor foci are confined to a narrow margin around the tumor (Holland R et al. 1985; Faverly et al. 2001). It is possible that breast-conserving surgery alone for these patients could provide a cure; however, it is not advisable to omit radiotherapy altogether, as this may result in higher local relapse rates (Fisher et al. 2002a,b). Therefore, partial breast irradiation (PBI) utilizing irradiation of the tumor bed with an associated margin in early breast cancer patients is being investigated.

A number of methods of PBI exist:

- External-beam radiotherapy (EBRT)
- Intraoperative radiotherapy (IORT)
- Brachytherapy

Irrespective of modality, the majority of treatments are prescribed using hypofractionated accelerated courses, which are termed accelerated partial breast irradiation (APBI). Determining the dose used and the expected toxicity for each modality requires knowledge of the radiobiologic concepts of both the tumor and the technique used.

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4.1 General Radiobiology Principles

The most commonly used radiobiological model is the linear quadratic (LQ) equation (Dale 1985; Joiner and van der Kogel 1997). This relates the total isoeffective dose to the dose per fraction and/or dose rate. Within this model, there are two assumed components of radiation damage characterized by the radiosensitivity coefficients α and β. The α-mediated component results from a single ionizing radiation event that simultaneously damages two individual targets. This nonrepairable damage increases in a linear pattern with dose, and is thus influenced by overall dose rather than fractionation or dose rate. The beta component (β) of the radiation damage is that resulting from two ionizing events which separately damage two targets. The separate, sublethally damaged targets may combine to form a lethal lesion. Although β-damage is indistinguishable from that created via the α-process, it increases with the square of the instantaneous dose and is influenced by fractionation and dose rate as well as overall dose.

The ratio, α/β, of the two radiosensitivity coefficients is a measure of how a tissue will respond to a change in total dose, fractionation or dose rate; it is also termed fraction sensitivity. For early-reacting normal tissues that express damage from radiotherapy in the days to weeks after irradiation, the α/β ratio is high (e.g., 10–20 Gy). For late-reacting normal tissues which express damage from radiotherapy in the months to years following irradiation, the α/β ratio is low (e.g., 0.5–6 Gy) (Steel 2002).

The individual single-target damage that is a precursor to full β-damage is potentially repairable and is usually called sublethal damage. Repair of sublethal damage during radiotherapy requires a full complement of repair enzymes and DNA damage detection proteins, in addition to adequate time to allow the full repair process to be completed. If a tumor cell has an acquired defect in its DNA repair pathway it is more likely than an adjacent normal cell to be killed by a low dose of radiation (Harrington et al. 2007). If repair does not occur before further sublethal damage occurs then lethal/unrepairable damage may result according to the β-mediated process described above. The repair half-time ($T_{1/2}$) is a measure of the time taken for half the maximum repair to occur. Some investigators suggest that the $T_{1/2}$ of late-responding normal tissue is between 1 and 1.5 h (Dale 1987; Pop et al. 1996), but in some cases it may be longer (Bentzen et al. 1999; Orton 2001). Some studies suggest that repair processes in late-responding normal tissues may have fast and slow components (Millar and Canney 1993; Fowler 1999).

The biologically effective dose (BED) is a useful LQ-based parameter for intercomparing the likely clinical and biological consequences of different external-beam and brachytherapy schedules. Even in its simplest form it employs the individual α/β ratio of a tissue and therefore the radiobiological effects of a treatment course can be calculated for each different tissue type. The standard BED equation can be modified to take into account other treatment factors, such as overall time, dose rate, etc., and is believed to be reliable over the range of range of fraction sizes and dose rates encountered in most radiotherapy regimens. The BED may also take account of the radiation quality of the beam, also termed the relative biological effectiveness (RBE).

Rosenstein et al. (2004) have provided a succinct and useful account of the effect of different APBI dose and fractionation schemes on the BED values for normal tissues and tumors. These values have not accounted for the changing dose heterogeneity within a target volume caused by different radiation techniques, and may result in the BEDs obtained using brachytherapy techniques being slightly higher than calculated (Dale et al. 1997).

4.2 The Radiobiology of Breast Cancer

The main role of radiotherapy in breast cancer is the eradication of subclinical disease. This means that the radiobiology of breast cancer can be difficult to determine, since a direct tumor response cannot be observed and breast cancer cells are generally resistant to growth in cell culture (Tutt and Yarnold 2006). Therefore, radiobiological characteristics have largely been derived from clinical studies of relapse patterns and toxicity following different radiotherapy schedules. Conventional external EBRT fractionation at 1.8–2 Gy day^{-1} has evolved largely empirically. All tumors were initially thought to have a high α/β ratio, around 10 Gy. However, the START A trial examining different fractionation schemes in breast cancer in the UK found that the α/β ratio for local relapse is 4.1 Gy (The START Trialists' Group 2008a), which is much closer to the α/β ratio of late-responding normal breast tissue, which is 3.4–3.6 Gy (Owen et al. 2006; The START Trialists' Group 2008a). Since a low α/β ratio means that a tissue has an increased sensitivity to fraction size, small changes in fraction size may produce relatively large changes in the effect of radiotherapy on tissues.

For tumors with α/β ratios in this range, it should follow that it is perhaps practically feasible to deliver fewer, larger fractions to a lower total dose to maximize local control but still predict an acceptably low late toxicity. This leads to an examination of the dose response of breast cancer. The EORTC boost trials have shown that increasing the dose of radiotherapy administered to the tumor bed significantly decreases the risk of local recurrence, particularly in younger women, but at the cost of increased moderate-to-severe fibrosis, especially at higher dose levels (Curran et al. 1998; Bartelink et al. 2007). In contrast, the START A trial showed an only 0.2% gain in local control per 2 Gy dose increase with a corresponding 5.2% rise in normal tissue effects, and thus concluded that there was little gain from dose escalation when the tumor control is over 95% (The START Trialists' Group 2008a). Whether these larger fractions can be delivered safely in a shorter overall time has also been examined. If the total dose is not adjusted then unacceptable late toxicity will result (Overgaard et al. 1987). However, when the total dose is adjusted downwards, equivalent local control and cosmesis are seen, though current follow-up times for these studies are too short to assess very late toxicity such as cardiac effects (Owen et al. 2006; The START Trialists' Group 2008b).

During radiotherapy of the breast, the organs at risk (OARs) are the heart, lung, soft tissue, skin, rib and contralateral breast. Irradiation of the heart may lead to late cardiovascular complications or, in more extreme cases, cardiac-related death (Taylor et al. 2006). The pathological response of the heart to radiation is characterized by a general accumulation

of collagen and a reduction in end-diastolic diameters of left auricles (Krüse et al. 2001). The incidence of radiation-related cardiac fatalities is 2–3 per 100 women treated over a 20-year period (Yarnold 2002). Volume effects are important, and the large variation in risk estimates from various studies suggests that sensitive substructures are present (Steel 2002). Although different radiotherapy techniques and different patient treatment positions may result in different levels of cardiac exposure (Hiatt et al. 2006), the greatest variability within a patient group is individual patient anatomy (Taylor et al. 2007). A suggested α/β ratio for heart is 3.7 Gy (Schultz-Hector 1992).

Lung complications of breast radiotherapy include acute pneumonitis, which usually occurs within 2–6 months of irradiation, and fibrosis, which can develop over a period of several years. As the lung also demonstrates a pronounced volume effect, it is only dose-limiting if large lung volumes (often involving both lungs) are irradiated (Gagliardi et al. 2000). Patient age is also important, with a higher normal tissue complication probability (NTCP) in older patients when similar lung volumes are irradiated (Gagliardi et al. 2000). Smoking history and previous lung damage must also be considered in NTCP estimation. The anatomical position of the lung irradiated may contribute to toxicity, with the lower lung being more likely to display late toxicity than the upper lung (Marks 2002). This may be important in APBI when utilizing techniques that allow a variation in the direction of the radiation exit path. For early responses (pneumonitis), the α/β ratio is probably around 4 Gy, whilst for longer-term induction of fibrosis it is rather lower: in the range 2–4 Gy (Bentzen et al. 2000).

4.3 Intraoperative APBI

Delivery of PBI at the time of surgery allows a large single fraction to be delivered with direct visualization of the tumor bed and displacement or shielding of uninvolved or dose-limiting tissues. Visualization of the tumor cavity avoids a “geographical miss”—which is always a risk with conventional EBRT techniques, even with CT imaging techniques (Landis et al. 2007)—thus potentially improving local control. However, use of IORT at the time of original surgery risks undertreatment of subgroups of patients at higher risk of recurrence. This risk can be minimized by careful patient selection using factors predictive of negative tumor margins, such as older age, small tumor size and ultrasound-guided localization of the tumor at the time of surgery (Schiller et al. 2008).

IORT is most commonly delivered using a single fraction of electrons or photons. When using large single fractions of radiation, the predictive power of LQ-based radiobiological modeling may become less reliable, since the model is progressively less accurate for fraction sizes above about 6 Gy. For single fractions, it is generally considered that the same amount of tumor cell kill will occur with about half to a third of the total dose used in conventional fractionated radiotherapy (Orecchia and Veronesi 2005). Immediate administration avoids the risk of tumor cell proliferation whilst awaiting radiotherapy or accelerated repopulation triggered by surgical intervention (Belletti et al. 2008). Whilst it is usually held that variations in overall treatment time may not have much influence on local control in breast cancer radiotherapy, there is certainly a detrimental effect with prolonged waits for

radiotherapy (Mikeljevic et al. 2004), implying that repopulation does occur over time (Wyatt et al. 2003). At the time of surgery there is a rich network of vasculature in the remaining tumor bed, as hypoxia has not yet set in. This may allow immediate radiotherapy to be more effective.

Intraoperative electron therapy has been used to deliver a homogeneous dose to a chosen target, usually 21 Gy to the 90% isodose surface, giving an average dose at the tumor bed of 22.5 Gy (Orecchia and Veronesi 2005). This single dose is reported as being equivalent to 56 Gy in conventional (1.8–2 Gy) fractionation, though this prediction used an α/β ratio of 10 Gy for tumors (Orecchia and Veronesi 2005). Intraoperative electron beams of energy 3–12 MeV are delivered at an average dose rate of 15–20 Gy min^{-1}. Normal tissue can be protected using aluminum–lead shields.

Intraoperative photon beams may be delivered using 50 kV X-rays at the tip of a 3.2 mm diameter tube with a spherical applicator. The tissue conforms to the applicator, so a high dose is delivered to the tumor bed whilst that to the normal breast tissue falls off very rapidly due to the low beam penetration. A prescription dose of 20 Gy to the tumor bed is typically used, falling to 5 Gy only 10 mm further away. The dose delivered at depth with intraoperative photon therapy is much lower than that delivered with other PBI techniques; however, the radiation quality of the beam must also be considered. The RBE of photons increases as the photon energy decreases. An RBE of up to 2.2 has been estimated for intraoperative photons in breast cancer; however, this is assuming an α/β ratio of 10 Gy for tumor cells. If the α/β ratio is closer to that of late-reacting normal tissue (3 Gy), then the RBE would be closer to estimations for late-responding normal tissue of 0.92 at the surface of the applicator and 1.45 at 10 mm in tissue (Herskind et al. 2005). These calculations were made assuming a $T_{1/2}$ for sublethal damage of 15 min; if the $T_{1/2}$ is in fact longer than this, the RBE would be proportionally higher.

Delivery of radiotherapy at the time of surgery may take advantage of biological conditions that give an added advantage to radiotherapy. Ionizing radiation is known to induce changes in the extracellular matrix (ECM) which persist for at least 30 years after radiation delivery, implying that radiation somehow affects the cell–ECM interactions to create an environment unsui-table for cancer cell growth (Cordes and Park 2007). Surgery itself may accelerate breast cancer cell growth; when surgical wound fluid was added to breast cancer cell lines, it was seen to stimulate growth, motility and invasion (Belletti et al. 2008). However, when surgical wound fluid harvested from a patient who had undergone intraoperative electron radiotherapy was added to the same cells lines, these effects were not seen. This may imply that, in addition to the direct tumoricidal effects of radiation, IORT may benefit from the wound microenvironment being made less favorable for cell growth and invasion.

4.4 External-Beam APBI

Three-dimensional conformal radiotherapy (3D CRT) for APBI is appealing because the technology of EBRT is well understood and more readily available than other APBI techniques. 3D CRT offers a more homogeneous dose distribution than intraoperative or brachytherapy PBI techniques, generally ranging from 95–107% of the intended dose

(ICRU 1993). However, the effect of this improved homogeneity must be accounted for in the prescription dose administered. This led to an increase in dose in the NSABP-B39 study from 34 Gy in ten fractions over one week for the brachytherapy APBI cohort to 38.5 Gy in ten fractions over one week for the 3D CRT APBI cohort. The risk of geographic miss is higher with 3D CRT techniques, resulting in a larger PTV margin or improved immobilization of the breast and tumor localization using prone positioning (Formenti et al. 2004) or tomotherapy techniques (Hui et al. 2004).

Careful estimation of biological equivalence must be made when selecting dose/fractionation schemes. Using 3D CRT with 30 Gy in five fractions over ten days, Formenti et al. predict equivalent tumor control to 50 Gy in 25 fractions over five weeks and equivalent late complications to WBRT plus boost (using an α/β of 4 Gy for tumor and 2 Gy for fibrosis) (Formenti 2005). Their calculation assumes that full repair of sublethal damage takes place between fractions, and that ten days is too short for significant cell proliferation to occur (Formenti et al. 2004). One concern is that most APBI regimens are compared for tumor control to a conventional WBRT regime of 50 Gy in 25 fractions, when in fact many WBRT schedules receive an additional 16 Gy boost to the tumor bed in order to improve local control (Bartelink et al. 2007). However, since this additional dose may be less important in older patients (Veronesi et al. 1993), delivery of a higher dose to the tumor bed may be less relevant in the generally older case-selected APBI population.

Generally, 3D CRT APBI with linac-generated X-ray beams results in significantly higher normal tissue doses than other APBI techniques, especially in the ipsilateral breast. Utilizing the unique properties of proton beams, namely a higher RBE (1.1) and sharp dose fall-off beyond the target volume, the volume of surrounding normal tissue irradiated could be reduced (Kozak et al. 2006). However, acute skin reactions may be increased due to there being higher entrance doses with protons than with photon beam radiotherapy. Electrons also demonstrate a rapid fall-off of dose at depth, but use of hypofractionated electrons alone may result in high rates of marked telangiectasia and fibrosis (Ribero et al. 1993). This may be overcome by the improved dosimetry seen when combining photon beams and electron beams (Taghian et al. 2006), though long-term follow-up is needed to assess late toxicity.

4.5 Interstitial Implant APBI

Three categories of brachytherapy were defined in the International Commission on Radiation Units and Measurements (ICRU) Report 38 (ICRU 1985):

- Low dose rate (LDR): a range of 0.4–2 Gy h^{-1}
- Medium dose rate (MDR): a range of 2–12 Gy h^{-1}
- High dose rate (HDR): over 12 Gy h^{-1}

Pulsed brachytherapy (PB) delivers a dose using short pulses of brachytherapy every 1–4 h in an attempt to achieve the optimization of dose available with an HDR stepping source combined with the toxicity profile associated with LDR brachytherapy. Although often

quoted, these definitions are very approximate and should been seen as providing no more than very general guidelines. In practice the dose-rate effect is governed as much by the time taken to deliver the treatment as by the dose rate per se. This is because the sublethally damaged lesions (which govern the observed magnitude of the dose-rate effect) may repair *during the ongoing treatment*, and the amount of such repair is time dependent. Since the treatment time is in turn related to the prescribed dose, it is clear that characterization of LDR, MDR and HDR cannot be achieved by considering dose rate alone (Dale and Fowler 2007).

Postoperative APBI using brachytherapy was initially developed using LDR multicatheter interstitial implants, at a typical dose of 45–50 Gy to the 100% isodose at a dose rate of 0.5 Gy h^{-1}. The implant time would be 90 h on average. On conversion to HDR, the LQ model was used to determine equivalence for tumor control and late toxicity for the commonly used treatment schedule of 34 Gy in ten fractions over one week (Arthur et al. 2003). This assumes a $T_{1/2}$ for sublethal damage of 1.5 h, which is longer than that assumed by other investigators (Herskind et al. 2005). This dose and fractionation scheme have also been used for the single-channel MammoSite catheter, though the effects of dose inhomogeneity from a single catheter may be result in a higher equivalent dose than using multiple interstitial catheters (Armpilia et al. 2006). A large variety of different HDR treatment schedules exist, for example the GEC ESTRO trial of APBI vs. WBRT uses 32 Gy in eight fractions bid or 30.3 Gy in seven fractions bid (http://www.apbi.uni-erlangen.de/outline/outline.html), and the Hungarian trial uses 36.4 Gy in seven fractions bid (Polgar et al. 2004). Using escalating doses of LDR brachytherapy, from 50 to 55 Gy and then to 60 Gy at a dose rate of 0.5 Gy h^{-1}, there was a nonsignificant trend towards increased fibrosis at the higher dose, with no difference in disease control (Lawneda et al. 2003). Although the study numbers were small, this may indicate that there is no benefit associated with dose escalation in this group of patients for local control, and possibly a cosmetic detriment.

The aim for a multicatheter interstitial implant is to achieve (as far as is possible) a homogeneous dose distribution avoiding large areas of overdose within the target volume. When using LDR sources of equal activity, all sources deliver the dose at a constant dose rate and treatment time to each point in the irradiated volume. Therefore, a relatively constant fractional cell kill is expected throughout the volume with isoeffect, mirroring (albeit in a nonlinear fashion) the isodose distribution. However, when using an HDR stepping source, the dose is generally delivered using varied dwell times, resulting in an equivalent overall dose achieved by a combination of different dose rates and different treatment times. Mathematical modeling of HDR interstitial implants has shown that treatment plans optimized to a homogeneous dose distribution may not provide homogeneous cell killing. Cells at the periphery of the implant show a fractional cell kill up to twice that at the implant center, where the dose delivery is more uniform. This effect was more marked in cell lines with short repair times. Cell kill was compromised with older, low-activity HDR sources (Manning et al. 2001).

In the absence of mathematical modeling, the dose homogeneity index (DHI) gives an indication of the homogeneity within an implant, and is calculated as follows:

$$\mathrm{DHI} = V_{100} - V_{150} / V_{100},$$

where V_{100} and V_{150} are respectively the tissue volumes receiving 100% and 150% of the prescribed dose. The higher the DHI, the more uniform the dose distribution within an

implant. A DHI of over 0.75 is recommended, with a value of >0.85 being ideal. The toxicity of multicatheter interstitial implants is significantly lower if the dose is more homogeneous within the target volume (Arthur et al. 2003; Wazer et al. 2006). The volume of the individual high-dose regions also appears to be important, with a large V_{150} and V_{200} (volumes receiving over 150% and 200% of the prescribed dose, respectively) contributing to increased rates of worse cosmesis and fat necrosis (Wazer et al. 2006). The administration of chemotherapy following the implant is associated with significantly worse cosmesis in both the HDR (Wazer et al. 2006) and LDR (Arthur et al. 2003) settings.

The MammoSite technique utilizes a single catheter to deliver a uniform dose to a circular cavity of depth 1 cm around the tumor bed. The stretching of the tissue caused by the MammoSite balloon results in an effective thickness of tissue treated of up to 2 cm around the lumpectomy cavity (Edmundson et al. 2002; Dickler et al. 2004). Of course, the optimal irradiated volume for PBI has not yet been established, and the inhomogeneous density of the remaining tumor cells cannot currently be predicted. The radiation dose may be delivered from a single dwell position in the center of the balloon or multiple dwell positions along the axis of the catheter. Using multiple positions decreases the effects of anisotropy from the HDR source, thereby improving dose coverage (Dickler et al. 2004). Both the dose distribution and the equivalent uniform dose (EUD) may change when multiple dwell positions are used (Dickler et al. 2004). With the inability to sculpt the radiation dose distribution, patients with unfavorable anatomic variations may receive higher doses to OARs than others with a similar tumor bed position (Khan et al. 2006). However, using radiobiological estimations for late chest wall toxicity in a cohort of 93 patients, no patients received doses of radiation to the rib that would be predicted to cause osteoradionecrosis (Dragun et al. 2005). Other balloon catheters with multiple channels are under investigation, and the differing radiobiologies of these will be interesting to explore, with an expectation of improved dose sculpting for OARs and therefore decreased EUDs and late toxicity due to the increased number of catheters (Dale et al. 1997; Armpilia et al. 2006; Niemierko 2007).

4.6 Conclusion

Understanding the radiobiological principles behind the different APBI techniques enables a more informed prediction of disease control and toxicity and enables quantitative comparisons between techniques and regimes. The current APBI dose and fractionation schemes appear to show very acceptable rates of disease control and cosmesis, but given the length of time for certain tissues (such as the heart) to reveal late effects of radiotherapy, a much longer follow-up is needed to assess full toxicity and equivalence to WBRT.

Patients vary in their response to a specific course of radiation. Translational research is becoming increasingly important in radiotherapy practice; for example, the finding of abrogation of the cell-stimulating effects of surgery by IORT may have profound implications for breast radiotherapy. In the future, translational research may give us the ability to identify genotypic and phenotypic factors (for example, microarray analysis may be used to demonstrate a genetic susceptibility to fibrosis or local relapse), which may enable us to predict which APBI technique may prove more suitable for an individual patient.

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Surgical Considerations in Partial Breast Irradiation

5

Alan Stolier

5.1 Introduction

Surgical involvement in breast irradiation is a new phenomenon. Although the practices of the surgeon and the radiation oncologist were linked through breast conservation therapy, the role of the surgeon was limited to "lumpectomy" and referral to medical and radiation oncologists. Patient selection criteria were limited to deciding whether clear margins could be obtained and judging the ultimate cosmetic outcome. With the initiation of accelerated partial breast irradiation (APBI), the subsequent release of the MammoSite Radiation Therapy System (Hologic, Inc.) in 2002, and encouraging early efficacy reports for this system, for the first time surgeons began to interact more closely with the radiation oncologist and participate more actively in the radiation treatment process (Keisch et al. 2003; Tsai et al. 2006; Benitez et al. 2006). As this new treatment approach filtered down through the medical community, surgeons actively sought out educational courses that would provide them with appropriate knowledge about APBI, including the fundamentals of radiation treatment, patient selection, and the technical aspects of device insertion. In the years following the first MammoSite trial (Keisch et al. 2003), surgeons have developed and refined techniques of balloon catheter placement and management, and made observations regarding their appropriate use. This chapter will focus on the issues faced by surgeons regarding candidates interested in pursuing APBI, discussing how the proper involvement of and interaction with the surgeon can optimize the outcome. Clinical scenarios and decision making regarding the use of the MammoSite, as well as potential situations where the utilization of the newer intracavitary devices and multicatheter interstitial brachytherapy may be advantageous, will be discussed.

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Table 5.1 Patient selection inclusion criteria recommended by the American Brachytherapy Society and the American Society of Breast Surgeons

Criteria	American Brachytherapy Society	American Society of Breast Surgeons
Age	≥50	≥45
Histology	IDC	IDC, DCIS
Tumor size (cm)	≤3	≤3
Node status	N0	N0
Margins	Negative	Negative

5.2 Patient Selection

Table 5.1 shows patient selection criteria as recommended by The American Brachytherapy Society (ABS) and the American Society of Breast Surgeons (ASBS). Because only part of the breast is to undergo irradiation, factors which increase the risk of ipsilateral breast tumor recurrence (IBTR) and occult multicentric foci (OMF) should be considered. Age <50 and extensive lymphovascular invasion (LVI) are factors that are known to increase the risk of IBTR (Dinshaw et al. 2005; Chia et al. 2004; Leitner et al. 1995). Tumors greater than 4 cm in diameter as well as papillary and micropapillary ductal carcinoma in situ (DCIS) have also been shown to be associated with an increased risk of OMF (Schwartz et al. 1989). From a more practical perspective, tumors >3 cm require significant excision volumes to ensure clear surgical margins, and the resultant cavities are rarely able to accept an intracavitary device.

Patients with ≥4 positive nodes are also at an increased risk of OMF, though the risk is unclear for 1–3 positive nodes (Fisher et al. 1986). There is currently no evidence to suggest that invasive lobular carcinoma is associated with either an increased risk of IBTR or OMF. Based on these considerations, current patient selection criteria include the following:

- Age ≥ 50
- Histology: invasive ductal and lobular carcinoma, DCIS
- Clear margins (widely clear for papillary and micropapillary DCIS)
- Negative nodes including N0i+
- Tumor size <3 cm

5.3 Tumor Location

Intracavitary and interstitial brachytherapy techniques are easily accomplished when the lumpectomy cavity is located within the central aspect of the breast, away from the skin and chest wall. Applicator placement is easily reproducible in this situation; however, if

the cavity is located in a subareolar location or in the axillary tail, inframammary fold or peripherally within the breast, it can be difficult to find a placement acceptable for radiation treatment delivery.

5.3.1 Subareola Tumors

Tumors located in the subareola region can be challenging when attempting to balance clear margins while maintaining a good cosmetic result. Trying to retain the nipple and a symmetrical areola usually results in thin skin flaps, making the use of intracavitary devices problematic. Removal of the nipple for lesions abutting the base of the nipple is a perfectly satisfactory approach and yields excellent outcomes (Fig. 5.1) (Wagner et al. 2007). In tumors where the nipple does not need to be removed, the use of radial incisions and removal of the skin overlying the lesion in an elliptical fashion is strongly advised. As opposed to periareola incisions, radial incisions result in little distortion around the nipple–areola complex. Because the use of intracavitary devices in the subareola location can be difficult, multicatheter interstitial brachytherapy should be considered. This technique can be used in most instances and is an excellent alternative when considering partial breast irradiation for patients with tumors in this location.

5.3.2 Axillary Tail

Tumors located in the axillary tail present special problems for the use of intracavitary devices. As can be seen in Fig. 5.2, breast fibroglandular tissue is on one side of the tumor and the loose fibrofatty tissue of the axilla is on the other. Balloon devices such as the MammoSite and the Contura (SenoRx, Inc.) may deliver undesirable doses of irradiation to the axillary fat pad. Moreover, in patients who have undergone sentinel node biopsy, there will be little tissue left to support the axillary side of the device, creating device

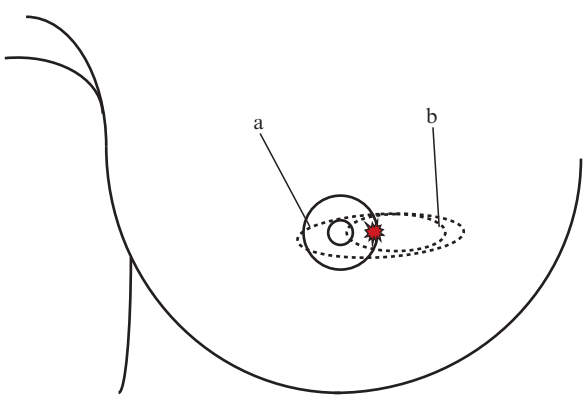

Fig. 5.1a–b Surgical approach to subareola tumors. **a** Removal of the nipple in tumors abutting the base of the nipple. **b** Radial incision removing an ellipse of skin

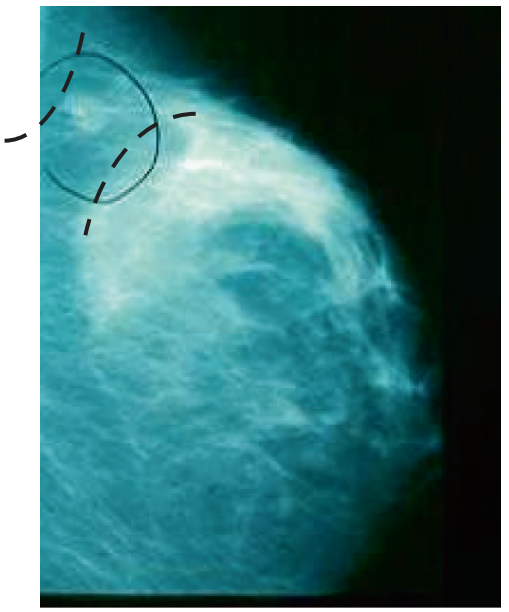

Fig. 5.2 Invasive ductal carcinoma in the axillary tail. Note the fibroglandular breast tissue on one side of the lesion and the fibrofatty breast tissue on the other

movement. Arm movement is also an issue for devices placed in the axillary tail, as devices may move in response to the pressure asserted by the overlying arm. In summary, patients who have lesions located in the axillary tail are poor candidates for APBI using intracavitary devices. However, multicatheter interstitial therapy is quite suitable for this location and serves as a good alternative to MammoSite or other similar intracavitary devices.

5.3.3 Inframammary Fold and Other Peripheral Locations

*S*imilar problems to those encountered for the axillary tail also apply to the use of intracavitary devices in the inframammary fold. One side of the device abuts the fibroglandular breast tissue, and the other the fatty tissue of the upper abdomen. Moreover, the weight of the breast lies on the device, causing unacceptable movement. Again the area is quite well suited to multicatheter interstitial therapy (Fig. 5.3). In the past, patients with tumors in other peripheral sites were also not ideal candidates for APBI, except when achieved with interstitial implants. This is due to a lack of tissue in these sites in many women, resulting in a lack of device-to-skin distance. Recently, however, additional devices have been developed that allow increased dosimetric control. Devices such as the SAVI (Strut Adjusted Volume Implant from Cianna Medical, Inc.) and ClearPath (North American Scientific Medical) that employ an “egg beater” configuration with multiple intracavitary catheters as well as the Contura multilumen balloon with five central lumen are, in many instances, able to overcome these issues (Fig. 5.4).

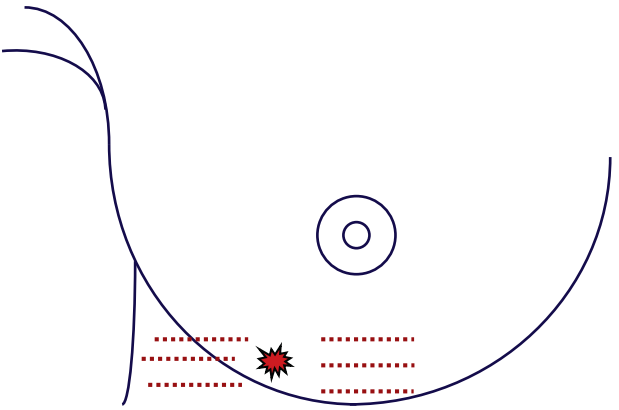

Fig. 5.3 Lesions in the inframammary fold are more suited to multi-catheter interstitial therapy than intracavitary devices

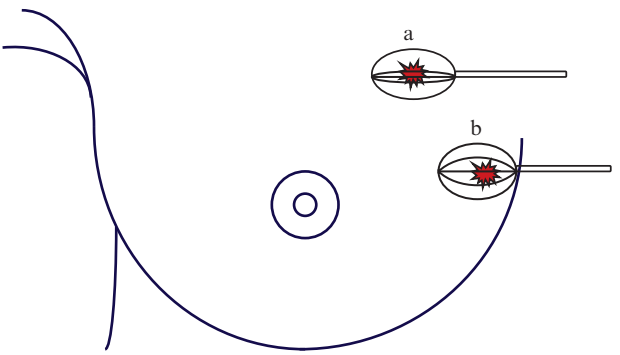

Fig. 5.4a–b The narrow skin bridge and lack of fibroglandular tissue can in many instances be overcome by using one of the newer intracavitary devices: **a** Centura; **b** Savi or Clearpath

5.4 Cavity Shape and Size

Cavity size can, in many instances, determine whether it is possible for a patient who is otherwise a candidate to undergo APBI. Figure 5.5 shows a hypothetical patient with an infiltrating ductal carcinoma and intraductal extension. If the excision occurs as in "A," then the cavity will indeed be appropriate for an intracavitary device or interstitial catheters. However, if the surgeon elects excision "B," the cavity will be inappropriately large for all available devices and will require an unacceptable number of interstitial catheters for a good outcome. It is not be unreasonable to assume that the ultimate cosmetic outcome is a function of cavity size. There is clearly a limit to lumpectomy volume in relation to breast size and shape where the resultant cosmetic outcome will be poor and breast conservation is therefore an inappropriate choice.

Re-excision of the lumpectomy cavity is often required to ensure that clear surgical margins are obtained. The need for re-excision varies widely, from 10 to 50% (Waljee et al. 2008; Fleming et al. 2004; Kaufman et al. 2004), and it is the removal of additional breast tissue

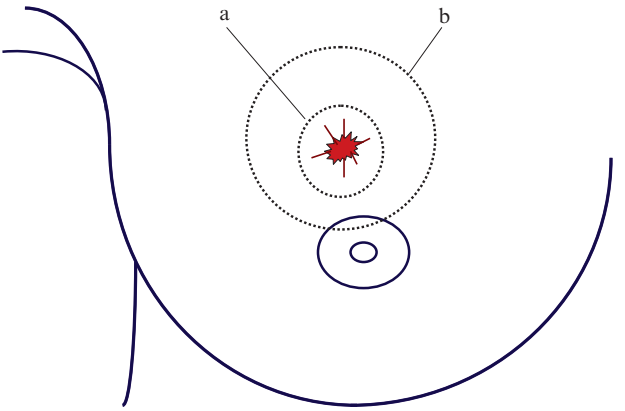

Fig. 5.5 Cavity size can in many instances determine the feasibility of APBI

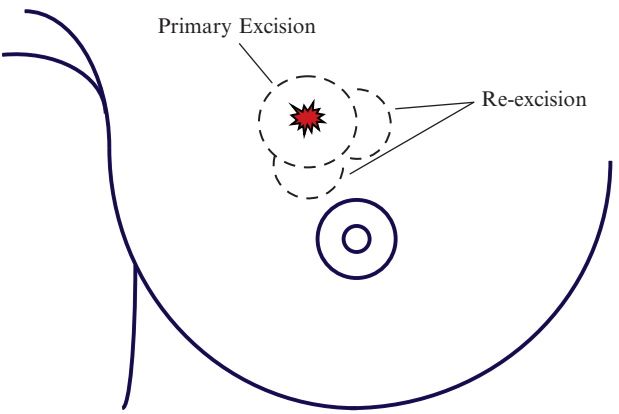

Fig. 5.6 Multiple re-excisions may make conformance of intracavitary devices more difficult

that may present a problem for APBI and intracavitary device placement as it makes it more difficult to obtain acceptable conformance. Although the increase in cavity size is a problem following re-excision, cavity shape irregularity may also be a challenge. Cavity shape irregularity usually results from the re-excision of one or two margins and not when the entire cavity is re-excised (Fig. 5.6). The re-excised cavity may result in an extremely irregular shape, reducing confidence in the ability to successfully place an intracavitary device. Depending on the time interval from surgery and the approach used for placement, these devices can still be utilized in these irregular cavities (Fig. 5.7). As is seen in Fig. 5.8, this successful case shows the device expanding the irregular edges of the cavity to conform to the spherical shape of the device, resulting in excellent conformance.

Ellipsoidal lumpectomy cavities commonly result from segmental mastectomies. This approach can be used in any patient with breast cancer but is more commonly encountered when treating patients with DCIS or in patients with an extensive intraductal component. Ellipsoidal devices are available for cavities of this shape. Multicatheter interstitial therapy is also an option.

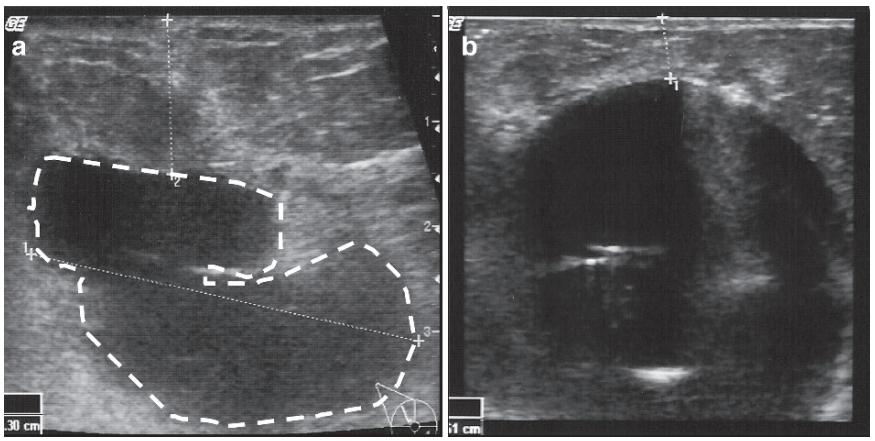

Fig. 5.7 **a** Postoperative breast ultrasound showing an irregular seroma cavity following re-excision. **b** Radiation balloon device expanded with good conformance in the seroma cavity

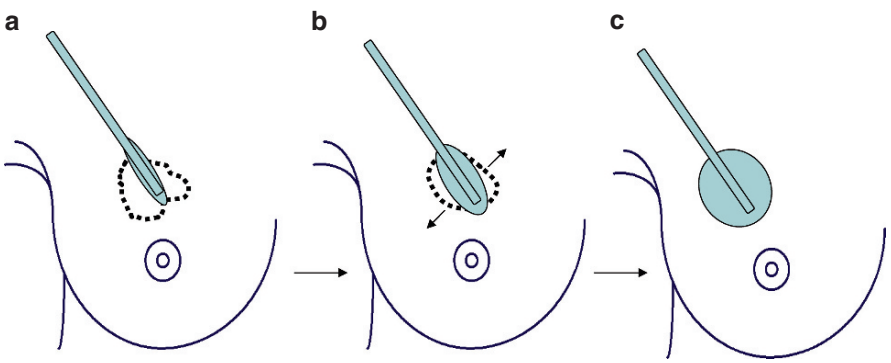

Fig. 5.8 Irregular lumpectomy cavities can in many instances be re-expanded by a balloon device, allowing for good tissue conformance. **a** Balloon device inserted; **b** partial expansion; **c** complete expansion

5.4.1 Surgical Approach with Wire Localization

In an ideal world, all lumpectomy excisions would appear as in Fig. 5.9. The lesion would be at the center of the excision with equal margins in all directions. This would clearly maximize the margins with the smallest excision volume. Unfortunately, in many instances, the lesions are placed eccentrically within the specimen. One common approach to wire localization that may result in marked eccentricity of the lesion is to place the surgical incision at the site of wire entry as opposed to over the lesion. Whereas some wires do pass directly in an anterior–posterior direction towards the lesion, many traverse the breast in a more tangential pathway (Fig. 5.10). An incision over the expected site of the lesion will in most instances result in a specimen that has the lesion more centrally placed.

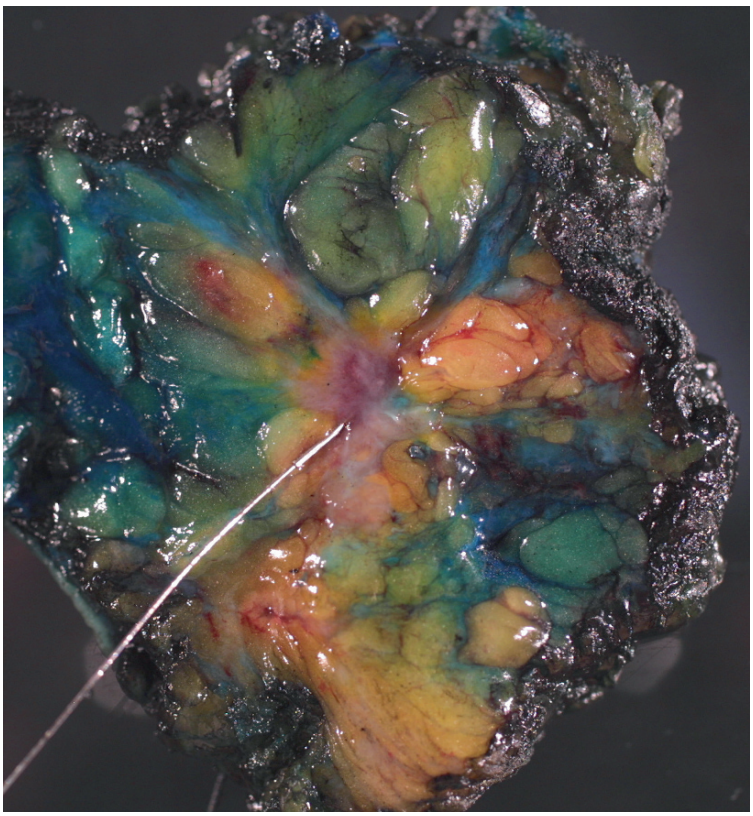

Fig. 5.9 Wire-localization lumpectomy with the lesion centered in the specimen

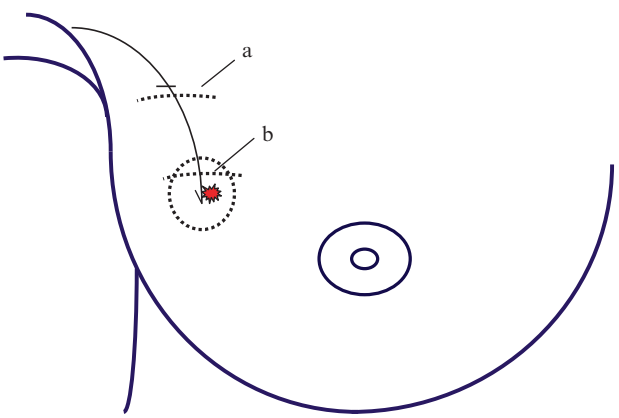

Fig. 5.10a–b Lumpectomy with wire localization. **a** Incision placed near the site of wire skin penetration. **b** An incision placed over the lesion may result in a more centrally placed specimen

5.5 Technical Considerations

When using the MammoSite, a single central lumen device, appropriate placement is essential to its success, as minimal dosimetric adjustment is possible. It is necessary to create a lumpectomy cavity that provides the opportunity for balloon symmetry, cavity conformance with the balloon surface, and a skin thickness of at least 5 mm (preferably 7 mm). Although the newer intracavitary devices have more dosimetric flexibility and are not limited by the fit of the balloon, a lumpectomy cavity with optimal geometry is still preferable. When using the MammoSite, the dose received by the skin is dependent on the overlying skin thickness. A minimum balloon surface to skin distance of ≥7 mm is necessary to reduce the risk of skin toxicity (Fig. 5.11). This can at times be a surgical challenge, particularly when tumors are in a superficial location. Even in situations where the tumor lies far from the skin, many surgeons lift rather superficial skin flaps prior to performing the lumpectomy. The importance of maintaining a good skin surface-to-device distance cannot be overstated. In the first 1,403 MammoSite cases recorded in a registry study, over half of the cases which could not undergo treatment after the balloon device was inserted did so because of an inadequate skin-to-device distance (Zannis et al. 2005). Surgical approaches for both superficial and deep breast tumors are suggested below.

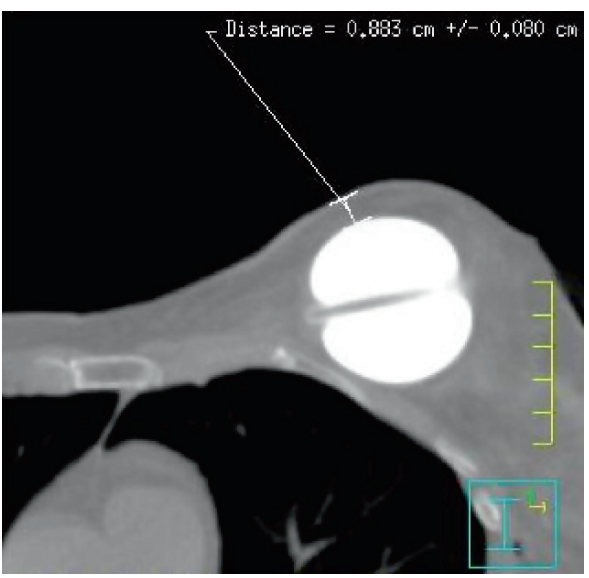

Fig. 5.11 Photo shows a MammoSite balloon in place. Skin distance is measured from the device to the closest skin site

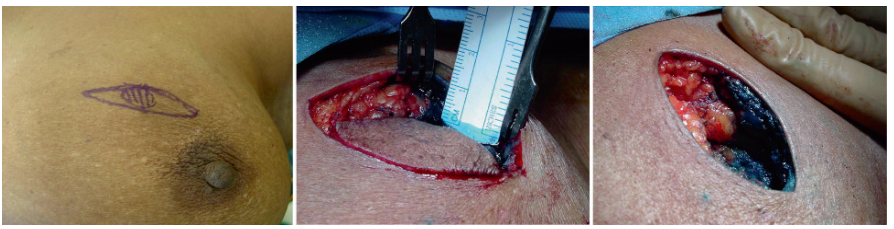

Fig. 5.12 Superficial tumors are best excised with an ellipse of overlying skin. This allows for a more substantial device-to-skin distance

5.5.1 Superficial Tumors

Removing an ellipse of skin and subcutaneous tissue over superficial tumors will, in many instances, allow the excision to occur at a deeper level while preserving a good skin bridge (Fig. 5.12). Newer devices such as the Contura, SAVI and ClearPath allow radiation oncologists to manipulate the radiation dose away from the skin, making the device-to-skin distance less critical. In all circumstances, the device-to-skin distance is an extremely important factor in determining the ultimate cosmetic outcome.

5.5.2 Deep Tumors

Cancers lying more than 1.5–2.0 cm from the skin are best excised by first incising through the skin, fat and fibroglandular tissue perpendicular to the tumor. Once an appropriate distance is reached, excision is then carried out (Fig. 5.13).

5.5.3 Balloon Symmetry

An asymmetrical balloon can result in the tissue on one edge of a balloon device receiving more than the prescribed dose of irradiation and the opposite side receiving less (Fig. 5.14). Balloon symmetry problems can result from factory defects, but this is relatively unusual. Balloon symmetry should always be checked, with the balloon fully inflated, prior to insertion. In many instances, asymmetry results from attempts to insert a balloon device into a cavity that is too small for the balloon, or into a cavity with sides that differ significantly in their ability to stretch (such as a cavity that abuts the chest wall).

When initially examined with ultrasound, some cavities will appear too small to hold an intracavitary device. It is not known if this was a seroma cavity that was initially adequate but closed down rapidly or a small excision. It is now necessary to find out if the cavity will stretch to accommodate the smallest available balloon, 35 cc. A rapid injection of 35 cc of saline under ultrasound will usually answer the question. If the cavity expands easily to accommodate the volume it will almost certainly accept a small balloon device.

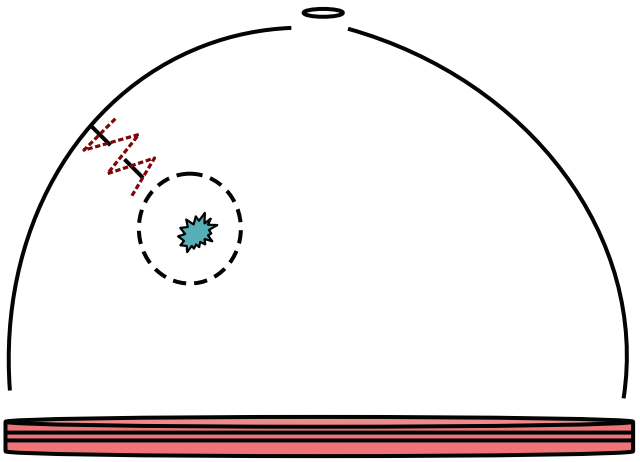

Fig. 5.13 Tumors lying deeper in the breast can be approached by first incising skin and breast tissue to an appropriate level prior to performing lumpectomy. The fibroglandular tissue can then be closed, providing a good device-to-skin distance

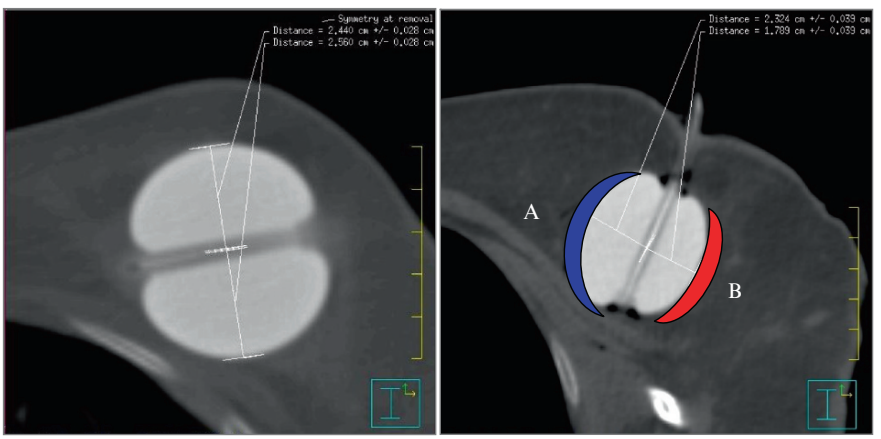

Fig. 5.14 CT scan 1 shows a symmetrical balloon device where measurements from the center to the outer edge are equal. CT scan 2 shows an asymmetrical balloon device resulting in the tissue adjacent to side A receiving less than the prescribed dose and B receiving more than the prescribed dose

Many cavities abutting the chest wall can easily accommodate an intracavitary device. However, in some instances, the unforgiving nature of the chest wall causes a balloon device to inflate asymmetrically. In such cases, the balloon will usually have to be removed and another approach taken. In other instances, a balloon can be inserted and overinflated, thereby stretching the cavity. Fluid is then withdrawn or a smaller balloon is inserted into the newly reformed cavity.

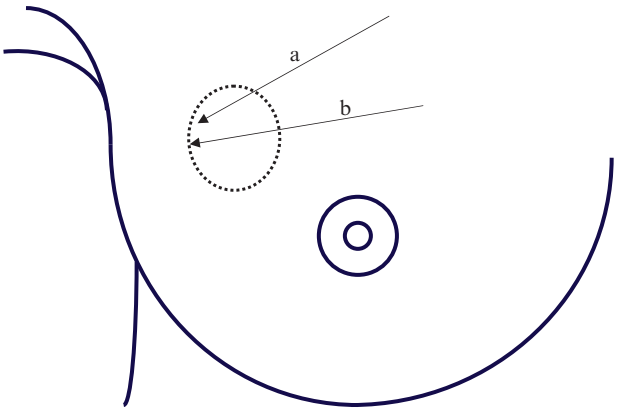

Fig. 5.15a–b An insertion path that does not enter the center of the cavity (**a**) may cause the device to become asymmetrical as it is expanded. The correct path of insertion (**b**) is at a right angle to the seroma cavity

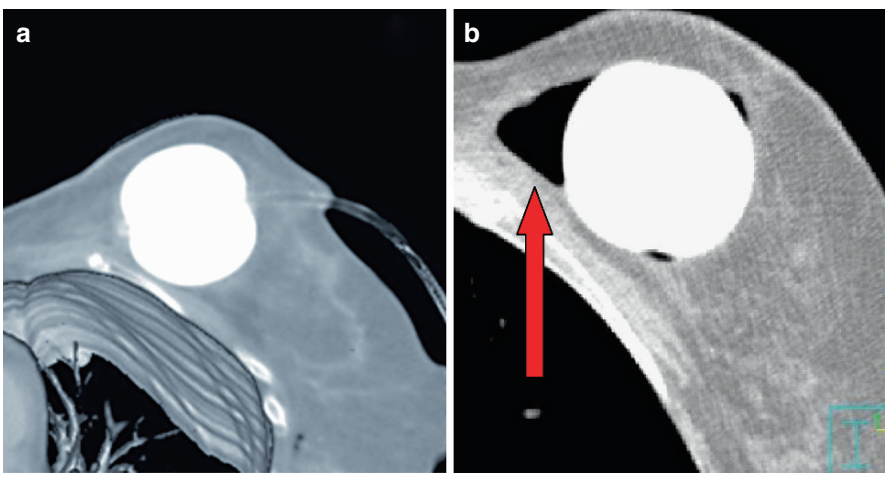

Fig. 5.16 CT scan **a** shows excellent tissue conformance. CT scan **b** shows poor conformance, with a large area of breast tissue not conforming to the intracavitary device

Balloon asymmetry can also result from a failure to insert a balloon device at right angles to the center of the cavity (Fig. 5.15). A device inserted near the edge of a cavity can result in asymmetric balloon inflation. Should this occur, the device needs to be withdrawn and reinserted towards the center of the cavity.

5.5.4 Conformance

When using a balloon device, conformance of tissue around the edge of the balloon is paramount in delivering a consistent dose of irradiation to all "at-risk" margins. In most

instances, good conformance results from selecting the correct device for the size and shape of the lumpectomy cavity. Small pockets of air or fluid around a device will usually resolve within 3–5 days, and patience is suggested. Larger pockets, as seen in Fig. 5.16, are usually unacceptable for treatment. In these instances, the issue is providing less than adequate treatment to a surgical margin that has been separated from the edge of the device. In Fig. 5.16, if the arrow is a surgical margin, it is located too far from the radiation source to receive an adequate dose of irradiation. Surgeons should also take care not to elevate the breast off the pectoralis muscle, as device inflation will elevate this portion of the breast, making it difficult to determine whether all margins will receive appropriate doses of radiation.

5.6 Impact of Oncoplastic Techniques on the Use of APBI

In an attempt to maintain the natural shape of the breast following lumpectomy, particularly larger segmental resections, "oncoplastic" techniques have gained favor (Kollias et al. 2008; Masetti et al. 2006; Anderson et al. 2005). Implicit in this approach is the rearrangement of breast tissue in order to eliminate dead space and seroma cavities. Reduction mammaplasty and mastopexy on the contralateral breast are also important components of the overall surgical approach. In its simplest and most commonly used form, breast tissue is mobilized and then advanced so that it may be reapproximated following lumpectomy (advancement mastopexy) (Fig. 5.17). In doing so, surgical margins are brought into approximation. In its more advanced form, local tissue flaps are used to eliminate the seroma cavity and reshape the breast. In some instances, large segmental resections can be performed through reduction mammaplasty incisions, with contralateral reductions performed either immediately or delayed. Although interstitial multicatheter radiation and partial-breast external-beam techniques are still possible, oncoplastic closures clearly eliminate the use of intracavitary devices.

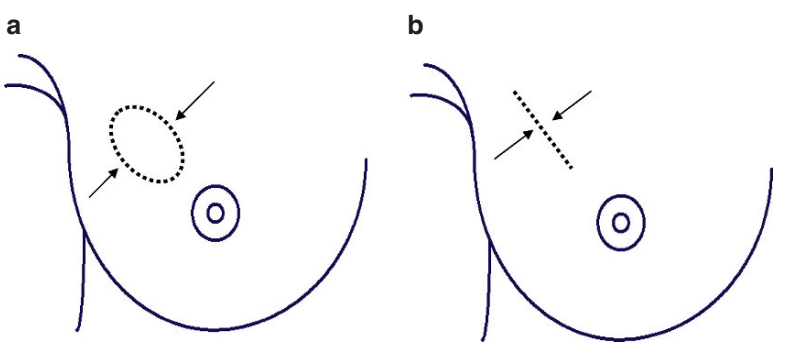

Fig. 5.17a–b Oncoplastic techniques (advancement mastopexy). **a** Breast tissue around the lumpectomy site is mobilized. **b** Closure of the lumpectomy cavity eliminates the seroma cavity and brings the surgical margins into approximation

5

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Physics of Accelerated Partial Breast Irradiation

6

Rupak K. Das and Bruce Thomadsen

6.1 Introduction

Breast-conservation therapy (BCT) is now widely accepted as a treatment option for most women with early-stage invasive breast cancer and most patients with ductal carcinoma in situ (DCIS) (Veronesi et al. 1986; van Dongen et al. 1992; Blichert-Toft et al. 1988; Sarrazin et al. 1989; Fisher et al. 1989). Despite a superior cosmetic outcome, BCT is complex and requires a treatment regimen of six weeks of daily external-beam radiation therapy to the whole breast. This often proves prohibitive for the working woman, elderly patients, and those who live a significant distance from a radiation treatment center. In addition, with the more frequent use of adjuvant, substantial delays can be incurred prior to the initiation of systemic chemotherapy if a conventional fractionated course of irradiation (XRT) is given first or in the delivery of locoregional XRT if chemotherapy is delivered beforehand. Most of the logistical problems associated with BCT relate to the protracted course of external-beam XRT delivered to the whole breast. Standard therapy after tumor excision generally includes five weeks of external-beam XRT to the whole breast (45–50 Gy), followed by an additional 10–15 Gy boost to the tumor bed.

Recently, accelerated partial breast irradiation (APBI) for breast cancer patients with brachytherapy or external beam as the sole radiation modality following lumpectomy has shown promising results for select early-stage breast cancer patients (Arthur et al. 2003; Kuske et al. 1994; Patel et al. 2003). In this technique, the radiation dose is delivered within and surrounding the original tumor site over 4–5 days, instead of the traditional six weeks of external beam to the entire breast. Both high dose rate (HDR) and low dose rate (LDR) brachytherapy as well as XRT have been used for APBI.

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D.E. Wazer et al. (eds.), *Accelerated Partial Breast Irradiation*,

6.2 Interstitial Brachytherapy

6.2.1 Low Dose Rate Implants

The physics of low dose rate brachytherapy are covered in many textbooks (for example, Williamson and Brenner 2008), so only the aspects of LDR brachytherapy pertinent directly to APBI, and not the general characteristics, will be included here. LDR breast brachytherapy as a boost to external-beam whole breast irradiation has been practiced for decades, particularly in Europe, although a few institutions in the USA use this technique. Summaries of the technique and dosimetry can be found in Calitchi and Marinello (1997) and van Limbergen and Mazeron (2002). Vicini et al. (1997) and Arthur et al. (2003) report on LDR implants for partial breast irradiation performed using both ^{192}Ir and ^{125}I sources. In the former study, ^{192}Ir ribbons were used to deliver a dose of 45 Gy at a rate of 0.5 Gy h^{-1}, while in the latter study ^{125}I ribbons were used to deliver a dose of 50 Gy at a rate of 0.52 Gy h^{-1}. Catheters were placed under image guidance (fluoroscope, ultrasound) with a template as guidance or freehand (the details of this are described in the section on implants). In both studies, the treatments were delivered as inpatient treatment for 4–5 days. At the end of the treatment, the radioactive seeds in the ribbons were removed and then the catheters were removed, and the patient was discharged with skin care instructions. More recently, Pignol et al. (2006) reported on permanent implants for partial breast irradiation. For radiation protection reasons they chose to implant ^{103}Pd sources due to the lower energy of the emitted X-rays (21 keV) compared with the alternatives (^{125}I with an effective energy of 28 keV or ^{131}Cs with an energy of 30 keV). They took the clinical target volume (CTV) to be the surgical cavity and surrounding fibrosis as seen in computed tomography (CT), and the planning target volume to be the tylectomy cavity plus a margin of 1 cm (except that this was limited to 5 mm from the skin and by the pectoralis). Patient selection limited the size of the original tumor to 3 cm in diameter. The implant was performed through the lateral side of the breast, and used a specially designed "hooking" needle to anchor the target (Pignol et al. 2004). Since prescribed dose was 90 Gy, the minimal peripheral dose covering the PTV equated to 50 Gy over two months using an α/β of 2 Gy^{-1}. Stranded sources were used to inhibit source migration. Calculations and measurements verified that the exposures to family members remained below 5 mSv for the duration of treatment. As with any permanent implant, the PTV exists to provide a margin so that the desired dose covers the CTV. Temporary LDR implants usually have more control over the placement of the sources, reducing the margins required around the CTV. In this report, after gaining experience with the procedure, on average, 87% of the prescribed dose covered the PTV and about 25% of the PTV received more than 200% of the prescribed dose. On average, 95% of the CTV received the prescribed dose (range 80–100%), but 33% received greater than 200%. Long-term results are not available at the time of writing, but the study dose shows the feasibility of this approach.

6.2.2 High Dose Rate Implants

In the HDR remote afterloader, a computer-driven single cable with a source (^{192}Ir; initial activity of 10 Ci) at the tip moves from each programmed treatment position (dwell position) in the catheter when the position-specific treatment time (dwell time) has elapsed. After treating each position in a given catheter, the source is retracted into the machine and transmitted into the next treatment catheter. Such a system, also known as stepping source remote afterloader, enables the planner to maximize the dose uniformity by varying the dwell time at each dwell position while minimizing the implant volume needed to adequately cover the target volume. High dose rate units are described in many textbooks (for example, Thomadsen and Das 2008), and so (as with LDR brachytherapy) only the aspects of HDR brachytherapy that are directly pertinent to APBI—and not the general characteristics—will be included here.

Within eight weeks of lumpectomy and axillary nodal evaluation, patients undergo an interstitial implant under local anesthesia with one of the techniques described below.

6.2.2.1 Interstitial Implant Techniques

Mammographic/Template-Guided Implant

In the prone, mammographic/template-guided method, an ultrasound is initially performed, allowing visualization and aspiration of the contents of the seroma followed by the injection of 4–5 cc of nonionic contrast and 3–4 cc of air, resulting in an air-fluid cavity that is well visualized on subsequent preimplant mammography. Next, the patient is positioned prone on the stereotactic biopsy table and the template is applied such that the surgical scar is located between the two templates and the contrast-enhanced cavity is centered on the template. A digital mammogram is obtained to assure coverage of the seroma. Usually, the field of view on a digital image is too small to include the whole implant volume, and a film image is taken. The target volume is demarcated on this image. The excision cavity is defined by surgical clips or radiopaque contrast filling the seroma as described above, with the PTV for the implant being defined as the volume encompassed by a 2 cm margin outside the lumpectomy cavity in all dimensions. The holes included in this region are used, and if the boundary of the PTV falls between holes on the template, the farthest hole is included. Figure 6.1a shows a mammogram with the template in place, and Fig. 6.1b shows the template pattern on a sheet of paper with the holes to be implanted marked on it. The template positions the needles 1.5 cm apart in offset rows, but also allows for additional needles between rows at the ends to prevent the eventual isodose surfaces from pulling into the implanted volume (scalloping). At the authors' institution, the average implant uses about 25 needles, but the range for template-guided implants falls between 14 and 34.

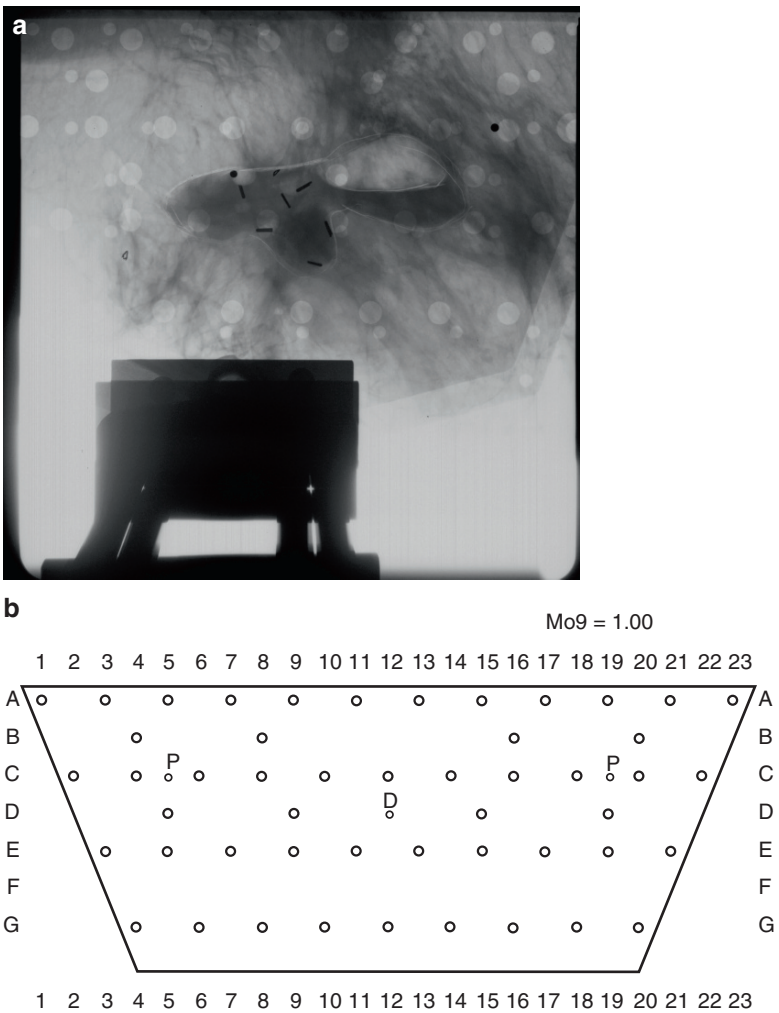

Fig. 6.1 **a** A mammogram with the guiding template in position

Following the localization, the template holes are numbed with local anesthetic. A thick guiding template is then attached to the system, ensuring parallel needle placement without deviation. Freehand needles are then placed in regions not covered by the template for optimal target volume coverage.

CT-Guided

CT can guide the placement of a template or freehand needle insertion. Vicini et al. (1999) reported that initial trials of such a technique were not as successful as they had hoped, but they felt that the methodology might simply have required more experience. Template-guided

approaches using CT face the problem of placing the template sufficiently close to the chest wall to implant needles behind the target. With the patient supine in the CT table, the breast flattens against the chest wall, so the deep coverage requires that the breast is lifted, as in the Virginia freehand technique, before template placement. Depending on the software available, visualizing the potential catheter tracks and selecting the needle holes to use can be very challenging. A freehand approach may make it easier to determine the needle location, but, unlike ultrasound placement, it fails to provide the live-time guidance to avoid deep structures.

Ultrasound-Guided Supine Technique

An alternate approach, the supine ultrasound-guided method, is used in situations where the template is difficult to use (medial lesions and smaller breast size). In this method, the target volume is first mapped out on the skin surface with ultrasound visualization of the lumpectomy cavity. Needle placement is marked on the skin, with a 1 cm interval. No template or contrast injection is utilized. Needles are placed in a similar fashion as described above, with a local anesthetic mixture used generously. Initially, a deep plane of needles is placed ideally just above the pectoralis major fascia with real-time ultrasound guidance. This is followed by at least one more superficial plane, resulting in a multiplane implant for adequate geometric coverage of the target volume.

Comparison of Implant Techniques

Regardless of the implantation approach, the final step requires that the needles are replaced with polyethylene tubing with a hemispherical button at each end. Extra attention is directed towards make sure that the button on the connector side of the remote afterloader is tight and flush to the skin.

In general, a prone implant uses more needles than a supine, although the needle tracks tend to be longer for the supine because the breast hangs for the implant when prone but flattens when supine. Figure 6.2 illustrates this. Despite these differences, the total treatment time remains fairly constant between the approaches.

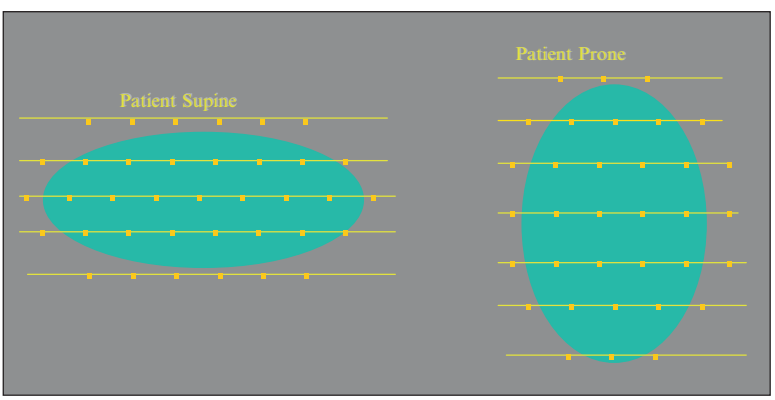

Fig. 6.2 Comparison of supine and prone implants

In general, the template approach is the simplest and most reproducible and requires the least training, while the ultrasound approach requires greater skill and experience on the part of the person placing the needles. Because the ultrasound-guided technique uses fewer needles, the dosimetric process takes less time.

6.2.2.2 Interstitial Dosimetry

Volume of Interest

When defining the target volume, the lumpectomy cavity is first delineated on each axial CT slice. Radiopaque material like Omnipaque or Hypaque, suitably diluted if injected into the lumpectomy cavity before the CT scanning or during catheter placement, enhances the visualization of the cavity and helps in the delineation. While the PTV for the implant uses a 2 cm margin around the seroma, the PTV for treatment planning is defined as the lumpectomy cavity with a 2 cm margin, modified anteriorly to 5 mm deep to the skin surface and also along the pectoral muscle. Dwell positions in each catheter are activated that fall within the PTV along with some additional margin, usually 5–8 cm. The margin provides more freedom to conform the dose to the planning target volume. With most planning systems, it is more time efficient to add extra dwell positions at this phase of the planning process, since adding extra dwell positions later may cancel out much of the work performed in-between. Dwell positions within 5 mm of the skin are never activated.

Tracking of Catheters

An en face photograph of the implant along with the breast is obtained at the time of the planning CT. Each numbered catheter/button is also identified in the en face picture, which is subsequently used to identify and reconstruct the catheters in the treatment planning system. Photographs of the entry and exit sides of the implant with the catheters numbered on the image also help to identify the catheters during the reconstruction. Scanning is performed after loading all of the catheters with CT-compatible wires, and the images are then transferred to the treatment-planning system.

In the treatment-planning computer, the catheters are identified based on the instructions from the system's manufacturer. After reconstructing the catheters, comparing image views from both ends of the catheter with the photographs taken at the time of the CT provides a quality assurance check for the reconstruction of the catheters.

Depending on the catheter type used and the HDR unit, the lengths of the catheters will need to be measured and entered into the plan.

Dose Optimization

The optimization options available depend on the treatment-planning system. Several good references cover the details of optimization (Ezzell and Luthmann 1995; Ezzell 2005;

Pouliot et al. 2005). Often, the optimization performed by the treatment-planning system will provide an approximate solution, but operator intervention may be required to finalize the plan. Most systems have manual optimization capabilities that allow isodose lines to be dragged to desired locations on the CT images. This process can conform the 100% dose well to the PTV while also facilitating 150% volume minimization. Prescriptions of 3.4 Gy for ten fractions or 4 Gy for eight fractions were prescribed to these basal dose points, and an isodose line was selected to cover the entire target as optimally as possible. Manual optimization on each CT slice was then done interactively by dragging the 100% isodose line to cover the target volume as conformally as possible while adjusting the 150% isodose line to minimize hot spots.

6.3 Intracavitary Volume Implants

An alternative to interstitial implants for the breast is intracavitary insertions using special applicators. The first of these was a balloon-catheter-based device called the MammoSite (Edmundson et al. 2002; Keisch et al. 2003). In the years following the introduction of the MammoSite, investigators developed several other approaches.

6.3.1 MammoSite (Hologic, Bedford, MA, USA)

The MammoSite consists of a balloon catheter that is placed in the tylectomy cavity by either a surgeon or a radiation oncologist. Descriptions of the device and the treatment process can be found in Chap. 14. The balloon may be placed at the time of surgery or in a separate procedure later. Placement at the time of surgery results in the removal of some applicators due to positive surgical margins. In the authors' experience, there is a slightly increased probability of trapped air pockets on the surface of the applicator, but no study has looked at this question.

6.3.1.1 General Dosimetric Principles for the MammoSite

Spherical MammoSite balloons generally use a single dwell position at the center of the balloon. This produces a circular dose distribution in the plane transverse to the source catheter (Fig. 6.3a), but one that is slightly retracted in the planes containing the catheter (Fig. 6.3b). The dominant factor for the dose distribution is simply the inverse square law, with tissue attenuation and inhomogeneities playing a secondary role. Figure 6.4 shows the dose as a function of distance from the surface of the balloon in a uniform, tissue-equivalent medium. Since the only dwell position is at the center of the balloon, the dose decreases continually with distance. As would be expected, the dose at the surface increases as the balloon diameter decreases (because the 1 cm distance to the prescription point makes a greater difference in relative terms for smaller radii). Figure 6.5 shows the volume in a

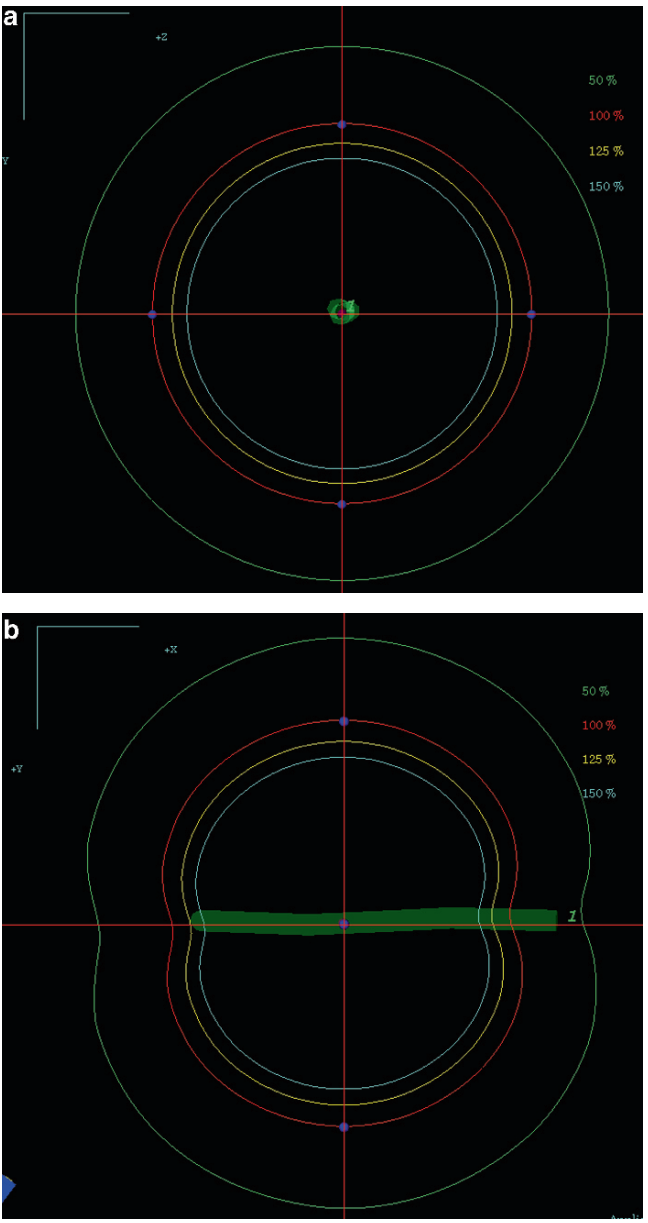

Fig. 6.3 **a** The dose distribution for a single dwell position in the transverse plane. **b** The dose distribution for a single dwell position in the axial plane

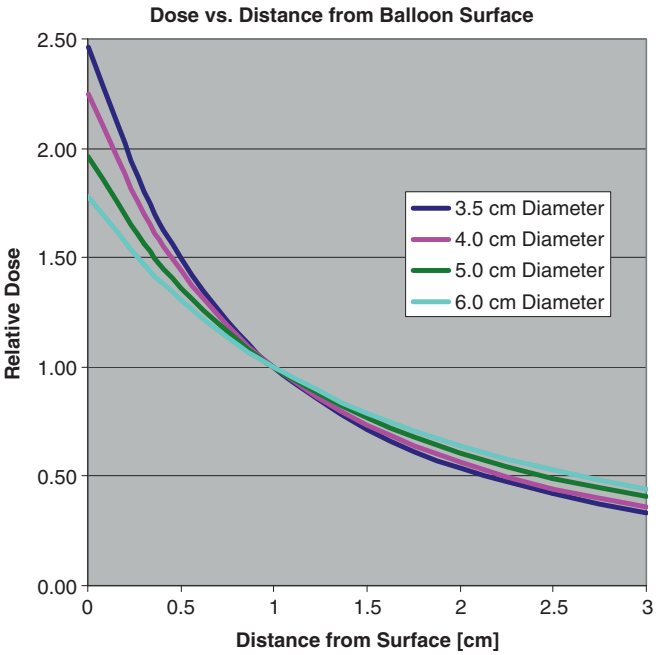

Fig. 6.4 The dose as a function of the distance from the surface of an intracavitary balloon catheter, relative to the dose at the prescription distance (1 cm) for radiation from a ^{192}Ir source

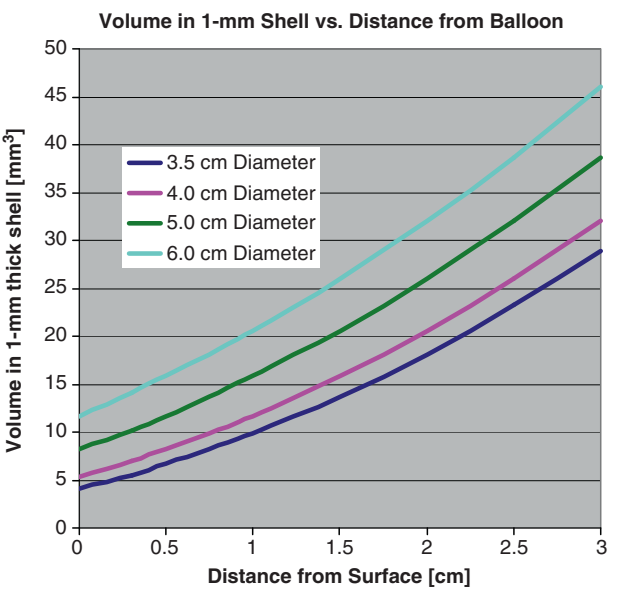

Fig. 6.5 The volume contained within a 1 mm shell as a function of distance from the surface of a balloon applicator for various balloon diameters

1 mm shell as a function of distance from the surface of the balloon for various balloon diameters. The shells near the surface contain small volumes, particularly for the small balloons, where the doses near the surface become quite large. Figure 6.6 displays the volume contained in the CTV (the V_{100}) and that in the 150% isodose surface (V_{150}). While the CTV increases markedly with balloon diameter, the V_{150} tends to almost plateau. Table 6.1 gives the values for the CTV, V_{50}, and the homogeneity index, defined as HI = ($V_{100} - V_{150} / V_{100}$), for several balloon diameters. Obviously, the best dosimetry comes from treatments that use the largest balloon diameter possible. All of the values in Fig. 6.6 assume that the entire CTV falls within the breast; that is, that neither the skin nor the pectoralis cut into the CTV.

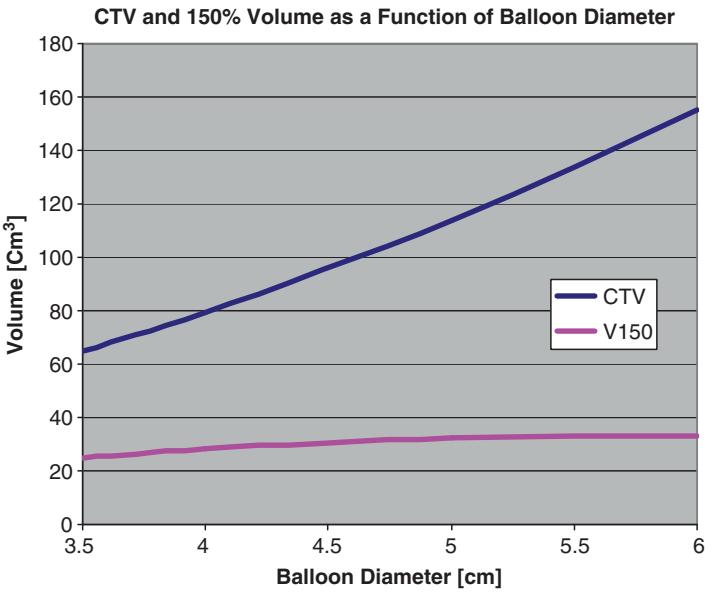

Fig. 6.6 The volume contained in the CTV (the V_{100}), and that in the 150% isodose surface (V_{150}) as a function of the balloon diameter, assuming neither the skin nor the pectoralis muscle cut into the CTV

Table 6.1 CTV, V_{150}, and homogeneity index (HI) for several balloon diameters

Balloon diameter (cm)	CTV (cm^3)	V_{150} (cm3)	V_{200} (cm3)	HI
3.5	64.6	25.0	8.3	0.61
4.0	79.5	28.0	6.5	0.65
5.0	114	32.3	–	0.72
6.0	155	32.8	–	0.79

Note that the 200% isodose surface occurs either at the surface of the balloon or inside the balloon for diameters of 5 and 6 cm

Only for the largest balloon does the homogeneity index approach the value for a typical interstitial implant of 0.8 or above.

Even with negative margins, there is some probability that malignant cells will reside outside the tylectomy border. While the highest probability of residual cancer cells exists nearest the border and decreases rapidly beyond about 1 cm (Holland et al. 1985), the probability does not fall to zero. Thus, while the prescribed dose for the MammoSite occurs 1 cm from the balloon, it may be important for the radiation to continue to deliver an only slightly reduced dose beyond that point.

6.3.1.2 Treatment Planning Rules

Acceptable treatment with a MammoSite requires careful attention to several aspects of the application during the treatment-planning process:

1. *Minimum distance to the skin*. The original guidelines for the use of the MammoSite recommended a minimum distance to the skin of 5 mm. For a 4 cm diameter balloon, this produces a skin dose of 144% based on just the inverse square law. The minimum distance then increased to 6 mm (giving 133%). While recommending that the minimum distance be greater than 7 mm, the NSABP/RTOG protocol allows treatment with only 5 mm (NSABP/RTOG 2005). Under no conditions should a patient be treated if the skin dose exceeds 150% of the prescribed dose.
2. *Applicator geometry*. The applicator should have the correct geometry (spherical or an ellipse with the correct aspect ratio, depending on the balloon used). Figure 6.7 shows a poorly shaped balloon. In this case, the tissue near the equator of the balloon

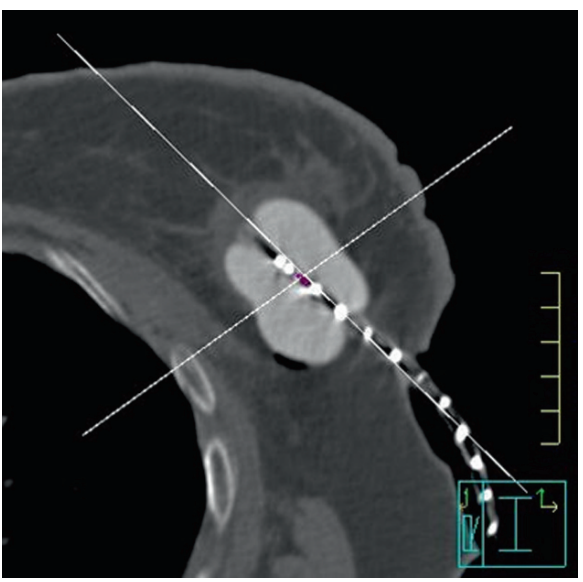

Fig. 6.7 A MammoSite application with poor conformance of the balloon with the intended spherical shape. (Image courtesy of Jeffrey Dorton)

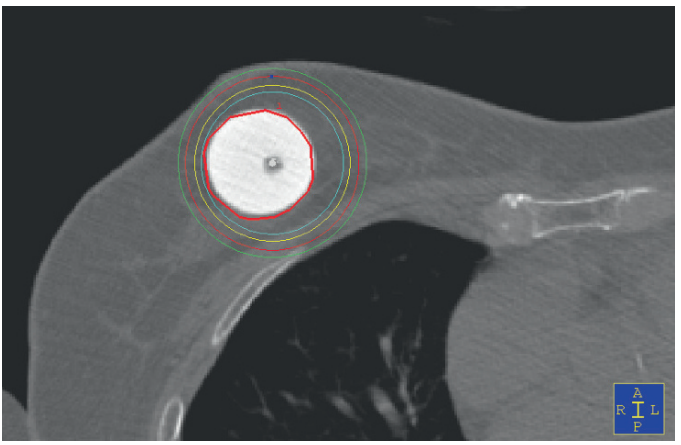

Fig. 6.8 A MammoSite application with the source path displaced to one side, exposing the medial tissues to excessive doses while not adequately treating those laterally

will receive doses much in excess of those expected and will likely suffer necrosis. The NSABP protocol specifies that the balloon's geometry must not deviate by more than 2 mm from the expected shape (NSABP/RTOG 2005).

3. *Source path*. The source path should be centered on the applicator. Figure 6.8 illustrates the effect of an off-center source track. Again, the tissue on the side of the balloon nearer to the source path will receive an excessive dose and will likely suffer necrosis. The target tissues on the opposite side will not receive adequate treatment.
4. *Voids*. The effect of voids—air pockets trapped on the surface of the balloon during placement—is not well understood. The voids clearly displace some target tissue, pushing it beyond the treatment radius (1 cm). How far and how much of the tissue moves is a matter of current research, and the answers are likely to be reported in the very near future. If any of the tissue is displaced by the same distance as the thickest radius of the void, then very small voids, 0.9 mm, would move some of the target tissue far enough from the sources that the dose falls below 95% of the prescription dose. It is not likely that the maximal tissue displacement is the same as the maximum thickness of the void. Whatever the displacement, the clinical effect on the treatment also becomes very unclear. The currently used practice for evaluating the effects of a void, as captured by the NASBP protocol, assumes that if the volume of the void remains less than 10% of the PTV "acceptable dose coverage can be achieved" (NSABP/RTOG 2005). No justification for this claim is included in the protocol or other literature.
5. *High-dose regions*. The NSABP protocol sets limits for the volumes enclosed by isodose surfaces that are significantly higher than the prescription dose (NSABP/RTOG 2005; Baglan et al. 2003). The volume raised to 150% of the prescription dose (V_{150}) must remain less than 50 cm^3, and that greater than 200% (V_{200}) must be less than 10 cm^3. From Table 6.1, these criteria should never be a limiting factor (or relevant).

6. *Dose to uninvolved breast*. Again, the protocol limits the dose to uninvolved breast tissues such that less than 60% of the breast receives greater than 50% of the dose.

Failure to pay attention to any of these criteria can lead to serious toxicity.

6.3.2 Contura (SenoRX, Aliso Viejo, CA, USA)

The Contura balloon applicator was developed to address some of the problems encountered with the MammoSite. The Contura is similar to the MammoSite except that, in addition to the central lumen, there are four additional source catheters that bow away from the central channel in the middle of the balloon (see Fig. 6.9). These additional catheters provide some ability to steer the radiation dose distribution away from the skin if the balloon lies closer than the standard 7 mm, or away from other structures such as ribs. Figure 6.10 shows just such a case and the resultant dose distribution after manual reoptimization. While the ability to modify the dose distribution is not great, it often seems to be enough to produce an adequate dose distribution from what would otherwise be an unsatisfactory insertion. While dispersing the source paths in an interstitial implant improves the homogeneity, in an intracavitary application the situation is different; the homogeneity index drops as steering of the dose distribution increases.

The dose shifting addresses criteria 1 through 3 in the list above. To try to reduce the problem with voids, the applicator has seven ports in the surface of the applicator through

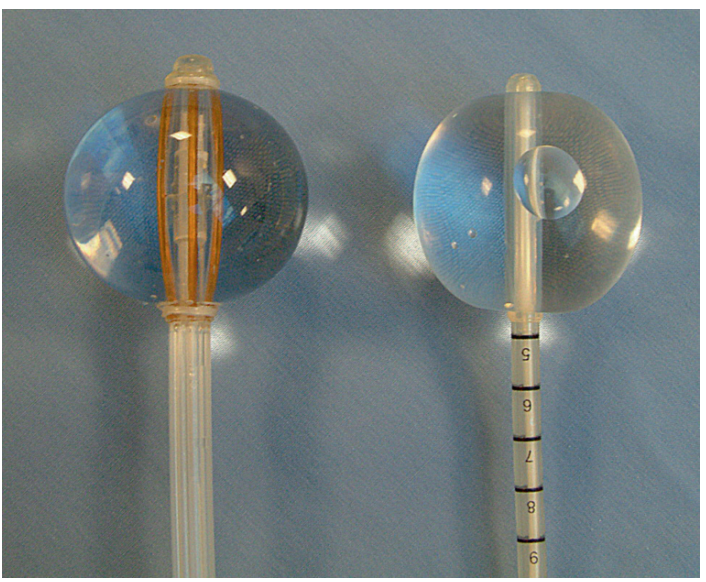

Fig. 6.9 The Contura applicator on the *left*, with multiple source paths within a balloon. On the *right* is the MammoSite

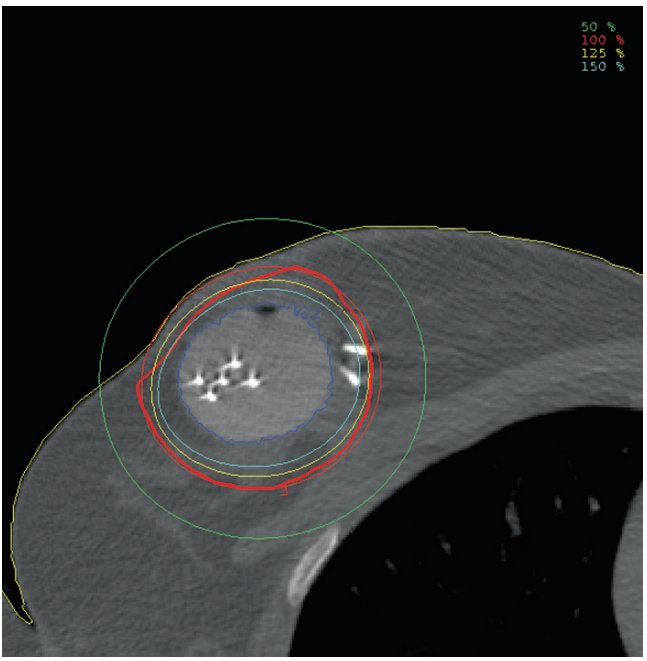

Fig. 6.10 A CT of the Contura in a patient with reduced weighting of the source tracks closest to the skin to reduce the dose

which air can be drawn, suctioning out the voids. While not all voids can be removed through this mechanism, it has proven successful in many cases.

6.3.3 ClearPath (NAS Medical, Chatsworth, CA, USA)

Sharing with the Contura the concept of having multiple source path catheters in the cavity, the ClearPath replaces the balloon with several stiffened catheters (as in Fig. 6.11). The ClearPath allows greater dispersion of the catheters away from the central catheter to provide more of an ability to steer the dose distribution. The cost of the increased steering is a worsening of the homogeneity. Figure 6.12 shows a typical dose distribution obtained with this device.

The lack of the balloon filling the cavity space raises two concerns. The first is the effect of the air in the cavity on the dose distribution. As of this writing, none of the commercial treatment-planning computers account for density variations in the patient. Thus, the true dose distribution is likely to be higher than that calculated. This variation may also change during the treatment course as fluid accumulates in or drains from the cavity. The other concern is the shape of the cavity and the resultant CTV. The struts do not hold the cavity in a sphere, which may be helpful if the cavity naturally assumes an irregular shape (although the balloon catheters usually make the cavity round), but this generally produces an irregular shape that then requires more modification of the dose distribution.

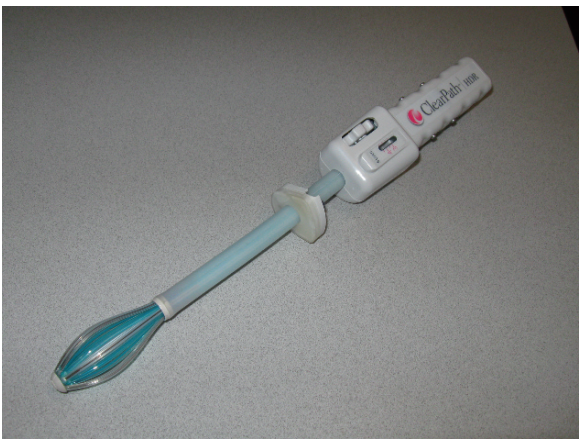

Fig. 6.11 The ClearPath applicator, with outer struts to hold the cavity open and inner struts for the source paths

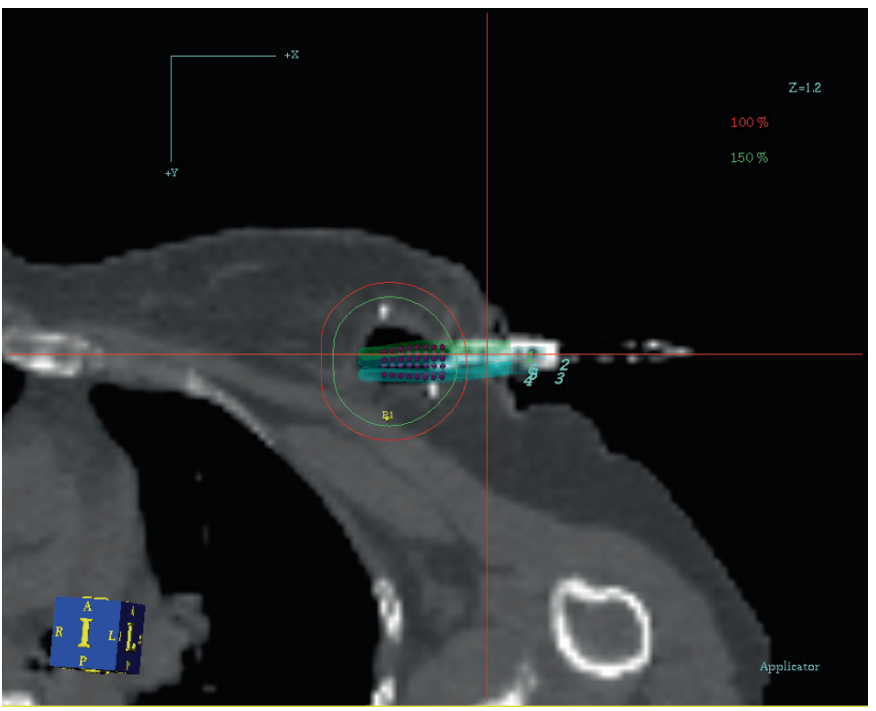

Fig. 6.12 A typical dose distribution with the ClearPath

6.3.4
SAVI (Cianna Medical, Aliso Viejo, CA, USA)

SAVI also uses dispersed source catheters in order to allow the dose distribution to be modified, but it uses the same source catheters to form the cavity shape. Figure 6.13 illustrates

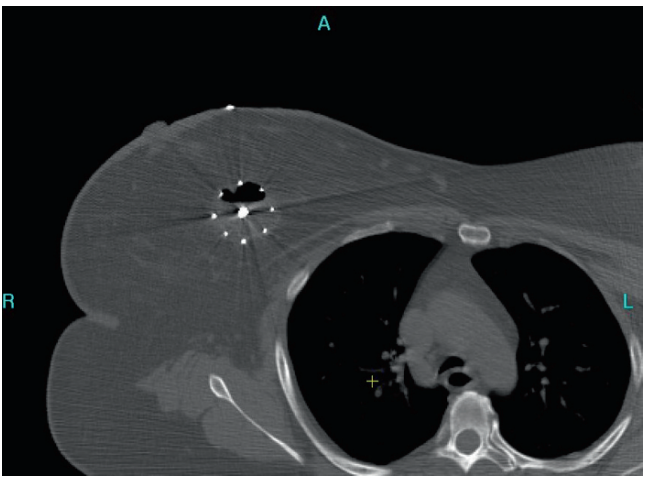

Fig. 6.13 The SAVI applicator with struts that act both as source paths and to hold the cavity open

this applicator and Fig. 6.14a shows a typical resulting dose distribution. Because the SAVI source paths lie in contact with the cavity wall, they yield the greatest ability to modify the dose distribution to the target locally of the three multipath applicators. Again this is a mixed blessing, because the variation in the dose distribution leads to a decrease in target homogeneity. In addition, because the source paths lie closer to the target distance, the relative penetration of the dose distribution beyond the prescription distance is also reduced.

Kitchen reported on the stability of the SAVI applicator in patients. In their practice, they image with CT before each fraction to evaluate the consistency of the applicator. Figure 6.14b shows an image in the same patient in approximately the same cut as Fig. 6.14a, and shows that the applicator rotated between fractions. Such a rotation may require recomputation of the dwell times.

As with the ClearPath, air in the cavity perturbs the dose distribution. Richardson has calculated that the air may increase the dose by about 6–8% (Richardson and Pino 2008). The perturbation is likely less than for the ClearPath because the dose to any tissue comes predominantly from the nearest catheter, reducing the amount of air the radiation traverses. The SAVI also appears to hold the cavity in a more uniform shape than the ClearPath.

6.3.5 Electronic Brachytherapy

While conventional brachytherapy uses radioactive materials (isotopic sources) to power the radiation engine for treatments, X-ray sources (electronic sources) provide an alternative. The units used for brachytherapy are either small enough to fit into an intracavitary catheter in the breast or are used for intraoperative irradiation at the time of tylectomy. Because these devices are relatively new and unfamiliar to many practitioners and are not presently

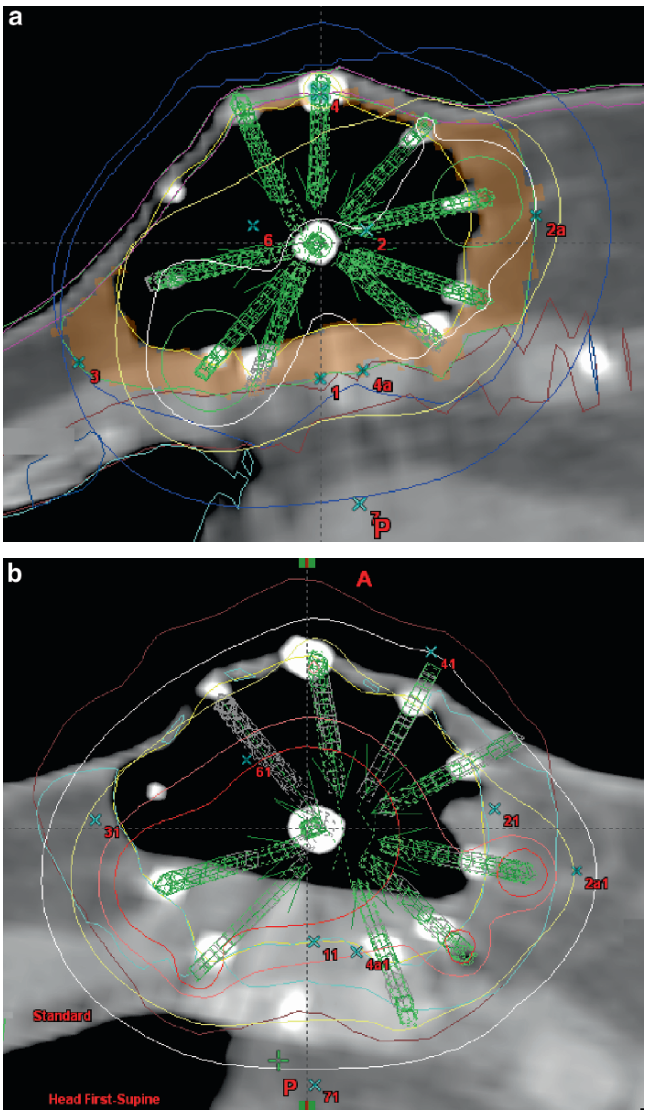

Fig. 6.14 **a** Typical dose distribution from the SAVI. **b** Image of the SAVI applicator in the same patient as in Fig. 6.14a, showing that the applicator rotated between treatments. Slide courtesy of Rebecca Kitchen, Aurora BayCare Medical Center Slide courtesy of Rebecca Kitchen, Aurora BayCare Medical Centre.

covered in most textbooks, a short description of the systems is warranted. Electronic brachytherapy devices mostly operate with an X-ray tube potential of 50 kVp, producing an effective energy of about 25–30 keV, an energy well below that of ^{192}Ir (with an effective energy of about 380 keV) or ^{169}Yb (93 keV). Advantages of these sources include:

- They protect nontarget tissues due to the more rapid fall-off in dose with distance compared with the isotopic sources. In particular, the dose from ^{192}Ir decreases according to the inverse square of the distance, because tissue attenuation and scatter mostly counteract each other over a range close to 6 cm. Alternatively, the radiation from the electronic source tends to decrease closer to the third power of distance.
- They allow radiotherapy personnel to remain with the patient during the treatment. Flexible shielding material (similar to lead-impregnated rubber) placed over the patient's breast during treatment reduces the radiation exposure in the room to levels compatible with occupancy. Some practitioners feel that this would be comforting to the patient, although this would be irrelevant in the intraoperative setting.
- They reduce the possibility of a major radiation event occurring due to a source becoming stuck in the patient. Because the radiation requires power to the X-ray tube, in the event of a problem, turning off the power stops the radiation from being produced and removes the need for an urgent response.
- There is a perception that there would be less stringent regulations for electronic sources than for isotopic ones.

Balanced against these advantages are the following considerations:

- *Dose inhomogeneity*. Due to the lower effective energy of the radiation, the dose at the surface of a balloon applicator in the breast will be higher than for an ^{192}Ir source. For example, a ^{192}Ir source delivers approximately 2.25 times the prescription dose at the surface of a 4 cm diameter balloon, while the surface dose becomes approximately three times the prescription dose for the X-ray source.
- *Decreased dose beyond the prescription distance*. While the more rapid decrease in dose for the electronic source protects neighboring normal structures, it carries a lower dose to more distant potential cancer cells. One cm beyond the prescription point, the dose with the X-ray source falls to 80% that of the ^{192}Ir. Three centimeters distal to the prescription distance, the probability of cancer cells remains about half that at the prescription distance (Holland et al. 1985). The dose beyond the prescription point may be critical to the success of this procedure, or it may not. Not enough is yet known about this issue to make a definitive statement.
- *Personnel remaining with the patient during treatment*. In the experience of the authors, very few patients have expressed any dissatisfaction with being alone during the treatment. More frequently, the patients enjoy meditating with music during the relatively short treatment.
- *Reducing the probability of an event*. The probability of excessive radiation exposure due to a stuck source is undoubtedly all but eliminated with the electronic source; however, the possibility of a source not progressing during treatment (in units that operate in that manner) remains. Neither of these types of events have a high probability with either radiation source. Some radiation oncologists have concerns about placing high-voltage cables in a patient, although the design of the X-ray units minimizes any hazard to the patient from electricity.
- *Reduced regulations*. At the time of writing, many states have yet to make regulations applicable to electronic brachytherapy. However, several have, and the Conference on Radiation Control Program Directors is in the process of issuing model regulations for the modality. Considering the regulations under consideration, it seems unlikely that the regulatory burden will be much different for electronic brachytherapy compared to isotopic.

- *Relative biological effectiveness (RBE)*. The RBE expresses the effectiveness of a given energy radiation at producing a biological effect compared with the effectiveness of radiation from a 250 kVp X-ray unit in producing the same effect. Radiation with energies significantly lower than 100 keV (the approximate effective energy of a 250 kVp X-ray unit) is more effective at producing many radiobiological endpoints. For diagnostic exposures, the RBE may be a factor of 2. In addition to the radiation energy, the value of the RBE depends on many factors, including the biological endpoint (and the species), the dose and the dose rate. When calculating the RBE, the values for α, β and the half-time for repair of sublethal cellular damage, μ, become important. Brenner et al. (1999) calculated the BRE for 40 kVp X-rays based on the spectrum of the beam for acute effects (α/β 7–10) and a single exposure of 12.5 Gy at 15 mm from the source, and found values of 1.24–1.38 compared with ^{192}Ir. They note that the RBE decreases with increased dose, and thus also increases with distance as the dose decreases. Fowler et al. (2004) calculated that the RBE for a high dose rate delivery of about 3 Gy would likely fall in the range of 1.3–1.5.

Comparing the X-ray system with the conventional HDR unit suggests no clear advantage of using one over the other, since they both have advantages. Currently the field includes two units.

6.3.5.1 Axxent (Xoft Inc., Fremont, CA, USA)

The Axxent system (Fig. 6.15) is a dynamic electronic brachytherapy device, a miniature X-ray tube that steps through a catheter in a manner similar to that of a radionuclide-based high dose rate unit. The tube operates with a peak potential of 50 kV, so the penetration of the beam is similar to that of ^{125}I. Figure 6.16 compares the dose as a function of distance for a ^{192}Ir source and the Axxent X-ray source. In the figure, both doses have been normalized to 3 cm from the source, corresponding to the prescription distance for a 4 cm diameter balloon. Due the greater decrease in dose with distance, the dose at the surface of the balloon is higher for the electronic source than for a ^{192}Ir source. As shown in Fig. 6.16, the dose at the surface of the balloon, as indicated by the black line, is three times the prescription dose for the X-ray and 2.25 times that for the ^{192}Ir. The dose beyond the prescription distance decreases more quickly for the X-ray source, which is a benefit for protecting the lung, heart and potentially reducing the skin dose, but does not irradiate potentially distant cancer cells as well as the conventional HDR unit.

Visualizing the MammoSite and the Contura balloons involves using dilute solutions of contrast, while the Axxent balloon catheter contains higher atomic number material in the wall. This avoids the need to fill the balloon volume with contrast, which would absorb much of the radiation at the lower X-ray energy, reducing the dose rate.

The X-ray tubes have a limited life. On average, one tube treats one patient or equivalent. If a tube expires during a treatment, it is simple to replace and does not increase the treatment time significantly. The output of the tube is calibrated before each use in an onboard well-type ionization chamber. The dose distribution exhibits greater anisotropy than a ^{192}Ir source, so multiple dwell positions are needed to form a uniform dose on the surface of a spherical balloon.

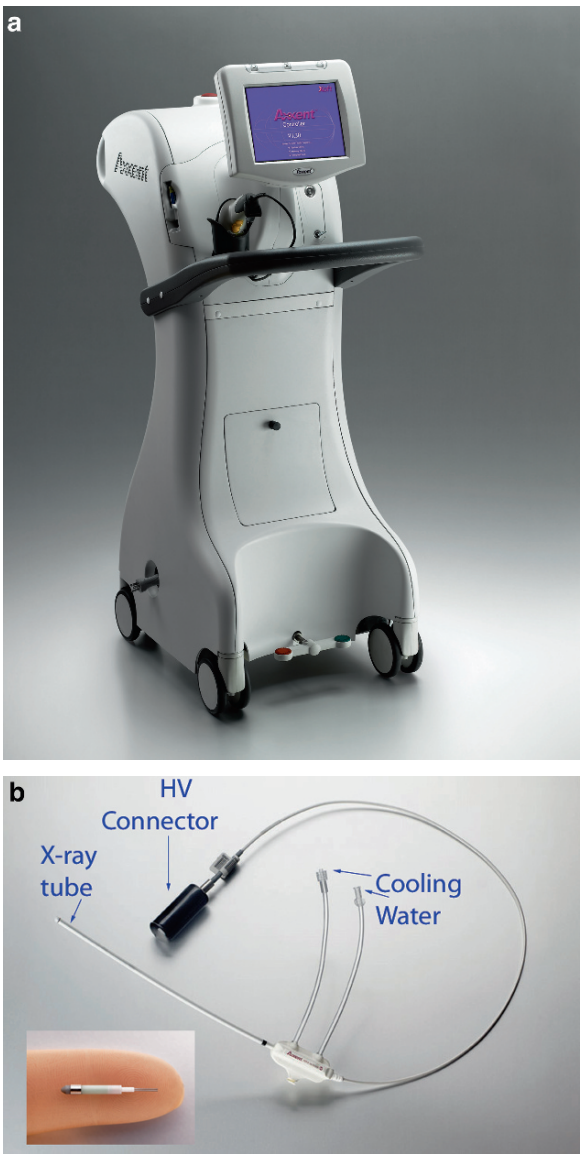

Fig. 6.15 The Xoft Axxent electronic brachytherapy unit, showing the unit as a whole (**a**) and the x-ray tube and cable (**b**). Figures courtesy of Xoft, Inc. Photos courtesy of Xoft, Inc.

The lower photon energy of the electronic source accentuates the effects of inhomogeneities in the target region. In the case of breast brachytherapy, the lung would be a large inhomogeneity that would result in higher relative doses within the lung of the radiation that reaches it. However, due to the low energy, little radiation should penetrate that far in

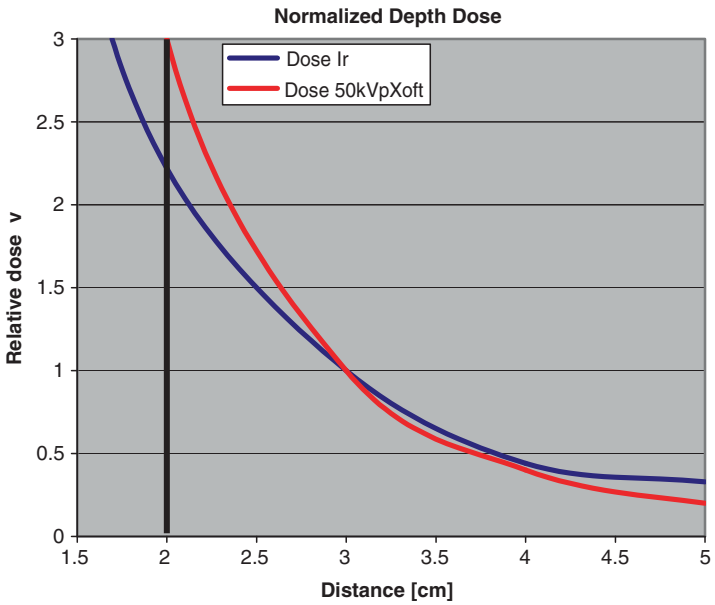

Fig. 6.16 A comparison of the dose as a function of distance for a ^{192}Ir source and the Xoft X-ray source operating at 50 kVp. The *black line* indicates the surface of a 4 cm diameter balloon. Both curves are normalized at the prescription distance, 1 cm distal to the balloon surface

most cases. Ribs also present as inhomogeneities, but with higher atomic numbers, and would have increased doses to the bone material, although the bone marrow should receive a lower dose than obtained with the conventional iridium sources. Air pockets trapped between the surface of the balloon and the inner surface of the tylectomy cavity should allow enhanced transmission of X-rays, which partially counteracts the effect of the increased distance on the dose to the target tissue pushed more distally by the pockets. The Axxent balloon does have vents on the surface to allow removal of air on the surface by suction, if the vents can be aligned with the air.

6.3.5.2 Intrabeam (Carl Zeiss, Oberkochen, Germany)

Another electronic brachytherapy system, the Intrabeam system (Fig. 6.17), is quite different from the Axxent. The Intrabeam has an electron gun on a stand that shoots the electrons through a long, straight, evacuated tube with a target at the end. Carefully shaping the target causes electrons striking the target to produce a mostly spherical dose distribution. As with the Axxent system, the Intrabeam operates at 50 kVp.

Fig. 6.17 The Carl Zeiss IntraBeam electronic brachytherapy unit, showing the unit as a whole (**a**) and the X-ray tube (**b**). Figures courtesy of Carl Zeiss Surgical GmbH, A Carl Zeiss Meditec Company

The Intrabeam system is used intraoperatively, by inserting a solid ball applicator over the long electron tube centered on the X-ray target and placing the applicator in the tylectomy cavity. Unlike the typical conventional HDR or Axxent approach of ten fractions, the Intrabeam TARGIT protocol calls for a single fraction, as used in stereotactic radiosurgery.

6.4 External Beam

External-beam treatments for whole breast irradiation have been a mainstay of radiotherapy for at least 80 years. Many techniques have been developed for whole breast and lymph node treatments—an indication that no technique was completely satisfactory. More recently, most treatments have included only the breast proper through the use of opposed tangential beams, for the same reason that partial breast treatments have come to the fore: the increase in patients with early-stage disease. While eliminating the lymph node coverage simplified whole breast treatments, good coverage, particularly at the margin, remains challenging due to the lack of rigidity of the breast.

6.4.1 Target Definition for External-Beam Approaches

Continuing the reduction in the volume of breast irradiated to PBI accentuates the problems of target localization and immobilization. Examples of external-beam approaches are given in Chaps. 16–18. Allowing the breast to assume a natural position as the patient reclines, results in fairly large changes in the spatial positioning and orientation of the breast following small variations in the patient's overall position. This translates into larger uncertainties in the location of the CTV and the need for larger margins around the CTV to form the PTV. A typical 4 cm tylectomy cavity may collapse to approximately 2 cm × 4 cm. Expansion for the CTV likely requires a 1.5 cm margin, making the CTV 5 × 7 cm^2. The margin for the PTV adds at least another 1 cm to the radius, for a target of 7 × 9 cm^2. A field of this size approaches that of the whole breast. Figure 6.18 shows a typical patient with the targets defined for an external-beam partial-breast treatment.

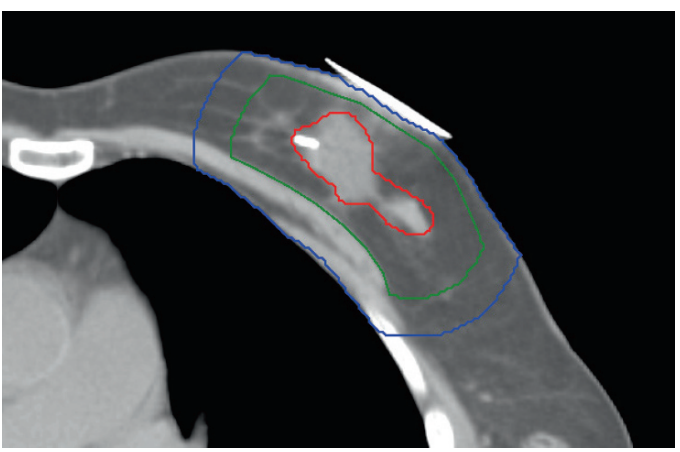

Fig. 6.18 A typical patient with the targets defined for an external-beam partial-breast treatment. *From inside out*: the tylectomy cavity with contrast; the clinical target volume; and the planning target volume. The *bright line to the anterior* is a wire on the surgical scar

6.4.2 External-Beam Techniques

Partial breast irradiation usually makes use of a three-dimensional conformal (3DC) technique or intensity-modulated radiotherapy (IMRT) (Edmundson et al. 2002; Keisch et al. 2003; Becker et al. 2006). The three-dimensional conformal approach, in essence, simply uses more than the conventional opposed tangential beams. The treatment may use fields at multiple angles, both gantry and couch, and/or fields within fields. All fields, of course, would be carefully shaped to protect tissues other than the target. For the most part, a simple tangential pair often serves as well for this treatment as more complex arrangements. IMRT uses multileaf collimators (MLC) to modulate the beam intensity through the field in order to sculpt the dose distribution and thus follow the target more closely and avoid other structures. While both techniques improve the conformance of the prescription dose to the target and avoid delivering high doses to neighboring tissues, the price paid is that increased volumes of the patient are irradiated to middle doses. Tomotherapy is an extreme case of IMRT where the source rotates around the patient as the patient moves through the gantry, with the MLC constantly changing. Here, particularly for women with large breasts, the doses to some normal structures may increase from middle doses to prescription dose. Figure 6.19 shows dose–volume histograms for the 3D conformal and IMRT plans. The IMRT plan does reduce the dose delivered to the breast other than the PTV and reduces the low-dose volume to the lung. However, the dose distribution assumes that the breast takes the same position day to day, which depends crucially on the

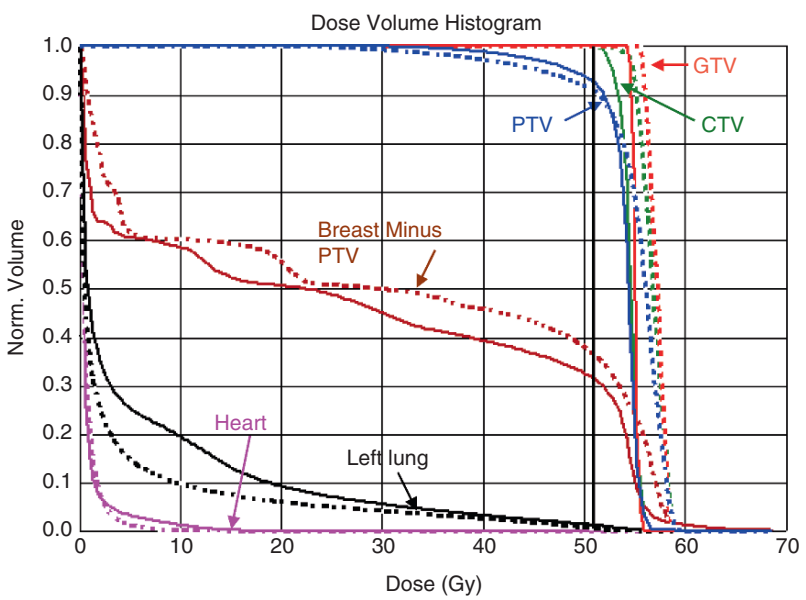

Fig. 6.19 Dose–volume histograms for a simple 3D conformal tangential pair (*solid line*) and IMRT (*dotted line*). The *vertical black line* indicates the prescription dose of 50.4 Gy

immobilization used (see below). The vertical line at 50.4 Gy indicates the prescribed dose. While it covers the CTV well, such that 100% of the CTV receives the prescribed dose, reasons for the expansion from the CTV to the PTV include the uncertainty in the positioning of the dose distribution. Thus, an evaluation of the coverage of the "target" must use the PTV rather than the CTV. Given that, the 3D conformal plan covers only 93% of the PTV, and the IMRT only 91%. The failure to cover more of the target volume mostly results from the low dose in the build-up region. The addition of bolus would solve this problem, but would increase the skin reaction, which (by intention) partial breast irradiation should avoid. Figure 6.20 shows typical isodose distributions for an external-beam treatment. It shows the problem of covering the volume near the skin. The difference between the partial-breast dose distribution in Fig. 6-c and that for a whole breast is slight.

Immobilization becomes critical for external-beam approaches. Many devices exist for assisting in positioning breast patients; almost all of them try to get the body and ipsilateral arm into a repositionable geometry. Figure 6.21 shows a typical device. The arm position sets the rotation of the body; but with the arm in the same location daily, the body may assume a range of locations, changing the position of the interior of the breast.

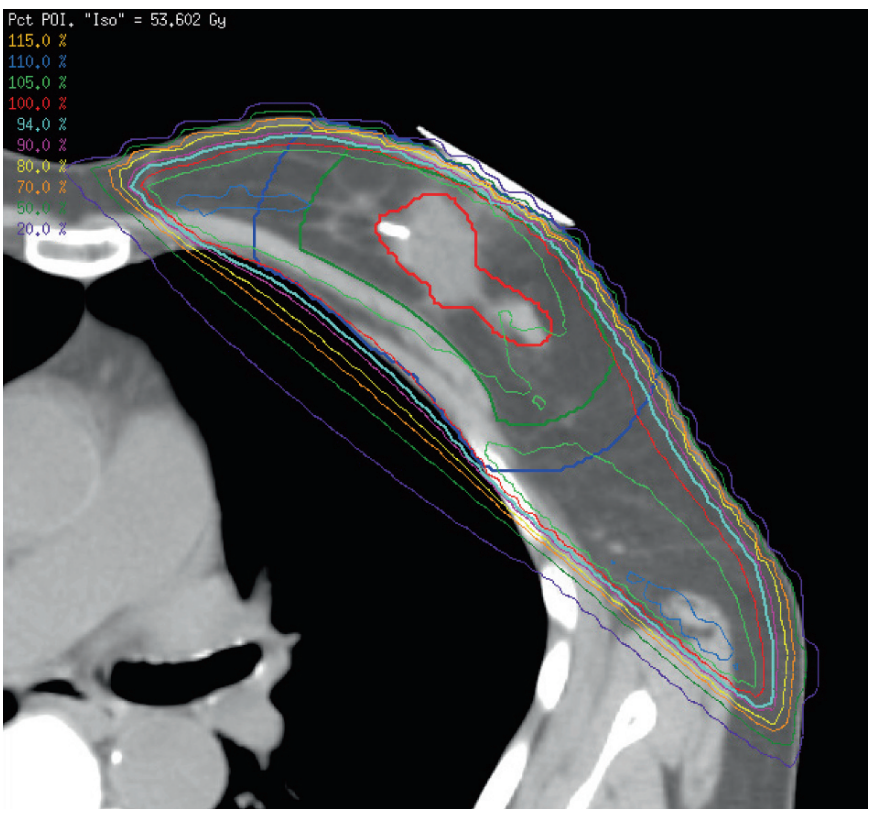

Fig. 6.20 Isodose distributions for various external-beam treatments for partial breast irradiation

Fig. 6.21 An immobilization device for breast irradiation. The arm position sets the rotation of the body, but with the arm in the same location daily, the body may assume a range of locations, thus changing the position of the interior of the breast. A body mold that comes up along the patient's sides to the mid-axilla provides improved reproducibility for the breast

A body mold that comes up along the patient's sides to the mid-axilla provides improved reproducibility for the breast.

Mindful of the problem of avoiding the lung with IMRT breast fields, Becker et al. investigated positioning the patient prone with the breast hanging through a hole in the couch. They found that the distance between the target and the lung increased by approximately 2 cm, reducing the dose to the lung by ab out a factor of three. There was no change in the distance to the heart for a left-sided tumor. While potentially beneficial for reducing

the lung dose, prone treatments present logistical challenges, particularly in terms of reproducible set up. Just as with the supine approach, small variations in body rotation result in marked differences in the location and orientation of the breast. Visualization of the breast to allow the detection and correction of any positioning problem becomes a difficult.

For all of these techniques, image guidance (IG) such as cone-beam CT or the use of implanted markers permits positioning imprecisions to be identified and corrected before treatment. However, such guidance often increases the dose to the contralateral breast, lung or heart.

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Quality Assurance for Accelerated Partial Breast Irradiation

7

Bruce Thomadsen and Rupak Das

7.1 Quality Management for Breast Brachytherapy

7.1.1 Quality Assurance During the Implantation Process

7.1.1.1 Interstitial Implants

Checking the Implantation Equipment

Quality management begins before the implantation procedure with an equipment check. Preferably, reusable equipment should be checked during the cleaning that follows the previous case. For template-based implants, it is particularly important to verify that all parts of the template system work correctly and were not broken. The templates themselves are made of relatively thin plastic; this is even true of the "thick" portions of many templates where much of the template material has been removed to make the plate lighter. As a result, the plate may suffer breakage, particularly near the edges, where the holes weaken the plastic. The rails on which the templates travel may also crack, although Frank breakage is rare for most of the materials used. A cracked rail could break during the subsequent implant, interrupting the procedure. Screws should be checked for correct operation and stripping. The conditions of each of these items should be carefully inspected. The packaging process should include verification that all parts are included.

Unfortunately (or fortunately), much of the implantation equipment comes sterilized, so physical inspection before the procedure is a difficult task. The main items that could affect the quality of the implant (template or otherwise) are the needles, the catheters and

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buttons. Should these materials be purchased in bulk and prepared at the facility, one of the references (Thomadsen 2000) provides detailed guidance on quality management for such supplies.

When the needles are replaced with catheters, each catheter should be checked visually for integrity. If the buttons that fix the catheter have numbers, the numbers should be checked for duplication. The most likely error would be to mistake a "6" and a "9," and there have been packs of buttons where two of the same number were packaged instead of one of each. If the numbers do not differentiate between the "6" and "9" other than by orientation, some marking, such as a decimal point after each, should be added to avoid confusion later.

Verification of the Target

Each of the implant techniques provides image-based guidance, and each also involves particular challenges. For template-based implants, template alignment is often the most time-consuming part of the procedure. Once aligned, the rest of the implantation proceeds fairly quickly. However, a poor alignment will make it very difficult to cover the target.

Target localization for a template-based implant is discussed elsewhere in this book. However, one important control measure is to ensure that the template and the images used for localization are not reversed. Most templates come with different markers on the right and left. Figure 7.1 shows a mammogram with the template in place. The right side shows two small markers, while the left side shows only one (as seen when the needles enter the template). This allows the parity of the images to be checked. The markers also indicate a given row and hole position; for example, on this template, the right marker indicates position 5 in row C.

Fig. 7.1 A mammogram with the template in place. Small ball bearings orient the image, with one on the *left* side, two on the *right* and three in the *center* when viewing as the needles enter the template. The ball bearings also indicate a particular row and hole

Implants performed under ultrasound (US), computed tomographic (CT) or magnetic resonance (MR) guidance make wrong-side errors in needle placement much less likely, but this increases the difficulty involved in assuring placement of the needles in even, parallel rows. For US guidance, the target is drawn as projected on the skin directly anterior. That means that the implant needles run in planes quite a distance from the transducer, adding to the difficulty involved in following the desired path. The images serve as the QA for the placement.

Alignment of the Needles

Because alignment of the needles during the implantation proper does involve quality control, it will not be discussed in this chapter. It is part ofZ the implantation technique discussed in Chaps. 11 to 13. Ensuring proper needle placement is the role of the guiding template or the guiding imagery.

Verification After Needle Placement

For all implants, regardless of the guidance approach, an image following insertion is always useful for verification. Such images can prevent erroneous treatment if a reversal of the guiding images was not detected previously, or the margin is inadequate. Figure 7.2 shows such an image for a template-based implant. Any question that the implant coverage is not as expected or that it may not give an adequate margin should be carefully investigated and resolved before breaking the sterile field.

A rule of thumb to follow for adequate coverage is to add needles to a margin if there is any question about the coverage. Extra needles placed during the procedure do not increase the discomfort of the patient. Unused needles can be removed easily later, but the addition

Fig. 7.2 A postimplantation image of a template-guided implant that is used to assure correct coverage of the target

of needles after localization has indicated uncovered regions is a much more difficult procedure and is uncomfortable for the patient.

7.1.1.2 Intracavitary Insertions

Checking the Intracavitary Equipment

The greatest concern about the equipment used for intracavitary breast insertions is a loss of fluid in the balloon. Such a loss would lead to breast tissue approaching the source closer than calculated and potentially receiving a large increase in dose. For a 4-cm diameter balloon, a 1-mm loss in radius produces a 10% increase in dose to the tissue at the balloon surface. Unfortunately, simply expanding the balloon before insertion is not the solution. Leaks may be slow, due to either poor seals at the syringe end of the balloon, through small holes or possibly diffusion, none of which would be observed during a short inflation before insertion. However, major balloon failures would be evident, and the manufacturer recommends inflating the balloons with about half the normal volume (about 60–90 cc) as a check for integrity (and tube patency) before insertion.[1] For insertions performed after the tylectomy, rather than during it, inflation before insertion can disrupt the smooth surface of the catheter, making insertion more difficult. Much of the quality management before treatment focuses on ensuring that the balloon diameter remains constant through the treatment.

Verification of Conformance with the Target

Intracavitary insertions eliminate many of the concerns associated with placing the sources in the target that accompany interstitial implants. In intracavitary applications, the balloon catheter is often placed into the cavity at the time of the tylectomy. Questions about the conformance of the applicator to the cavity must wait for the localization phase of the procedure. Cases where the catheter is placed later require that the cavity is still visible under imaging. Healing may cause the positioning of the balloon at the center of the cavity to be compromised, and this mispositioning would not be detected on the planning CT images. In addition, if the use of the balloon catheter was not planned at the time of surgery, the shape of the cavity formed may not be compatible with the use of the catheters. US imaging can sometimes be used to verify the correct positioning of the catheter during insertion in such cases, but only where the cavity can still be seen.

7.1.2 Quality Assurance During Localization and Reconstruction

The discussion of localization and treatment planning in this chapter assumes the use of CT or MR imaging. Two-dimensional radiographic imaging fails to distinguish either the

[1] Appreciation is extended to Gregory Edmundson for discussion on this topic.

target or normal structures such as skin or lungs. Larger volumes of the patient must be treated to provide a reasonable assurance that the target is covered, and yet such coverage is not assured. This is especially true for intracavitary treatments, where radiographic images fail to identify situations that can cause injury to the patient.

7.1.2.1 Interstitial

Regardless of the position of the patient during implantation, treatment is almost always delivered with the patient supine. Localization requires the patient to assume the same position as during treatment. Alternatively, if the bore of the imaging device (CT or MR) restricts the patient's position, treatment should be in the same position as localization. The positions of the catheters will differ from the nice controlled array that existed during the implantation procedure, but due to optimization during treatment planning, the differences in catheter position seldom make any difference.

Preparing the Catheters for Imaging

Before creating the images, the catheters should have markers placed in them. The catheters show up on the images as dark spots, although it is sometimes difficult to visualize the actual end of the catheter. The uncertainty over the end position is aggravated by the interslice resolution. Special markers that indicate the end position of the source assist in obtaining the correct source positions for treatment planning. The limiting resolution of the slice thickness and interslice separation affects the accuracy of the calculation in all cases. If the catheters run perpendicular to the cuts, the positions of the catheters are well defined but the positions of the dwells along the catheter become uncertain due to the slice thickness (assuming contiguous slices). If a catheter falls entirely in a slice, the dwell positions in the catheter are easily located, but the position of the catheter perpendicular to the slice becomes less certain.

The thickness of the breast changes over the duration of the treatment. Initially when a template is used, it takes some time after the removal of the template for the breast to relax from the compression and assume a normal shape. The breast also swells during and for a time after implantation. Because of these changes, the buttons fixing the catheters in place should not be fastened too tightly immediately after the implant. By the next day—a common time for localization imaging—the breast will have reduced towards its normal size. However, during the course of treatment, the breast usually swells again in response to the radiation, becoming noticeable by about the third day of treatment. Thus, at the time of localization, the buttons should again not be fastened too tightly. Buttons that can slide along the catheter can be snugged at the time of localization, and the pressure released as the breast swells. Button that fix solidly to the catheters must leave room for swelling. The changing contour of the breast during the course of treatment poses problems for the correct localization of dwell positions. As the catheters shift in the breast, the distance from the center of the target to either the entry or the exit buttons (whether they are fixed

or adjustable) does not stay constant. To complicate the situation still further, the target is seldom centered in the breast. Since there is no easy way to adjust for the change in the relative positions of the catheters with respect to the target, the margin in the direction of the catheter must include this uncertainty upon expanding the clinical target volume (CTV) to the planning target volume (PTV) (ICRU 1993; ICRU 1999). The overall uncertainty can be approximately 1 cm. For consistency, it is probably best to always keep the fixed ends of the catheters (distalmost with respect to the source travel) against the skin, both during the localization and during treatments.

Catheter Numbering

Catheter identification is, of course, important when inputting data into the treatment planning system and during catheter connection. We have already discussed catheter labeling in a previous section. When data are entered into the treatment planning system, it is useful to have photographs from both the tip end and the connector end. Figure 7.3 shows a photograph of the tip end. One of the easiest and surest ways to establish which exit button corresponds to which entrance catheter number is to watch for the marker to show at the bottom of the catheter (most catheter allow seeing the shadow of the marker in the center of the button) or to feel the marker hit the bottom of the button during the insertion of the imaging markers. The photograph provides a comparison with a three-dimensional end-on view that can be used to verify that the catheters were correctly identified.

Checking the Lengths of the Catheters or Catheter Inserts

The length to the first dwell position sets all subsequent positions, and must be correct for the correct positioning of the dose distribution. In systems where the transfer tubes connect

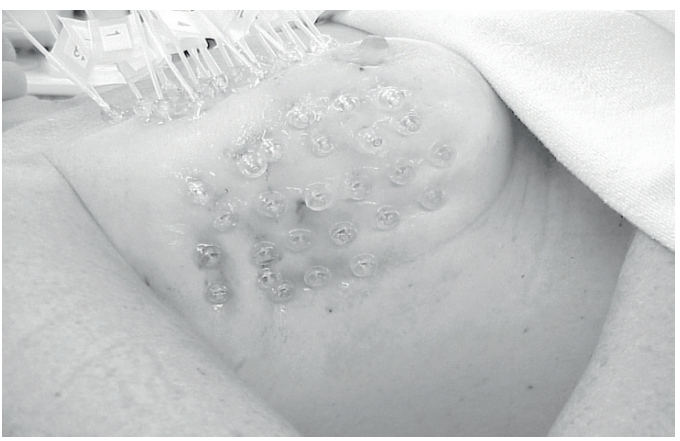


Fig. 7.3 A photograph of the exit side of an implant showing the catheter numbering as found from the entrance side

directly to the catheters, and the catheters may be cut to arbitrary lengths, the distance to the end of the catheter must be measured. This can be done by inserting a wire down the transfer tube with the catheter connected and measuring the length of the wire. However, when using this method, one must know the offset from the end of the transfer tube to the zero point of the afterloader, as well as the distance from the tip of the source cable to the center of the activity, and any margin required beyond the end position of the source cable to accommodate extra travel on the part of the check cable on some units. A better alternative is to use a tool sold by the manufacturers that performs this measurement. Figure 7.4a shows the tool marketed by Nucletron (Veenendaal, Netherlands) that connects to a transfer tube and catheter. It consists of a wire connected to a scale that directly reads the length of source travel. Units with "end-seek" functions, where the check cable travels to the end of the catheter and records the distance as well as manual tools such as that shown in Fig. 7.4a can both be confused by kinks or unexpected resistance in the catheter. An approximate knowledge of the expected distance helps to prevent reading misinterpretations in such cases.

A different class of catheter systems uses special inserts that are attached to the transfer tube that slides into the catheter. The inserts have a constant length, so the length of the catheter becomes irrelevant. One should bear in mind, though, that this simply shifts the task of length verification from checking the catheters to checking the inserts. However, it is easier to perform this check than to check the length of the catheter. For the most part, checking the length of the inserts simply involves comparing the inserts to a standard insert that has been verified previously. Figure 7.4b shows a simple comparison. Of course, the comparison is only useful after verifying the length of the standard insert.

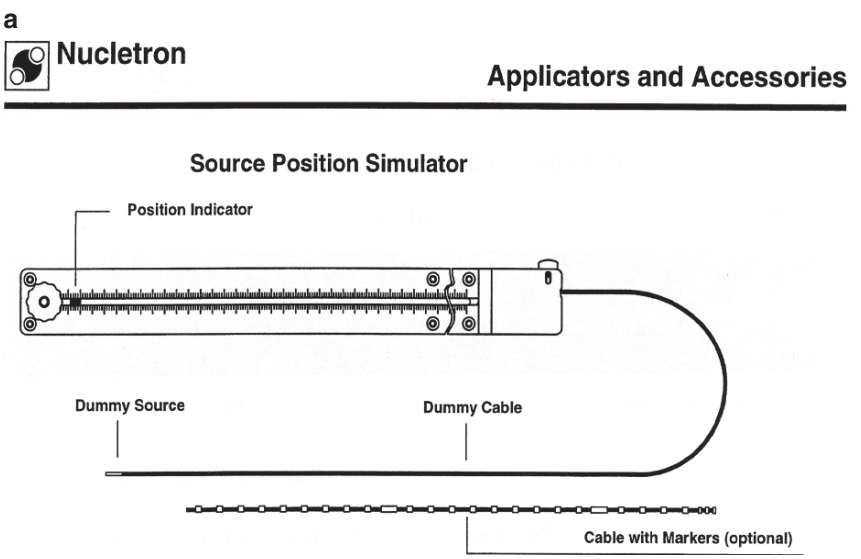


Fig. 7.4 **a** A tool for determining the length to the first dwell position (courtesy of Nucletron BV, Veenendaal, Netherlands)

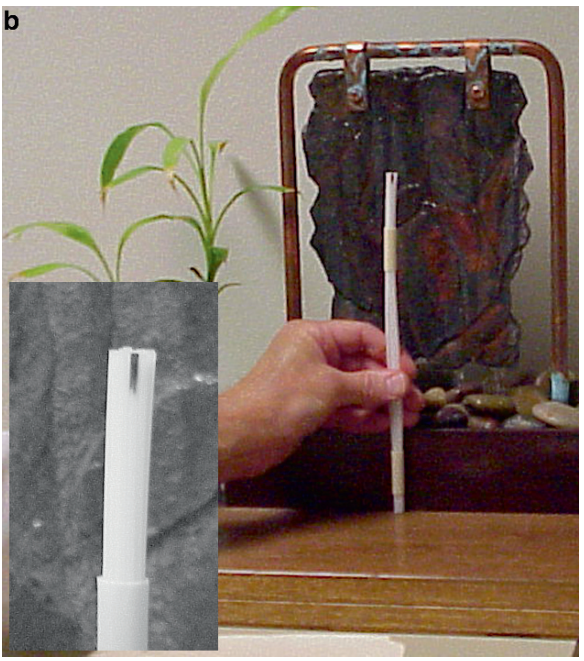


Fig. 7.4 (continued) **b** Comparison of the lengths of catheter inserts to a standard, verified insert

7.1.2.2 Intracavitary

Verification of Length

The length becomes a much more critical parameter for intracavitary treatments than interstitial treatments. With interstitial treatments, one catheter with an erroneous length alters the dose distribution locally around that catheter but does not usually make a large difference to the overall dose distribution. With an intracavitary treatment, particularly one that uses a single dwell position, any shift in the position of the source causes an equal shift in the dose distribution. A 1-mm misplacement in the length produces a 10% variation in dose at the surface of a 4 cm diameter balloon. Thus, verifying the length to locate the source becomes of paramount importance, and it becomes essential to use a special localization marker that indicates the location of the first dwell position. At the time of treatment, coincidence between the dwell position and the center of the balloon again requires verification, as discussed below.

Verification of the Filled Diameter

Determining the correct balloon diameter requires as much care as determining the length because similar errors produce the same unwanted results. During the localization procedure, the diameter of the balloon is not checked other than to compare its size on the CT or MR

to that expected given the filling. Before treatment, the balloon is checked to ensure that the diameter is the same as that measured during the localization. The balloons should never be used with diameters that are smaller than their specified range (for example a 4–5 cm balloon filled only to a diameter of only 3.5 cm). Doing so would likely result in the balloon losing sphericity.

Appropriateness of Application

Many aspects of the application can result in inappropriate or even dangerous dose distributions, and must be screened for during localization.

Shape

The surface of the balloon should be regular. Significant variations from the correct spherical or ellipsoidal shape constitute grounds to abort the procedure. The anisotropy of the source's dose distribution does allow for some constriction along the axis compared with the transverse direction, but such differences should remain within 3 mm.

Voids

One of the most common problems is voids at the surface of the balloon. Air pockets can be trapped during applicator insertion, and these can shift target tissue away from the balloon and out of the range of the prescribed isodose surface. A void 0.8 mm in radial height reduces the dose to the most distant target tissue to 95% for a 4-cm diameter balloon, and a void with a radial height of 1.6 mm reduces the dose to 90%. Volumetric assessment, looking at the volume of the void as a fraction of the target volume, does not indicate much sensitivity to the effects of voids. The same 4-cm diameter balloon produces a treatment volume of 80 cm^3 in the 1 cm wide rim (not counting the volume of the balloon). If we use a volumetric-based criterion to evaluate the effect of a void, to get 10% of the volume pushed out of the treatment volume (the Rind around the applicator balloon) would require an 8-cm^3 void, which would have a radius of 1.6 cm if the void was hemispherical. Obviously, the minimum dose criterion is more stringent.

Voids often seem to resolve over time. However, resolution may result from either the tissue refilling the void and contacting the balloon or, as is often the case, fluid filling the void and leaving the target tissue at a distance from the balloon. CT images cannot distinguish between these cases, so the patient should be imaged using MR before deciding to initiate treatment. Placement of a vented catheter along the surface of the balloon to allow any air to escape partially defeats the point, because the venting catheter also pushes the target tissue out of the treatment volume. Some catheters have vents built into the wall of the balloon, allowing the trapped air to be suctioned, thus improving the conformality. The placement and number of venting holes does limit the ability to reach all possible void positions; however, by rotating the balloon, most locations are made accessible.

One mitigating aspect of the treatment modality is that the dose does not fall off very quickly. Even though they do not receive the treatment dose, tissues that are moved 1.5 mm from the surface still receive about 90% of the prescribed dose. This slow gradient does provide some margin. Some recent investigations have suggested that voids may not cause as much change in the dose to the target tissues as previously thought.

Distance to Skin, Pectoralis, Lung, and Heart

As discussed in a previous chapter, intracavitary treatment of the breast will deliver higher doses to the skin than will interstitial. The skin dose should remain below 150% of the treatment dose. For this to hold, the margin between the surface of the balloon and the skin, δ, must remain

$$\delta \geq 8.2\,\text{mm} - 0.18\,r_{\text{balloon}}, \tag{7.1}$$

where r_{balloon} indicates the radius of the balloon. For a 4-cm diameter balloon, the margin must be at least 4.6 mm. The general rule to allow for a safe margin is to have at least a 5 mm margin. While there is less concern over the pectoralis muscle than the skin, it is usually considered prudent to apply this same margin to the muscle. The dose to the lungs, and more so to the heart, seldom becomes high enough or covers a large enough volume to raise concerns.

7.1.3 Quality Assurance of the Treatment Plan

Today, almost all treatment planning systems have the ability to import CT/MRI/US images through a local area network (LAN). The delineation of critical structures like the heart and lungs and the definition of PTV by adding margins to the lumpectomy cavity have aided conformal treatment plans tremendously. The utilization of a dose–volume histogram (DVH) for the region of interest to relate clinical outcome and toxicities (Kestin et al. 2000), as well as the ability to achieve a homogeneous dose distribution using optimization tools in order to reduce telangiectasias and fat necrosis (Roston and El-Sayed 1987; Clarke et al. 1983) have provided the radiation oncologist with powerful tools to make clinical decisions when making the patient's treatment plan. Finally, quality assurance (QA) for a complex HDR treatment plan with a single stepping source has always been a challenge to the physics community. A good and efficient QA program for planning and delivering treatment is extremely important and is necessary to treat patients safely.

7.1.3.1 Interstitial

Target Coverage

Ideally, both the lumpectomy cavity and the target volume should be covered by the prescription isodose line. Figure 7.5 shows a 3D view of one such plan. As is seen from the figure, the 100% isodose cloud (blue) covers the lumpectomy cavity (deep pink) and also the PTV (light pink). In order to analyze the total coverage in 3D, a DVH must be generated. Figure 7.6 shows the integral DVH for 100% of the lumpectomy cavity, with a volume of 19.9 cc totally covered by the 100% isodose line. For the PTV, 95.4% of the target (volume: 230.5 cc) is covered (i.e., 220 cc is covered by the prescription dose of

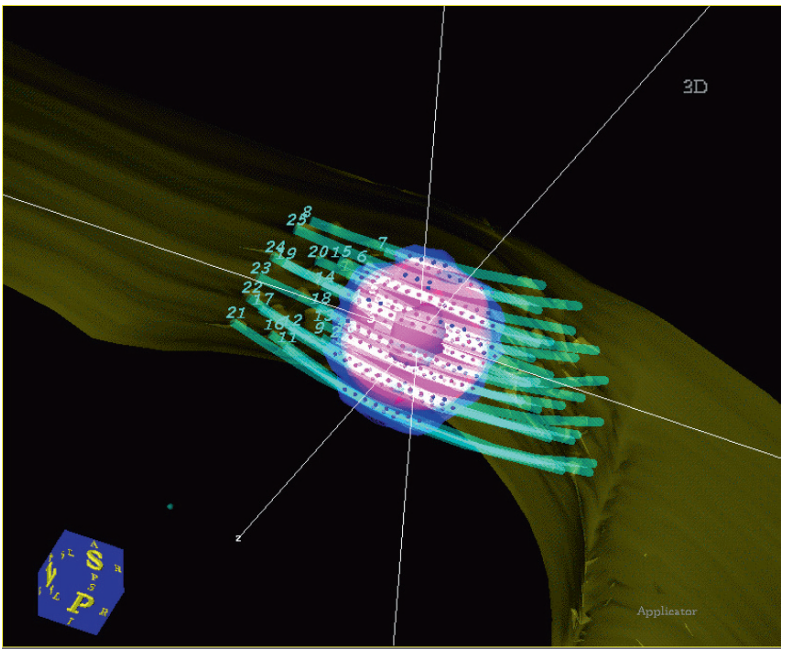
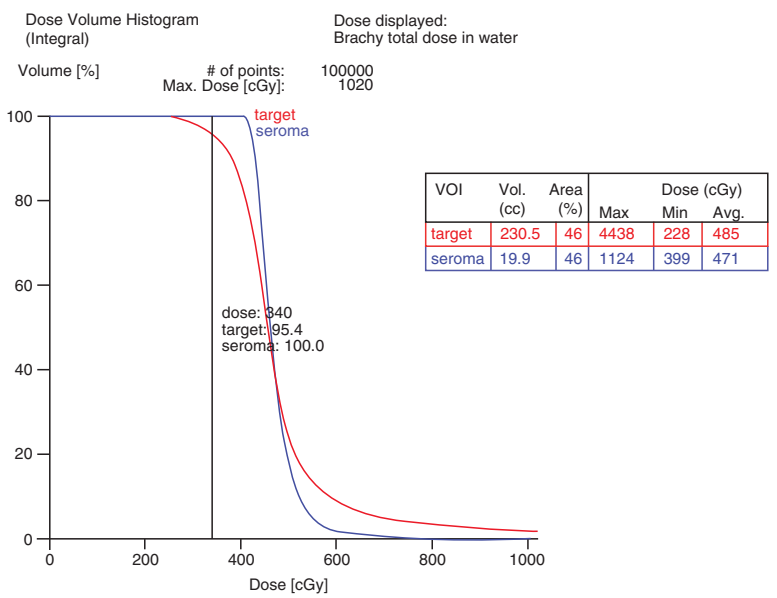


Fig. 7.5 A 3D view of the dose distribution with the lumpectomy cavity (*dark pink*) and the planning target volume (*light pink*)



VOI	Vol. (cc)	Area (%)	Dose (cGy) Max	Min	Avg.
target	230.5	46	4438	228	485
seroma	19.9	46	1124	399	471

Fig. 7.6 Integral dose–volume histogram of an interstitial breast implant

3.4 Gy per fraction). Critical structures like heart, lungs, skin, and contralateral breast can also be delineated, and their DVHs can be generated to aid the physician in determining the best treatment plan.

High-Dose Volume

In any interstitial brachytherapy implant, the tissue around the radioactive source will be "hot." However, the extent of this hotspot can be minimized by implanting catheters that are equidistant (1–1.5 cm) from one another. When optimizing the dose distribution, great care should be taken to distribute the "hot spot" (150% isodose line) among as many dwell positions as possible, rather than among just a few. A rule of thumb is not to allow two adjacent 150% isodose surfaces to coalesce or touch each other. A "good" or "optimal" implant with adequate catheters should be able to maintain this rule.

Uniformity Indices

One measure of the uniformity of dose distribution in a brachytherapy implant is termed the dose homogeneity index (DHI), defined as

$$\mathrm{DHI} = \frac{V_{100} - V_{150}}{V_{100}}, \tag{7.2}$$

where V_{100} and V_{150} are the volumes covered by the 100% and 150% isodose surfaces, respectively. This has been used to ensure that the level of dose homogeneity for the implant is as high as possible (Wu et al. 1988). A DVH is generated for the implant in order to derive V_{100} and V_{150} and thus calculate the DHI. The ideal value for the DHI is 1.0, which is impossible in practical terms since there will be some hot spots around the source.

Conformality Index

The target volume and the volume covered by the 100% isodose surface, V_{100}, should be as conformal as possible. Mathematically, a conformality index (CI) can be defined as (ICRU 1993; Das and Patel 2005)

$$\mathrm{CI} = \frac{\text{Target volume} \cap V_{100}}{\text{Target volume} \cup V_{100}}. \tag{7.3}$$

The CI can be calculated as

$$\mathrm{CI} = \frac{\text{Volume of PTV covered by 100\% isodose line}}{V_{100} + \text{Volume of PTV not covered by 100\% isodose line}}. \tag{7.4}$$

In an ideal implant, the CI should equal 1.0, indicating perfect conformance between the 100% isodose surface and the target volume. As explained above, a DVH for the brachytherapy implant and an integral DVH for the 3D treatment plan are required to derive V_{100} and the volume of PTV covered/not covered by the 100% isodose line.

Another measure of the conformality of an implant is the conformality number,

$$\mathrm{CN} = \left(\frac{\text{Volume of the CTV receiving the prescribed dose}}{V_{100}} \right) \left(\frac{\text{Volume of the CTV receiving the prescribed dose}}{{}_{\mathrm{CTV}}V} \right). \tag{7.5}$$

The first factor in the equation evaluates how efficiently the dose distribution is placed in the target, while the second considers the coverage of the target.

Skin Dose

For breast interstitial implants, a high dose to the skin can be detrimental to the cosmetic outcome, and could lead to long-term complications in certain cases where the skin dose is very high. A quality assurance program to restrict the skin dose to a certain percentage of the prescription or the PTV to be at a certain depth below the skin (often taken as 5 mm) is essential. Figure 7.7 shows how a PTV generated by adding a 2 cm margin around the

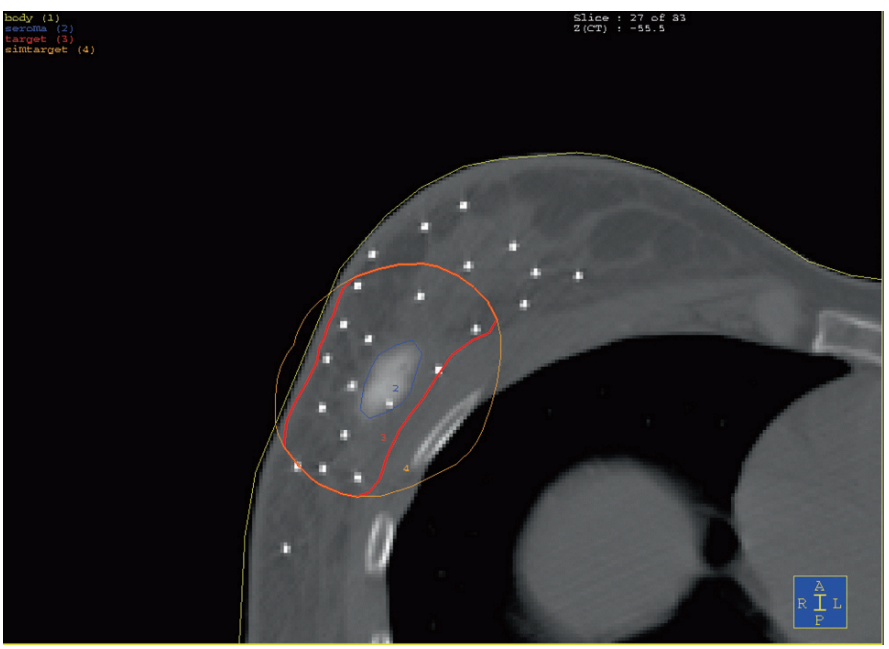


Fig. 7.7 Limiting the expansion of the seroma (*blue*) to the target (*red*) by the skin and pectoralis muscle

lumpectomy cavity is then modified to be 5 mm below the skin, which generally restricts the dose to the skin to about 80% of the prescription dose (Das et al. 2004).

Dwell Time as a Function of Volume

All remote afterloaders utilize stepping source technology, which enables the planner to maximize the dose uniformity while minimizing the implant volume needed to adequately cover the target volume. Such flexibility creates a challenge when it comes to verifying the optimized calculations with practical manual calculation techniques that take only a few minutes and at the same time detect significant errors. The Nuclear Regulatory Commission considers a difference of 20% between the administered dose and calculated dose a medical event (NRC 2005). Commonly, variations of greater than 5% in external-beam treatments are felt to potentially compromise outcomes. While the accuracy of brachytherapy treatments is less well defined, there is clearly a need for a quick method to verify the accuracy of an optimized plan. Using the Manchester volume implant table, the calculated irradiation time can very easily be used as a quality assurance parameter for the HDR computed time.

Table 7.1 shows the Manchester volume implant table, with column 3 corrected for modern units and factors and the conversion from mgRaEq-h/1000R to Ci s Gy^{-1}, (Williamson et al. 1994), while Table 7.2 gives the elongation factors as they were originally published (Paterson and Parker 1938).

Table 7.1 Integrated decays needed to deliver a dose R_v (Williamson et al. 1994)

Volume (cm^3)	mg Ra Eq-h/1000R	R_v (Ci s Gy^{-1})
0	463	314
80	633	429
100	735	498
140	920	624
180	1,087	737
220	1,243	843
300	1,529	1,037
340	1,662	1,127
380	1,788	1,212

Table 7.2 Elongation factors (Paterson and Parker 1938)

Ratio of length/diameter	Correction factor
1.5	1.03
2.0	1.06
2.5	1.10
3.0	1.15

For a given treatment volume (V_{100}), the irradiation time in seconds needed to deliver a prescription dose in grays with a source activity in curies is given by

$$\text{Time (s)} = \frac{\text{R}_V\ (\text{Ci s Gy}^{-1}) \times \text{Elongation factor} \times \text{Prescribed dose (Gy)}}{\text{Activity (Ci)}}. \tag{7.6}$$

The time calculated from (7.6) can then be compared with the treatment planning time. A recent study of 50 breast interstitial plans showed that the two times agree within ±7% of each other (Das et al. 2004).

Lengths

As noted above, in an interstitial implant with many catheters of different lengths, great care should be taken when measuring the lengths of these catheters along with the transfer tubes. The accurate transfer of the measured length of each catheter to the treatment planning system is crucial, and requires a quality assurance check. Moreover, maintaining a record of these lengths and verifying the recorded length against the programmed length before each treatment are essential tasks, since any discrepancy results in a totally different dose distribution to the PTV. One vendor (Nucletron Corporation) has come up with a fixed-length catheter system (Comfort Catheter), as shown in Fig. 7.8. Even though the button-to-button distance of the catheter can vary, the length of the plastic tube that is inserted into the catheter is fixed. Instead of measuring the length of each catheter, a premeasured length applicable to all catheters can be used, reducing the simulation time. As noted in Sect. 7.1.2.1, the lengths of the inserts must be verified instead.

7.1.3.2 Intracavitary

Target Coverage

Just as in interstitial implants, integral DVH analysis should be performed for breast intracavitary implants in order to evaluate the volume of the PTV (surface of the balloon +1 cm)

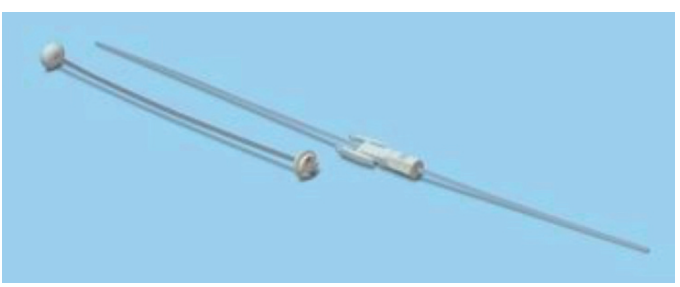


Fig. 7.8 Comfort catheter (courtesy of Nucletron B.V., Veenendaal, Netherlands)

covered by the prescribed dose. The assumption that the lumpectomy cavity and the balloon are isocentric and congruent does not hold for all patients. In those situations, the V_{100} and the PTV do not overlap, and an integral DVH is the ideal tool for clinical decisions.

Uniformity Indices

For intracavitary implants, (7.2) can be modified to

$$\mathrm{DHI}_{\mathrm{intracavitary}} = \frac{V_{100} - V_{150}}{V_{100} - V_{\mathrm{balloon}}}, \tag{7.7}$$

where the volume of the balloon (V_{balloon}) needs to be assessed either by measuring the amount of fluid injected in the balloon or by consulting the integral DVH after delineating the balloon in all of the CT slices. For the MammoSite (Hologic, Inc., Bedford, MA, USA) balloon, the DHI increases as V_{balloon} increases.

Skin Dose and Dose to Other Structures

Unlike interstitial implants with multiple catheters, each with several active dwell positions, intracavitary applicators like MammoSite have one active dwell at the center of the balloon. Conforming the V_{100} to the PTV and reducing the doses to critical structures like skin, heart, and lungs is not an option. Great care should be taken to analyze the DVHs of the skin and other critical structures before making a clinical decision.

Dwell Time as a Function of Distance

Since the prescription point is determined from the center of the balloon to the equatorial surface of the balloon +1 cm, a manual calculation of the time given by the point source equation (7.8) can be performed to compare the predicted time to the treatment planning time.

$$\mathrm{Time\,(s)} = \frac{\mathrm{Prescription\ dose} \times r^2}{\Lambda S_{\mathrm{k}}\, g(r)}, \tag{7.8}$$

Here, with the values for the ^{192}Ir source given in parentheses, Λ is the dose rate constant (1.12 cGy μGy^{-1} m^{-2}), S_{k} is the air-kerma strength (μGy m^2 h^{-1}), $g(r)$ is the radial dose function (1.02), and r is the radius of the balloon +1 cm. Usually the times agree within ±5%.

Length

For a MammoSite balloon, the center of the balloon preferably needs to be located by a source simulator and an imaging device. Diluted radio-opaque material that is strong enough to visualize the surface of the balloon yet weak enough to see the dummy source

of the source simulator can help to locate the center of the balloon on the image as well as to establish the length required for the source to be positioned at the center. The Axxent balloon contains contrast material in the walls of the balloon to assist in visualization, since the presence of contrast in the balloon volume would severely attenuate the low-energy X-rays.

7.1.3.3 Quality Assurance at the Time of Treatment

For both interstitial and intracavitary treatments, the first step is to assure that the patient assumes the same position on the treatment table as during localization. Variations in position can produce variations in catheter geometry and thus in dose distribution.

7.1.3.4 Interstitial

Program Verification

Data are transported from the treatment planning system to the treatment console station by either a LAN or electronic memory devices. After the data have been transported, the values included in the program for patient name, total treatment time, step sizes or dwell locations, catheter lengths, and dwell times should be checked before the first treatment. For the most part, this check verifies that the correct plan has been imported into the treatment unit, since file corruption usually results in an unusable file rather than a usable one with modified data. However, it is not unwise to check the program. For subsequent fractions, not every dwell time needs to be checked; only as many as necessary (or the overall time) to assure that the correct program is loaded.

Connection of the Catheters

Correctly connecting the catheters is, of course, essential if the correct treatment is to be provided. Errors in catheter connection can occur either when connecting the transfer tubes to the treatment unit or when connecting the catheters to the transfer tubes. If more than one set of transfer tubes is available for catheter connection (e.g., for different lengths to the first dwell position), selection of the correct set of tubes should be one of the verification procedures. Many potential errors when connecting the transfer tubes to the treatment unit tend to be prevented by design; for example, skipping a hole when inserting the tubes into the indexer. Such a mistake would cause the unit to pause during treatment until the tubes were moved to fill the empty location. It is possible to mix up the tubes: any tube may go in any hole. However, any error in the order must actually be *two* errors; for example, inserting tube #12 into hole #2 would leave hole #12 without a corresponding tube unless tube #2 is placed in there, making the error less likely.

Mistakes when connecting the transfer tubes to the catheters are more likely, particularly when more catheters are treated than transfer tubes (i.e., holes in the indexer). In such cases, the catheters from 1 through to the highest number on the indexer are treated in a first set. Then, after disconnecting these catheters, the next numbers in line are connected. This process is repeated until all of the catheters are treated. With cases requiring multiple sets of connections, mistakes where catheters from different sets are connected become a hazard. For example, when connecting the first set, catheter #32 could mistakenly be connected to hole #2 (or #3, depending on what the person connecting sees).

After connecting the catheters to the transfer tubes, but before initiating treatment, the catheters must be moved so that the buttons on the exit side of the patient abut the skin, as they were for localization imaging. Section 7.1.2.1 discusses this issue in more depth.

Early in a breast brachytherapy program, a facility may wish to perform a patency check on all of the catheters before starting the treatment in order to ensure that the treatment doesn't get stuck because a catheter has a kink. However, with experience, increased confidence in the procedure will probably lead to this step being skipped. We have never had a catheter that the check cable found to be kinked or blocked. (The check cable frequently detects connections that are not secured, but these are easily corrected.) Even without checking all of the catheters before initiating treatment, the unit will still check each catheter immediately before sending the source.

7.1.3.5 Intracavitary

All of the abovementioned checks for interstitial treatments should be performed for intracavitary treatments too, along with the following extra checks.

Volume Check

Before each treatment, an image of the balloon should be acquired to make sure that the volume of the balloon is the same as during localization, that the balloon has not collapsed, or that fluid from the balloon has leaked. Figure 7.9a shows fluoroscopic images of a MammoSite balloon in two patients. A ruler with small opaque spheres (1 cm apart) is placed at the same level as the center of the balloon in order to help determine the diameter of the balloon. Ensuring that the ruler lies at the same distance as the balloon can be difficult, and variations in the focus-to-ruler distance will lead to incorrect magnification factors for the image of the balloon, and possibly mistakes when interpreting the balloon diameter. Figure 7.9b shows an US image of a Contura (SenoRX, Aliso Viejo, CA, USA). The US verification takes about one minute in total.

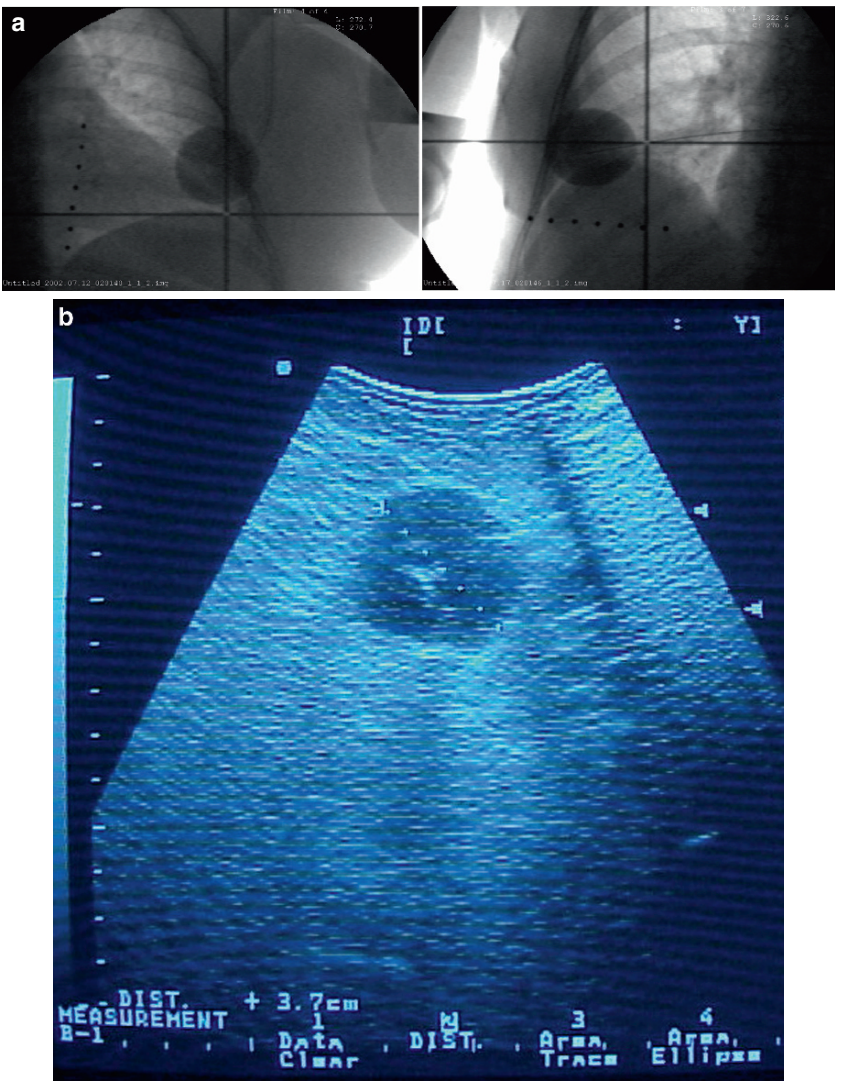


Fig. 7.9 (**a**) Fluoroscopic image of Mammo Site balloons in two patients, a ruler with small opaque spheres (1 cm apart) is placed at the same level as the center of the balloon, helping determine the diameter of the balloon. The image on the right also shows the source traveling to the center of the balloon. (**b**) An ultrasound image of a Contura applicator for verification of the diameter

Correct Location of Source

A check that the source has traveled to the center of the balloon should also be performed before each treatment. Figure 7.9a also shows the programmed check cable run to the center of the balloon before the radioactive source run.

7.1.4 Post-treatment Verification

Immediately after the end of treatment, the operator must check the patient with a radiation detector to verify the complete retraction of the source. If a source, or part of a source, remained in the patient after treatment it would deliver a sufficient dose locally to cause injury to the tissues after a minute. After each treatment has finished, the contents of the treatment report should be verified, including the length of each channel, the total irradiation time, and the individual dwell time.

7.2 Quality Management for External-Beam Partial Breast Irradiation

While whole breast irradiation has been practiced successfully (for the most part) for decades, and localization and positioning have become routine, the tolerances for positioning in partial breast irradiation have tightened considerably (see Chap. 6). Unlike the brachy therapy approaches, where the applicator forces the dose distribution to conform to the target, matching the dose to the target is a critical challenge in external-beam treatments. Thus, the application of quality control to such treatments is an indispensable link in the treatment chain.

7.2.1 Quality Control During Patient Positioning

7.2.1.1 Immobilization and Stability

Traditionally, the lasers in the treatment room have been the most important tools used in the localization of the whole breast, while many radiation centers use breast boards for immobilization and stability. In partial breast irradiation, the PTV is generated by the expansion of the CTV by a margin that includes the patient positioning error. Since setting up with lasers is not a highly accurate approach, daily patient positioning error increase, the margin required to expand the CTV to the PTV (see Chap. 6). This leads to a larger PTV, which ultimately defeats the aim of partial breast treatment. Breast boards or molds along with imaging on the linear accelerator should be chosen for immobilization and stability.

7.2.1.2 Clearance

Clearance becomes a problem with external-beam breast patients at two steps. The first problem with clearance occurs at the CT unit during imaging for treatment planning. When using a breast board, such as shown in Fig. 6.21, the patient will often not fit into the bore of the unit in the desired treatment position. Failure to attain the correct position during

this imaging results in poor conformance of the treatment plan to the execution. To mitigate the problem of positioning the patient on a breast board in the conventional treatment position (with the head of the board raised), modern treatment planning usually allows good treatment plans with the patient completely supine. Problems with patient clearance at the CT become obvious during the imaging session, and only propagate to degrade the treatment quality if the problems are ignored.

Clearance again becomes an issue when setting the fields developed during the planning phase. Particularly with multifield conformal or IMRT plans, beam orientations that produce desirable dose distributions in the computer may occur at combinations of angles that pose problems. Three common problems are: (i) the beam passes through parts of the couch before the patient, attenuating the beam in unplanned (and often unknowable) ways; (ii) the beam passes undesirably through part of the patient on the way to the target (e.g., through or too near to the contralateral breast, shoulder or chin); (iii) the beam exits through an organ at risk, possibly outside of the CT image sets. Such problems usually only occur with novel beam orientations.

Clearance could potentially be a problem with wedges or physical blocks, but with the common utilization of multileaf collimators and dynamic or universal wedges, those problems have now become rare.

7.2.2 Quality Control During Treatment Planning

Regardless of the treatment approach used (either three-dimensional conformal or intensity-modulated), the quality assurance approach used for the treatment plan remains the same:

1. Determine if the plan adequately satisfies the treatment objectives
2. Test the plan for quality and errors

Chapter 6 discusses the differences in treatment planning for the two modalities. The discussion provided below will assume that there is a conventional quality assurance program for external-beam treatment plans, as well as one for IMRT.

7.2.2.1 Evaluating the Adequacy of the Plan

Most evaluation for external-beam treatment planning uses the parameters V_{100}, V_{95}, and D_{100}, or these quantities with selected subscripts. The "V" quantities were discussed above, and indicate the volume of the CTV (or PTV, or an organ at risk) that receives at least the percentage of the prescribed dose denoted by the subscript. The "D" quantities indicate the dose that covers the percentage of the target (or organ) specified by the subscript. Figure 7.10 shows the DVH in Fig. 6.19 with these typical quantities illustrated. These quantities are actually used more to determine the treatment, particularly during the optimization of IMRT, than to evaluate the plan. The first check considers if the treatment plan satisfies the requirements for the target volume. As discussed in Chap. 6, external-beam treatments

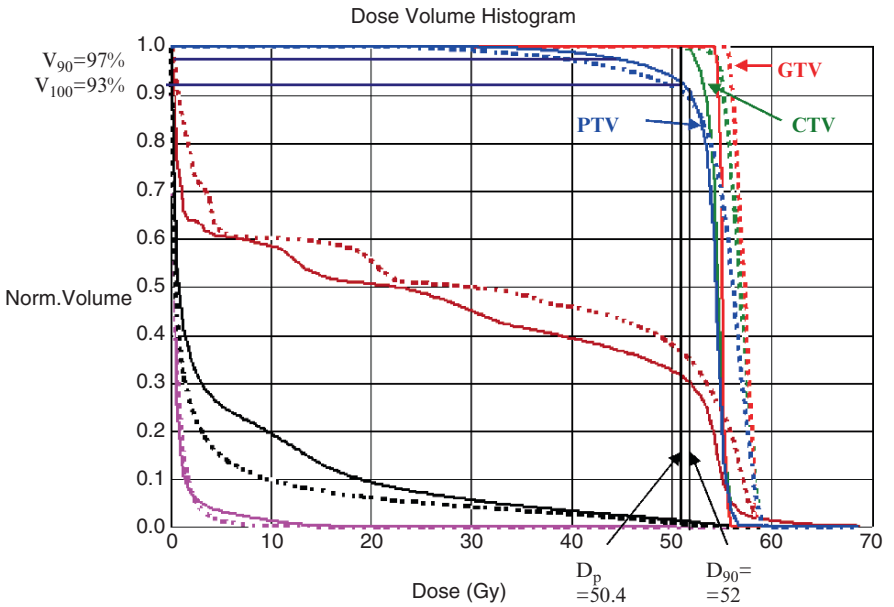


Fig. 7.10 A DVH with the dosimetric evaluation quantities indicated

require greater margins when expanding the CTV to form the PTV than do brachytherapy plans; however, the desired dose distribution must still cover the PTV to the extent specified by the "*V*" and "*D*" quantities in the prescription.

The second part of the evaluation entails ensuring that excessive doses are not supplied to the neighboring organs at risk (the lungs, heart, and skin in the case of partial breast irradiation). At the time of writing, a committee of the American Society for Radiology Oncology is compiling information to use in order to draw up recommended tolerance doses for various organs and parts of organs. When published, this reference will provide guidance when evaluating plans.

7.2.2.2 Testing a Plan for Quality and Errors

Again, this chapter assumes that a facility has a quality management program for the treatment planning system and the treatment planning process, so only the aspects that are of particular interest for partial breast irradiation will be addressed. The evaluation in the previous section simply asked if the plan did what was requested. While there are many possible plans for a given patient's treatment, some adequate plans may be markedly better than others in various respects, since most treatment planning involves compromises. The evaluation quantities recommended for brachytherapy in Eqs. 7.4 and 7.5 are also useful for external-beam treatments. An external-beam plan will have a much greater dose uniformity

than a brachytherapy plan simply because it contains no radioactive sources where the dose approaches infinity. However, particularly for IMRT, the target dose uniformity may suffer greatly as the optimization program attempts to create a dose distribution that covers the entire periphery and avoids the organs at risk. While (7.2) does not generally provide useful information, a modified version of this equation where the high-dose level is reduced from 150% to something closer to 110% may. Typical values for this modified DHI and the conformality indices would have to be based on the institution's experience. For the external-beam DVH shown in Fig. 6.19, the DHI obtained using 110% as the high-dose level is 0.61.

These indices can detect some errors in the treatment plan, but not those related to plans calling for performance that the treatment unit cannot provide. Examples of such problems include IMRT static (step-and-shoot) plans with segments that are exposed for too few monitor units to establish a stable dose rate, or dynamic (sliding window) plans that call for incompatible combinations of multileaf collimator blade movement or machine output. Establishing the performance limitations of an accelerator is an important part of commissioning it. At the beginning of an IMRT program, checking that the planned fluence map is achieved provides assurance that planned treatments can be delivered. After validating the planning and delivery process, the continued measurement of fluence maps serves no function.

7.2.3 Quality Management at the Time of Treatment

The in-room lasers can be used for initial alignment as the patient is prepared for daily treatment. Once that is achieved, cone beam computed tomography (CBCT) should be used to align the patient. In the absence of CBCT, portal images should be taken in order to confirm the alignment of the patient, both orthoganal positioning images and one beam image per day.

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Overview of North American Trials

8

Rakesh R. Patel and Sushil Beriwal

8.1 Introduction

A major paradigm shift in locoregional management of breast cancer in the last two to three decades has been the acceptance of lumpectomy and whole breast irradiation as a viable alternative to mastectomy. Similarly, axillary nodal evaluation has shifted in many centers from more extensive level I–II dissections to more limited sentinel node mapping procedures. The idea is to minimize morbidity, optimize cosmesis, and maintain treatment outcomes. Pathologic and clinical data suggest that the vast majority of ipsilateral breast recurrences occur in the vicinity of the index lesion, and remote recurrences are uncommon whether whole breast irradiation is delivered or not, thereby lending credence to the concept of partial breast irradiation. The more limited treatment volume allows safe delivery of an accelerated hypofractionated regimen over a truncated course of one week. This effort represents yet another paradigm shift from standard whole breast tangential external beam radiation therapy to investigations of accelerated partial breast irradiation (APBI).

Several reports utilizing APBI have shown promising early outcomes with few local recurrences, minimal toxicity, and excellent cosmetic outcomes. Several methods of APBI are being investigated: brachytherapy involving multiple interstitial catheters, a single intracavitary balloon, novel hybrid applicators, noninvasive stereotactic brachytherapy, external beam radiation either in the supine or prone position utilizing photons, electrons, or protons, as well as multiple methods of intraoperative irradiation. All of these share a common thread of treating a more limited volume, allowing a higher dose per fraction, and resulting in a shortened overall treatment course; however, these modalities all differ logistically for the patient, they have distinct technical advantages and challenges in radiation

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delivery, and perhaps more importantly, they afford different volumes of irradiated breast tissue. There is still very little published information on treatment planning techniques and the quality assurance measures utilized to assure that the target volume is adequately covered. Differences in target volume definition (variable margin around the surgical cavity), variable target delineation methods, as well as inconsistent methods of treatment planning have meant that a standard method of dosimetry is yet to be defined. Without this information, it is difficult to know if the results obtained in each study are dependent on the implant technique, dosimetry, differences in follow-up, or selection criteria. The more frequent use of 3D CT planning has allowed more rigorous comparisons between the techniques both within and between institutions. Dose optimization of implants by interactive graphics has allowed excellent target volume coverage and concurrent assessment of dosimetric quality, thereby instilling confidence that the dose is delivered to the desired partial breast region. The results of studies with modern planning systems, systematic QA and stringent patient selection criteria have thus far been promising.

There are excellent and mature experiences of APBI from multiple European centers in addition to ongoing multicenter trials that will be further outlined elsewhere. The ongoing NSABP B39\RTOG 0413 Phase III randomized trial comparing conventional whole breast irradiation with APBI allows patients to be treated with 3D external-beam, multicatheter interstitial brachytherapy or balloon brachytherapy on the APBI arm. The initiation of this pivotal trial was based on the compilation of many experiences around the globe with significant technical advancements as well as improvements in treatment planning systems. In this chapter, key aspects of these published APBI trials from North America with each of these three treatment methods are highlighted. Alternative approaches to APBI and associated clinical rationale and outcome data are presented in later chapters of this text.

8.2 Patient Selection

In order to compare published trials between centers and between modalities, the selection criteria should be well defined. The American Brachytherapy Society (ABS) and the American Society of Breast Surgeons (ASBS) have each recommended patient selection criteria and treatment guidelines. Both selection criteria are more conservative than the published literature and ongoing randomized trials have allowed. Both require negative margins, no axillary nodal involvement, and only nonlobular invasive breast cancer (IBC). There are differences in minimum age (45 years vs. 50 years), maximum tumor size (3 cm vs. 2 cm), and allowance of ductal carcinoma in situ (DCIS; no vs. yes) between ABS and ASBS, respectively.

Several other selection criteria have been more controversial and have been debated vigorously; outcome analysis from the various experiences should prove useful in elucidating this issue. These factors include positive nodes, as the treatment of the axilla with external beam irradiation in patients with one to three positive nodes remains controversial. A randomized RTOG trial set up to answer this question closed early due to poor accrual. Clearly, APBI can only be warranted when the draining lymphatic regions are

confidently deemed to be at sufficiently low risk that they can be excluded from the radiation portal. Many would not routinely encompass the axilla in this subset of patients, and thus would allow more limited volumes if there was no compelling risk of residual microscopic disease such as extracapsular spread. Others would treat comprehensively in high-risk node-negative patients as well. Another group of patients with limited data include those with intraductal disease (DCIS). There is some pathologic evidence that patients with DCIS have a higher risk of multicentric disease, especially in the context of an extensive intraductal component (EIC). More recent pathologic data suggests that lumpectomy alone may be sufficient in select patients with widely negative margins, thereby refuting the notion that DCIS patients require wider volume treatment. Additionally, there is limited data revealing a multicentric recurrence pattern in DCIS patients after lumpectomy irrespective of whether whole breast irradiation is administered. Similarly, patients with lobular carcinoma have been excluded in some series due to the heightened suspicion of multicentricity. Although clinical and pathologic data support smaller lesions with negative margin status, the specific maximal tumor size and minimal negative margin extent required are also not uniformly agreed upon and will require longer-term data from clinical trials.

The completed RTOG 95-17 and the ongoing NSABP B-39/RTOG-0413 randomized trials allow a more diverse population of women to be treated with APBI. The eligibility includes unicentric, small lesions (≤3 cm), all carcinoma histologies including lobular and DCIS, positive nodes (≤3 positive with no extracapsular spread), and negative margins ("no tumor on inked margin"). Distinct selection criteria used in each of the studies will be mentioned in the sections that follow (Table 8.1).

8.3 Interstitial Technique

The first APBI technique that was developed and is associated with the most mature results is the multicatheter, interstitial brachytherapy approach. The initial implementation of this method dates back several decades, when it was performed at the time of lumpectomy and used as a boost in conjunction with whole breast irradiation. The technique and indications have evolved significantly to its current use as a sole modality following lumpectomy, as described in the several studies below (Table 8.2). The premise is to place multiple needles/catheters through the breast tissue surrounding the lumpectomy cavity seroma correlating with the region at highest risk of harboring residual microscopic disease. The total number of catheters used is based on the size of the seroma cavity, which involutes over the several weeks following surgery. Generally, basic brachytherapy principles are followed during implantation, and needles are spaced uniformly to optimally cover the planned target volume while minimizing hotspots and proximity to normal tissues. This can require anywhere from 15 to 25 catheters in a given patient. The flexible catheters remain in the breast for the duration of the treatment course and are generally well tolerated with minimal discomfort. Following the outpatient procedure, treatment planning is performed to confirm proper coverage. Recent advances in catheter placement techniques

Table 8.1 APBI trials: patient selection and dosimetric criteria

Institution	Tumor size (cm)	Nodes	EIC	Margin definition	Technique	RT details	Target definition (cm)	Median no. of needles
Interstitial series								
Ochsner	<4	Yes	Yes	Neg	HDR/LDR	32–34 Gy/8–10 fx or 45 Gy/4 days	2–3	15
WBH	<3	Yes	No	≥2 mm	HDR/LDR	32–34 Gy/8–10 fx or 50 Gy/4 days	1–2	14
Tufts/Brown	<5	Yes	Yes	≥2 mm	HDR	34 Gy/10 fx	2	16
Univ. Kansas	<2	No	No	Neg	LDR	20–25 Gy/24–48 h	1	NR
RTOG 95-17	<3	Yes	No	Neg	HDR/LDR	34 Gy/10 fx or 45 Gy/4 days	2	16
VCU	<3	Yes	No	Neg	HDR/LDR	34 Gy/10 fx or 45 Gy/4 days	1–2	15
UW	<3	Yes	No	Neg	HDR	32–34 Gy/8–10 fx	1.5–2	22
MGH	<2	No	No	Neg	LDR	50–60 Gy/4–5 days	3	14
External beam								
WBH	<3	No	No	≥2 mm	3–5 Field, supine	38.5 Gy/10 fx	1.5 + 1	–
NYU	<2	No	No	≥2 mm	2-Field, prone	30 Gy/6 fx/10 days	1.5–2 + 0.7	–
MGH	<2	No	No	≥2 mm	3–4 Field, supine	32 Gy/8 fx	1.5 + 1	–
MammoSite								
FDA trial	<2	No	No	≥2 mm	HDR	34 Gy/10 fx	1	–
ASBS	<2	No	No	Neg	HDR	34 Gy/10 fx	1	–
MWH	<2	No	No	≥2 mm	HDR	34 Gy/10 fx	1	–
WBH	<2	No	No	≥2 mm	HDR	34 Gy/10 fx	1	–
Rush	<5	No	No	≥2 mm	HDR	34 Gy/10 fx	1	–

NR, not reported; *EIC*, extensive intraductal component; *IBTR*, ipsilateral breast tumor recurrence; *WBH*, William Beaumont Hospital; *RTOG*, Radiation Therapy Oncology Group; *VCU*, Virginia Commonwealth University; *UW*, University of Wisconsin; *MGH*, Massachusetts General Hospital; *NYU*, New York University; *NEMC*, New England Medical Center; *FDA*, Federal Drug Administration; *ASBS*, American Society of Breast Surgeons; *MWH*, Magee-Womens Hospital of UPMC

Table 8.2 APBI results: interstitial brachytherapy series with >2 years median follow-up

Institution	No. patients	Median follow-up (months)	5-Year IBTR (total)	5-Year IBTR (elsewhere)	Cosmesis (good/ excellent)	Grade 3/4 toxicity
WBH	199	96	1.6 (10 year = 3.8)	0.8	92	0
Ochsner	164	84	2.5	1.2	75	8
Tufts/Brown	33	83.9	6.1	6.1	88	33
RTOG 95-17	99					
HDR	66	78	3	2	NR	4
LDR	33	85	6	3		
UW	273	48.5	2.9	2.9	93	8.9
Univ. Kansas	25	47	0	0	100	NR
VCU	44	42	0	0	80	14
MGH	48	23	0	0	92	12.5

NR, not reported; *IBTR*, ipsilateral breast tumor recurrence; *WBH*, William Beaumont Hospital; *RTOG*, Radiation Therapy Oncology Group; *UW*, University of Wisconsin; *VCU*, Virginia Commonwealth University; *MGH*, Massachusetts General Hospital

as well as an increased number of brachytherapy schools have led to more reproducible implantations. Specifically, advancements in image-guidance measures such as CT, ultrasound, and stereotactic digital mammography have been instilled into this APBI method. The pairing of advanced 3D CT-based dosimetry with geometric volume optimization has further improved target volume delineation, coverage, and dose homogeneity. As with all complex brachytherapy, including prostate and gynecologic, quality implantation does require a learning curve for radiation oncologists (including additional time, skill, and often specialized training), and this in turn has led to this method being deemed "technically challenging." However, it appears that, in comparison to other APBI modalities, it affords the greatest control and tailoring of radiation dose delivery to variations in lumpectomy cavity size, shape, or location within the breast, while potentially minimizing doses to normal tissues.

When reviewing studies regarding interstitial implants, it is important to realize that there has been significant disparity in the methods of performing these implants between physicians and institutions. One important difference is in target definition, which consists of two critical components, target delineation and implant volume. The target delineation method is important, as there is still no consensus on which technique is preferred, thereby rendering comparisons between reports in the literature less accurate. Some have advocated using surgical clips to define the seroma cavity, others have used contrast injection into the seroma to guide needle placement with digital mammography, and yet others have used the unenhanced seroma cavity that is visualized via CT or ultrasound guidance. The implant volume can also differ, with some reports suggesting a 1 cm expansion while others favor a wider 2 cm expansion. Considerable differences in the treatment planning process used also remain. Several reports have confirmed that CT-based treatment planning allows excellent visualization of the lumpectomy cavity and normal structures, thereby

improving target volume delineation and optimizing coverage relative to conventional orthogonal film dosimetry. However, CT-based planning with geometric optimization tools has only become common relatively recently, and early reports all used plain film 2D dosimetry.

8.3.1 William Beaumont Hospital

Vicini and colleagues at William Beaumont Hospital have played a pivotal role in providing rigorous APBI data using several different methods. Their most mature results have been obtained with interstitial brachytherapy and included a cohort of 199 women with stricter selection and treatment criteria than the Ochsner group (Vicini et al. 2003). Inclusion criteria were age ≥40 years, tumor size ≤3 cm, and no EIC or lobular histology. Following lumpectomy and axillary node dissection in all patients, margins had to be clear microscopically by ≥2 mm. While women with ≤3 involved nodes were initially allowed (12% of patients enrolled), this was later restricted to no positive nodes once evidence had emerged of potential survival benefits with chest wall radiotherapy in premenopausal women with one to three involved nodes in the randomized postmastectomy trials (Overgaard et al. 1997; Ragaz et al. 1997). The average tumor size was small at 1.2 cm. Most patients had widely negative margins, with 88% of patients having margins ≥2 mm and 55% having margins ≥10 mm. Patients were treated with either LDR brachytherapy to a total dose of 50 Gy continuously over five days (120 women, 1993–1995) or with HDR brachytherapy to a total dose of 32 Gy in eight fractions BID over four days or 34 Gy in ten fractions BID over five days (71 and 8 women, respectively, 1995–1999) (Baglan et al. 2001). The planning target volume (PTV) was defined as a 1- to 2-cm margin around the lumpectomy cavity, with catheters placed either at the time of the initial lumpectomy or postoperatively. Uniquely, a rigid template system was used and kept in place during the treatment course in most women, which differs from other centers, where a template system may be used during the implant procedure but it is replaced with flexible catheters for the duration of treatment. The majority of these patients were treated using the 2D plain film dosimetry available at the time, with 33% having received double-plane implants and 66% with triple-plane implants. The average number of catheters was 14 (range, 8–18).

Combined results from both phases of the trial were excellent at a median follow-up of 5.7 years. A total of 199 patients were treated and compared in a matched-pair analysis with patients receiving conventional whole breast irradiation. There were only five ipsilateral breast tumor recurrences (IBTRs) for a five-year local recurrence rate of 1.2% with an elsewhere recurrence rate of 0.6%. In addition, the patients tolerated the treatment well with minimal complications and no acute grade 3 or 4 toxicity. However, the incidence of fat necrosis has increased over time (11% at five years) (Benitez et al. 2004). An update of this series was reported with a median follow-up of surviving patients of 8.6 years, of which 53 patients had more than ten years of follow-up. The ten-year actuarial rate of local recurrence was 3.8%, and the nodal recurrence risk was 1.6%. The type of local recurrence

was analyzed with a polymerase chain reaction-based loss of heterozygosity assay; 83% of recurrences were classified as clonally related (Vicini et al. 2007a).

8.4 Tufts/Brown/Rhode Island

In a multiple-institution series by Tufts-NEMC, Rhode Island Hospital and Brown University led by Wazer and colleagues, 32 women with 33 breast cancers were enrolled in an interstitial brachytherapy trial between 1997 and 1999 (Wazer et al. 2001). They allowed both T1 and T2 tumors (mean size, 1.3 cm) and required tumor-free margins of ≥1 mm (55% had ≥2 mm margins). Age was not restricted, although most women were postmenopausal with a mean age of 63 years. DCIS and ILC were excluded, but a high proportion of patients had EIC (55%) as well as up to three positive lymph nodes (27%). Catheter placement was either via a freehand technique at the time of lumpectomy or was postoperative. The PTV goal was the lumpectomy cavity plus a 2 cm margin. An average of 16 catheters were placed (range, 8–25) and kept 5–7 mm from the skin. All patients received HDR brachytherapy to 34 Gy in ten twice-daily fractions over five days. In an excellent analysis of dosimetric correlation with toxicity, fat necrosis was proportionally associated with larger tissue volumes receiving fractional doses of 340, 510, and 680 cGy.

In a separate report with 58 months of median follow-up, the five-year crude local recurrence rate was 3% (Wazer et al. 2002). Cosmetic results were judged good to excellent in 91% of patients. 33% had RTOG/EORTC-defined grade 3 or 4 subcutaneous toxicity (three patients with grade 3 and 11 patients with grade 4). Both the total number of dwell positions and the fractional volume of irradiated tissue at each isodose level were significantly associated with grade 3 or 4 toxicity. There was a trend toward a higher risk of clinically evident fat necrosis and women that received Adriamycin-based chemotherapy. An updated analysis at a median follow-up of 83.8 months demonstrated an actuarial five-year local recurrence rate of 6.1% (all elsewhere failures in the breast) (Kaufman et al. 2007). Fat necrosis, pain, and cosmesis appeared to improve with longer follow-up, whereas subcutaneous toxicity worsened and skin toxicity stabilized. Further outcome analysis from experiences such as these should allow more accurate dose volume constraints to be employed while treatment planning to minimize higher grade and symptomatic toxicities.

8.4.1 The Ochsner Clinic

The earliest experience of APBI utilizing interstitial brachytherapy can be traced to Kuske and colleagues at the Ochsner Clinic. At the time, the method was termed the "wide-volume" interstitial brachytherapy technique due to the larger number of catheters used (often >20) and the volume of breast tissue irradiated compared to the earlier European studies (King et al. 2000). Fifty women with 51 breast cancers were treated between 1992 and 1993.

Selection criteria included early-stage breast cancer patients following lumpectomy with unicentric Tis, T1, and T2 ($T \leq 4$ cm) lesions and negative surgical margins according to the NSABP definition, and up to three involved lymph nodes were allowed. Although eligibility was broad, 45% of lesions were occult, and the mean size was only 1.4 cm. Brachytherapy catheters were placed intraoperatively at the time of lumpectomy using a freehand technique (45% of patients) or by a closed technique via ultrasound guidance (55% of patients). The target volume was defined as being an expansion of at least 2 cm beyond the lumpectomy cavity, which often encompassed a substantial proportion of the breast tissue. The mean number of catheters was fifteen. Patients were treated with either low dose rate (LDR) to 45 Gy over four days or with high dose rate (HDR) to 32 Gy in eight twice-daily outpatient fractions over four days. In a matched-pair analysis with similar patients treated with whole breast external-beam irradiation, the results were quite favorable at a median follow-up of 75 months. There were one and five local failures in the brachytherapy and external beam arms, corresponding to crude IBTR rates of 2% and 5%, respectively ($p = 0.24$). There were also three nodal recurrences in the APBI group, which at 6% is slightly higher than would be expected for isolated recurrence after external-beam radiation after a negative level I/II lymph node dissection (Harris et al. 2003). Most physicians would not routinely treat the axillary nodes to higher doses in this subset of patients, and thus it is possible that these recurrences may not have been avoided by standard whole breast tangent beams. In an updated report, 160 patients with a median follow-up of 84 months were presented. The five-year IBTR rate was 2.5%, with 1.2% being elsewhere failures outside the partial breast volume. At 20 months median follow-up, 75% of women receiving brachytherapy had good to excellent cosmetic results; however, 8% of patients developed grade 3 or 4 toxicity and ultimately required surgical intervention for complications related to radiotherapy.

8.4.2 University of Wisconsin

One of the largest experiences in the country has been reported by Patel and colleagues from the University of Wisconsin (Patel et al. 2008). Between 2000 and 2005, 273 patients were treated with HDR-APBI (247 multicatheter interstitial, 26 MammoSite balloon). Selection criteria were broad and included patients with unicentric, Tis-T2, N1 (≤3 cm tumor size; 0–3 nodes positive with no extracapsular extension), negative surgical margins, and a negative postlumpectomy mammogram. There were no age criteria, or exclusions based on histology (lobular and DCIS were allowed). The median tumor size was 1.1 cm. Two techniques, prone template with digital mammographic and template guidance on the stereotactic biopsy table as well as supine freehand with real-time ultrasound guidance, were used for catheter placement (Patel and Das 2006). The target volume was defined as the surgical cavity delineated by Omnipaque contrast and/or surgical clips with a 1–2 cm margin modified to at least 5 mm deep to the skin surface or at the pectoral fascia. The group implemented CT-based 3D treatment planning in early 2002, thereby allowing more accurate target delineation, improved geometric coverage of

the target volume with optimization, and dosimetric verification (Das et al. 2004). The first 88 pts had orthogonal film dosimetry and were excluded from the dosimetric analysis. All patients were treated with fractionated HDR brachytherapy delivered in the supine position to a dose of 32–34 Gy in 8–10 twice-daily fractions over 4–5 days. At a median follow-up of 30 months, the crude rate of total ipsilateral breast failure was 1.4% (four patients). 96.5% of patients had good/excellent cosmesis at twelve months (22.7% and 73.8% with good and excellent scores, respectively). The procedure was well tolerated with minimal acute toxicity. The rate of symptomatic fat necrosis was 8.9% (24 patients). The target volume coverage with CT planning was excellent. Importantly, the overall implant volume was larger than in other series, with the median number of catheters being 22 (range: 10–37) (Patel et al. 2005).

In an updated report, the patients were separated into two groups: high-risk patients who satisfied one or more of the "high-risk" criteria (age <50 years, estrogen receptor negative, and/or positive lymph nodes; $n = 90$), and low-risk patients who comprised the remainder of the cohort ($n = 183$). The median follow-up of the entire cohort was 48.5 months. No significant difference was found in outcomes at five years between the low- and high-risk groups, with a local control rate of 97.8% vs. 93.6%, a crude local recurrence rate of 2.2% ($n = 4$) vs. 4.4% ($n = 4$), and an overall survival rate of 92.1% vs. 89.5%, respectively. All of these were elsewhere failures outside the treated volume. These clinical data support the inclusion of a "higher-risk" population in the ongoing studies attempting to expand the patient selection for APBI.

8.4.2.1 RTOG 95-17

This Phase II multicenter cooperative group study evaluating interstitial brachytherapy enrolled 99 patients between 1997 and 2000 (Kuske 2002). Selection criteria were broad and had no age limitations, allowed unifocal tumor sizes to up to 3 cm, required clear margins ("no tumor on ink"), and allowed women with up to three involved lymph nodes with no extracapsular extension. Patients with DCIS and invasive lobular cancer were excluded. APBI was delivered using either LDR with 45 Gy delivered over 3.5–5 days (33%) or with a HDR dose of 34 Gy in ten fractions over five days (66%). The PTV was intended to be a 2 cm margin around the lumpectomy cavity with a 5 mm minimum separation from the skin and chest wall. Most implants were multiplane (two to three planes). The median number of catheters was 16. The procedure was well tolerated in both cohorts with 2% and 9% grade 2 toxicity in the HDR and LDR patients, respectively. There was minimal grade 3 or 4 toxicity (4%).

More recently, Arthur et al. (2008) have published an update with five-year outcomes. At a median follow-up of 6.1 years, the IBTR rate was 3%, with a regional lymph node failure rate of 5% for the HDR group, while the LDR group had a breast failure rate of 6% and a regional relapse rate of 0% at a median follow-up of 6.2 years. Importantly, the elsewhere failure rate was low at 2% and 3% for the HDR and LDR cohorts, respectively. This early trial validated the feasibility of conducting a multi-institutional APBI trial and should contribute clinical outcome data in a meaningful manner with extended follow-up.

8.4.3 Virginia Commonwealth University

Arthur et al. (2003) at Virginia Commonwealth University treated 44 women with interstitial multicatheter brachytherapy from 1995 to 2000. Their selection criteria were similar to those of RTOG 95-17, allowing tumors <4 cm (median size, 1.2 cm), with no age restrictions (median age 62 years), allowing limited positive nodes (18%), and requiring negative surgical margins (72% of women had margins >2 mm). DCIS and lobular histologies were initially included; however, pure DCIS and node-positive patients were ultimately excluded. Most patients had catheters placed postoperatively. PTV was defined as the lumpectomy cavity plus a 2 cm margin except where limited by skin or the chest wall. An average of 14.7 catheters were placed primarily using a freehand technique with CT and fluoroscopic guidance. Patients received either LDR brachytherapy to a total dose of 45 Gy at 50 cGy h^{-1} or HDR for a total dose of 34 Gy in ten BID fractions.

At a median follow-up of 42 months, there were no local or regional recurrences. Good to excellent cosmetic results were achieved in 79.6% and 90% with LDR and HDR, respectively. Toxicity was minimal, although 14% (six patients) had cosmesis-altering fibrosis in the high dose treatment region. Additionally, 43% of women receiving Adriamycin-based chemotherapy after brachytherapy developed a recall reaction that led to a deterioration in cosmesis.

8.4.3.1 University of Kansas

Twenty-five women were treated at the University of Kansas by Krishnan et al. (2001) from 1993 to 1998. The selection criteria included patients aged ≥60 years, tumors ≤2 cm, and negative surgical margins. The mean tumor size was 1 cm. DCIS, EIC, and women with positive lymph nodes were excluded. The total dose was significantly lower than the other APBI series at 20–25 Gy over 24–48 h with LDR brachytherapy. Similarly, the minimum PTV margin was also smaller than other interstitial series at 1 cm around the tumor bed. All patients had their catheters placed intraoperatively at the time of lumpectomy. At a median follow-up of 47 months, there were no local, regional, or distant recurrences. Patient tolerance was excellent, with no reported cases of RTOG grade 3 or 4 toxicity noted, and good to excellent cosmetic results in all patients.

8.4.4 Massachusetts General Hospital

Significant information about the impact of implant volume and dose on potential risk of toxicity and cosmetic outcome was first reported by Lawenda and investigators at Massachusetts General Hospital. In their published series, 48 patients were enrolled between 1997 and 2001 (Lawenda et al. 2003). The eligibility criteria for the trial were more stringent than those mentioned previously, and included patients with tumors ≤2 cm size with no DCIS, EIC, LVI, or positive nodes. An average of 14 (range, 10–16)

brachytherapy catheters were placed. The PTV was formed by a 3 cm margin around the lumpectomy cavity, usually in two or three planes. Patients were treated at three separate dose levels of 50, 55, and 60 Gy, respectively, with LDR brachytherapy. At 23-month follow-up, there were no local, regional, or distant recurrences. Cosmesis was good to excellent in 91.8% of patients. RTOG grade 2 or 3 complications were most common in the group with the largest treatment volume, >203 cm^3 (27%). Significant fibrosis was noted in four patients (8.3%). 17.4% had biopsy-proven fat necrosis.

8.5 MammoSite Balloon

Due to the invasiveness, the implant technique variability and the perceived technical challenge of multicatheter interstitial implants, an alternative method for APBI was developed using an intracavitary balloon catheter treatment device, the MammoSite Radiation Therapy System (RTS; Hologic Inc., Bedford, MA, USA). This was originally designed to simplify the brachytherapy procedure, thus lessening the learning curve while improving the reproducibility of dosimetric coverage of the target volume. The system consists of a single catheter located centrally within a balloon that is placed in and inflated within the lumpectomy cavity. The balloon can be inflated to a sphere of either 4–5 cm or 5–6 cm in diameter, although additional sizes and elliptical shapes have been developed. The device can be placed either at the time of lumpectomy in the operating room or postoperatively with the cavity closed; however, initial experience with the intraoperative approach suggests that it results in higher infection rates and the persistence of seroma (Watkins et al. 2008). Also, the lack of known final pathologic margin status has led to the recommendation of postoperative balloon placement. Early experiences have revealed several additional quality assurance measures that are necessary to improve optimal delivery. After inflation, balloon catheter placement is evaluated to assure balloon symmetry, an overlying skin distance of ≥7 mm, and tissue conformance with the balloon surface.

An important distinguishing factor from multicatheter brachytherapy is the target volume encompassed by the prescription isodose line. The treatment is delivered from a single centralized HDR source to a distance of 1 cm circumferentially from the surface of the balloon, while most of the published interstitial studies have used more extensive margins on the seroma cavity (1–3 cm). Despite the differences, Edmundson and coauthors showed that the mean PTV of the patients treated with the MammoSite device was 112.1 cm^3, compared with 98.3 cm^3 for patients treated with multicatheter-based interstitial brachytherapy at the same institution (Edmundson et al. 2002). To further compare, Dickler et al. (2004) found that the volume of breast tissue treated by the MammoSite device was equal to the volume encompassed by a mean 1.6 cm margin around the lumpectomy cavity because of compression of breast tissue caused by the balloon. This implies that the effective volume of postoperative breast tissue may be similar in many cases for an intracavitary balloon and an interstitial APBI approach.

Some have advocated the use of multiple dwell positions to enhance the conformality of the isodose distribution; however, most of the data presented have employed the single central dwell position method (Streeter et al. 2003). Thus far, patient tolerability has been

Table 8.3 APBI results: MammoSite brachytherapy series

Institution	No. of Patients	Median follow up (months)	IBTR (total)	Cosmesis (good/excellent) (%)
FDA trial	43	65.5	0	81.3
ASBS registry trial	1,440	30.1	1.4%	93
MWH	92	30	0%	NR
Rush	70	26.1	5.7%	NR
VCU compilation	483	24	1.2%	91
MUSC	90	24	2.2%	90
WBH	80	22	2.9%	88.2
Multi-institutional DCIS	100	36	4%	95

NR, not reported; *IBTR*, ipsilateral breast tumor recurrence; *FDA*, Federal Drug Administration; *ASBS*, American Society of Breast Surgeons; *MWH*, Magee-Womens Hospital of UPMC; *VCU*, Virginia Commonwealth University; *MUSC*, Medical University of South Carolina; *WBH*, William Beaumont Hospital

excellent, with minimal complications aside from high catheter pull-rate and initial infection rates. These have declined as experience has mounted, patient selection has improved and clinical and dosimetric factors have been determined. The early to intermediate outcome data from the ASBS registry study and multiple single institutions are promising, and the following sections briefly review these results (Table 8.3).

8.5.1 FDA Study

The MammoSite RTS was cleared by the US Food and Drug Administration (US FDA) in May 2002 based on results from an initial Phase I/II trial designed to test the safety and performance of the device. The initial experience was reported by Keisch and colleagues and consisted of patients treated at a total of nine institutions. Selection criteria were more conservative than the interstitial APBI counterparts and included women aged >45 years with tumor size ≤2 cm, negative lymph nodes, and negative surgical margins (Keisch et al. 2003). Women with pure DCIS, EIC, and ILC were excluded. Fifty-four patients had the device inserted, and 43 of these patients were eventually treated. The majority of the catheters that were pulled were secondary to issues of poor tissue conformance (seven patients) and inadequate skin thickness (two patients), and resulted in no treatment. The catheter was placed with an open technique in 34 patients and with a postoperative closed technique in the other 20 patients. The prescription dose was 34 Gy in ten fractions delivered BID over five days and prescribed to 1 cm from the balloon surface. A minimum skin-to-balloon surface distance of 5 mm was required for treatment. Device performance, complications,

and cosmesis were assessed. The infection rate was 9.3%, including severe mastitis in one patient and abscess in another patient.

Of the 43 treated patients, 36 patients were followed for a median of 5.5 years from time of catheter placement with no local or regional recurrence (Benitez et al. 2007). The presence of a seroma was reported more frequently with open vs. closed cavity placements (50% vs. 17.4%, $P = 0.0483$). Asymptomatic fat necrosis was identified in 4 of 43 patients and telangiectasia was identified in 39.5% of the treated patients, which is relatively high and may potentially increase as the data matures. Retraction of the breast and/or nipple was reported in 20.9%. Both telangiectasia and retraction occurred more frequently in patients with a skin spacing of less than 7 mm vs. ≥7 mm ($P = 0.0422$ and 0.0458, respectively). Cosmetic outcomes of good to excellent were achieved in 81.3% at last follow-up visit. Furthermore, the cosmetic outcomes were improved, with increased skin spacing exhibiting statistical significance as a continuous variable ($P = 0.0248$).

8.5.2 American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial

After clearance of the device by the FDA for clinical use in May 2002, a registry trial was initiated concurrently by the manufacturer. The goals and objectives of the trial were to provide a method to prospectively, objectively, and systematically collect data on the clinical use of the brachytherapy applicator. A total of 1,440 patients (1,449 cases) with early-stage breast cancer who were undergoing breast-conserving therapy were treated with the MammoSite device to deliver APBI (34 Gy in 3.4 Gy fractions). Of these, 1,255 (87%) had IBC (median size = 10 mm), and 194 (13%) had DCIS (median size = 8 mm). One hundred twenty-three (9%) had explantation of the device before initiation of brachytherapy. The primary reasons for premature explantation, as reported by investigators, included poor skin spacing (43 patients; 35% of explanted cases) and nonconformance to cavity (35 patients; 28% of explanted cases). Median follow-up at the time of the last report was 30.1 months. Twenty-three (1.6%) cases developed an IBTR for a two-year actuarial rate of 1.04% (1.11% for IBC and 0.59% for DCIS). No variables were found to be associated with IBTR. Six (0.4%) patients developed an axillary failure. The percentages of breasts with good to excellent cosmetic results at 12 ($n = 980$), 24 ($n = 752$), 36 ($n = 403$), and 48 months ($n = 67$ cases) were 95%, 94%, 93%, and 93%, respectively. Breast seromas were reported in 23.9% of cases (30% in open-cavity implants and 19% in closed-cavity implants). Symptomatic seromas occurred in 10.6% of cases, and 1.5% of cases developed fat necrosis. A subset analysis of the first 400 consecutive cases enrolled was performed (352 with IBC, 48 DCIS). With a median follow-up of 37.5 months, the three-year actuarial rate of IBTR was 1.79%. The treatment efficacy, cosmesis, and toxicity three years after treatment with APBI using the MammoSite device in this multi-institution setting are good and similar to those reported with other forms of APBI with similar follow-ups (Vicini et al. 2008).

8

8.5.3 VCU Compilation

Nine institutions participated in a pooled analysis of data evaluating the clinical experience of the MammoSite RTS for delivering APBI (Cuttino et al. 2008). Between 2000 and 2004, 483 patients were treated with the MammoSite RTS to 34 Gy delivered in ten fractions. Treatment parameters were analyzed to identify factors affecting outcome. Median follow-up was 24 months (minimum of one year). Overall, infection was documented in 9% of patients, but the rate was only 4.8% if the catheter was placed after lumpectomy. Six patients (1.2%) experienced an in-breast failure; four failures occurred remote from the lumpectomy site (elsewhere failure). Cosmetic results were good to excellent in 91% of patients. Treatment parameters identified as significant on univariate analysis were tested in multivariate regression analysis. The closed-cavity placement technique significantly reduced the risk of infection ($p = 0.0267$). Infection was associated with an increased risk of fair or poor overall cosmesis ($p = 0.0009$). A skin spacing of <6 mm increased the risk of severe acute skin reaction ($p = 0.0178$) and telangiectasia ($p = 0.0280$). The use of prophylactic antibiotics reduced the risk of severe acute skin reaction ($p < 0.0001$). The use of multiple dwell positions reduced the risk of severe hyperpigmentation ($p = 0.0278$). The authors concluded that the MammoSite RTS seems to have acceptable toxicity rates and cosmetic outcomes, comparable to those with whole breast radiotherapy. Based on these data, the closed-cavity placement technique, the use of prophylactic antibiotics, the use of multiple dwell positions, and a minimum skin spacing of 6 mm all seem to improve overall patient outcome.

8.5.3.1 Rush University

The largest published single-institution experience comes from Dowlatshahi and colleagues from Rush University, and included 129 patients that had a balloon placed, of which 112 patients underwent treatment (Dowlatshahi et al. 2004). The inclusion criteria were broad, allowing women >40 years, stage T1–T2, node negative or positive, negative surgical margins, plus DCIS, EIC, and ILC.122. The primary reason for not treating was poor balloon/cavity conformance and inadequate balloon/skin spacing. Overall, the balloon was very well tolerated after the initial 24 h. Six patients developed wound infections. At six months follow-up, 80% of patients had good to excellent cosmesis. In an updated analysis of treatment failures after MammoSite breast brachytherapy, the group identified five treatment failures in the 70 patients with a median follow-up of 26.1 months (Chen et al. 2007). Of these, three in-breast failures were more than 2 cm away from the original surgical bed, one failure was directly adjacent to the original surgical bed, and one failure was in the axilla with synchronous distant metastases. Two out of three elsewhere failures were in a patient with lobular histology and in a patient aged <45 with node-positive disease. The surgical bed failure was in a patient with EIC with negative margins. The failure data emphasize the importance of patient selection when offering partial breast irradiation.

8.5.3.2 Medical University of South Carolina

Dragun et al. (2007a) reported on the cosmetic outcomes for the first 100 patients treated at Medical University of South Carolina with a median follow-up of 2 years. Cosmesis was excellent in 62 (68.9%), good in 19 (21.1%), fair in 8 (8.9%), and poor in 1 (1.1%) patient. Using stepwise logistic regression, the factors that predicted for excellent cosmesis were as follows: absence vs. presence of infection (p = 0.017); absence vs. presence of acute skin toxicity (p = 0.026). There was a statistically significant association between acute skin toxicity (present vs. absent) and balloon-to-skin distance (<8 vs. >8 mm, p = 0.001). Factors that did not predict for cosmesis were age, balloon placement technique, balloon volume, catheter days in situ, subcutaneous toxicity, and chemotherapy or hormonal therapy.

The same group reported on post-treatment mammographic findings on patients who received MammoSite brachytherapy (Dragun et al. 2007b). A total of 126 mammograms from a cohort of 38 patients who underwent MammoSite breast brachytherapy and post-treatment mammographic were analyzed. The minimum and median follow-ups were 6 and 28 months, respectively. Of the 126 mammograms analyzed, 22 (17%) were classified as BI-RADS category 2, 93 (74%) as category 3, 10 (8%) as category 4, and 1 (0.8%) as category 5. Further descriptions of the BI-RADS 3 studies were: 61 (65%) "surgical changes," 30 (32%) seromas, and 2 (2%) dystrophic calcifications. Additional interventions followed ten (11%) of BI-RADS 3 studies, all revealing benign findings. All BI-RADS 4 or 5 studies led to needle aspiration (three) or breast biopsy (eight). Two biopsies were positive for malignancy, and both were classified as elsewhere breast failures. This study suggests that the mammographic architectural patterns observed after partial breast irradiation and potential differences with respect to those traditionally seen following whole breast radiotherapy are yet to be well characterized.

8.5.3.3 William Beaumont Hospital

Chao et al. (2007) have published early outcomes of 80 patients of stage 0 (n = 23), I (n = 46), and II (n = 11) treated with MammoSite brachytherapy with a median follow-up of 22 months. There were two local recurrences for a three-year actuarial rate of 2.9%. Upon molecular-based clonality assay evaluation, both recurrences were found to be clonally related. Younger age at diagnosis was the only variable associated with local recurrence (continuous variable, p = 0.044; categorical variable [<55 years vs. ≥55 years], p = 0.012). The percentages of patients with good/excellent cosmetic results at 12 and 36 months were 96.9% and 88.2%, respectively. Patients with an applicator-to-skin spacing of <7 mm and those who received adjuvant systemic chemotherapy exhibited lower rates of good to excellent cosmetic results, though the association was not statistically significant. The overall incidences of symptomatic seromas and any seromas were 10% and 45%, respectively. Upon univariate analysis, intraoperative placement of the MammoSite (open approach), larger applicator size, and increasing balloon volume were found to be risk factors

for seroma formation ($p < 0.01$). The overall incidence of fat necrosis and infections was 8.8% and 11.3%, respectively. The early results from this study show levels of efficacy, cosmesis, and toxicity similar to those observed with other forms of interstitial APBI at this length of follow-up.

8.5.3.4
Magee-Womens Hospital of UPMC

In the report by Agarwal et al., a total of 125 patients underwent catheter placement for MammoSite HDR brachytherapy, with 108 patients successfully completing treatment. Open placement was used in 85 patients and closed in 40 patients. Median follow-up was 11 months for the open group and 5 months for the closed group. The treatment was well tolerated. A recent update with a median follow-up of 30 months showed persistence of seroma (clinical and/or radiological) in 67% patients. The only clinical or dosimetric variable predictive for seroma was intraoperative placement of the catheter (84% vs. 47%, $p = 0.005$). Telangiectasia in the treatment area was observed in nine patients. The median time of appearance of telangiectasia was 23 months (range 4–52 months). Telangiectasia was significantly increased in patients with maximum skin doses of ≥100% (41% vs. 2%, $p = 0.0002$) and ≥125% (71% vs. 6.7%, $p = 0.0001$). There were no local failures. The study again emphasizes the importance of adequate skin distance as a surrogate for lower skin dose for better cosmetic outcome (Soran et al. 2007).

8.5.3.5
Tufts/New England Medical Center

Data from the same institution comparing outcomes between different APBI techniques are limited. One such report from investigators at Tufts-New England Medical Center led by Wazer compared toxicity in 75 women receiving HDR interstitial brachytherapy vs. that seen in 20 women receiving intracavitary brachytherapy (Shah et al. 2004). Twenty percent of patients (seven patients) had the procedure aborted prior to treatment due to either balloon rupture, hemorrhage, or inadequate skin thickness. In their series, grade 2–4 subcutaneous fibrosis was significantly less with the intracavitary vs. interstitial brachytherapy method (10% vs. 32%). An important distinguishing point is that a much smaller volume of breast tissue was irradiated with the balloon technique (101 cc vs. 176 cc). The authors compared the volumes receiving 100% (34 Gy), 150% (51 Gy), and 200% (68 Gy) and concluded that the reduced fibrosis in the intracavitary patients was due to the smaller treatment volumes. However, when only multicatheter brachytherapy patients that did not have anthracycline-based chemotherapy were compared to intracavitary therapy, the toxicity difference was insignificant. The MammoSite patients had consistently greater skin dose and thus resulted in significantly higher mild erythema (42.9% and 17.3% with interstitial, respectively). Whether this will lead to higher rates of telangiectasias, fibrosis, or dermatitis remains unknown. The dose homogeneity index (DHI), which is a reflection of the hotspots in the high dose region, was less with balloon brachytherapy than with HDR

interstitial brachytherapy (0.73 vs. 0.83, $p < 0.001$). A longer follow-up will be needed to discern factors correlating with specific outcomes, thus allowing rigorous dosimetric constraints to be identified that can be used during treatment planning to minimize late toxicity while optimizing local control rates.

In a separate study of 38 patients treated with intraoperative MammoSite catheter placement at the time of lumpectomy or re-excision, the same group reported that the overall rate of any detectable seroma was 76.3%. Persistent seroma (>6 months) occurred in 26 (68.4%) of 38 patients, of whom 46% experienced at least modest discomfort at some point during follow-up. Of these symptomatic patients, three required biopsy or complete cavity excision, revealing squamous metaplasia, foreign body giant cell reaction, fibroblasts, and active collagen deposition. Of the analyzed dosimetric, clinical, and treatment-related variables, only body weight correlated positively with the risk of seroma formation ($p = 0.04$). Postprocedural infection correlated significantly ($p = 0.05$) with reduced risk of seroma formation (Evans et al. 2006).

8.5.3.6 St. Vincents

Richards and colleagues from St. Vincent's Cancer Center recently reported on their initial experience with the MammoSite balloon (Richards et al. 2004). This included 32 patients with a median follow up of 11 months. Selection criteria included stage 1–2 patients with negative surgical margins. No acute toxicities occurred during the five days of treatment. Although all skin reactions were confined to the region overlying the balloon, 25% developed bright erythema and patchy moist desquamation. They also reported a high infection rate of 16%, which may have been attributable to the minimal recommended catheter care when the device was initially implemented. Cosmesis was good to excellent in 86% of cases.

8.5.3.7 MammoSite for DCIS

Twelve institutions participating in this Phase II clinical study reported preliminary results and evaluation of the MammoSite balloon catheter as the sole method of delivering partial breast irradiation to the lumpectomy bed with breast-conserving surgery in patients with pure DCIS (Benitez et al. 2006). A total of 133 patients have been enrolled and 100 patients have successfully completed the prescribed radiation therapy. Patients who met the following criteria were selected for enrollment into the study: age 45 years or older, unicentric pure DCIS, mammographic lesion of 3 cm or less, negative margins as defined by 1 mm or more, a postoperative final gross pathologic size of tumor of 5 cm or less, clinically node negative, and a postlumpectomy mammogram showing the absence of any residual suspicious microcalcifications. The mean follow-up period at the last published report was 9.5 months (range, 1–24 months). It was well tolerated, with an excellent to good cosmetic rate in 95% of the patients and a 6% infection rate. In the recent update of this study presented at

the San Antonio Breast Conference 2007 with a median follow up of three years, four recurrences were noted. All four recurrences were noninvasive at this point. Each recurrence had at least one or more risk factors for a high USC/VNPI score, a high nuclear grade, or comedo necrosis. There were no recurrences in nuclear grade 1 or nuclear grade 2 patients without comedo necrosis.

In the ASBS registry trial, 191 patients with DCIS were enrolled, among whom fifteen patients were excluded from analysis because of device- or patient-related factors; seven patients were excluded after receiving a radiotherapy boost, thus leaving 169 patients available for study (Jeruss et al. 2006). Follow-up information was available for 158 patients. The average length of follow-up was 7.35 months. Forty-three patients had at least one year of follow-up. Patients with a device-to-skin distance of ≥7 mm had the best cosmetic results. Patients with a device-to-skin distance of ≥7 mm also had a lower incidence of radiation dermatitis. Data on 43 patients who were followed up for at least one year confirmed these findings. No patient in the study had experienced a recurrence. In the recent update, the three-year actuarial local control for the first 48 patients with DCIS was 100%.

In a subset analysis of the William Beaumont experience of 23 patients with DCIS treated using MammoSite, one had local recurrence with a three-year actuarial local control of 95%. Accelerated partial breast irradiation is now being explored as a possible treatment option for patients with DCIS, with the goal of providing similar local control to whole breast RT but with reduced morbidity (and potentially improved quality of life). These early outcomes are encouraging, and support the continued investigation of this approach for low-risk patients.

8.6 External-Beam APBI

Given the technical challenges and skill levels required for an invasive brachytherapy procedure, external-beam APBI approaches have also been investigated. The advent of 3D-CT-based treatment planning with highly conformal dose distributions and visualization and monitoring of the target volume has allowed several reports of clinical feasibility to be published (Baglan et al. 2003; Formenti et al. 2004). The noninvasive and more accessible external-beam treatment makes the corresponding APBI course significantly more convenient for both patients and treating physicians. However, there are still several important challenges associated with this approach (as compared to brachytherapy) that are being investigated. An important factor is that the integral normal tissue dose can be significantly increased, especially for ipsilateral breast tissue. This is due to concerns regarding target delineation, target motion due to respiration, and daily set-up variability. Alternate immobilization techniques have been utilized, including prone positioning, alpha cradle bras, and respiratory gating. Whether the higher integral dose will lead to increased long-term side effects remains to be seen. Rigorous dose–volume constraints have been proposed and will be evaluated in ongoing trials to assess the feasibility and safety of this approach, thereby making it more readily applicable in the clinical setting.

Table 8.4 APBI results: external beam radiation

Institution	Number	Median follow up (months)	IBTR	Cosmesis (good/excellent) (%)
NYU	78	28	0	92
WBH	91	24	0	90
MGH	20	12	0	100

NR, not reported; *IBTR*, ipsilateral breast tumor recurrence; *WBH*, William Beaumont Hospital; *NYU*, New York University; *MGH*, Massachusetts General Hospital

Limited data from North America have been reported on this technique so far, and further follow-up data are awaited to generate comparisons with the more established APBI methods. However, experiences thus far have revealed high feasibility with minimal acute toxicity (Table 8.4). In addition to a few single-institution series using variable techniques, a RTOG multi-institutional study has been completed and is outlined in the following section.

8.6.1 William Beaumont Hospital

Investigators at William Beaumont Hospital led by Vicini and colleagues were instrumental in complementing a long-term APBI experience with breast brachytherapy with 3D conformal APBI. In a small pilot study, nine patients were enrolled with similar criteria, such as a brachytherapy protocol of age >40 years, tumor size <3 cm, invasive ductal histology, negative margins >2 mm, and negative axillary nodes (Baglan et al. 2003). Details of the complex treatment planning process include either a four-field (right breast) or five-field (left breast) noncoplanar beam arrangement with 6 MV photons. The clinical target volume (CTV) definition was similar to that for brachytherapy at 15 mm beyond the surgical cavity; however, an additional 10 mm was added to form the PTV (5 mm to account for normal respiration and 5 mm added for daily set-up variation). The surgical cavity was defined by the presence of surgical clips placed at the time of lumpectomy. A similar dose fractionation scheme was initially used at 34 Gy in ten fractions over five days, but was later escalated to a total dose of 38.5 Gy to account for the inherent homogeneity of the dose distribution in comparison to the brachytherapy plans. The group recently updated the analysis of 91 consecutive patients treated with APBI using the 3D-CRT technique (Vicini et al. 2007b). The median follow-up was 24 months. Twelve patients were followed for ≥4 years, 20 for ≥3.5 years, 29 for >3.0 years, 33 for ≥2.5 years, and 46 for ≥2.0 years. No local recurrences developed. Cosmetic results were rated as good to excellent in 100% of evaluable patients at ≥6 months ($n = 47$), 93% at 1 year ($n = 43$), 91% at 2 years ($n = 21$), and in 90% at ≥3 years ($n = 10$). Erythema, hyperpigmentation, breast edema, breast pain, telangiectasias, fibrosis, and fat necrosis were evaluated at 6, 24, and 36 months after treatment. All factors had stabilized by three years post-treatment, with grade

I or II rates of 0%, 0%, 0%, 0%, 9%, 18%, and 9%, respectively. Only two patients (3%) developed grade III toxicity (breast pain), which resolved with time. Delivery of APBI with 3D-CRT has resulted in minimal chronic (≥6 months) toxicity to date, with good to excellent cosmetic results. Additional follow-up is needed to assess the long-term efficacy of this form of approach.

8.6.2 New York University

Dr. Formenti and researchers from New York University have also explored external-beam APBI (Formenti et al. 2004). However, they have focused on treating select women in the prone position to minimize the effect of respiratory motion while displacing normal structures. A dedicated prone table was constructed to facilitate such positioning. Eligibility for the trial was restricted to postmenopausal women who had refused to undergo standard radiotherapy. Patients were also required to be newly diagnosed with nonpalpable pT1 tumor, pN0 breast cancer, lack of EIC, negative margins of at least 5 mm, and estrogen receptor positive tumors. A dose of 6 Gy per day was delivered in five fractions to a total dose of 30 Gy over ten days (Monday, Wednesday, Friday, Monday, and Wednesday). CT planning was carried out with patients in the prone position on a dedicated table with the intent to include ≤25% of the breast tissue in the PBI field. This dose and fractionation schedule was calculated by radiobiological modeling and was predicted to be as effective in terms of tumor control as 50 Gy in 25 fractions while maintaining a risk of fibrosis at the tumor bed comparable to that of a standard regimen of 60 Gy in 30 fractions. Field arrangements were designed to completely avoid the contralateral breast, lungs bilaterally, heart, and thyroid. The postoperative cavity was defined as the CTV, with a 1.5 cm margin added to determine the PTV. The authors initially reported on 47 patients with 18 months of follow-up, and recently updated to 78 patients with a median follow-up of 28 months. Median age was 67.5 years (range: 52–88 years) and median tumor size was 0.9 cm (range: 0.1–1.9 cm). Medial length of follow-up was 28 months (range: 1.2–71 months). To date, none of the patients has recurred. Thirty-five patients have a duration of follow-up of at least 28 months. Twenty (57%) had no detectable toxicities, six (17%) had residual asymmetry related to surgery, and nine (26%) had detectable radiation-related toxicities. Cosmesis was evaluated by both doctors and the patients. Patients described their cosmetic results as "excellent" in 16/35 (46%), "good/excellent" in 9/35 (26%), "good" in 7/35 (20%), and "fair" in 3/35 (8%). These are comparable to the rates reported by PBI studies using brachytherapy techniques.

8.6.3 MGH

The group from MGH has published a feasibility study and initial clinical experiences with proton, three-dimensional, conformal, external-beam partial breast irradiation (3D-CPBI) (Taghian et al. 2006). Twenty patients with stage I breast cancer were treated with proton

3D-CPBI in a Phase I/II clinical trial. Patients were followed at 3–4 weeks, 6–8 weeks, six months, and every six months thereafter for recurrent disease, cosmetic outcome, toxicity, and patient satisfaction. At a median follow-up of 12 months (range: 8–22 months), no recurrent disease had been detected. Global breast cosmesis was judged by physicians to be good or excellent in 89% and 100% of cases at six and 12 months, respectively. Patients rated global breast cosmesis as good or excellent in 100% of cases at both six and 12 months. Proton 3D-CPBI produced significant acute skin toxicity with moderate to severe skin color changes in 79% of patients at 3–4 weeks and moderate to severe moist desquamation in 22% of patients at 6–8 weeks. Telangiectasia was noted in three patients. Three patients reported rib tenderness in the treated area, and one rib fracture was documented. At the most recent follow-up, 95% of patients reported total satisfaction with proton 3D-CPBI. Based on the study results, the authors concluded that proton 3D-CPBI offered good to excellent cosmetic outcomes in 89–100% of patients at six- and 12-months follow-up and nearly universal patient satisfaction. However, proton 3D-CPBI, as used in this study, did result in significant acute skin toxicity, and may potentially be associated with late skin (telangiectasia) and rib toxicity. Because of the dosimetric advantages of proton 3D-CPBI, technique modifications are currently being explored in order to improve acute skin tolerance.

8.6.4 RTOG 0319

Building on the initial Beaumont experience by Vicini and colleagues, a multi-institution Phase I/II study, RTOG 0319, examined the feasibility of 3D conformal external-beam partial breast irradiation (Vicini et al. 2005). Selection criteria were similar to those in the previous RTOG 95-17 APBI trial of interstitial brachytherapy and included patients with unifocal, invasive nonlobular histology, size ≤3 cm, negative margins ≥2 mm, and ≤3 positive nodes with no extracapsular spread. Patients were treated to a dose of 38.5 Gy in ten fractions (3.85 Gy per fraction) over five days. The CTV included the lumpectomy cavity plus a 10- to 15-mm margin bounded by 5 mm from the skin surface and the lung–chest wall interface. The PTV included the CTV plus a 10 mm margin. There were four cases with major variations (all four related to normal tissue DVHs exceeding 5% of the specified limit). A total of 32 cases with minor variations in treatment plans were detected (16 related to normal tissue DVHs exceeding the specified limits [by ≤5%], six related to suboptimal coverage of the PTV, and ten related to both). There were six cases with no variations. Of the 51 evaluable patients, one additional major variation was noted (PTV receiving <93% of the prescription dose). An additional five cases with minor variations in treatment plans were detected (three related to normal tissue DVHs exceeding the specified limits [by ≤5%], one related to suboptimal coverage of the PTV, and one related to both). There were three more cases with no variations. APBI using 3D conformal external beam radiation therapy was shown in this preliminary analysis to be technically feasible and reproducible in a multi-institutional trial using exceptionally strict dosimetric criteria. The successful completion of and credentialing process for this trial formed the template for and was the impetus for the ongoing Phase III NSABP B39/RTOG 0413 trial.

8.7 Conclusion

A rapid evolution in APBI has taken place on both sides of the Atlantic Ocean in the past decade. Clearly, the concept of an accelerated, more limited irradiated volume approach represents one of the most important potential paradigm shifts in breast cancer treatment, and will likely allow many more women access to breast conservation therapy in a cost- and time-effective manner. However, rigorous analysis of evidence gained from single institution and cooperative group trials will be required before this can be considered the new standard of care. Paramount to its success are appropriate patient selection criteria, as studies with poor selection have witnessed higher than acceptable local control rates. Although slightly different amongst institutional series presented in this chapter, there is consistency in that the best results are seen in patients with small tumor size, negative margins, and minimally involved nodes. Clearly, if a patient is not a candidate for breast conservation therapy with tangential whole breast irradiation alone, excluding the draining lymphatics, then they should be excluded from regimens that further reduce the volume of breast tissue irradiated.

There remains a significant difference between the three primary methods of APBI outlined in this chapter: multicatheter brachytherapy, balloon brachytherapy and external-beam therapy. The highlighted differences include the amount of tissue irradiated, the technical challenge involved in radiation delivery and planning, as well as the logistics for the patient (such as the level of invasiveness). Also, the level of data supporting each modality varies, as only the multicatheter approach has published outcome data extending beyond five years, and has been compared to matched or historical controls treated with whole breast irradiation. The others have shown excellent feasibility and tolerability with minimal acute toxicity, and the efficacy data are mounting steadily. Clearly, the ongoing Phase III NSABP B39/RTOG 0413 trial (which allows treatment with any of these three methods on the APBI arm) will allow controlled analysis between them, but more importantly it will facilitate comparisons with the current standard of care of whole breast radiotherapy.

Further outcome analysis linking toxicity with dosimetric parameters is needed to allow the development of tighter dose–volume constraints that can be employed during treatment planning. The advent of CT-based treatment planning has allowed significant advancements in target delineation, dosimetric coverage, and quality assurance measures, which in turn have spawned several next-generation APBI methods. These refined methods will likely further improve the therapeutic ratio of target coverage vs. conformal avoidance of normal tissues, while ultimately expanding the eligibility of APBI for patients. It is likely that the situation where there is just one superior method of APBI suitable for all patients will change, as the optimal technique will clearly need to be tailored to the individual patient. From the evidence presented in this review chapter, it appears that modern APBI represents a viable alternative treatment option for carefully selected women with early-stage breast cancer.

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An Overview of European Clinical Trials of APBI

9

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9.1 Introduction

In the last two decades, there has been increasing interest in Europe in treating selected patients with early-stage breast cancer with accelerated partial breast irradiation (APBI) using external-beam irradiation (EBI) (Magee et al. 1996; Ribeiro et al. 1993), interstitial brachytherapy (BT) (Cionini et al. 1995; Clarke et al. 1994; Fentiman et al. 1991, 1996, 2004; Johansson et al. 2008; Mayer and Nemeskéri 1993; Ott et al. 2004, 2005, 2007; Polgár et al. 2002, 2004a, 2005, 2007, 2008; Póti et al. 2004; Samuel et al. 1999; Strnad et al. 2004), or intracavitary (MammoSite) BT (Niehoff et al. 2006a,b). In this chapter, we will give an overview of these European clinical trials of APBI, including their implications for optimal patient selection, target definition, treatment technique, and quality assurance (QA). Finally, we will discuss the development and status of the new European Multicentric Phase III APBI trial conducted by the Breast Cancer Working Group of the Groupe Européen de Curiethérapie–European Society for Therapeutic Radiology and Oncology (GEC–ESTRO). European experience with intraoperative radiotherapy for APBI is discussed elsewhere (see Chap. 12).

9.2 Early European APBI Trials

Several European centers pioneered the use of different APBI regimens for unselected patients in the early 1980s (Cionini et al. 1995; Clarke et al. 1994; Fentiman et al. 1991, 1996, 2004; Mayer and Nemeskéri 1993; Póti et al. 2004). However, results in all but one of these early studies were poor, with high local recurrence (LR) rates (Table 9.1). The high rates of local failure seen in these early APBI studies reflect inadequate patient selection critera and/or a

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Table 9.1 Results of early European APBI trials

Institution	Technique	RT scheme (dose in Gy × fraction no.)	Median FUP (years)	Total LR % (n)	TR/MM % (n)	EF (%)	Annual LR (%)	Cosmesis exc./good (%)
Christie Hosp. (Magee et al. 1996; Ribeiro et al. 1993)	ELE	5 × 8	8	20 (69 of 353)	NR	NR	2.5	NR
Uzsoki Hosp. (Mayer and Nemeskéri 1993; Póti et al. 2004)	MDR	50 × 1	12	24 (17 of 70)	17 (12 of 70)	7 (5 of 70)	2	50
Guy's Hosp. I (Fentiman et al. 1991, 1996)	LDR	55 × 1	6	37 (10 of 27)	33 (9 of 27)	4 (1 of 27)	6.2	83
Guy's Hosp. II (Fentiman et al. 2004)	MDR	11 × 4	6.3	18 (9 of 49)	14 (7 of 49)	4 (2 of 49)	2.9	81
Florence Hosp. (Cionini et al. 1995)	LDR	50–60 × 1	4.2	6 (7 of 115)	2 (2 of 115)	4 (5 of 115)	1.4	NR
Royal Devon/Exeter (Clarke et al. 1994)	HDR	20 × 2; 8 × 4; 6 × 6	1.5	16 (7 of 45)	9 (4 of 45)	7 (3 of 45)	10.7	95
All patients			1.5–12	18 (119 of 659)	11 (34 of 306)	5 (16 of 306)	1.4–10.7	50–95

APBI, accelerated partial breast irradiation; *FUP*, follow-up period; *LR*, local recurrence; *TR/MM*, true recurrence / marginal miss; *EF*, elsewhere failure; *MDR*, medium dose rate; *LDR*, low dose rate; *HDR*, high dose rate; *NR*, not reported

Table 9.2 Results of early breast conservation trials using conventional whole breast irradiation

Institution	Study period	WBI dose (Gy)	Boost dose (Gy)	Median FUP (years)	LR (%)	Annual LR (%)
NCI (Jacobson et al. 1995)	1979–87	45–50.4	15–20	10	18[a]	1.80
W. Beaumont Hosp. (Pass et al. 2004)	1980–85	45	15	12.3	21[b]	1.75
EORTC 10801 (Van Dongen et al. 1992)	1980–86	50	25	8	13[c]	1.63
Christie Hosp. (Magee et al. 1996)	1982–87	40	0	8	13[c]	1.63
Ontario (Clark et al. 1996)	1984–89	40	12.5	7.6	11.3	1.48
Uzsoki Hosp. (Lövey et al. 1994)	1986–90	50	10–20	3.8	5.5	1.45
Uzsoki Hosp. (Lövey et al. 1994)	1986–90	50	0	3.8	10.7	2.82

WBI, whole breast irradiation; *FUP*, follow-up period; *LR*, local recurrence
[a] 10-Year actuarial rate
[b] 12-Year actuarial rate
[c] 8-Year actuarial rate

suboptimal treatment technique and a lack of appropriate QA procedures (Polgár et al. 2004b, 2005). Note that these results are quite similar to those obtained in earlier breast conservation trials using conventional whole breast radiotherapy (Table 9.2) (Clark et al. 1996; Jacobson et al. 1995; Lövey et al. 1994; Pass et al. 2004; Van Dongen et al. 1992), which suggests that this problem was not due to the omission of irradiation of the whole breast.

9.2.1 Christie Hospital's External-Beam APBI Trial

The first APBI trial using EBI was conducted at the Christie Hospital in Manchester, UK, between 1982 and 1987 (Magee et al. 1996; Ribeiro et al. 1993). Patients were randomly assigned to receive either 40–42.5 Gy electron beam irradiation in eight fractions to the tumor bed only (limited field, LF, group), or 40 Gy whole breast plus regional photon irradiation (wide field, WF, group). The eight-year actuarial LR rate was significantly higher in the LF group than in the WF group (25% vs. 13%). However, there was no significant difference in disease-specific survival between the two groups (73% vs. 72%). The average field size used in the LF arm was 6 × 8 cm, and no attempt was made to localize the excision cavity by means of surgical clips or CT-based treatment planning. Note that the majority of ipsilateral breast recurrences were in the treated quadrant. Patients with tumor sizes of up to 4 cm (75% T2) were enrolled in the study, and axillary dissection was omitted. Specimen margins were not evaluated microscopically, and no adjuvant systemic therapy was administered. The authors concluded that with improved patient selection and technique refinement, radiotherapy restricted to the tumor bed may provide an adequate local treatment.

9.2.2 Uzsoki Hospital's Cobalt-Needle Study

One of the first prospective APBI studies using interstitial implants was conducted in Hungary at the Uzsoki Hospital between 1987 and 1992 (Mayer and Nemeskéri 1993; Polgár et al. 2005; Póti et al. 2004). Due to the limited availability of modern teletherapy equipment and the lack of ^{192}Ir wires in Hungary, special ^{60}Co sources were designed and manufactured to allow manual afterloading of interstitial BT catheters. (These ^{60}Co needles were used in the late 1980s to replace the conventional ^{226}Ra needles previously used in Hungary, in order to increase the radiation safety of the staff and allow more patients to have the option of breast-conserving therapy.) During this period, 70 patients were treated with these needles following conservative surgery, without using whole breast irradiation (WBI) (Póti et al. 2004). Any patient with a pathologic T1 or T2 tumor that was clinically unifocal was eligible. A median of five (range 2–8) catheters with an active length of 4 cm were implanted into the tumor bed (which was not delineated by surgical clips or by the use of CT) in a single plane without template guidance. A dose of 50 Gy was prescribed at 5 mm from the surfaces of the sources, given in a single session of 10–22 h at a rate of 2.3–5.0 Gy h^{-1} (medium dose rate, MDR). The volume included within the reference isodose surface was quite small (median 36 cm^3).

The first interim analysis of this series was published in 1993 (Mayer and Nemeskéri 1993). With a median follow-up time of 3.8 years, eight of 44 patients (18%) had developed a LR. Because of poor cosmetic results (a high incidence of changes in skin pigmentation, development of telangiectasias, and fibrosis), the study was closed in 1992 (Mayer and Nemeskéri 1993; Póti et al. 2004). Updated 12-year results for this series showed that the crude LR rate was 24%, with 59% of patients having grade 3 or 4 complications (Póti et al. 2004).

The investigators noted that modern imaging methods (mammography and ultrasound) were not available during this particular study period in their hospital's health-care area (Mayer and Nemeskéri 1993). Therefore, most patients did not have pre- or postoperative mammographic evaluation. The vast majority of pathology reports did not contain important information such as pathologic tumor size and the presence of multifocality. Hence, it is likely that even their very limited predefined patient-selection criteria were frequently violated. Other important pathological factors were also not assessed, such as pathological axillary node status (unknown for 80% of patients) and margin status (unknown for all patients). Hence, perhaps many or most of the patients treated in this study would not be considered eligible for breast-conserving therapy today. Therefore, it is likely that the high rate of LR in this study was due to having persistent (not recurrent) tumors due to inadequate patient selection criteria and radiological and pathological evaluation, as well as a very small and inadequate implant volume. The high rate of toxicity may have resulted from giving a high total dose (86–134 Gy low dose rate, LDR, equivalent dose) delivered within a short overall treatment time without fractionation. American, Japanese, and European experts have declared that the defects in the Uzsoki Hospital's study cannot be used to disparage the concept of APBI, if properly performed (Polgár et al. 2004b, 2005; Vicini et al. 2004). Despite its obvious limitations, the annual LR rate of 2% reported in this study is quite similar to those observed in other early breast conservation trials using WBI

(Table 9.2). In addition, the pioneering experience of the Uzsoki Hospital subsequently served as a basis for the development of more successful APBI series at the National Institute of Oncology, Budapest, later on (Polgár et al. 2002, 2004a, 2005, 2007, 2008).

9.2.3 Guy's Hospital Studies

Fentiman et al. (1991, 1996, 2004) also explored the feasibility and limitations of partial breast BT in two consecutive pilot trials performed at the Guy's Hospital, London, UK. In the first study, conducted from May 1987 to November 1988, 27 patients were treated with LDR implants using rigid needles (Fentiman et al. 1991, 1996). The target volume included a 2 cm margin around the tumor bed. Doses were prescribed using the Paris dosimetry system with a dose of 55 Gy given over 5–6 days using manually afterloaded ^{192}Ir wires. The authors stated that a systematic QA procedure was not used at that time. With a median follow-up of six years, ten of 27 patients (37%) experienced recurrence in the treated breast (Fentiman et al. 1991). All relapses were within the irradiated volume, except in one patient. None of the patients developed breast fibrosis, and only one patient had telangiectasias. The cosmetic outcome was good or excellent in 83% of patients.

A second Guy's Hospital study enrolled 50 patients between 1990 and 1992 (Fentiman et al. 2004). Patient selection criteria, surgical and implant techniques were similar to the first Guy's Hospital series except for three aspects. First, only patients aged 40 or older were eligible. Second, to reduce radiation exposure to medical and nursing staff, a MDR remote-controlled afterloading system employing ^{137}Cs was used to give a total dose of 45 Gy in four fractions over four days. Third, 92% of patients received adjuvant systemic therapy. At a median follow-up of 6.3 years, eight of 49 eligible patients (18%) developed a breast relapse, which was located in the index quadrant in seven (78%). Only one LR (4%) occurred among patients with lesions smaller than 2 cm, while the rate was 35% for patients with tumors of 2 cm or larger. Cosmetic outcome was considered excellent or good in 81% of patients.

With hindsight, it is easy to see that there were many flaws in the design of these trials, particularly with regard to surgical technique and patient selection. No attempt was made to achieve a wide excision, either grossly or microscopically. As a consequence, the surgical margins were involved in 56% of patients in the first study and in 43% of patients in the second. Although only patients with tumors measuring no more than 4 cm in diameter were eligible for the first study, there were three patients with larger tumors. Furthermore, in the first study, 11 patients (41%) had tumors containing extensive intraductal component (EIC), and 12 patients (44%) had positive axillary lymph nodes; in the second study, 44% of patients had positive nodes.

9.2.4 Florence Series

Between 1989 and 1993, Cionini et al. (1995) in Florence, Italy treated 115 patients with T1-2N0-1 tumors with quadrantectomy, axillary dissection and LDR BT of the entire

quadrant and the nipple, giving a dose of 50–60 Gy using ^{192}Ir implants. Young patients (52% of the population was premenopausal), patients with positive or unknown margins (15%), and patients with infiltrating lobular carcinoma (20%) were included in the study. Patients with positive axillary nodes (38%) received chemotherapy or tamoxifen. At a median follow-up of 50 months, seven breast recurrences (6%) were observed (two in the tumor bed and five elsewhere in the breast). The five-year actuarial LR, disease-free survival (DFS), and overall survival (OS) rates were 6%, 83%, and 96%, respectively. Cosmetic outcome and side effects were not reported.

9.2.5 Royal Devon/Exeter Hospital Series

In a pilot study performed at the Royal Devon and Exeter Hospital in the United Kingdom, fractionated high dose rate (HDR) interstitial BT was used to treat the quadrant after tumor excision in 45 patients (Clarke et al. 1994). Patients selected for BT alone had tumors smaller than 4 cm, grade 1 or 2 tumors, and clear or close margins. Three different fractionation schedules were used: 20 Gy given in two fractions; 28 Gy given in four fractions; and 32 Gy given in six fractions. The crude LR rate was 15.6% at 18 months. A true recurrence/marginal miss within the treated volume was observed in four patients, and three patients had elsewhere failures. However, this study was also limited by the surgical techniques and pathological reports used, as axillary dissection was not performed routinely, and in many cases detailed histologic findings were not available. Cosmetic outcome was excellent in 95% of patients.

9.3 Contemporary European APBI Trials

Based on the controversial results of earlier studies, a number of European groups created APBI trial protocols incorporating strict patient selection criteria and systematic QA procedures. As a result, the outcomes of these studies have been much improved (Table 9.3) (Johansson et al. 2008; Ott et al. 2004, 2005, 2007; Polgár et al. 2002, 2004a, 2005, 2007, 2008; Samuel et al. 1999; Strnad et al. 2004).

9.3.1 Ninewells Hospital's Study

Samuel et al. (1999) reported their experience of a small pilot study (11 patients) performed in Dundee, Scotland using perioperative double-plane LDR ^{192}Ir implants. The mean reference dose (prescribed according to the Paris system) was 51 Gy (range 46–55 Gy). Stringent patient selection criteria were used. Eligible patients had a single unilateral tumor with a diameter of 2 cm or less. Women with EIC-positive, multifocal cancers or invasive lobular carcinomas were excluded. All patients were older than 40 years. Only one patient had

Table 9.3 Results of contemporary European APBI trials

Institution	Technique	RT scheme (dose in Gy × fraction no.)	Median FUP (years)	Total LR % (n)	TR/MM % (n)	EF (%)	Annual LR (%)	Exc./good cosmesis (%)
HNIO, Budapest I (Polgár et al. 2004b, 2008)	HDR	4.33 × 7; 5.2 × 7	11.1	8.9 (4 of 45)	0 (0 of 45)	8.9 (4 of 45)	0.80	78
Örebro Med. Centre (Johansson et al. 2008)	PDR	50/0.83[b]	7.2	6.0 (3 of 50)	2 (1 of 50)	4 (2 of 50)	0.83	56
HNIO, Budapest II (Polgár et al. 2007, 2008)	HDR	5.2 × 7	6.8	4.5 (4 of 88)	2.3 (2 of 88)	2.3 (2 of 88)	0.66	81
HNIO, Budapest II (Polgár et al. 2007, 2008)	ELE	2 × 25	6.8	5.0 (2 of 40)	2.5 (1 of 40)	2.5 (1 of 40)	0.74	68
Ninewells Hosp. (Samuel et al. 1999)	LDR	46–55 × 1	6	0 (0 of 11)	0 (0 of 11)	0 (0 of 11)	0	91
Germany/Austria (Ott et al. 2007; Strnad et al. 2004)[a]	PDR/HDR	50/0.6[b]; 4 × 8	4	2.2 (6 of 274)	1.1 (3 of 274)	1.1 (3 of 274)	0.55	92
MammoSite Kiel-HNIO (Niehoff et al. 2006b)[c]	HDR	3.4 × 10	5	0 (0 of 11)	0 (0 of 11)	0 (0 of 11)	0	45
MammoSite Multicentric (Niehoff et al. 2006a)	HDR	3.4 × 10	1.2	0 (0 of 28)	0 (0 of 28)	0 (0 of 28)	0	76
All patients			1.2–11.1	3.5 (19 of 547)	1.3 (7 of 547)	2.2 (12 of 547)	0–0.83	45–94

FUP, follow-up period; *LR*, local recurrence; *TR/MM*, true recurrence / marginal miss; *EF*, elsewhere failure; *MDR*, medium dose rate; *LDR*, low dose rate; *HDR*, high dose rate; *ELE*, electrons; *HNIO*, Hungarian National Institute of Oncology; *NR*, not reported

[a] Updated results by Strnad

[b] Total dose/pulse dose

[c] Updated results by Niehoff

positive surgical margins, and all but one patient were pathologically node-negative. At a median follow-up time of 67 months, there were no LR or breast cancer-related deaths. Cosmetic results were felt to be satisfactory as judged by the authors in all patients, except for one patient who developed an abscess.

9.3.2 Örebro Series

The first APBI study using pulsed dose rate (PDR) BT was begun in December 1993 at the Örebro Medical Centre in Sweden (Johansson et al. 2008). Inclusion criteria included being age 40 years or older with a unifocal breast cancer measuring 5 cm or less (with 80% of patients having tumors ≤2 cm) without an EIC, which was excised with clear inked margins, and up to three positive axillary lymph nodes (although 88% of patients were node negative). Freehand plastic tube implants were used to cover the PTV, defined as the excision cavity plus 3 cm margins. Fifty patients were treated to a total dose of 50 Gy, using pulses of 0.83 Gy delivered over five days. At a median follow-up time of 86 months, only three patients (6%) developed LR. Two of them (4%) occurred outside the treated volume. The seven-year actuarial LR rate was 4%. Moderate (Grade 2) and severe (Grade 3) fibrosis located in the treatment volume were reported in 18% and 8%, respectively. Grade 2 and 3 telangiectasias developed in 14% and 8% of patients, respectively. Fat necrosis was seen in ten patients (20%). Six of these patients (12%) had both symptoms and mammographic findings, and four patients (8%) were asymptomatic. The authors were not able to demonstrate any significant correlation between different dosimetric parameters (V_{100}, V_{150}, V_{200}, and DHI) and fat necrosis. Only one patient (2%) developed chronic pain in the breast and was subsequently treated by mastectomy. The oncology nurse scored the cosmetic outcome as good or excellent in 56% of the patients. However, the authors noted that surgical factors (volume reduction, deformation, scaring) were associated with cosmetic failure at least in 44% of the cases.

9.3.3 National Institute of Oncology (Hungary) Studies

Between 1996 and 1998, 45 selected patients with early-stage invasive breast cancer were treated with APBI using interstitial HDR implants at the National Institute of Oncology (NIO), Budapest, Hungary (Polgár et al. 2002, 2004a, 2005, 2008). Patients were eligible for sole BT if they met all of the following conditions: unifocal tumor; tumor size ≤20 mm (pT1); microscopically clear surgical margins; pathologically negative axillary nodes or only axillary micrometastases (pN1mi); histological grade 1 or 2; and technical suitability for breast implantation. Exclusion criteria were: pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; or the presence of EIC. During surgery, the boundaries of the excision cavity were marked with titanium clips. Implantation was performed 4–6 weeks after surgery under local anesthesia. A preimplant radiographic simulation was performed using a template placed on the breast in order to determine the entry and exit

points of the implant strand from a "needle's-eye" view. The PTV was defined as the excision cavity (delineated by the surgical clips) plus a margin of 1–2 cm. Single-, double-, and triple-plane implants were performed on 3, 34, and 8 patients (7%, 75%, and 18%), respectively. After all the rigid guide needles were implanted, they were replaced with flexible plastic tubes. Dose planning was based on a three-dimensional reconstruction of the locations of catheters, surgical clips, and skin points. Two postimplant isocentric radiographs were taken on a simulator with variable angles and the radiographic films were used for digitizing the positions of catheters (Fig. 9.1). A total dose of 30.3 Gy (n = 8) or 36.4 Gy (n = 37) in seven fractions over four days was delivered to the PTV. The mean volume encompassed by the 100% isodose surface was 50 cm^3. Only seven patients (16%) received adjuvant tamoxifen therapy.

A 12-year update of this study was reported, including comparison with the results of a control group treated during the same time period with conventional breast-conserving therapy (Polgár et al. 2004a, 2008). The control group comprised 80 consecutive patients who met the eligibility criteria for APBI, but who were treated with 50 Gy WBI with (n = 36) or without (n = 44) a 10–16 Gy tumor bed boost. The crude rates of total ipsilateral breast failure were 8.9% (4 of 45) and 10% (8 of 80) in patients treated with multicatheter BT and WBI, respectively. The 12-year actuarial rate of ipsilateral breast recurrence was not significantly different between patients treated with APBI (9.3%) and WBI (11.1%). There were no significant differences in either the 12-year probability of DFS

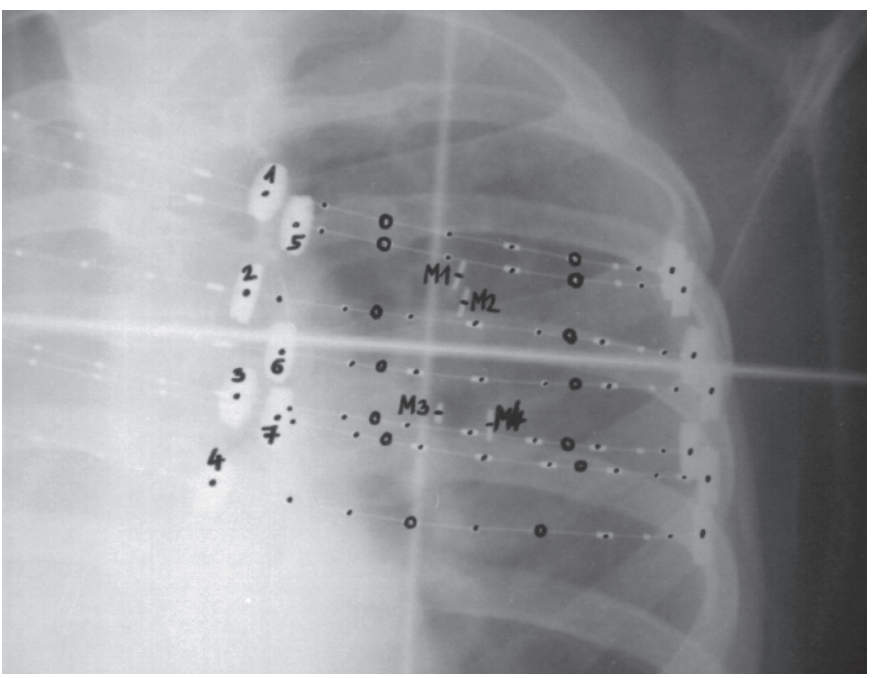

Fig. 9.1 Radiographic verification of a typical two-plane implant for the Phase II Hungarian APBI study (M1–M4 are surgical clips; small circles denote first and last active source positions)

(75% and 74%, respectively) or cancer-specific survival (91% and 89%, respectively). Three out of four patients with isolated breast recurrences in the APBI group underwent a second breast-conserving surgery followed by 46–50 Gy of whole breast radiotherapy. (Only one patient was treated by mastectomy.) So far, there has been no further LR in these three patients, yielding a 98% mastectomy-free survival rate for patients treated with APBI. In contrast, three patients (4%) in the control group underwent salvage mastectomy. The rate of excellent or good cosmetic results was 78% in the APBI group and 67% in the control group (p = 0.045). Similar incidences of fat necrosis were identified in both the APBI (38%) and control (31%) groups (p = NS). Only one patient (2.2%) in the APBI group developed symptomatic fat necrosis and underwent re-excision.

Based on the encouraging results of the first NIO study, a randomized study was conducted between 1998 and 2004 at the same institution in Budapest (Polgár et al. 2002, 2005, 2007, 2008). Initial eligibility criteria were similar to those for the previous study, although following the publication of the European Organization for Research and Treatment of Cancer (EORTC) boost trial in 2001, patients aged 40 years or younger were excluded. In addition, the trial allowed patients with breasts that were technically unsuitable for performing interstitial implantation to enroll and be treated with an external-beam (EB) approach. By May 2004, 258 eligible patients had been randomized to receive either 50 Gy WBI (n = 130) or partial breast irradiation (PBI, n = 128). The latter consisted of either 36.4 Gy (given over four days using seven fractions of 5.2 Gy each) with HDR multicatheter BT (n = 88) or limited-field electron irradiation (n = 40), giving a dose of 50 Gy in 25 fractions (prescribed to the 80% isodose line) over five weeks. One-, two-, three-, or four-plane implants were performed in one (1%), 47 (55%), 37 (43%), and one (1%) patient(s), respectively. The mean volume encompassed by the reference isodose surface was 62 cm^3. The majority of the patients in both arms (70%) received adjuvant hormone therapy.

The five-year results of the Hungarian randomized trial were published in 2007 (Polgár et al. 2007). In the most recent analysis, at a median follow-up time of 6.8 years, there was no significant difference in local and regional tumor control, disease-free, cancer-specific or distant metastasis-free survival between the two treatment arms (Tables 9.3 and 9.4) (Polgár et al. 2008). The rate of excellent to good cosmetic results was 77% in the PBI group (81% after HDR-BT; 68% after EB) and 65% in the control group ($p_{WBI/PBI}$ = 0.024).

In a separate analysis, the four-year actuarial rates of fat necrosis were 31.9%, 36.5%, and 17.7% after WBI, HDR-BT and EB, respectively (Lövey et al. 2007). However the incidence of symptomatic fat necrosis was not significantly different after WBI (8.5%), HDR-BT (11.4%), and EB (7.5%). Among the evaluated patient-, tumor-, and treatment-related

Table 9.4 Seven-year actuarial results of the Budapest Phase III trial (Polgár et al. 2008)

Treatment arm	LR % (n)	RR % (n)	CSS %	DFS %	DMFS %
Partial breast irradiation	5.1 (6 of 128)	1.6 (2 of 126)	96.2	86.3	91.0
Whole breast irradiation	3.3 (4 of 130)	1.7 (2 of 129)	93.9	89.0	92.3
p value	0.53	0.99	0.45	0.65	0.94

LR, local recurrence; *RR*, regional recurrence; *CSS*, cancer-specific survival; *DFS*, disease-free survival; *DMFS*, distant metastasis-free survival

variables, only bra cup size was significantly associated with the incidence of fat necrosis. In the HDR-BT group, there was no correlation among specific implant parameters (V_{100}, V_{150}, DHI, number of catheters, and implant planes) and the actual rate of fat necrosis.

9.3.4 German–Austrian Multicentric Trial

In the year 2000, four institutions decided to start the first European multi-institutional Phase II trial to investigate the effectiveness and safety of APBI (Ott et al. 2004, 2005, 2007; Polgár et al. 2005; Strnad et al. 2004). Radiation oncology departments from the University Hospitals of Erlangen and Leipzig from Germany and the University Hospital of Vienna and the Barmherzige Schwestern Hospital of Linz from Austria recruited 274 patients between November 2000 and April 2005.

Patients were eligible for APBI if they had histologically confirmed breast cancer, a tumor diameter ≤3 cm, complete resection with clear margins of 2 mm at least, pathologically negative axillary lymph nodes (pN0), or singular nodal micrometastasis (pN1mi) with at least nine lymph nodes removed and histologically examined, no evidence for distant metastasis or contralateral breast cancer, ECOG performance status ≤2, estrogen and/or progesterone receptor positive tumors, and patient age ≥35 years. Patients were excluded from the protocol if they initially showed a multicentric invasive growth pattern, poorly differentiated or undifferentiated tumors, had postoperative residual microcalcifications, an EIC, lymph vessel invasion, or unknown, involved or close margins.

After breast-conserving surgery, an interval of 4–6 weeks was designated for wound healing and for proper histological analysis of the tumor specimen to guarantee the selection of appropriate patients. PBI was solely performed as multicatheter BT according to the rules of the Paris system (Figs. 9.2 and 9.3). The median duration of the interval between surgery and BT was 59 days (range 4–159). The tumor bed was localized through the use of surgical clips, preoperative mammography and ultrasound examination and/or postoperative planning CT scans. In contrast to the USA and some other European countries, where the surgical cavity remains open, breast-conserving surgery is performed with a closed cavity in Germany and Austria. In the case of closed-cavity surgery, CT-based planning often does not lead to a clear delineation of the target volume; therefore, it was not stipulated in the protocol. The PTV was confined to the tumor bed plus a safety margin of 2–3 cm in each direction, if possible. Two- or three-plane implants were used in 57.7% and 42.3%, respectively. The median number of afterloading tubes was 13 (range 6–18). Treatment planning was done with either CT scans or conventional radiographs taken with a simulator. Dose specification was performed according to the Paris system. The reference isodose was defined to 85% of the mean central dose (MCD). Implant volumes for all 274 patients were 75.0 ± 34.3 cm^3 (range 22.4–205.1 cm^3) enclosed by the reference isodose (V_{ref}), 14.7 ± 6.9 cm^3 (range 5.3–54.0 cm^3) for the volume V_{150} (1.5 × reference isodose), and 8.6 ± 3.6 cm^3 (range 3.2–23.5 cm^3) for the volume of $V_{1.5 \times MCD}$. The median dose homogeneity index (DHI) was 0.81 (range 0.49–0.91). The prescribed reference dose in HDR BT was 32 Gy in eight fractions of 4 Gy twice daily with an intraday interval of at least 6 h. The prescribed reference dose in PDR BT was 49.8 Gy in 83 fractions of 0.6 Gy every

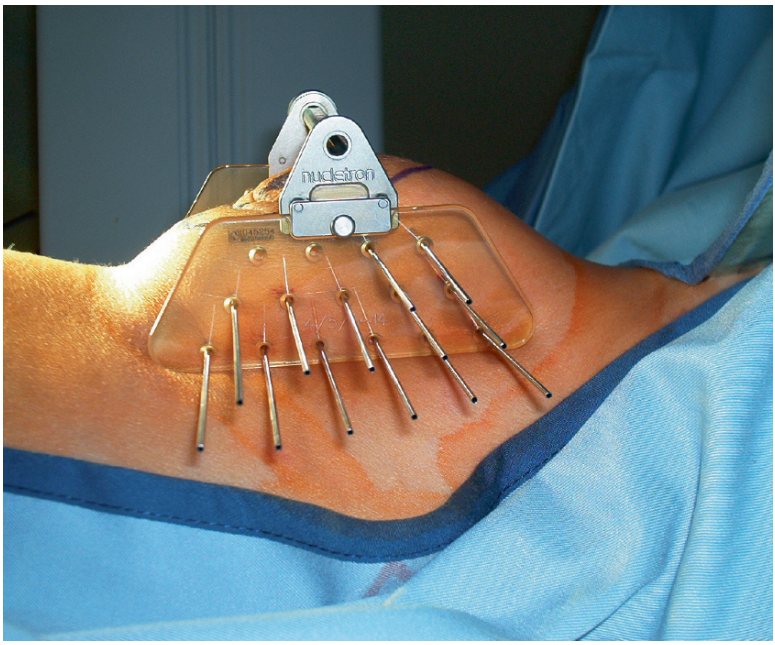

Fig. 9.2 Template-guided insertion of steel needles into the left breast

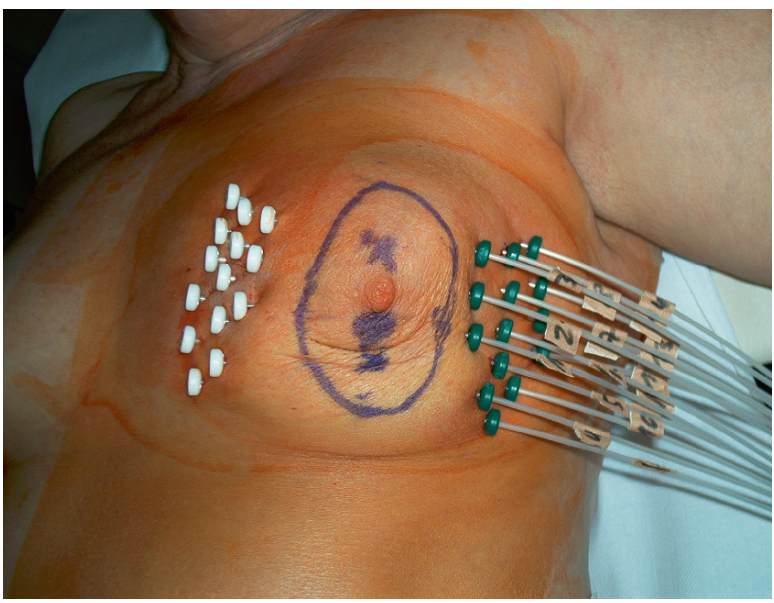

Fig. 9.3 Interstitial multicatheter breast implant in the same patient as shown in Fig. 9.2. The steel needles have been replaced by 14 flexible afterloading tubes

hour. Total treatment time was four days. PDR and HDR BT were performed in 63.6% and 36.4% of the patients, respectively.

Preliminary results of the trial have already been published (Ott et al. 2004, 2005, 2007; Strnad 2004). According to the last update of this study (unpublished results from V. Strnad and O.J. Ott, June 2008), six patients (2.2%) had developed ipsilateral breast recurrence after a median follow-up of 48 months, yielding a four-year actuarial LR rate of 0.6%.

Data on perioperative complications and side effects were available in all of the 274 patients. Bacterial infection was developed in six patients (2.2%). The incidence of hematoma was also 2.2%. Acute toxicity was low: 3.6% of the patients experienced mild and 1.1% moderate radiodermatitis. To date, late toxicity has been mild: 5.1% of the women experienced hypersensation or mild pain related to the tumor bed, and 1.1% intermittent but tolerable pain. Mild dyspigmentation of the skin above the BT implant was found in 2.2% of the cases. Grade 1 fibrosis was palpated in 14.2%, and grade 2 and 3 fibrosis in 9.5% and 0.4% of the patients in the region of the surgical scar. Grade 1 telangiectasia of the involved skin was found in 10.2%, and grade 2 and 3 telangiectasia in 4.7% and 2.2% of the women, respectively.

Ott et al. (2005) investigated the incidence of fat necrosis in a subgroup of patients (n = 33) treated in the German–Austrian study. At a median follow-up of 35 months, the incidence of fat necrosis was 15.2%, and no patient underwent surgical intervention because of fat necrosis-related pain.

Data on cosmetic outcome were available for all patients. At a median follow-up of 48 months, physicians judged the cosmetic results to be excellent or good in 92%, and fair in 8% of the women. Patients subjectively judged the cosmetic outcome to be excellent or good in 91.6%, fair in 6.9%, and poor in 1.5%. Immediately before the beginning of BT, physicians and patients declared that the cosmetic outcome was good to excellent in 93.4% and 91.5%, respectively. This indicates that the use of multicatheter BT did not significantly impact on cosmetic outcome after a median follow-up of four years.

Recruitment for the German–Austrian Phase II trial was stopped in April 2005. The four participating institutions concentrate their energy on the randomized GEC–ESTRO Phase III APBI trial (Polgár et al. 2005).

9.4 European MammoSite Brachytherapy Trials

APBI with interstitial BT using multicatheter systems requires a high level of experience in all members of staff. For that reason, a new and simple BT system was developed in the USA (Edmundson et al. 2002). The MammoSite Radiation Treatment System (RTS) is a dual-lumen spherical balloon catheter. One lumen allows the balloon to be inflated to a diameter of 4–5 cm; the other provides a pathway for the ^{192}Ir source. The advantage of this system is that only one applicator is implanted to perform fractionated radiotherapy of the tumor bed, in contrast to interstitial BT, which requires up to 20 needles. Since 2002 this system has been available for commercial use. In the US, the system is used by many institutions in their daily practice. In Europe, several feasibility studies have been initiated to investigate the practicability and safety of the system (Niehoff et al. 2006a,b).

Table 9.5 Implanted patients in European MammoSite studies listed by countries

	Primary	Boost	Not treated	Total
Germany	10	2	7	19
Italy	13	–	2	15
Hungary	1	11	1	13
Switzerland	2	3	–	5
Austria	2	–	–	2
All countries	28	16	10	54

Most of these trials were designed to test the device as the sole method of APBI and for delivering a boost dose in combination with whole breast EBI.

Up to June 2005, MammoSite applicators had been implanted in 54 patients in different institutions in Europe (Table 9.5) (Niehoff et al. 2006a). Eligibility criteria for the sole modality (boost modality in parentheses) were: age ≥60 years (boost: age ≥40 years); tumor ≤2 cm (boost: ≤2.5 cm); invasive ductal histology; grade 1–2 (boost: grade 2–3); margins ≥5 mm (boost: negative margins); applicator placement within ten weeks of final lumpectomy procedure; excision cavity with one dimension of at least 3.0 cm. In contrast to the US studies (Benitez et al. 2007; Chao et al. 2007; Chen et al. 2007; Cuttino et al. 2008; Dragun et al. 2007; Vicini et al. 2008), a skin–balloon distance of at least 7 mm was demanded. Exclusion criteria were: presence of EIC; pure intraductal cancer (pTis); lobular histology; multifocal or multicentric lesions; or collagen vascular disease. The implantation, treatment planning and treatment performance was similar to the US trials described in Chap. 14. The applicators were preferably implanted during the final lumpectomy. In one institution, a drain was inserted into the cavity to prevent air bubbles and hematoma, and to maintain optimal tissue conformance to the balloon surface. For sole MammoSite therapy, a total dose of 34 Gy in ten fractions (prescribed at 1 cm from the balloon surface) was delivered over 5–7 days. In the boost group, a total dose of 10–20 Gy was delivered with a fraction dose of 2.5 Gy over 2–4 days. In both groups, two daily fractions were delivered with a minimum of 6 h between fractions. Patients were treated with various commercially available HDR remote afterloading machines.

Overall, 54 patients were enrolled in the European studies. Out of 54 implanted patients, ten (18.5%) had to be excluded from the clinical trial. The most common reason for exclusion was the final pathology. At the final decision, 28 patients were eligible for BT alone and 16 patients were treated with a boost BT followed by whole breast EBI.

No LRs have been reported after a mean follow-up of 14 months (range 3–31 months) (Niehoff et al. 2006a). One patient died of intercurrent disease two years after the treatment, and another disease-free patient suffers from stomach carcinoma. In all patients the anatomic position of the device in relation to the skin and to the chest wall was verified before and during the treatment. With the daily fluoroscopic simulations, a balloon rupture was detected in two patients, one prior to and one during the course of treatment. One patient was excluded; the other patient finished the treatment after the reimplantation of a new balloon. The devices were returned to the manufacturer for analysis, and in each case

the balloon damage was consistent with contact with a suturing needle or suture material. Because of this, we recommend cavity closure with a deflated balloon.

CT-based treatment planning is required to define the balloon–skin distance and to detect air pockets and hematoma. An insufficient skin distance of less than 7 mm leads to an overdosage at the small skin vessels. A subgroup analysis of the 32 German and Hungarian patients showed that the mean balloon–skin distance was 12 mm (range 5–43 mm), and this was strongly correlated with the breast cup size (Niehoff et al. 2006a,b). Calculated mean skin dose was 97% (range 38–132%) of the reference dose, and treatment with the MammoSite device resulted in significantly higher skin doses compared to conventional multicatheter BT (Major et al. 2006). Mean lung dose was also higher for MammoSite BT. For the Hungarian and German patients, the D_{90} (minimum dose to 90% of the target volume) was 98% (range 84–112%), which is higher than that reported in the literature (Edmundson et al. 2002). The DHI of 0.70 (range 0.55–0.83) was similar to the mean DHI (0.63) obtained using multicatheter BT.

Air pockets and hematoma of more than 3 mm lead to an underdosage of relevant breast tissue. The air gap volumes of 31 patients were analyzed in the German–Hungarian study. The measured mean air gap volumes with or without a drain were 0.01% (range 0–2%) and 0.97% (range 0–4.8%) of the PTV, respectively ($p = 0.01$).

Side effects in patients ($n = 24$) treated in Germany and Hungary are listed in Tables 9.6 and 9.7. The most common early toxicities were mild or moderate erythema, hyperpigmentation in the high skin dose area, and seroma formation. Other less common events were: mastitis, serosanguineous leakage, abscess, edema, pain, and fistula formation. Five serious adverse events were recorded, three of which were device related (two abscesses and one fistula). Patients who developed an abscess show only minor cosmetic deterioration at a follow-up of one year.

Antibiotic prophylaxis and stringent wound care recommendations appear to be indispensable. No abscess was seen after the introduction of antibiotic prophylaxis. The infection

Table 9.6 Early side effects of 24 patients irradiated*

	Primary ($n = 11$)	Boost ($n = 13$)	All patients ($n = 24$)
Side effects	*N* (%)	*N* (%)	*N* (%)
Erythema	9 (82)	12 (92)	21 (88)
Hyperpigmentation	8 (73)	12 (92)	20 (83)
Seroma	5 (45)	9 (69)	14 (58)
Abscess	1 (9)	1 (8)	2 (8)
Mastitis	1 (9)	0 (0)	1 (4)
Desquamation	2 (18)	0 (0)	2 (8)
Fistula	1 (9)	0 (0)	1 (4)
Edema	2 (18)	1 (8)	3 (13)
Serosanguineous leakage	1 (9)	0 (0)	1 (4)
Pain (any grade)	0 (0)	4 (31)	4 (17)

*Subgroup analysis of the German–Hungarian MammoSite study (updated unpublished results by Niehoff et al.)

Table 9.7 Late side effects and cosmetic results at last follow-up of 24 patients irradiated*

	Primary ($n = 11$)	Boost ($n = 13$)	All patients ($n = 24$)
Side effects	*N* (%)	*N* (%)	*N* (%)
Telangiectasia	7 (64)	6 (46)	13 (54)
Hyperpigmentation	6 (55)	2 (15)	8 (33)
Fibrosis (any grade)	4 (36)	10 (77)	14 (58)
Fat necrosis	5 (45)	8 (62)	13 (54)
Pain (any grade)	1 (9)	4 (31)	5 (21)
Persistent seroma	0 (0)	1 (8)	1 (4)
Excellent/good cosmetic result	5 (45)	6 (46)	11 (46)

*Subgroup analysis of the German–Hungarian MammoSite study (updated results by Niehoff P et al.)

rate (12%)—including abscess (8%) and mastititis (4%)—in the German–Hungarian study was similar to that reported by others (Benitez et al. 2007; Chao et al. 2007; Cuttino et al. 2008). In the initial US MammoSite study, the infection rate was 9.3%, including abscess in one patient (2.3%) (Benitez et al. 2007). The Beaumont group reported an overall infection rate of 11.3%, including mastitis, cellulitis, or abscess (Chao et al. 2007).

The balloon surface to skin distance is a critical point in terms of avoiding toxicity. In Europe, a minimum skin distance of 7 mm was allowed. Van Limbergen et al. (1989) reported that the risk of telangiectasia is increased when doses for the subcutaneous skin vessels exceed 46 Gy. Van Limbergen et al. (1987, 1990) also emphasized that any overlapping of the high dose areas of the interstitial implants with the upper 5 mm of the subcutaneous tissue should be avoided. Turreson (1990) reported that there is an interval of five years before telangiectasia appears. According to our preliminary analysis, in the German–Hungarian Trial, 26% (37% in the primary and 16% in the boost group) of patients developed telangiectasia after a mean follow-up of 20 months (Niehoff et al. 2006c). An update after a mean of 48 months (Table 9.7) showed a telangiectasia rate of 54% (64% in the primary, and 46% in the boost group). High rates of teleangiectasia (range 17–39.5%) were also observed in US MammoSite studies (Benitez et al. 2007; Cuttino et al. 2008). Therefore, in Europe we suggested that the use of the MammoSite system should be avoided for patients with a balloon-to-skin distance of less than 15 mm (Niehoff et al. 2006c). Due to the flexibility of dose shaping with multicatheter BT, we prefer interstitial implants for those patients with an inadequate (<15 mm) skin distance using the MammoSite applicator.

Based on the early European experience, the MammoSite device is simple and safe to handle. The acceptance of the system by the patients is very high, and we believe that the device offers an alternative method of postoperative partial breast brachytherapy for a highly selected group of patients. As yet, in Europe the issue of reimbursement has generally not been solved. In most European countries, the high costs of the applicator are not refunded by the health insurer. However, additional studies are planned in different European countries to test new intracavitary breast applicator systems.

9.5 European (GEC–ESTRO) Multicentric Randomized APBI Trial

Based on the success of the Hungarian and German–Austrian studies of APBI, a Phase III multicentric APBI protocol has been developed by the Breast Cancer Working Group of the GEC–ESTRO (Polgár et al. 2005). As long-term results beyond five years proving that multicatheter BT can be used with adequate reproducibility, low toxicity, and appropriate local control are only available for interstitial implants, it has been decided that only interstitial HDR/PDR BT will be allowed for the APBI arm of this European multicentric Phase III trial.

The first patient was randomized in May 2004 at the European Data Center in Erlangen, Germany. To date, fourteen centers from seven European countries—Austria (Vienna), Czech Republic (Brno), Germany (Erlangen, Kiel, Leipzig, Luebeck, Regensburg, Rostock and Wuerzburg), Hungary (Budapest), Spain (Barcelona and Valencia), and Switzerland (Bern)—have activated the protocol.

Patients in the control group are treated with 50 Gy whole breast EBI plus a 10 Gy electron boost (Fig. 9.4). Patients in the APBI arm are treated with HDR or PDR multicatheter BT. The primary end-point of the study is LR as a first event within five years. The scientific hypothesis to be assessed and statistically tested is "nonrelevant noninferiority" of the experimental treatment. Compared to the estimated 4% five-year LR rate in the control arm, an absolute increase of up to 3% (e.g., 7%) in the APBI arm is regarded as being nonrelevant noninferior. For adequate statistical power, 1,170 patients will be enrolled, based on the desire to detect a difference of 3% in LR rates between the arms. Secondary end-points will address overall, disease-free and distant metastasis-free survival, contralateral breast cancer, early and late side effects, cosmesis, and quality of life. Eligibility criteria include unifocal ductal carcinoma in situ (DCIS) or invasive carcinoma of the breast, tumor size ≤3 cm, microscopic negative margins of at least 2 mm (5 mm for DCIS or invasive lobular carcinoma), no EIC, no lymphovascular invasion, no more than one micrometastasis in axillary lymph nodes (pN1mi), and patient age ≥40 years. Patients are stratified before randomization according to the treatment center, whether they have DCIS or invasive carcinoma, and menopausal status. The QA program for partial breast BT includes preimplant PTV definition by surgical clips and/or preimplant CT image-based preplanning of the implant geometry (Fig. 9.5). The PTV is defined as the excision cavity plus a 2 cm margin

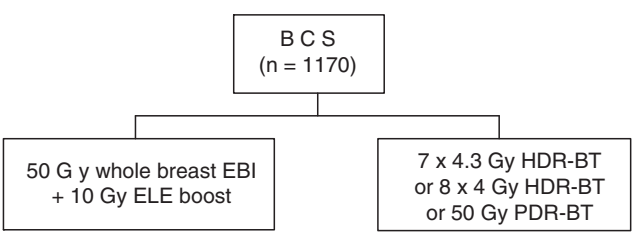

Fig. 9.4 Scheme of the GEC–ESTRO multicentric randomized APBI trial (BCS, breast-conserving surgery; EBI, external-beam irradiation; ELE, electron; HDR-BT, high dose rate brachytherapy; PDR-BT, pulse dose rate brachytherapy)

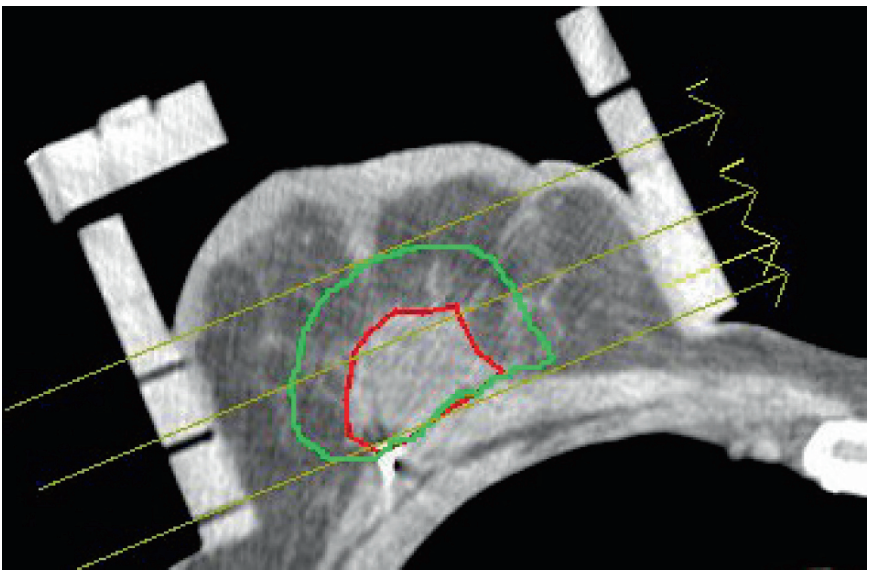

Fig. 9.5 CT-based preplanning of the implant geometry for multicatheter brachytherapy (red line denotes the excision cavity, green line the PTV, yellow arrows the preplanned implant planes)

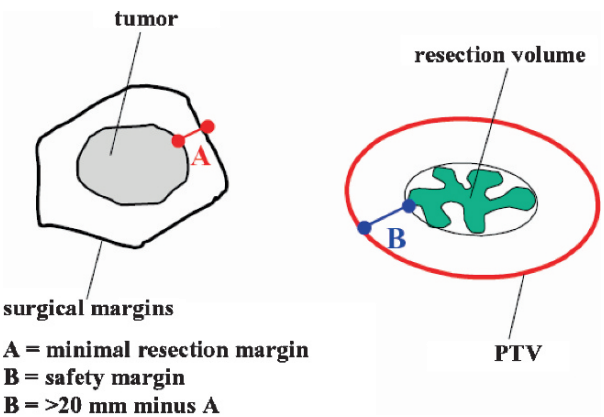

Fig. 9.6 PTV definition for the GEC–ESTRO multicentric randomized APBI trial

minus the minimum clear pathological margin (Fig. 9.6). Postimplant CT scans are mandatory for the documentation of target coverage and dose homogeneity (Fig. 9.7). Acceptable treatment parameters for CT image-based treatment planning include:

- DVH analysis of the target coverage confirming that the prescribed dose covers ≥90% of the PTV (coverage index ≥0.9)
- Dose nonuniformity ratio (DNR) ≤0.35
- Maximum skin dose <70% of the prescribed dose

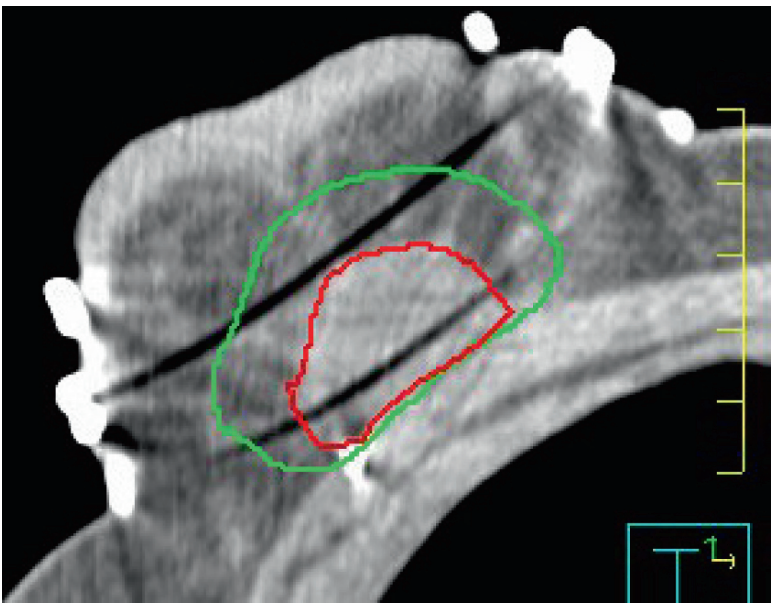

Fig. 9.7 PTV definition in postimplant CT scan for multicatheter brachytherapy (red line denotes the excision cavity, green line the PTV)

The GEC–ESTRO APBI trial is financially supported by a grant from German Cancer Aid (Deutsche Krebshilfe) for a study period of four years between 2005 and 2009. To date (June 2008), 983 patients have been randomized.

9.6 Summary and Future Directions

APBI is an attractive treatment approach with considerable advantages over standard whole breast radiotherapy. Earlier European APBI studies with less than satisfactory results failed to identify the ideal subset of patients and/or applied suboptimal treatment techniques. Indeed, by modern pathological and surgical standards, the majority of patients treated in those earlier APBI studies were not acceptable candidates even for conventional breast-conserving therapy. Consequently, the results of these "negative" APBI trials only prove that radiotherapy confined to the surgical bed with localization uncertainties is not appropriate treatment for unselected patients, and reinforce the need for meticulous QA. Contemporary European APBI trials have been based on this hard-won lesson. These series, which used multicatheter or MammoSite BT with strict patient-selection criteria and systematic QA procedures, resulted in an annual LR rate ranging between 0% and 0.83%. The five- to twelve-year results from single-institution Phase I/II APBI studies and the seven-year results of the Hungarian Phase III trial certainly support the continuation of the current European multicentric Phase III trial. Issues of patient selection, PTV definition,

total dose, and fractionation will be addressed and refined in such randomized trials. As data from this and other trials mature, they will hopefully support the implementation of APBI into routine clinical practice.

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The Phase III Trials: Obtaining Definitive Answers

10

Douglas W. Arthur

Through the past 15 years, several single-institutional trials in Europe and the United States have been published with results that maintain that the use of APBI yields acceptable toxicity and comparable local control to standard breast conservation therapy with whole breast irradiation (Vicini et al. 2007; King et al. 2000; Kaufman et al. 2007; Arthur et al. 2008; Polgar et al. 2007). Follow-up in these trials exceeds five years, and the numbers of patients included in these trials amount to a combined several hundred patient experience. These trials have helped to provide the data required to allow initial definition of patient selection criteria and the development of basic rules for treatment delivery and quality assurance for those physicians who choose to offer APBI in their clinical practice (Arthur et al. 2002; American Society of Breast Surgeons 2009). However, it must be recognized that the concept of APBI challenges the present standard treatment paradigm for early-stage breast cancer and introduces new treatment concepts that include target volume reduction to a partial breast target and the intensification of the treatment fractionation scheme to deliver the total dose in five days or less. To fully understand the impact of these new concepts and the role of APBI in the management of early-stage breast cancer, additional data is needed. This additional information can only be obtained through properly designed clinical trials and a joint effort by all physicians in supporting these trials.

There are presently seven Phase III trials that have been initiated with the purpose of addressing whether radiation treatment with an accelerated partial breast irradiation approach following breast-conserving surgery is an acceptable alternative to treatment with conventional whole breast radiotherapy, Table 10.1 (Polgar et al. 2007; Vicini et al. 2004; Strnad 2004; Orecchia et al. 2003; Coles and Yarnold 2006; Whelan et al. 2006). The basic question of in-breast disease control addressed in each protocol is consistent; however, variations in technique, patient selection and target definition exist, securing the opportunity to refine accelerated partial breast irradiation based on the outcome from

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Table 10.1 Accelerated partial breast irradiation Phase III trials

Trial	Accrual goal	Standard arm	Experimental arm	Total treatment days
NSABP B-39/ RTOG 0413 (Vicini et al. 2004)	4300	WBI 45–50 Gy in 25 fx (optional boost to ≥60 Gy)	1) Multicatheter APBI (34 Gy in 10 fx), or 2) MammoSite APBI (34 Gy in 10 fx), or 3) 3D-CRT APBI (38.5 Gy in 10 fx)	5
GEC-ESTRO (Polgar et al. 2005)	1170	WBI 50–50.4 Gy in 25–28 fx followed by 10 Gy boost	Multicatheter technique. 1) HDR 32 Gy in 8 fx, or 2) HDR 30.3 Gy in 7 fx, or 3) PDR 0.6–0.8 Gy/hr to 50 Gy	2.5–4
EIO ELIOT (Orecchia et al. 2003)	1,200	WBI 50 Gy in 25 fx followed by 10 Gy boost	21 Gy intraoperative with electrons	1
TARGIT (Holmes et al. 2007)	2,200	WBI 50 Gy in 25 fx (optional 10 Gy boost)	20 Gy intraoperative with 50 kV X-rays; Intrabeam applicator	1
United Kingdom IMPORT LOW (Coles and Yarnold 2006)	1,935	WBI 40 Gy in 15 fx	External-beam technique. 1) 36 Gy in 15 fx WBI with simultaneous delivery of 40 Gy in 15 fx to a partial breast target, or 2) 40 Gy in 15 fx to partial breast only	15
Canadian RAPID (Whelan et al. 2006)	2,128	WBI 50 Gy in 25 fx or 42.5 Gy in 16 fx (optional 10 Gy boost)	External-beam technique. 3DCRT APBI (38.5 Gy in 10 fx)	5
NIO Budapest, Hungary (Polgar et al. 2007)	258	WBI 50 Gy in 25 fx	HDR multicatheter 7 × 5.2 Gy, or partial breast electron beam 50 Gy in 25 fx	4 or 25

NSABP, National Surgical Adjuvant Breast and Bowel Project; RTOG, Radiation Therapy Oncology Group; GEC–ESTRO, Groupe European de Curietherapie–European Society for Therapeutic Radiology and Oncology; HDR, high dose rate; PDR, pulsed dose rate; EIO ELIOT, European Institute of Oncology: intraoperative radiotherapy with electrons; TARGIT, targeted intraoperative radiotherapy; IMPORT LOW, intensity modulated and partial organ radiotherapy: low-risk disease; RAPID, randomized trial of accelerated partial breast irradiation; NIO, National Institute of Oncology; fx, fractions; kV, kilovolts; WBI, whole breast irradiation

these protocols. Two of the Phase III trials, both now completed, were conducted at single institutions, while five are multi-institutional.

The first Phase III trial to be initiated was opened in 1998 at the National Institute of Oncology in Budapest, Hungary (Polgar et al. 2007). In this trial, 258 patients were randomized between whole breast irradiation (50 Gy in 25 fractions) and partial breast

irradiation, and treated with either a high dose rate multicatheter technique (7 × 5.2 Gy) or an electron beam to a partial breast target (50 Gy in 25 fractions) for those judged unsuitable for brachytherapy. Inclusion criteria represented a conservative approach and patients were required to meet all of the following criteria: infiltrating ductal carcinoma only, unifocal tumor, wide excision with microscopically negative margins, no evidence of extensive intraductal carcinoma, tumor size ≤ 2 cm, histologic grade 2 or less, cN0, pN0 or pN1mic (single nodal micrometastasis > 0.2 mm and ≤ 2.0 mm). This trial was closed to accrual in 2004, so that the institution could devote all resources towards the European Phase III trial that was to start soon (discussed below). Outcome results from the trial have recently been reported with a median follow up of 66 months. At this follow-up interval, the five-year actuarial rates of local recurrence were 4.7% and 3.4% in the partial breast and whole breast treatment arms, respectively ($p = 0.50$) (Polgar et al. 2007).

In 2000, a second Phase III trial was opened to accrual at the European Institute of Oncology in Milan, Italy. Building on their experiences with both breast conservation therapy and intraoperative electron radiotherapy, the ELIOT (intraoperative radiotherapy with elections) Phase III trial was developed and initiated. With an initial enrollment goal of 1,200 patients, patients have been randomized between standard whole breast irradiation (50 Gy in 25 fractions and 10 Gy tumor bed boost) and intraoperative electron irradiation to a limited, partial breast, field (21 Gy in 1 fraction). Inclusion criteria include infiltrating, unifocal breast disease of tumor size ≤ 2.5 cm. Patients receiving any previous treatment at an outside institution, presence of comorbid factors (i.e., connective tissue disorders) and those patients with tumor locations unsuitable for intraoperative electron treatment delivery were excluded (Orecchia et al. 2003). This trial has now closed after reaching accrual goals, and outcome reports are anxiously awaited.

A second Phase III trial focused on intraoperative adjuvant radiotherapy delivery is presently ongoing. This trial centers on the intraoperative delivery of soft X-rays (50 kV) with the Intrabeam Photon Radiosurgery system (Zeiss Inc., Oberkochen, Germany). Patients in this trial, TARGIT (targeted intraoperative radiotherapy trial), are randomized between standard whole breast irradiation (50 Gy in 25 fractions with optional 10 Gy boost) and intraoperative treatment (20 Gy in one fraction to the surface of the tumor bed). This is a multi-institutional trial with an accrual goal of 2,200 patients. To be considered for trial enrollment, patients must be ≥ 35 years old with operable invasive breast cancer (T1–3, N0–1, M0) suitable for breast conservation surgery. Patients are excluded if the tumor is found to be nonunifocal, if neoadjuvant chemotherapy is used, if positive axillary lymph nodes are documented, or if extensive intraductal and/or invasive lobular cancer is present (Holmes et al. 2007). Accrual continues at 16 institutions located throughout the world.

Two trials were opened in 2006 and continue to accrue patients: the IMPORT LOW (intensity modulated and partial organ radiotherapy for low-risk disease) trial and the Canadian-based RAPID (randomized trial of accelerated partial breast irradiation) trial. The IMPORT LOW trial has been initiated through the Royal Marsden Hospital, United Kingdom (Coles and Yarnold 2006). The trial builds upon their successful experience with accelerated, hypofractionated, whole breast irradiation. Patients are randomized between whole breast irradiation (40 Gy in 15 fractions) and two test arms. The first test arm receives 40 Gy in 15 fractions to a partial breast target only. The second test arm delivers 40 Gy in 15 fractions to a partial breast target, with the remainder of the breast volume receiving a

simultaneous 36 Gy in 15 fractions. Patients acceptable for enrollment in this trial are considered low risk for disease recurrence and are defined as age ≥ 50 years old, primary breast conserving therapy, tumor size < 2 cm, invasive nonlobular histology only, unifocal grade 1 or 2, minimal microscopic margin of resection ≥ 2 mm, no lymph vascular invasion, and axillary node negative (Coles and Yarnold 2006).

The second trial that opened in 2006, the Canadian RAPID trial, utilizes the 3D-conformal external-beam technique as the only partial breast treatment technique. A total of 2,128 patients are to be enrolled and randomized between whole breast irradiation (either 42.5 Gy in 16 fractions or 50 Gy in 25 fractions in the case of large breast size; 10 Gy boost irradiation is permitted with either fractionation scheme) and 3D conformal, external-beam, accelerated partial breast irradiation receiving a total dose of 38.5 in ten fractions delivered twice a day for five days. Eligibility criteria include women who are found to have ductal carcinoma in situ only or invasive breast disease that has been resected with negative margins and with negative axillary node status. Patients are excluded if they are <40 years old, tumor size is ≥ 3 cm, histology is lobular carcinoma only, or if they have multifocal disease (Whelan et al. 2006).

The remaining two large, multi-institutional Phase III clinical trials are also actively accruing; one in Europe and one in the United States. They are both designed to definitively compare APBI with whole breast irradiation in a prospective randomized fashion and to further define the role of APBI in the management of early-stage breast cancer. The European Brachytherapy Breast Cancer GEC-ESTRO (Groupe Europeen de Curietherapie, European Society for Therapeutic Radiology and Oncology) Working Group has opened their multicenter Phase III trial, 16 institutions from several European countries, with a goal of randomizing 1,170 women between standard whole breast irradiation and accelerated partial breast irradiation utilizing multicatheter brachytherapy, see Fig. 10.1 (Strnad 2004). This trial has been statistically designed as a noninferiority trial. With a patient accrual goal of 11,170, the study is powered with a significance level set to 0.05 to detect greater than the set nonrelevant 3% increase in local failure rate above the five-year in-breast failure reference value of 4%. If the local failure rate in the APBI arm does not exceed 7%, then APBI will be judged to be "noninferior" to adjuvant whole breast irradiation.

The National Surgical Adjuvant Breast and Bowl Project (NSABP), jointly with the Radiation Therapy Oncology Group (RTOG), opened a Phase III trial in the United States in May of 2005. This trial will also compare standard whole breast radiotherapy to APBI utilizing multicatheter brachytherapy, MammoSite balloon brachytherapy or the 3D-conformal external-beam technique, see Fig. 10.2 (Vicini et al. 2004.). This trial is statistically designed as a trial of equivalence. Based on previous NSABP trial data, the estimated ten-year cumulative incidence of in-breast recurrence is 6.1% for the population to be included in this trial, and the variance from this result set is an acceptable ± 3%. If the risk of in-breast tumor recurrence following APBI relative to the risk of in-breast tumor recurrence following whole breast irradiation (WBI) is ≥ 1.5, then APBI will be defined as being inferior to WBI. If the risk of in-breast tumor recurrence following APBI relative to the risk of in-breast tumor recurrence following WBI is ≤ 1/1.5 (0.667), then WBI will be defined as being inferior to APBI. If APBI is not inferior to WBI and WBI is not inferior to APBI, then APBI will be defined as being equivalent to WBI.

Initiated in May of 2005, the NSABP B39/ RTOG 0413 trial quickly increased its

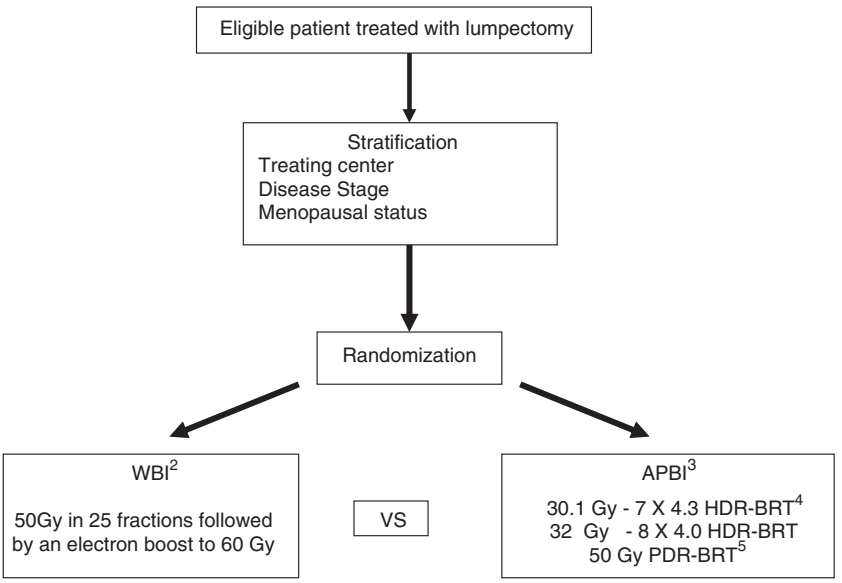

Fig. 10.1 GEC–ESTRO (Vicini et al. 2007) Multicenter Phase III Trial. *1*, Groupe Europeen de Curietherapie European Society for Therapeutic Radiology and Oncology; *2*, whole breast irradiation; *3*, accelerated partial breast irradiation; *4*, high dose rate brachytherapy; *5*, pulsed dose rate brachytherapy

accrual rate, stabilizing at an average rate of approximately 160 patients enrolled per month. As the initial accrual goal of 3,000 total patients was approached, a review of the spectrum of patients enrolled revealed that the majority had lower risk characteristics. The statistical design was based on a spectrum of patients that had been encountered on previous protocols with a mix of both higher- and lower-risk features, yielding an anticipated in-breast failure rate of 6.1%. With a much lower than expected enrollment of patients with higher-risk features, the actual anticipated in-breast failure rate was projected to only be 4.4%. If the trial had completed accrual at 3,000 patients, then statistically the trial would have been severely underpowered, thus leaving the definitive answers sought in jeopardy. As a result, changes to total patient accrual and patient eligibility were proposed to and accepted by the National Cancer Institute that will allow the trial to preserve statistical validity. On 30 December 2006, the total patient accrual goal was increased to 4,300 and the patient eligibility criteria restricted to only include women with higher-risk features: women < 50 years old or women ≥ 50 years old who have infiltrating disease with 1–3 positive nodes and/or estrogen receptor negativity.

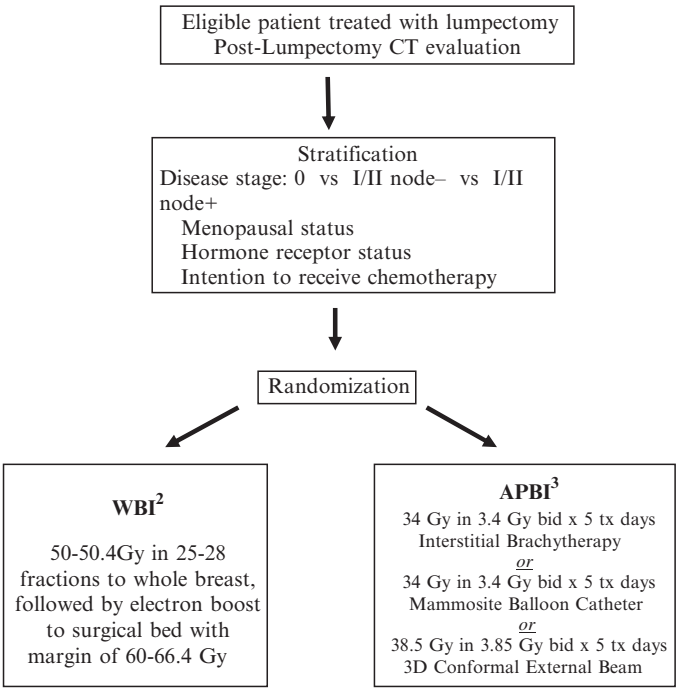

Fig. 10.2 NSABP B39/RTOG 0413 protocol schema. *1*, National Surgical Adjuvant Bresat and Bowel Project B39 & Radiation Therapy Oncology Group 0413; *2*, whole breast irradiation; *3*, accelerated partial breast irradiation

The primary objective in both the European and American Phase III trials is to determine if local control is equivalent between accelerated partial breast irradiation and whole breast irradiation. Secondary objectives are also similar in that acute and late toxicities will be reviewed, cosmetic outcomes compared, quality of life differences evaluated, and failure patterns (including distant metastasis free survival, disease-free survival, and overall survival) assessed. The key components of successful partial breast irradiation are patient selection, target delineation, technique, dosimetry, and quality assurance. These components are clearly outlined in the European Phase III trial (GEC-ESTRO multicenter Phase III trial) and the American Phase III trial (NSABP B-39/RTOG 0413). Upon reviewing these trials, many similarities are appreciated, subtle differences are seen, and both trials are constructed to generate important additional and required information on accelerated partial breast irradiation. The remainder of this chapter is devoted to a review of the key aspects of these two trials, highlighting their similarities and differences.

10.1 Patient Selection and Study Eligibility

Proper conservative patient selection appears to be crucial to the success of APBI, but clear boundaries of inclusion and exclusion criteria are yet to be fully tested. The goal of patient selection is to identify those patients without a significant risk of harboring microscopic disease outside the immediate vicinity of the lumpectomy cavity. Although the patient selection criteria published by the ABS and ASBS appears appropriate, this set of criteria is conservative and may exclude many appropriate patients. The American and European Phase III trials are designed to explore the bounds of patient selection, and both Phase III trials have broadened the inclusion criteria; see Table 10.2. Patients will be stratified at the time of randomization. There will be stratification for disease stage and menopausal status in both trials, with the GEC-ESTRO multicenter Phase III trial additionally stratifying for treatment center, and the NSABP B39/RTOG 0413 additionally stratifying for hormonal receptor status and intent to receive chemotherapy; see Figs. 10.1 and 10.2.

The GEC-ESTRO multicenter Phase III trial only includes patients who are ≥ 40 years old, tumors which are unifocal/unicentric and histopathologically assured to be ≤ 3 cm, all invasive histologies, and ductal carcinoma in situ (DCIS) alone. DCIS lesions are only

Table 10.2 NSABP B39/RTOG 0413 and the GEC-ESTRO Phase III trials: core patient eligibility criteria

	NSABP B39/RTOG 0413[a] **	GEC-ESTRO[b] Multicenter Phase III Trial
Patient age	All ages	≥40 years old
Tumor size	≤3 cm	≤3 cm
Histology	All invasive histologies	All invasive histologies
	Ductal carcinoma in situ	Ductal carcinoma in situ (Van Nuys prognostic index[c] < 8 only)
Margin status	Negative (no tumor extending to inked margin)	Nonlobular invasive histologies > 2 mm
		Invasive lobular carcinoma > 5 mm
		Ductal carcinoma in situ > 5 mm
Node status	pN0–pN1	pN0–pN1mic negative or microscopic involvement only
	0–3 Positive nodes	
	Extracapsular extension negative	

[a] National Surgical Adjuvant Breast and Bowel Project B39 & Radiation Therapy Oncology Group 0413; [b] Groupe Europeen de Curietherapie European Society for Therapeutic Radiology and Oncology; [c] Silverstein et al. (2003);
** This reflects the initial eligibility criteria; restrictions to higher-risk patients were imposed 12/30/06

eligible if they are classified as low or intermediate risk as defined by a Van Nuys Prognostic Index of < 8 (Silverstein 2003). Clear margins of resection of a confirmed 2 mm in any direction must exist, and if the histology is lobular or DCIS, then this margin must be at least 5 mm. For invasive histology, axillary lymph node evaluation should be by dissection with a minimum of six axillary lymph nodes if positive, or by a negative sentinel node, and the resected nodes must be negative or with no greater than microscopic involvement (pN1mi). Additional exclusion criteria include evidence of lymphatic invasion, vascular invasion and/or extensive intraductal component (EIC).

Eligibility criteria for NSABP B39/RTOG 0413 are similar but less restrictive. When initiated, this trial included all ages, unifocal/unicentric tumors that are histopathologically assured to be ≤ 3 cm, and included all invasive histologies and the entire spectrum of ductal carcinoma in situ (DCIS). As noted above, changes in the eligibility criteria were employed to assure statistical validity. Margins of resection must be clear; however, the NSABP definition of clear (no tumor extending to and involving the inked margin) is used for all histologies. Axillary lymph nodes require evaluation in invasive histologies, and either a sentinel node negative or greater than six lymph nodes on dissection is required. Patients must be node negative, or no greater than three positive lymph nodes involved without evidence of extracapsular extension. The presence of lymphatic invasion, vascular invasion or an extensive intraductal component will not be used as exclusion criteria and will not be reported in this trial.

10.2 Target Delineation

As the postlumpectomy radiation target decreases from the whole breast to partial breast, the precision of target delineation becomes increasingly important. A universally accepted target definition has not been established, and the present definitions used vary depending on physician preferences and biases, specific pathologic findings, and the treatment technique used. The partial breast target has most often been defined as a 1–2 cm margin of normal breast tissue beyond the lumpectomy cavity, bounded by breast tissue extent. Although the definitions are within a range of only 1 cm, this can represent a significant volume of breast tissue, and it is the burden of further investigation to identify a universally accepted definition. Visualizing the cavity and clearly delineating the target is essential for APBI to be successful. Originally, target delineation was based on clinical parameters. This can often be misleading and is considered unacceptable by contemporary standards. Both Phase III trials require clear radiographic visualization of the lumpectomy cavity. The GEC-ESTRO multicenter Phase III trial recommends surgical clip placement at time of lumpectomy to accurately define the cavity. If the clips are present, then any form of imaging to locate and visualize the target is acceptable. CT is recommended and preferred, but in cases where surgical clips have not been placed, CT evaluation is mandatory. In the NSABP B39/RTOG 0413 trial, surgical clips are optional

and CT evaluation for cavity localization and target delineation is required in all cases. Any patient where the cavity is not clearly visualized is considered ineligible in both trials.

Once the location of the clinical target volume has been established, the planning target volume (PTV) must then be defined. In the European trial, an elegant approach is used. In this trial, the PTV is defined using a "safety margin" of 2 cm beyond the original tumor. This safety margin is the amount of normal breast tissue beyond the edge of the tumor in all directions that is to be treated. This is the expanded treatment target and is to be restricted to 5 mm below the skin surface and 5 mm above the ribs. This 2 cm treatment distance is covered through a combined surgical margin and designed radiation target; see Fig. 10.3. For instance, a cavity with a medial surgical margin clear by 1 cm, a superior surgical margin clear by 5 mm, and all other surgical margins clear by 2 mm would result in an eccentric PTV covered by a radiation dose that would extend from the cavity edge 1 cm medially, 1.5 cm superiorly, and 1.8 cm in all others directions. This requires thorough pathologic evaluation, documentation and communication. The opportunity to customize the radiation target based on the extent of surgery provides the potential for treating smaller volumes of normal breast tissue.

The American trial uses a simplified approach but must deal with the challenge of equating target coverage goals between three different partial breast treatment techniques. The goal is to treat a 1.5 cm distance from the cavity edge, 5 mm below the skin surface anteriorly, and the chest wall and pectoralis muscles posteriorly; see Fig. 10.4a. In the case of multicatheter brachytherapy, target coverage is achieved with proper catheter placement and radioactive source dwell positioning; see Fig. 10.4b-A. Target coverage with MammoSite

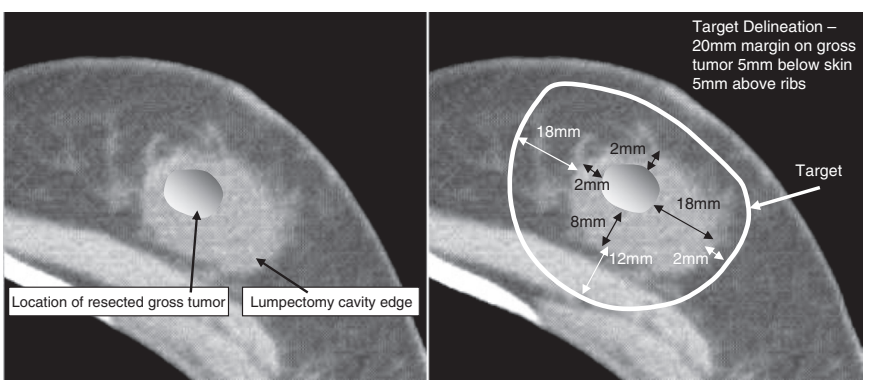

Fig. 10.3 GEC-ESTRO Multicenter Phase III target definition. *GEC-ESTRO*, Groupe Europeen de Curietherapie European Society for Therapeutic Radiology and Oncology

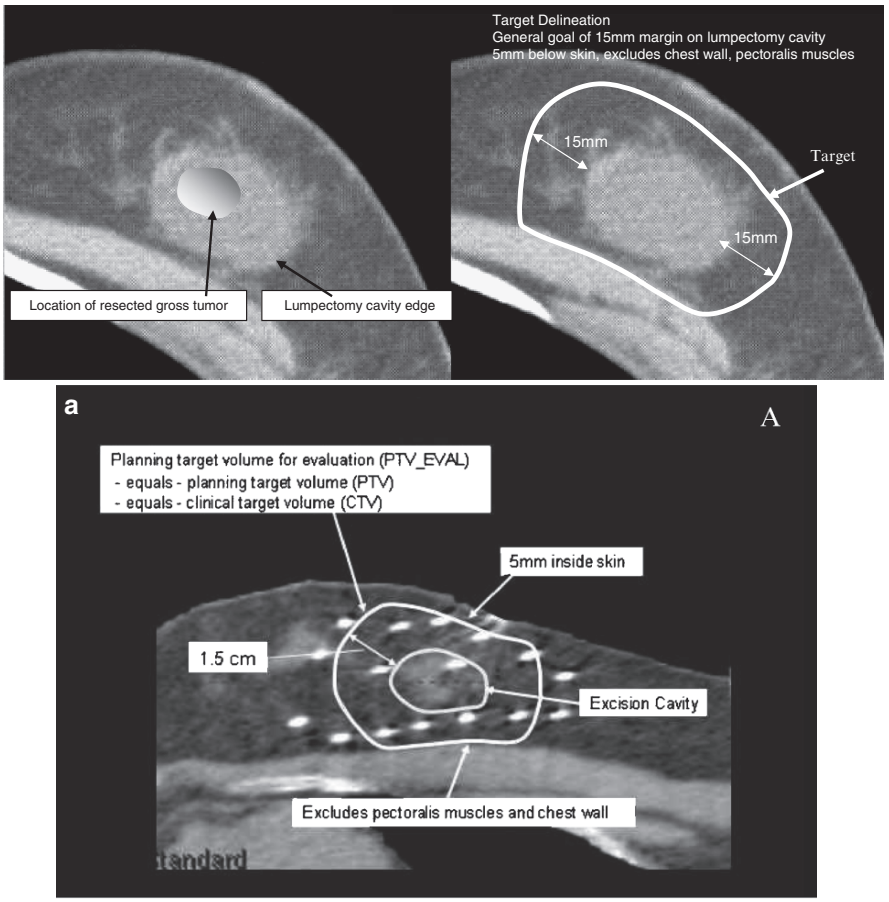

Fig. 10.4 **a** NSABP B39/RTOG 0413 target definition: general goals. *NSABP*, National Surgical Breast and Bowel Project; *RTOG*, Radiation Therapy Oncology Group

brachytherapy is not as adaptable as multicatheter brachytherapy and can only safely treat to a nominal 1 cm distance from the balloon surface; see Fig. 10.4b-B. However, it is known that the actual treatment distance reaches beyond 1 cm due to the stretching, conforming and compacting effect that the inflation of the balloon has on the surrounding targeted breast tissue (Edmundson et al. 2002). This is dependent on the postsurgical size and shape of the lumpectomy cavity and cannot be controlled, but actual treatment distances beyond 1 cm that approach 1.5 cm are expected in the majority of cases. 3D-CRT presents a unique challenge that is not confronted with brachytherapy techniques: the need to account for breathing motion and set-up error. When treating with 3D-CRT, the protocol defines the clinical

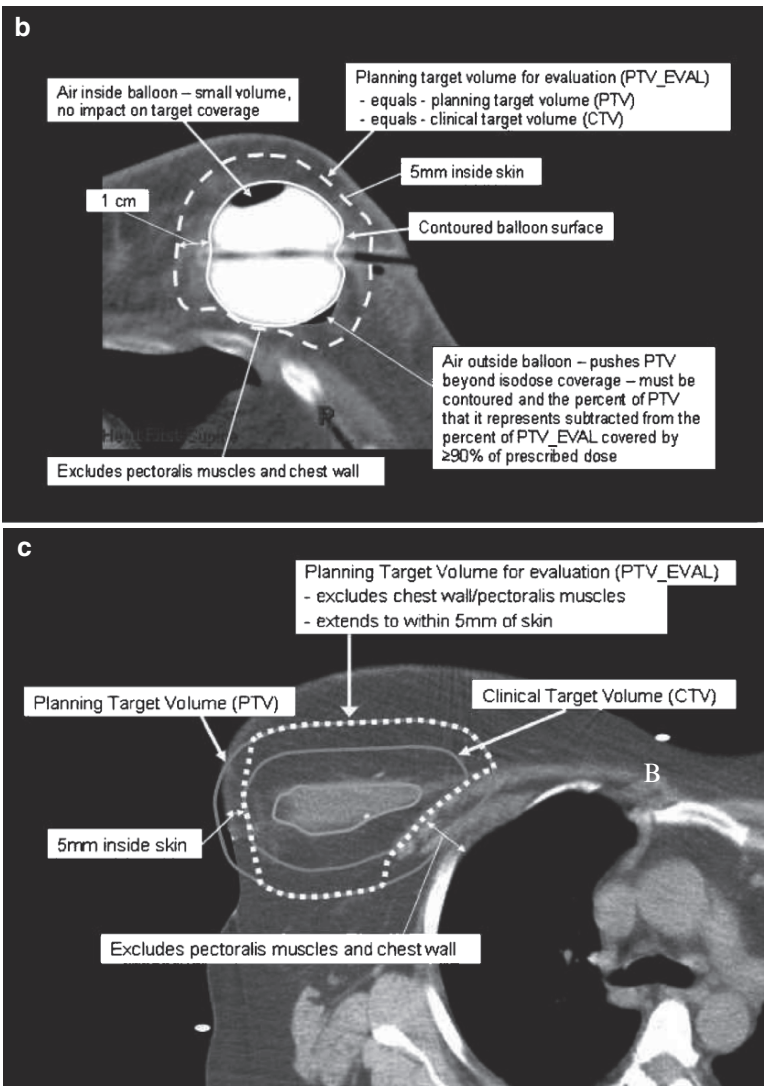

Fig. 10.4 (continued) **b** Target definition specifics for NSABP B39/RTOG0413 treatment techniques. *A*, Multicatheter brachytherapy; *B*, MammoSite brachytherapy; *C*, 3D-conformal external-beam radiotherapy. *NSABP*, National Surgical Breast and Bowel Project; *RTOG*, Radiation Therapy Oncology Group

target volume as a 1.5 cm expansion beyond the cavity edge, but adds an additional 1 cm to define the PTV in order to account for potential variations in target coverage due to breathing motion and set-up error; see Fig. 10.4b-c. This results in a larger volume of breast tissue receiving radiation as compared to brachytherapy techniques.

10.3 Technique and Dosimetry

The largest distinction between NSABP B39/ RTOG 0413 and the GEC-ESTRO multicenter Phase III trial is the technique of delivering partial breast irradiation and the dose delivery schemes used. Intraoperative dose delivery techniques are not included in either study, reflecting the investigators desire for complete pathologic evaluation to assure eligibility prior to protocol enrollment as well as the need for clear target delineation and confirmation of dose delivery to the target. Interstitial multicatheter implants have been the predominant method investigated to date in Europe, and this is the only method of partial breast irradiation that is used in the GEC-ESTRO multicenter Phase III trial. The dose delivery schemes allowed reflect the European experience with APBI. Low dose rate brachytherapy is not allowed; investigators have a choice of high dose rate (HDR) or pulsed dose rate (PDR). If HDR, they can then treat with a total dose of 32 Gy in eight fractions treating twice daily over four days, or a total dose of 30.3 Gy in seven fractions treating twice daily. The PDR dose scheme is 0.6–0.8 Gy/hour to 50 Gy (1 pulse/hour, 24 hours/day). All brachytherapy plans require imaging on a simulator or CT scanner. Dose parameters to assure dose homogeneity and the reporting of the dose distribution characterization are clearly outlined. Dose coverage goals include confirmation that 100% of the prescribed dose covers 90% of the target and that the maximum skin dose is < 70% of the prescribed dose.

Multicatheter brachytherapy is also one of the techniques that can be used for APBI in the NSABP B39/RTOG 0413 trial. Despite the long history of multicatheter brachytherapy within the United States, it is recognized that this approach can be technically challenging and far less appealing to patients due to the appearance and potential pain. In response, the MammoSite Radiation Treatment System was developed in an attempt to simplify breast brachytherapy for both the physician and patient. As a result, the MammoSite Radiation Treatment System has become the dominant method of delivering APBI in the United States and will also be included as an APBI treatment method. Lastly, 3D-CRT will also be included in the American trial. Utilizing CT planning for the design of multiple conformal external beam fields, this technique has been developed to provide a noninvasive method of APBI.

After eligibility determination and enrollment, patients will be randomized between standard whole breast radiotherapy and APBI. If randomized to APBI, the treating physician will choose which APBI technique should be used: multicatheter brachytherapy, MammoSite brachytherapy, or 3D-CRT. The decision will be based on facility preference, patient preference, and technical feasibility for that unique case. In each of the two brachytherapy approaches, the dose delivery scheme has been standardized to a total dose of 34 Gy delivered in ten fractions twice daily over five days. Brachytherapy dose delivery is inherently nonhomogeneous and so an increase in dose is required to properly adjust the homogeneous dose delivery scheme of 3D-CRT to a dose delivery scheme that is radiobiologically equivalent. The dose scheme calculated to provide equivalence and used in the Phase I/II RTOG 0319 protocol is a total dose of 38.5 delivered in ten fractions twice daily over five days. All APBI plans require CT-based planning. Dose parameters to assure dose homogeneity and the reporting of the dose distribution characterization are clearly

outlined. Dose coverage goals include confirmation that 90% of the prescribed dose covers 90% of the target, that skin dose is controlled, and that, when treating with 3D-CRT, the dose to surrounding normal tissues is restricted to defined dose volumes.

10.4 Quality Assurance

Standard breast conservation therapy, where standard WBI follows lumpectomy, has proven to be successful and so it is our responsibility to assure that APBI maintains comparable in-breast control and toxicity rates. The ethical predicate to do no harm is thus very high, and so the quality assurance procedures applied in both trials are stringent. Quality control dominates both trials, preventing unacceptable toxicity and ensuring a meaningful comparison between results. Dosimetric parameters governing target coverage and dose homogeneity are thorough, with details provided within each protocol. In the GEC-ESTRO multicenter Phase III trial, the traditional approach of submitting requested dosimetric information is used and site visits are planned. Measured and calculated parameters are provided for data collection and subsequent review, as well as to compare with clinical outcome.

The quality assurance program of the NSABP B39/RTOG 0413 trial is based on an innovative electronic data submission system developed and managed by the Image-Guided Therapy Center (ITC). The CT data set for each APBI case is submitted to the ITC for review and evaluation, where normal tissue structures and target volumes are checked for accuracy, and the dosimetric target coverage and dose homogeneity are evaluated to assure that guidelines are followed. These cases are reviewed by members of the ITC and the principal investigators of the study. The complexity of the guidelines is recognized and so a system of monitoring was developed to help sites quickly understand all of the details involved. This all starts with a credentialing process that consists of two questionnaires and CT-based test cases. The questionnaires test the facility's capabilities and assess the physician's understanding of the protocol. A CT-based test case is planned and digitally submitted for each APBI technique to be offered at the facility. Once the site is credentialed, accrual may begin. The first case from each facility for any of the three APBI techniques to be offered is to be submitted for rapid review. The rapid review process allows for the case to be evaluated prior to treatment initiation in order to assure that all of the parameters and guidelines have been followed and thus that the patient will be treated according to the protocol. Immediate feedback to the site is important to correct any observed deviation from the protocol. The subsequent four cases from that facility for that technique will be reviewed in a timely (five days) fashion. After the first five cases are complete, all five cases are reviewed and recommendations to either proceed with continued enrollment or to repeat the review process are provided. Once the first five-case review process is cleared, additional reviews of completed cases occur at random. The process is efficient and provides immediate feedback to the treating facility in a timely manner that guarantees that each case will be treated according to the protocol.

10.5 Conclusion

The management of early-stage breast cancer remains an area of active research. Standard breast conservation therapy is now well established, but the logistics of traditional whole breast adjuvant irradiation limit the widespread use of breast conservation. A modern review of clinical and pathological data suggests that adjuvant radiation of the entire breast is unnecessary, and indicates that partial breast therapy may be appropriate, thus opening up the possibilities of APBI. After more than ten years of experience, definitive data regarding the role of APBI have not yet been generated. With two Phase III trials completed and five more underway, there is now the promise that the basic questions surrounding accelerated partial breast irradiation and its comparison to conventional whole breast irradiation will be definitively addressed. Additionally, it is the role of these Phase III trials to further define and potentially expand the patient selection criteria, to elucidate which dosimetric parameters are critical to success, and to clarify which APBI technique is appropriate in which situation.

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The Virginia Commonwealth University Technique of Interstitial Brachytherapy

11

Laurie W. Cuttino and Douglas W. Arthur

11.1 History

The multicatheter interstitial technique was the brachytherapy technique used at the inception of accelerated partial breast irradiation (APBI), and is the technique that has been employed in all mature institutional experiences to date (Vicini et al. 2003a,b; King et al. 2000; Arthur et al. 2003b; Kuske et al. 2004; Cionini et al. 1993; Krishnan et al. 2001; Lawenda et al. 2003; Polgar et al. 2002, 2004; Arthur and Vicini 2005). The multicatheter technique is a universal technique that can be applied in any patient presentation provided the lumpectomy cavity is readily identifiable. Any lumpectomy cavity size, shape and location within the breast can be approached with a multicatheter technique.

While the newer APBI techniques of the MammoSite Radiation Treatment Delivery System (RTS) and three-dimensional conformal radiotherapy (3D-CRT) are gaining in popularity, they are not technically universal and they cannot be used in all patients, as there are boundaries on the use of this device (Baglan et al. 2003; Vicini et al. 2003c; Keisch et al. 2003a,b). The MammoSite RTS requires a close working relationship between the surgeon and radiation oncologist to assure that the lumpectomy cavity creation provides the opportunity for proper balloon catheter placement, allowing for balloon symmetry, inflation size and skin spacing (Arthur and Vicini 2004). In addition, cavity location and small breast size may present as limitations. The 3D-CRT technique faces unique challenges, as appropriate field design may not be possible due to cavity size and cavity location. Additionally, the need and ability to counter breathing motion and daily set-up error is yet to be thoroughly understood.

The only obstacle that multicatheter brachytherapy confronts is the ability to place the catheters in an appropriate distribution to assure dosimetric target coverage, and this obstacle can be overcome with an appropriate approach to catheter placement. The essential

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component in any multicatheter technique is image guidance. Although this can be achieved with ultrasound, stereotactic mammography or computed tomography (CT), CT offers the advantages of being universally applicable and improving the efficiency of the procedure process. This chapter describes the CT image guidance technique used at the Virginia Commonwealth University (Cuttino et al. 2005).

Initially, multicatheter breast brachytherapy was employed as a boost following standard whole breast radiotherapy and performed in the operating room using a freehand insertion technique. Typically performed at the time of lumpectomy, the physician often implanted without final tumor histology, nodal and margin status being available, complicating patient selection and target definition. Catheters were placed by direct visualization of the open lumpectomy cavity and/or with intraoperative fluoroscopic guidance subsequent to closure of the cavity. Postcompletion of the procedure, catheter placement evaluation and dosimetric planning were performed with orthogonal films and two-dimensional treatment planning. Target delineation and dosimetric coverage of the target was difficult, relying heavily on experience and a degree of speculation. Improvements in technique were not possible until three-dimensional brachytherapy planning software became commercially available and CT-based treatment planning became more widely accessible.

To demonstrate the importance of CT-based treatment planning, Vicini et al. reported on a series of eight patients who underwent multicatheter APBI using standard intraoperative cavity insertion techniques (Vicini et al. 1998). Although CT-based treatment planning was not available at this time, a postoperative CT scan was obtained in these eight patients for visual verification that the surgical clips (with an appropriate margin) were within the boundaries of the implant needles. These CT scans were later used for retrospective dosimetric analysis and determination of target coverage through three-dimensional planning recreations of the treatment delivered. Despite meticulous catheter placement technique, without image guidance they found that a significant proportion of the target volume did not receive the intended prescribed dose. They reported that the median proportion of the target volume (the lumpectomy cavity plus a 1 cm margin) receiving the prescribed dose was only 68%. This clearly demonstrates the need for improved catheter placement techniques and verification of dosimetric target coverage prior to treatment initiation.

Image-guided catheter placement is possible using CT, ultrasound, or stereotactic mammography. At VCU, a CT-guided placement technique was developed to assure target coverage and improve procedure efficiency (Cuttino et al. 2005). The procedure is performed entirely in the Radiation Oncology Department's CT-simulation suite, allowing complete procedure-scheduling control and decreasing time away from the department. This technique has proven feasible regardless of breast size, cavity shape, target location, overlying skin thickness, and whether or not surgical clips are present. As the quality of the implant construction is evaluated prior to procedure completion, an inexperienced brachytherapist can reliably obtain excellent target coverage in each case. In contrast to an experienced brachytherapist, those initiating a brachytherapy program may take additional time but will also achieve excellent results. With additional experience, the time needed to complete the procedure quickly decreases. In outline form, the procedure consists of a preprocedure evaluation, patient preparation, stainless steel trocar placement with intermittent CT guidance, flexible catheter exchange, final CT acquisition, and CT-based 3D treatment planning.

11.2 Implantation Technique

11.2.1 Preprocedure Evaluation

To assure an efficient and successful implant, an appropriate flow from consultation (which determines patient eligibility and technical feasibility) to the procedure and treatment delivery should be well planned. At the time of initial consultation, each potential patient undergoes a CT scan in the Radiation Oncology Department to evaluate the lumpectomy cavity and determine patient eligibility and technical feasibility for APBI. This preimplant CT scan is evaluated with 3D planning software, at which time the lumpectomy cavity is delineated. With both a 3D rendering of the cavity with respect to the ipsilateral breast as well as representative transverse slices, an initial design and approach for the multicatheter implantation can be determined that addresses catheter number, number of catheter planes and the optimal direction of placement. This information is printed and available at the time of the procedure and becomes a permanent part of the patient's medical record.

11.2.2 Patient Preparation

The VCU technique focuses on the use of the CT simulator (Fig. 11.1). Although this technique could also be carried out on a diagnostic CT scanner, moving the procedure outside

Fig. 11.1 CT simulator with optional fluoroscopy available

the department compromises the benefits of procedural control and efficiency to some degree. The procedure starts with proper patient positioning. With the patient supine, the goal is to optimize access to the target site to facilitate catheter placement. This is best accomplished with the breast appropriately exposed, which is typically achieved by placing a wedge cushion under the ipsilateral shoulder and torso and tucking the ipsilateral arm low on the patient's side. Once the patient is positioned, a test run through the CT scanner is needed to avoid future CT acquisition difficulties during the procedure.

Proper patient comfort can be achieved with several different methods, and each patient may require a different level of anesthesia. As a result of our early experience with multicatheter breast implantation and the inability to predict a patient's anesthetic requirements, we have opted to incorporate the help of the mobile anesthesia team. This allows us to concentrate on completing the implant accurately and efficiently while the anesthesiologist monitors the patient and concentrates on patient comfort. Through a balance of conscious sedation and local anesthetic, patient comfort is effectively achieved. Once the patient is positioned and IV access established, the patient is prepped and draped in a sterile fashion. Although this is a minor procedure, infection of the breast in the face of APBI can be a difficult entity to manage, and so it is recommended that considerable attention should be paid to ensuring that a sterile technique is used. It is our custom to closely model the sterile technique used in an ambulatory surgical setting, and as a result have avoided any difficulties with breast infection to date.

11.2.3 Catheter Placement

Catheter orientation and direction of placement are individualized for each case in order to minimize the number of catheters needed to achieve target coverage and to optimize patient comfort. The positions of the catheter entrance and exit planes are determined using the 3D rendering and transverse CT images obtained at the time of consultation. These planes are drawn onto the skin with a sterile marking pen (Fig. 11.2). Once the size and location of the implant are delineated, the local anesthetic can be administered. Several degrees of local anesthesia have been applied with success using 2% lidocaine or a mixture of equal parts 2% lidocaine and 0.5% bupivacaine. Sodium bicarbonate can be added to reduce the discomfort that accompanies injection. In all patients, local anesthetic is applied subcutaneously along the skin marks where the catheters will enter and exit (Fig. 11.3). The degree to which anesthetic is needed deep within the implant volume is dependent on the success of the conscious sedation and the patient's pain threshold. Caution must be exercised so as not to exceed recommended limits of lidocaine or, if using increased volumes of diluted lidocaine, not to use excessive volumes that may temporarily distort the geometry of the target, which may complicate treatment planning or require the patient to return on a subsequent day for final CT acquisition and treatment planning. Typically, anesthetic is needed deep within the implant volume in addition to subcutaneous injection. This can be achieved by injecting a controlled volume around the periphery of the implant target, as surgeons do prior to lumpectomy, or with supplementary lidocaine injected through the open-ended trocar if a sensitive area is identified when placing.

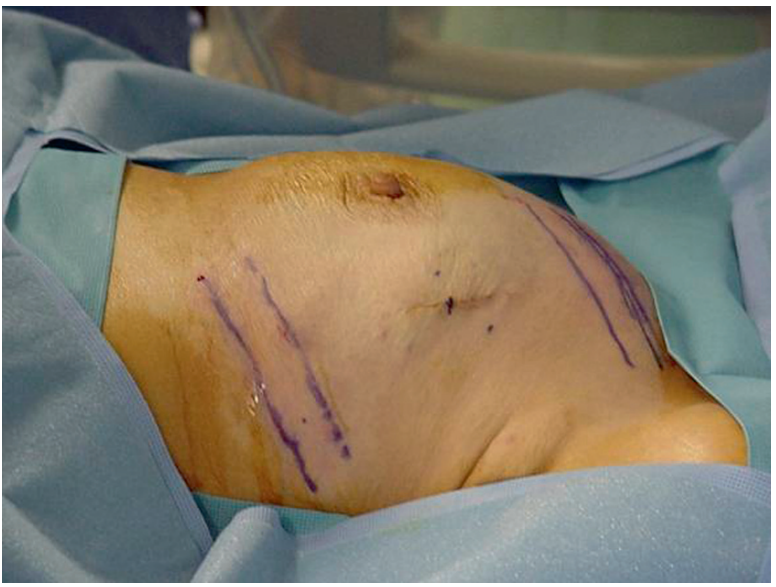

Fig. 11.2 Catheter exit and entrance planes are based on preimplant CT and delineated on the patient's skin for guidance

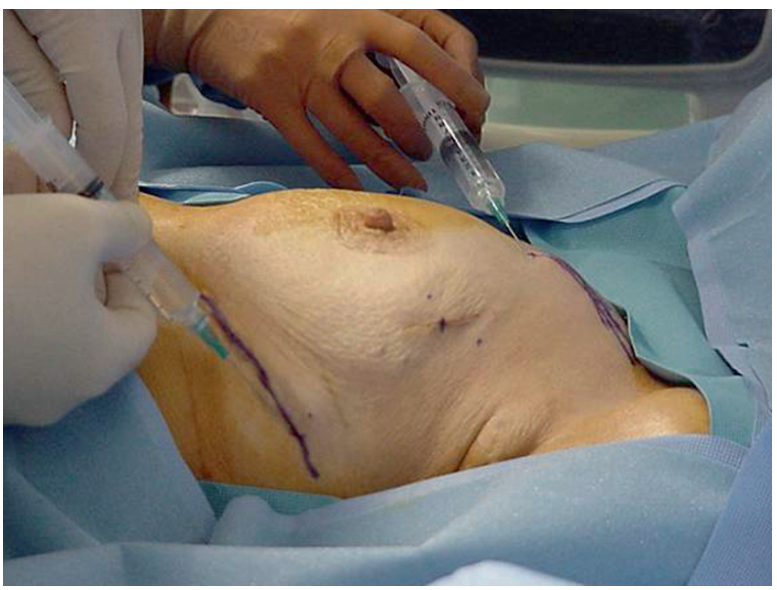

Fig. 11.3 Local anesthetic is placed subcutaneously to assure painless skin entrance and exit. Additional anesthetic is injected within the breast peripherally around the implant target

Standard, commercially available stainless steel trocars with sharply beveled tips are used to establish the tract through the breast tissue prior to exchange with flexible afterloading catheters. For CT visualization and efficiency, all trocars are placed in the breast and positions are adjusted as necessary until the final positions have been verified and approved. Trocars can be cleaned, sterilized, and reused for additional procedures before requiring replacement, but the tips are quickly dulled and single use is recommended. The method of deep catheter placement varies from the method of superficial catheter placement and, provided a few simple guidelines are followed, can help to achieve placement goals. To accurately and safely place a deep catheter, the breast is firmly grasped (compressed) and lifted off the chest wall so that the trocar can be placed deep into the lumpectomy cavity while avoiding chest wall structures (Fig. 11.4). This technique will decrease the breast tissue distance that the trocar will traverse and provide the necessary control over catheter depth and direction. In contrast, superficial catheters require placement so that the catheter-to-skin distance can be controlled along the course of the trocar. This is achieved by "flattening" the skin surface so that the trocar can easily be placed, and a consistent depth along its path is achieved with pressure from a flat hand after the superficial catheter enters past the skin (Fig. 11.5). A standardized approach to trocar placement and implant construction has proven helpful and is based on the experience of the brachytherapist. It is recommended that those that are new to the technique should first place two deep-plane trocars and one superficial trocar as close to the level of the lumpectomy cavity as possible. After these three initial catheters are placed, a CT scan should be obtained for an initial

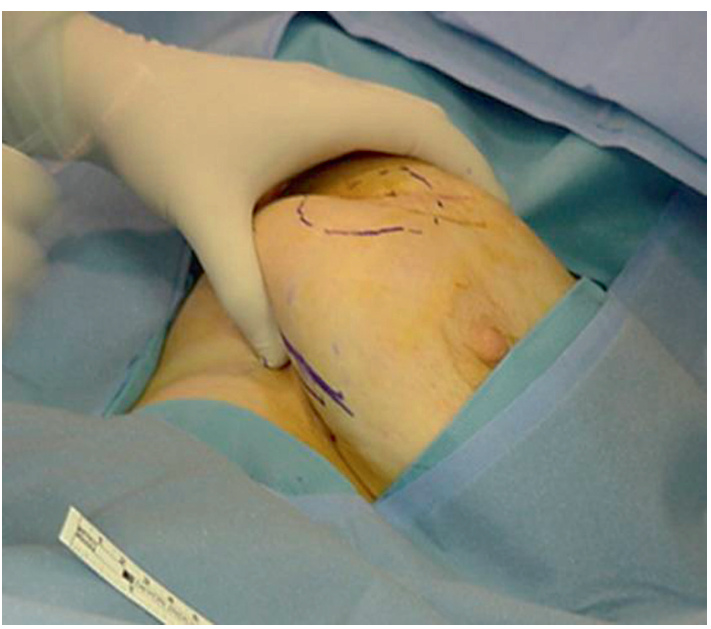

Fig. 11.4 Deep-plane catheter placement. Compression with lift of breast improves control of trocar placement for accurate placement

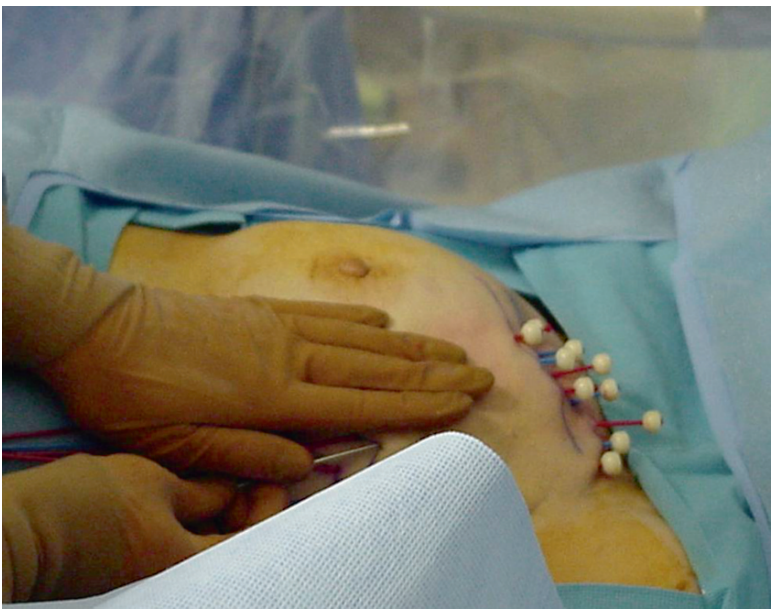

Fig. 11.5 Superficial-plane catheter placement. Utilizing a flat hand, the contour of the breast is controlled to allow the trocar to be placed at a consistent distance from the skin along its course

evaluation of trocar orientation with respect to lumpectomy cavity and target coverage goals. This is a focused CT, scanning over a minimal distance using 5 mm slices for rapid completion. The position of the trocars relative to the lumpectomy cavity is noted. If necessary, these positions can be adjusted. The remaining trocars are then placed to complete the deep and superficial planes, pausing for CT evaluation for guidance as needed. With experience and preprocedure CT evaluation guidance, the need for periodic CT scans can be reduced to first obtaining a CT to evaluate the completed deep plane (Fig. 11.6), adjusting if needed, and then obtaining another after the implant has been completed (Fig. 11.7).

Trocars are placed according to the standard principles of brachytherapy implant design (Zwicker et al. 1999; Zwicker and Schmidt-Ullrich 1995). Generally, trocars should be placed 1.0–1.5 cm apart, and the plane should extend 1.5–2.0 cm beyond the lumpectomy cavity. If the distance between the superficial and deep planes exceeds 3 cm, then a central plane is added. A typical implant will require between 14 and 20 trocars. Once all trocar positions have been reviewed on a CT scan and approved, the trocars are exchanged for flexible afterloading catheters. The catheters are secured in place with a locking collar (Fig. 11.8). Skin sutures are not required. The catheters are then trimmed with sterile scissors at a consistent length. Each catheter length is then carefully measured and recorded. Once all catheters are in their final positions and cut to length, a final CT is performed. Thin metal wires are threaded into each catheter to facilitate tract visualization on the final CT scan. This scan encompasses the entire treated breast in 3 mm slices. Knowing that all treatments will be delivered with the patient in exactly the same position as that in which the final CT was obtained, the position is noted for future reference. The final CT data set

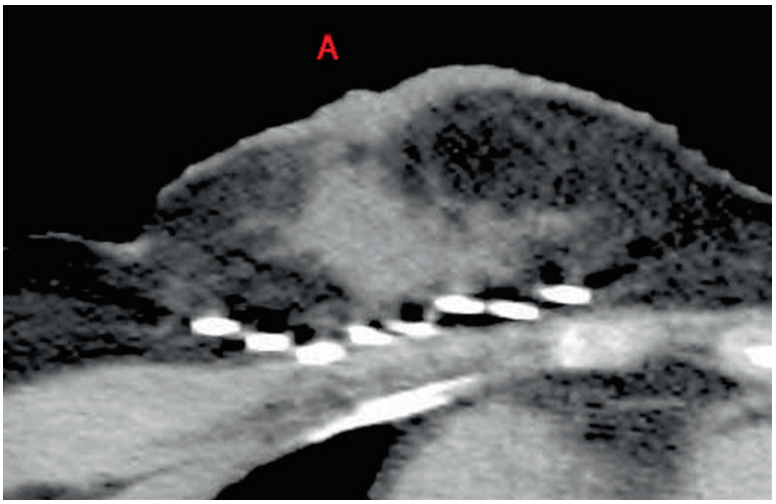

Fig. 11.6 CT scan for initial evaluation of trocar placement. Along the course of the deep-plane trocar, the relationship of the catheter to the chest wall and lumpectomy cavity is noted, and adjustments to trocar location are made as necessary

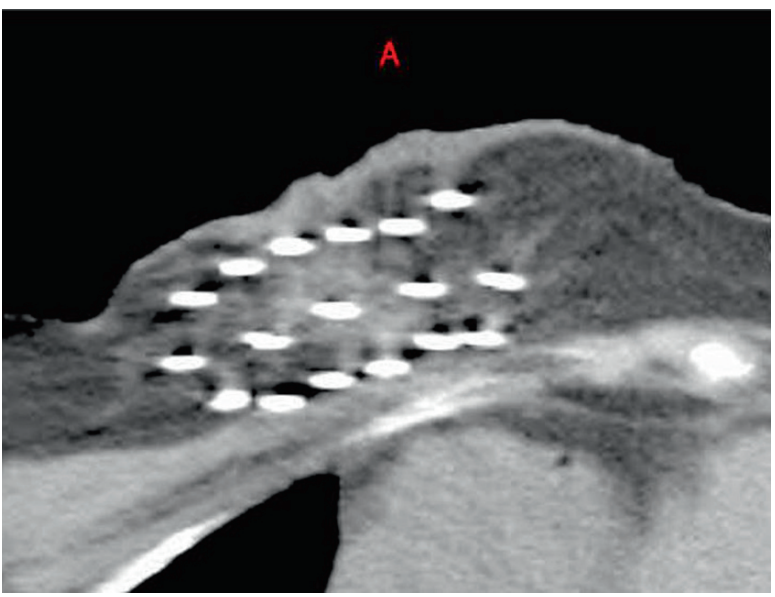

Fig. 11.7 CT scan for evaluation after implant construction for final assessment prior to flexible catheter exchange

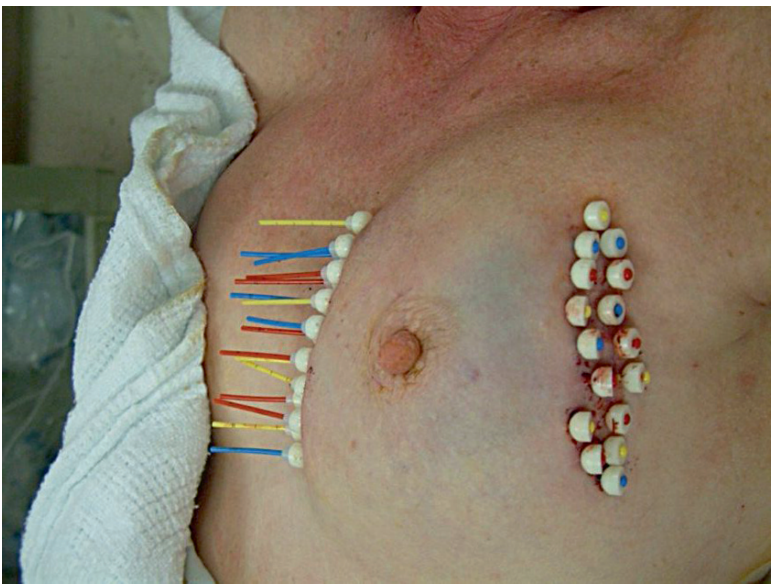

Fig. 11.8 External view of completed implant

is then transferred to the brachytherapy planning software. An experienced radiation oncologist typically requires 2–4 CT scans and completes the entire procedure in less than 60–90 min.

Following the completion of the implant, the patient is observed in the department for approximately 1 h. During that time period, the implant site is cleaned and dressed and instructions for catheter care are reviewed. Patients are discharged home with prescriptions for ten days of an oral antibiotic and pain medication as needed. Pain medication is rarely needed, and if so, rarely for longer than the first 1–2 days. Most discomfort is easily managed with nonsteroidal anti-inflammatory medications.

11.3 Dosimetric Guidelines

Dosimetric guidelines have evolved over time. Using CT-based 3D brachytherapy treatment planning software, target volumes are delineated and dwell times are determined in order to achieve dosimetric coverage goals (Fig. 11.9). Once a planning treatment volume (PTV) defined as the lumpectomy cavity plus a 2.0 cm margin is utilized, our present standard is that the PTV is defined as the lumpectomy cavity expanded by 1.5 cm and bounded by the extent of breast tissue, the chest wall structures, and to within 5 mm of the skin. Dosimetric guidelines that direct dwell positions and times are influenced by the goals of target coverage and dose homogeneity. Although 100% of the dose delivered to 100% of the target is the goal, this is difficult to achieve due to inherent errors in lumpectomy cavity

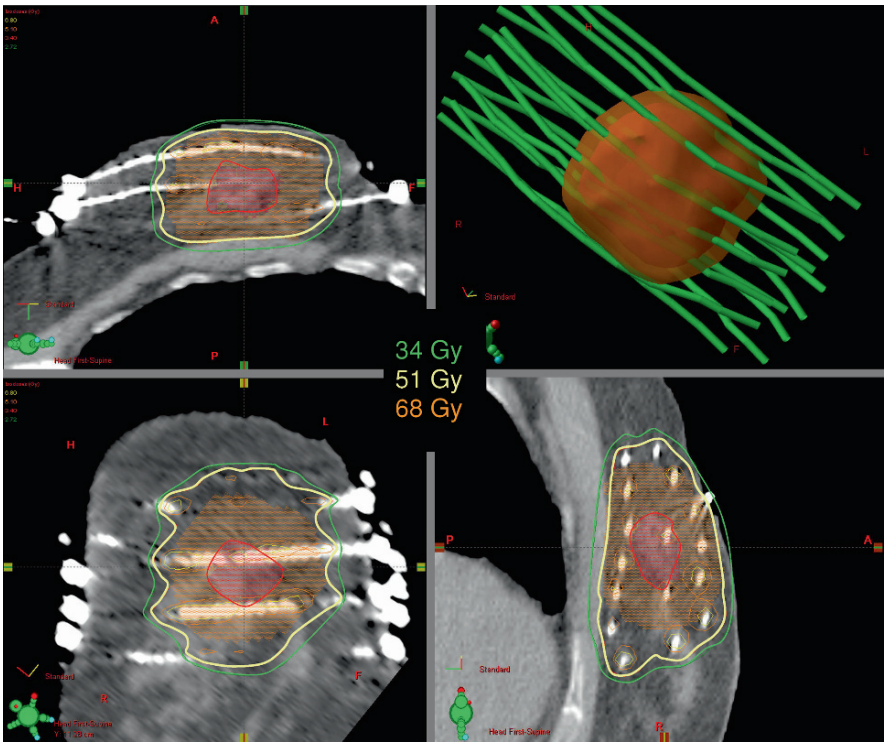

Fig. 11.9 CT-based 3D treatment planning for multicatheter interstitial brachytherapy. The lumpectomy cavity is outlined in *red*, and the target is shaded in *orange* (target is defined as the lumpectomy cavity with a 1.5 cm expansion)

and PTV delineation. A realistic goal is that 90% of the target receiving 90% of the dose is acceptable, and >95% of the target receiving >95% of the dose is desirable. Most current protocols require that 90% of the PTV receives at least 90% of the prescription dose.

The dose distribution of a multicatheter implant has been associated with toxicity, illustrating the importance of dose homogeneity (Arthur et al. 2003a; Wazer et al. 2002). For this reason, two absolute dose–volume histogram (DVH) parameters have been established that are reproducibly achievable with proper catheter placement. These parameters include a DVH analysis evaluating how much tissue receives doses exceeding 100% of the prescription dose, and a dose homogeneity index (DHI) defined as the ratio of the absolute volume of tissue receiving 150% of the prescription dose to the volume receiving 100% (V_{150}/V_{100}) (Wu et al. 1988). The first parameter is based on limiting the volume of breast tissue receiving 200% of the prescribed dose (V_{200}) and limiting the volume of breast tissue receiving 150% of the prescribed dose (V_{150}). With a prescription dose of 34 Gy in ten fractions, this represents the volumes of tissue receiving fraction sizes of 6.8 Gy and 5.1 Gy, respectively. As these parameters are dependent on data utilizing a specific prescription dose, 34 Gy delivered in ten fractions, it is unclear as to how this should be extrapolated to alternative dose fractionation schemes. However, when using 34 Gy in ten fractions, it is

recommended that V_{200} should not exceed 20 cc, and that V_{150} should not exceed 70 cc. However, with proper technique, these parameters are easily respected, with the V_{200} rarely exceeding 15 cc and the V_{150} rarely exceeding 50 cc. DHI is an associated entity that reflects the relative sizes of the areas receiving a dose greater than the prescribed dose. To avoid toxicity, the DHI should exceed 0.75.

Low dose rate brachytherapy for breast cancer has been abandoned at VCU in favor of high dose rate (HDR) brachytherapy, as this offers improved control of dosimetry, radiation safety, and the ability to deliver treatment as an outpatient. Standard treatment at VCU now consists of treating with a commercially available HDR brachytherapy remote afterloader equipped with a ^{192}Ir HDR source and utilizing a treatment scheme comprising 3.4 Gy fractions given twice daily over five days, for a total prescription dose of 34 Gy.

11.4 Results

Although target coverage and dose homogeneity can be improved through CT-based treatment planning software and dose optimization, there is a limited degree of dose improvement that can be achieved with 3D treatment planning. The manipulation of dwell position and times cannot compensate for poor implant geometry, thus stressing the importance of image-guided catheter placement and immediate postoperative CT imaging.

To evaluate the feasibility and dosimetric reliability of the VCU CT-guided method of catheter insertion, a dosimetric comparison of APBI cases completed before and after the initiation of the CT-guided method was performed (Cuttino et al. 2005). In this evaluation, 29 patients were identified as having the necessary data available for complete comparison. All patients presented with early-stage invasive breast cancer, were treated with high dose rate partial breast brachytherapy following lumpectomy, and had CT scans of the brachytherapy implant available for analysis. All 29 patients were treated to 34 Gy delivered in ten twice-daily fractions over five days. The daily interfraction interval was 6 h. Treatment was performed using an HDR afterloading device with a 5–10 Ci ^{192}Ir source. Catheter placement was completed by one of two approaches.

From 1995 to 2000, 15 patients had catheters placed in the operating room, where catheters were placed with traditional methods based on clinical evaluation and aided by orthogonal fluoroscopic films. Dosimetric planning was two dimensional and derived from orthogonal films of the implant obtained the day following catheter placement. Homogeneity and target coverage were evaluated at the coronal and cross-sectional views at the center of the implant as well as at representative cross-sectional views above and below the center of the implant. The dosimetric goal was to deliver 100% of the prescription dose to the lumpectomy cavity, as delineated by the six surgical clips, plus a 2 cm margin in all directions, restricted by the anatomical extent of breast tissue. From 2000 to 2002, 14 patients had catheters placed with CT guidance in our department, and dosimetry planned with 3D planning software (Brachyvision Planning System, Varian, Palo Alto, CA, USA) based on the final CT scan obtained at the completion of the procedure. The lumpectomy cavity was first contoured, and this volume was expanded by 1 cm and designated the planning target volume 1 cm (PTV1 cm). Similarly, planning target volume 2 cm (PTV2 cm) was

delineated by expanding the contour of the lumpectomy cavity by 2 cm. These volume expansions were bounded by the extent of the breast tissue. Three dosimetric goals were established to evaluate overall implant quality as represented by target coverage and dose homogeneity. Target coverage was determined as being acceptable if 100% of the prescribed dose was delivered to >95% of PTV 1 cm, and >90% of the dose was delivered to > 90% of PTV2. Dose homogeneity was deemed acceptable if the dose homogeneity index (DHI) was >0.75. In this study, DHI was defined as $(V_{150}\%–V_{100}\%)/V_{100}\%$, where $V_{100}\%$ is the absolute volume of tissue receiving 100% of the prescribed dose, and $V_{150}\%$ is the volume receiving 150% of the dose.

To facilitate a comparison between the two catheter placement techniques, it was necessary to retrospectively reconstruct the implants from the traditional catheter placement cohort within the 3D treatment planning software. The postcatheter placement CT scans from this cohort were entered into the 3D planning system, and the volumes for the lumpectomy cavity, PTV1 cm and PTV2 cm were delineated. Dose–volume histograms analyzing dose delivered to normal breast tissue volumes were generated for the purpose of comparing the quality of implants constructed with the traditional catheter placement technique and the CT-guided catheter placement technique. The percentage of the PTV1 cm volume covered with 100% of the dose, the percentage of the PTV2 cm volume covered with 90% of the dose, and the DHI were generated for each case and compared.

In this comparison, the CT-guided technique proved superior in achieving an optimized brachytherapy implant according to the parameters used in this study. When the CT-guided technique was used, the percentage of implant cases that satisfied all three dosimetric goals increased from 42% to 93%. Mean dose coverage, defined as the percentage of PTV2 cm receiving 90% of the prescribed dose, increased from 89% to 95% ($p = 0.007$), and the mean DHI increased from 0.77 to 0.82 with the new technique ($p < 0.005$). There was a correlation between the improved dosimetry achieved and the cosmetic outcome and risk of fat necrosis in this small group of patients, but the findings need confirmation in a larger group of patients for the dosimetric improvements to definitively translate into clinical outcome.

11.5 Conclusion

Multicatheter interstitial brachytherapy was the original technique used to deliver APBI and the technique with which the concept of APBI was initiated. Although newer techniques (MammoSite RTS and 3D-conformal radiation therapy) have now been established with the promise of simplifying APBI, these techniques have not yet been shown to be as universal as the multicatheter approach. Among all of the APBI techniques reported, the multicatheter technique continues to be the most adaptable and universally applicable approach, and can be applied regardless of breast size or lumpectomy cavity size, shape or location. If a treatment center desires the ability to offer APBI to any patient that is eligible, then the ability to appropriately construct a multicatheter implant continues to be necessary—even if this option is held in reserve until the newer forms of APBI have been shown to be unable to meet dosimetric goals of target coverage.

The VCU method of CT-guided catheter insertion ensures that optimal implant geometry is confirmed at the completion of the procedure, therefore avoiding the need for additional time in the department and minimizing the time to treatment initiation. Through a direct dosimetric comparison, the VCU method of CT-guided catheter insertion has been shown to improve target coverage and dose homogeneity as compared to non-image-guided techniques (Cuttino et al. 2005). With the assurance of optimal catheter placement, subsequent catheter manipulation is avoided, and the need to rely on creative dwell time manipulation due to suboptimal catheter placement is minimized. The CT-guided catheter placement technique is a reliable method of implant construction resulting in reproducible target coverage and dose homogeneity that promises to translate into improved disease control and reduced toxicity.

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Accelerated Partial Breast Irradiation: The William Beaumont Hospital Technique of Interstitial Brachytherapy

12

Peter Y. Chen

12.1 History

Tremendous strides in the treatment of early-stage breast cancer have resulted in the implementation of breast-conservation therapy (BCT). Indeed, the most important impetus has been Class I evidence based on randomized Phase III clinical trials which have proven the equivalency of BCT compared to mastectomy with published results from selected trials out beyond 20 years (Arriagada et al. 1996; Blichert-Toft et al. 1992; Fisher et al. 2002; Jacobson et al. 1995; VanDongen et al. 2000; Veronesi et al. 2002). Additionally, a meta-analysis of randomized trials involving over 7,000 patients treated with breast-conserving surgery with or without adjuvant breast radiation therapy (RT) has shown a significant 19% reduction in local recurrence in favor of adjuvant RT (Clarke et al. 2005):

Although these data are compelling, only 10–60% of women who are candidates for BCT actually receive such treatment (Morrow et al. 2001; Nattinger et al. 2000). Many factors contribute to this underutilization of BCT, including travel distance to a radiation therapy center, toxicity, time, and inconvenience of delivering 6–7 weeks of daily external-beam radiation therapy (EBRT) to the whole breast following partial mastectomy.

In an effort to circumvent the obstacles to BCT, provide the breast-conserving option to more women, and improve the quality of life of breast cancer patients treated with breast conservation, in March 1993 we began a pilot study to treat selected early-stage breast cancer patients with accelerated partial breast irradiation (APBI) using an interstitial low-dose rate (LDR) brachytherapy implant with ^{125}I sources as the sole RT modality (Vicini et al. 1997, 1999). In June 1995, a parallel trial of outpatient high dose rate (HDR) brachytherapy as the single source of RT was begun (Baglan et al. 2001). Both the LDR and HDR treatment regimens have the same eligibility criteria of age >40, infiltrating ductal carcinoma ≤3 cm in maximal dimension, negative surgical margins ≥2 mm, and surgically staged axilla with ≤3 positive nodes (in 1997, this latter criterion was changed

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to negative nodes based upon the documented survival benefit of regional along with local RT plus systemic adjuvant therapy in node-positive women after mastectomy compared to chemotherapy alone from the Danish and British Columbia trials) (Overgaard et al. 1997, 1999; Ragaz et al. 1997).

All patients underwent a partial mastectomy to achieve negative surgical margins of at least 2 mm along with axillary nodal sampling; if adequate margins were not attained at the initial operative procedure, re-excision of the partial mastectomy site/cavity was undertaken.

12.2 Physics

The dosimetric goal of the brachytherapy implantation, whether LDR or HDR, was to cover the partial mastectomy excisional cavity with a 1–2 cm margin of normal surrounding breast tissue. This was done with the interstitial implant placed via either an open or a closed cavity technique, the former at the time of initial surgical excision or at re-excision, and the latter in a delayed fashion after all histopathological findings were confirmed, with a brachytherapy implant done under a second, separate anesthesia using CT and ultrasonic guidance.

12.2.1 LDR Dosimetry

The LDR implants were template guided to enable interstitial placement of one, two, or three planes of afterloading catheters to be loaded with ^{125}I seeds. Dosimetric planning consisted of placement of multiple inert sources into each afterloading catheter to assist in 3D geometric localization. Anterior/posterior and lateral radiographs were taken at the time of simulation for computerized reconstruction. The Nucletron Planning System (Nucletron BV, Veenendaal, The Netherlands) was used for isodose calculations. With the use of ^{125}I seeds, the dose homogeneity of the implant volume was optimized by adjusting the spacing of seeds in the individual catheters (Clarke et al. 1989). A dose of 50 Gy delivered at 0.52 Gy h^{-1} was prescribed as a minimum dose within the prescription volume; a dose constraint of having no contiguous area (i.e., confluent around multiple catheters) of 150% of the prescribed dose in the central plane isodose distribution was instituted for every LDR patient (Vicini et al. 1997).

No ^{125}I sources were placed in the proximal or distal ends of the afterloading catheters, beyond the treatment volume. The radioactive seeds were placed a minimum of 5–7 mm from the skin surface in order to prevent excessive dose from being delivered to the skin.

12.2.2 HDR Dosimetry

From 1995 to 2005, all HDR brachytherapy implants were template-based, using afterloading needles that were not replaced by flexible catheters. Thus, the implantation geometry for this decade of HDR breast brachytherapy was rigid, with consistently straight paths

within the volume of interest allowing for better uniformity of radioactive source distribution and resultant dosimetry. A postimplant CT scan was obtained to verify adequate coverage of the target volume and provide 3D dose–volume data.

At the time of simulation, orthogonal plain films were taken to allow for 3D reconstruction of the needle implant. The target volume was the partial mastectomy excisional cavity plus a 1–2 cm margin of normal breast tissue. The Nucletron Planning System generated the treatment plan and isodose distribution. With a standard step size of 5 mm, the HDR Iridium-192 source dwell times were optimized to deliver a uniform dose throughout the target volume. Due to the straight needle geometry of each implant with the consistently equal spacing between the interstitial needles afforded by the rigid template, a library of standard isodose plans was available to provide a very close approximation to the formally planned dosimetric distribution for each individual patient. Avoidance of excessive skin dose was achieved by restricting the closest dwell position to the skin at a distance of 5 mm. The target volume received a minimum dose of either 32 Gy in eight fractions of 4 Gy delivered twice daily (BID) over four consecutive days or 34 Gy in 10 fractions of 3.4 Gy BID over 5 days. The minimal interfraction time interval was 6 h.

Since the fall of 2005, the interstitial needles have been replaced with flexible catheters. These interstitial HDR afterloading catheters continue to be placed with the guidance of a rigid template in the same manner as when the needles remained within the treated breast for APBI.

12.3 Implantation Technique

Since April 1995, all such interstitial brachytherapy implants for breast APBI have been done via the HDR technique. Those implants done via LDR followed a similar placement technique except for replacement of the interstitial needles by afterloading catheters, which were later loaded with ^{125}I sources.

The procedure of needle placement is performed with either an open cavity at the time of partial mastectomy/axillary nodal procedure or as a closed cavity with a preplanning CT scan done prior to the time of interstitial needle placement. Whether open or closed cavity, the goal is to implant a volume 1–2 cm beyond the excised cavity; although such margins are achievable in width, length, cephalad and caudad directions, these margins may not be attained in the deep and superficial planes (this due to the anatomical limits of the chest wall and overlying skin).

The desired minimum distance from the superficial plane of needles to the skin is 5 mm; if the implanted superficial row is less than this distance, that plane of needles may not be required. The underlying chest wall limits the deep plane; indeed, if the excised cavity is down to the pectoralis fascia, the deep plane of needles may need to be inserted just deep to the musculature. If, in the judgment of both the surgeon and the radiation oncologist, the deep plane of needles may not adequately cover the deep extent of the target volume, the interstitial procedure may need to be aborted.

All implants with the interstitial needle technique at Beaumont are template-based (Fig. 12.1). The templates have 13 needle apertures in the two-plane system: seven deep and six superficial, with an intraplane distance of 1.4 cm and a spacing of 1.5 cm between needles.

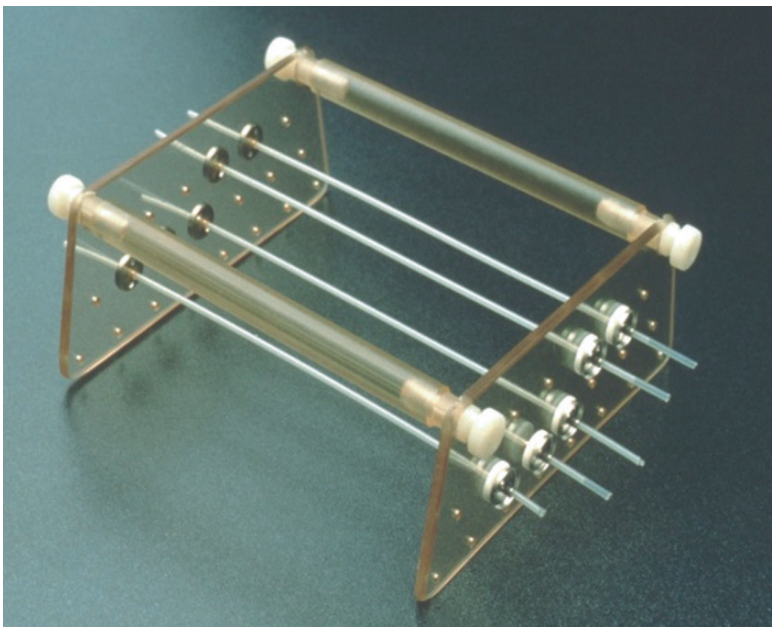

Fig. 12.1 Brachytherapy template

The three-plane HDR template consists of seven deep, six intermediate and five superficial needle apertures arranged in the same distance configuration as the two-plane system. For generous anatomical breasts, Beaumont has a specially machined template with interplane and needle distances of 2 cm configured in three planes with 18 apertures.

12.3.1 Open Cavity Technique

After the axillary procedure and the partial mastectomy (or re-excision) are completed, the reference radiation oncologist enters the operative suite. The radiation oncology service ascertains that surgical clips are placed to delineate all borders of the excisional cavity. These are placed to delineate the cephalad, caudad, medial, lateral, as well as the anterior and posterior margins. With a surgical marking pen, the margins of the excised cavity are projected onto the skin and outlined.

Based on the location and depth of the partial mastectomy site, a rigid two- or three-plane breast brachytherapy template is selected; connecting bars of variable length (i.e., 12, 14, 16, 18, or 20 cm) are chosen. Once fastened together, the template with connecting bars is orientated along the excisional site to assure adequate coverage width-, length-, and depth-wise.

Due to the just completed axillary procedure, the template is angled away from the apex of the axilla to avoid placing undue pressure/trauma on the axillary incisional wound.

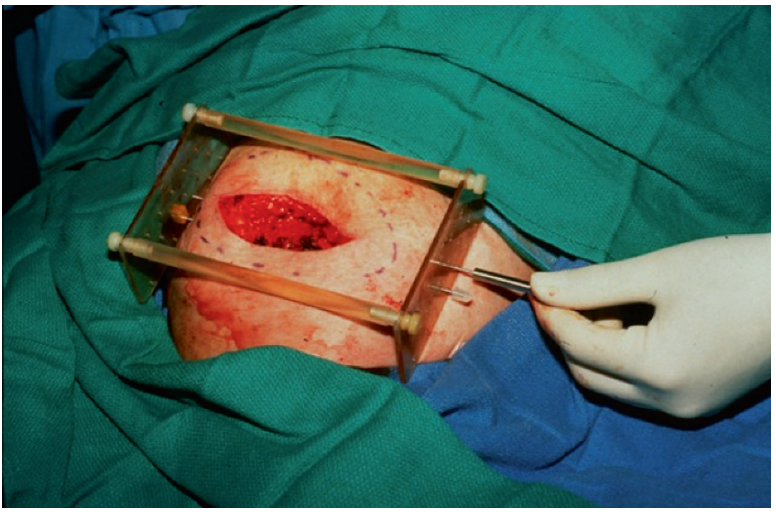

Fig. 12.2 Central needles placed first

The deep row of needles is inserted with the central-most needle placed first to allow for proper alignment of the template in relation to the excised cavity (Fig. 12.2). The direction of needle insertion into the breast tissue is done from lateral to medial, such that the open end of the needle is situated laterally; this allows for the connection of the HDR transfer cable in a lateral position to minimize the in-transit dose to the patient without the transfer cables crossing over the patient.

Once the template is confirmed as being anchored by the central-most needle for adequate coverage of the cavity in all directions, the remainder of the deep-plane needles are placed. Upon completion of the deep row of needles, the surgeon may desire to close the cavity before the intermediate and superficial planes of needles are inserted. If this is the case, the placement of a single central intermediate as well as superficial plane needle is undertaken to assure that the entire depth of the cavity is appropriately covered and visualized before surgical closure of the cavity is achieved. Indeed, if the superficial breast tissue is noted to be beyond the extent of what the template would cover, slight manual compression of the overlying breast may then allow for adequate coverage of the more superficial tissue.

If cavity closure is to be done upon completion of the interstitial procedure, the intermediate and superficial plane needles are inserted under direct visualization to assure adequate cavity coverage. As each needle is inserted, a yellow H clamp is placed on the sharp needle end to secure it in place. The open needle end is closed off with a sterilization cap (Fig. 12.3). Since the fall of 2005, the interstitial needles have been replaced with flexible afterloading HDR catheters; after all of the needles have been extracted the template is removed, leaving the HDR interstitial catheters in place within the excisional cavity.

Prior to the closure of the wound cavity, the surgeon is requested to confirm the appropriateness of the interstitial HDR needle placement; if any needles need repositioning, this can be accomplished prior to the closure of the cavity. DuoDerm pads are applied to relieve

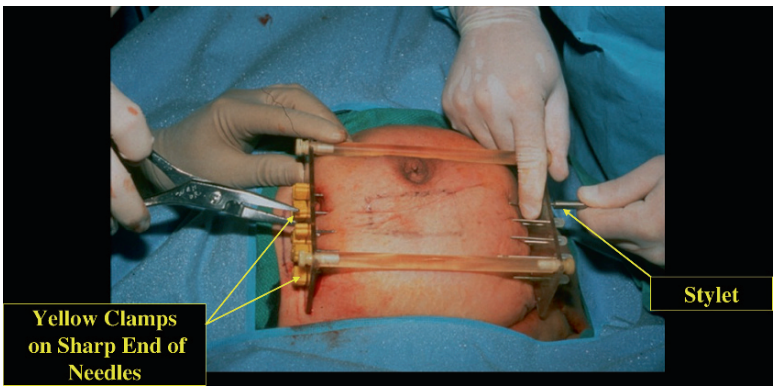

Fig. 12.3 Open cavity technique: securing the implant

any pressure points caused by the template; bacitracin is applied at each of the entrance/exit skin sites of the interstitial needles. Again, since 2005, the interstitial needles have been replaced with afterloading catheters that remain in place within and about the excisional cavity with the removal of the template; thus, the need for the DuoDerm pads has presently been obviated.

Two ABD pads are used to dress the site of interstitial implantation. A specialized Velcro-type brassiere is given to the patient for use during the duration of the interstitial application. A course of antimicrobial therapy is maintained for the duration of the brachytherapy treatments and for 7–10 days afterwards.

A dosimetric simulation and a postimplant CT scan are obtained within 24–48 h. The surgical specimens are sent to pathology, and a minimum turnaround time of 48 h is needed to adequately process the submitted specimens. If not all of the pathological criteria are met for treatment via interstitial brachytherapy alone, the interstitial brachytherapy is converted to boost irradiation (at 400 cGy × three or 340 cGy × four fractions), which is then followed by a course of whole breast EBRT.

12.3.2 Closed Cavity Technique

Any potential candidate for a closed cavity interstitial implantation must have had cavity delineating clips placed at the time of the partial mastectomy/ipsilateral axillary procedure. Seven to ten days after the lumpectomy, the patient returns for a preplanning CT scan with fiducial markers placed on the breast of interest (Fig. 12.4). Radio-opaque angiographic catheters are placed and taped longitudinally onto the involved breast. A central catheter is placed along the nipple, followed by a series of such markers spaced 2 cm apart to cover the full extent of the breast, both medially and laterally (Fig. 12.4).

A free-breathing CT scan is obtained for the purposes of delineating the clinical target volume as well as preplanning with a virtual template. Upon the completion of the CT

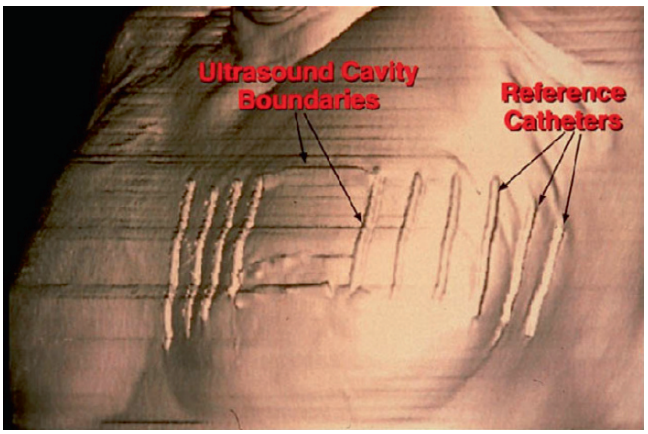

Fig. 12.4 Closed cavity technique

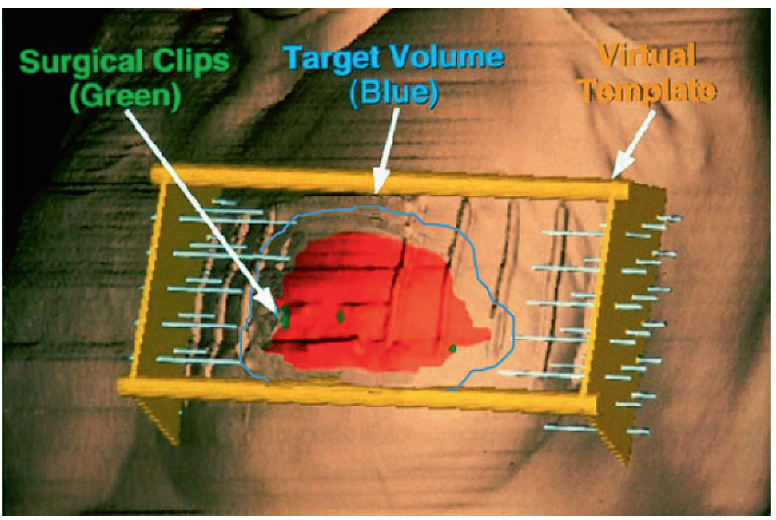

Fig. 12.5 Closed cavity technique II

scan, the excisional cavity is outlined on all of the CT slices. Once this information has been inputted, a virtual simulation is undertaken. Through the efforts of the dosimetry staff, a virtual template with virtual needles of an appropriate length are used to simulate the forthcoming implantation (Fig. 12.5) (Vicini et al. 1998).

On anatomically rendered 3D reconstructed images of the skin surface, the orientation of the virtual template as well as the entry and exit points of the virtual needles are well defined in relation to the previously placed radio-opaque fiducial markers; various parameters needed to perform the implantation are obtained, such as the angulation of the

template, the length of the needles required, and the depth needed to adequately cover the deep margin of the excisional/partial mastectomy cavity (Fig. 12.5).

Paper printouts are made of the virtual treatment plan(s), including the anatomical data of entry/exit sites of the needles, template angulation, and depth of the implant required; all of these are taken to the operating room on the day of closed cavity placement.

Under general anesthesia, the implantation is undertaken with the guidance of the virtual treatment plan along with real-time intraoperative ultrasound (DeBiose et al. 1997). Based upon the parameters of the virtual plan, the appropriate template (whether two or three planes) and the proper length of needles are selected. Longitudinal stippled marks are placed on the skin of the breast of interest to correspond to the prior fiducial opaque markers used in preplanning. An intraoperative ultrasound unit is then employed to delineate the margins of the excisional cavity, and this is outlined on the skin with a surgical marker pen.

Using the technical details of the virtual plan, the template is orientated across the involved breast via the longitudinal marks on the breast skin corresponding to the virtual fiducial markers. Via ultrasound guidance, each needle of the deep plane is inserted under constant ultrasound viewing to assure adequate depth of placement and that the needles are implanted no deeper than the chest wall (ideally, ultrasound can monitor the entire placement of each deep-plane needle in relation to the underlying chest wall and lung) (Fig. 12.6). The remaining deep-plane needles are then placed, again under the guidance of ultrasound.

One intermediate and one superficial plane needle are inserted under constant ultrasound viewing to assure that the depth of the cavity is adequately covered by the three planes; if the superficial tissues are not appropriately implanted, manual compression of the breast may be required to achieve adequate needle placement. The remaining intermediate and superficial plane needles are then implanted. As in the open cavity procedure, once each needle is inserted, a yellow H clamp is placed on the sharp needle end and a

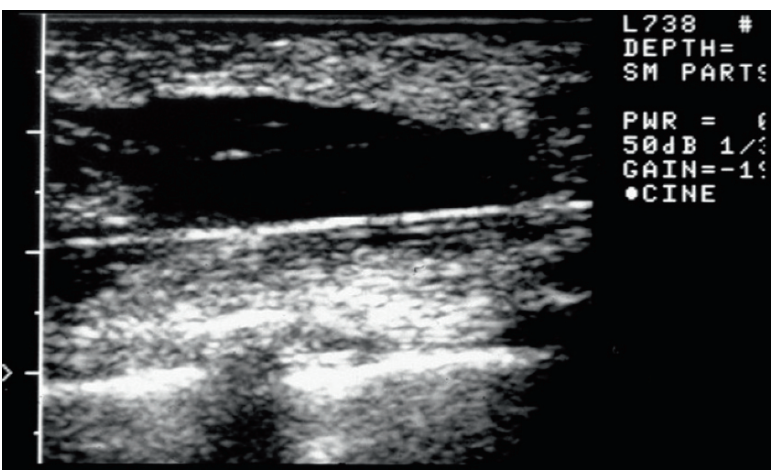

Fig. 12.6 Intraoperative ultrasound image of interstitial needle placement

sterilization cap is placed on the open needle end. Just prior to terminating the procedure, the completed interstitial implant is viewed one more time with the ultrasound unit.

As in the open technique, DuoDerm is applied to relieve any pressure points caused by the template. Bacitracin is applied at each of the entry/exit sites of the HDR needles. The template/implant is dressed with two ABD pads. The patient will remain on antibiotics for the duration of the implantation, as well as an additional 7–10 days post implant. Since 2005, as described for the open interstitial implantation technique, the needles have been replaced with afterloading interstitial catheters; once these are confirmed as being clinically appropriate for coverage of the excisional cavity, the template is removed, serving only to guide the equidistant spacing of the catheters.

As with the open technique, a postimplantation CT scan is obtained at 24–48 h to assure adequate coverage of the clinical/planning target volume (Fig. 12.7). Final dosimetric calculations with optimization may be performed on the CT-acquired data set. The patient is instructed not to shower, engage in contact sports, or sit in the front seat of the car when she travels in for the twice-daily treatments.

The dose prescription for the HDR breast protocol is either 400 cGy per fraction × 8, for a total of 3,200 cGy prescribed to the clinical target volume given on a twice-daily schedule with a minimal interfraction time interval of 6 h, or 340 cGy twice daily × 10, for a total dose of 3,400 cGy. Prior to each fraction, needle positions (or presently catheter positions) are reverified in reference to the skin; this is done by caliper measurements of the template-to-skin distances of each needle or via a Mylar overlay that delineates the entrance point of each needle through the skin.

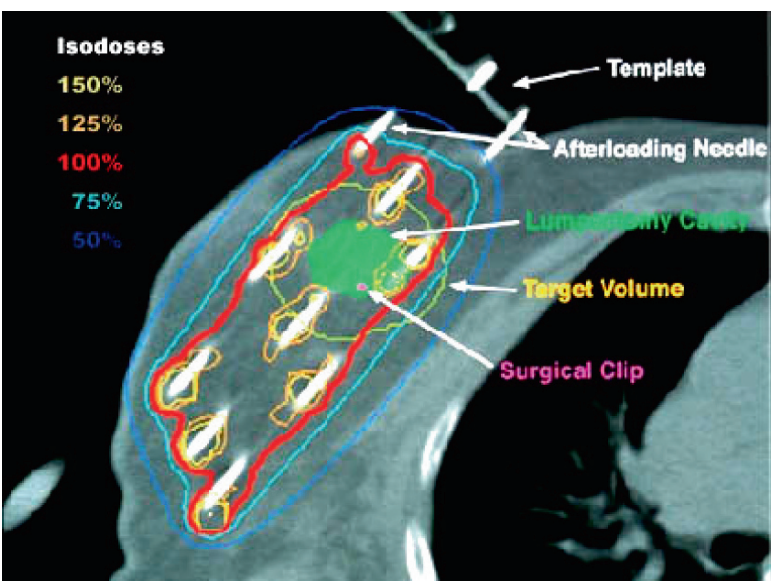

Fig. 12.7 Dosimetric treatment planning

12.4 Clinical Results

Between 1993 and 2007, 209 patients have been treated at William Beaumont Hospital with interstitial brachytherapy alone (120 with LDR, 79 with HDR rigid needles, and 10 with HDR flexible catheters). With a median follow-up of 9.4 years for the cohort of 209 patients, the five-year actuarial local recurrence rate is 1.6%, with an elsewhere breast failure rate of 0.6%. To compare potential outcome differences based upon the volume of breast irradiated, the initial 199 interstitial brachytherapy alone patients were matched with 199 patients treated with whole breast radiation therapy. The match criteria included tumor size, lymph node status, patient age, margins of excision, estrogen receptor status, and use of tamoxifen. The rate of local recurrence was not statistically different between the two groups, with whole breast radiotherapy demonstrating a recurrence rate of 1% vs. those receiving partial breast irradiation, with a similar 1% risk of local recurrence ($P = 0.65$). Also, no significant statistical differences were seen in the five-year actuarial cause-specific survival of 97% vs. 97% ($P = 0.34$) and overall survival 93% vs. 87% ($P = 0.23$) between whole breast and accelerated partial breast alone treated patients (Vicini et al. 2003).

The same cohort of 199 patients treated with APBI via either LDR or HDR interstitial brachytherapy underwent an updated matched-pair analysis with ten-year follow-up (Antonucci et al. 2008). Each APBI patient was matched with one whole breast irradiated patient treated at William Beaumont Hospital, the latter drawn from a database of 1,503 patients consecutively given whole breast treatment along with cone-down boost radiation therapy over 6.5 weeks to a median dose to the tumor bed of 60 Gy. Match criteria were identical to those used in the earlier analysis. With a median follow-up of 9.6 years (range 0.3–13.6) for surviving patients, no statistically significant differences in the ten-year actuarial rates of ipsilateral breast tumor recurrence or regional failure were found between whole breast irradiation and APBI patients (4% [95% CI 1.3–6.7%] vs. 5% [95% CI 1.5–8.5%], $p = 0.48$; and 0.5% [95% CI 0–1.5%] vs. 1.6% [95% CI 0–3.4%], $p = 0.3$, respectively). There were no statistically significant differences in ten-year actuarial rates of distant metastases (9% [95% CI 4.9–13.1%] vs. 5% [95% CI 1.7–8.3%], $p = 0.08$). Additionally, there was no difference in cause-specific survival (93% [95% CI 89.3–96.7%] vs. 95% [95% CI 91.3–98.7%] $p = 0.34$) or contralateral breast failure (8% [95% CI 4.1–11.9%] vs. 4% [95% CI 0.5–7.5%], $p = 0.19$) between whole breast treated and APBI patients, respectively.

In defining the type of ipsilateral breast tumor recurrence, clinical information has been supplemented by molecular clonality assays to delineate the nature of the breast recurrence on a subcellular basis. Clinically, ipsilateral breast recurrences are classified by the location in relation to the original index lesion; that is, a true recurrence/marginal miss within or immediately adjacent to the primary index tumor site or an elsewhere failure localized several centimeters from the primary site (Recht et al. 1985). However, such clinical estimates of the type of recurrence are inaccurate in more than one-third of all cases. Molecular clonality studies can subtype ipsilateral breast recurrences into those clonally related (true recurrence/marginal miss) or clonally distinct (elsewhere) (Goldstein et al. 2005).

Of the ipsilateral breast recurrences in the 199 APBI patients, eight such recurrences were noted, of which five were true recurrences of the primary tumor and three were new distinct cancers. Four contralateral breast failures were documented. In combining all of the matched-pair patients from this updated analysis ($n = 398$), a Cox proportional hazard regression was performed to analyze the breast failures. No use of adjuvant tamoxifen, decreasing age, and estrogen receptor negative status were statistically significantly associated with the development of any ipsilateral breast tumor recurrence ($p = 0.04$, 0.01, and 0.05, respectively). Decreasing age was associated with the development of clonally distinct failures ($p = 0.02$), and lack of tamoxifen use was associated with contralateral breast failures ($p = 0.02$). Elective treatment of the whole breast had no additional benefit in reducing the rate of development of any type of ipsilateral breast tumor recurrence (Antonucci et al. 2008).

In terms of toxicities and cosmetic outcome, the toxicity parameters examined in our cohort of patients included breast edema, erythema, fibrosis, hyperpigmentation, hypopigmentation, breast pain, telangiectasia, and fat necrosis. Toxicities were graded using the Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group (ECOG) late radiation morbidity scoring scheme (Cox et al. 1995) for skin, subcutaneous tissues, pain, radiation dermatitis, and dermatology/skin from the Common Toxicity Criteria (CTC) version 3.0. As per the guidelines of CTC version 3, toxicities were graded using the acute/chronic radiation morbidity scale: Grade 0 = no observable radiation effects; Grade I = mild radiation effects; Grade II = moderate radiation effects; Grade III = severe radiation effects. Cosmetic evaluation was based on standards as set forth by the Harvard criteria (Rose et al. 1989). An excellent score was given when the treated breast looked essentially the same as the contralateral untreated breast. A good score was assigned for minimal but identifiable radiation effects of the treated breast. Scoring a fair result meant that significant radiation effects were readily observable. A poor score was used for severe sequelae of normal tissue.

Breast toxicities including pain, edema, erythema, and hyperpigmentation were almost always mild and diminished over time (Table 12.1). Breast pain diminished from 27% at six months to 8% at five years. Breast edema decreased from 50% (six months) to 12%

Table 12.1 Toxicities with resolution or stabilization over time with interstitial catheter needle-based brachytherapy

Interval	≤6 months n = 165			2 years n = 128			FU > 5 years n = 79		
Toxicity/grade	I	II	III	I	II	III	I	II	III
Breast pain (%)	27	0	0	13	1	0	8	1	0
Breast edema (%)	50	1	0	12	0	0	6	1	0
Erythema (%)	35	1	0	11	0	0	11	0	0
Hyperpigmentation (%)	67	2	0	39	2	0	37	0	0
Fibrosis (%)	22	1	0	48	2	1	46	5	1
Hypopigmentation (%)	18	0	0	34	0	0	38	0	0

I, mild; *II*, moderate; *III*, severe

(two years) to 6% (five years). Similarly, erythema demonstrated the following pattern: 35% at six months to 11% at two years with stabilization thereafter. Hyperpigmentation followed a similar downward trend in frequency: 67% (six months) to 37% (five years). All of these were statistically analyzed by Pearson's chi-square analysis and were not found to be chance occurrences (Chen et al. 2006).

Breast sequelae that increased until the two-year mark and stabilized included breast fibrosis (22% to 48% to 46% at six months, two years and five years, respectively) and hypopigmentation (18%, 34%, and 38% at six months, two years and five years). Note that any slight degree of periscar induration was scored as mild fibrosis regardless of whether postsurgical changes may have contributed or not. Nearly all of the pigmentary changes, whether hyper- or hypopigmentation, were mild and pinpoint rather than diffuse and corresponded to the sites where the LDR catheters or HDR needles had been placed. Likewise, chi-square analysis supported the contention that these trends were real. The time-course trend of hypopigmentation followed that of fibrosis, with an increase in frequency out to two years and then a plateau occurring as time progressed further. However, beyond five years, breast fibrosis increased in frequency such that by the median follow-up interval of 9.4 years for the cohort of 209 patients, 53% of patients had palpable periscar induration of any degree, the majority of which was mild (Chen, 2009).

Fat necrosis and telangiectasia increased with the passage of time out to five years, although fat necrosis remained relatively low in frequency (9% at two years; 11% at five years). The median time to occurrence of fat necrosis was 5.5 years (range of 0.25–8.2 years). Telangiectasias, nearly all of which were grade I, were evenly distributed between the LDR and HDR treatment modalities at five years, being 34% for both LDR and HDR ($p = 0.983$). At the latest update with a median follow-up interval of nearly 9.5 years, fat necrosis remains at 11%, with mild telangiectasias having plateaued at 34%. Thus, although the previously reported trend of increasing percentages of both fat necrosis and telangiectasia occurs up to the five-year mark, beyond five years, both fat necrosis and telangiectasia stabilize with the passage of time, similar to the trend demonstrated by the other morbidities listed in Table 12.1, but with a delayed time to stabilization beyond the five-year mark (Chen et al. 2006, 2009).

Good to excellent cosmetic outcomes were noted in 95–99% of patients depending on the time point of assessment (Table 12.2). Assessment at six months revealed a large percentage of good scores (85%). However, between six months and two years, the incidence of excellent scores increased from 10% to 29%. Comparison of cosmetic results at

Table 12.2 Cosmesis: cosmetic outcome over time with APBI

≤6 months *n* = 165			2 years *n* = 128			≥5 years *n* = 79		
Excellent	**Good**	**Fair**	**Excellent**	**Good**	**Fair**	**Excellent**	**Good**	**Fair**
10%	85%	1%	29%	68%	2%	33%	66%	1%
Total 95%			Total 97%			Total 99%		

Total percentage equals excellent and good outcomes combined
4% and 1% of unreported cosmesis for ≤6 months and 2 years, respectively

the two- and five-year intervals demonstrated a stabilization of scores, with the percentage of excellent scores increasing at five years. This trend of increasing excellent cosmetic outcome is seen out towards the 9.5-year mark, with the percentage of excellent cosmesis up to 35% from the 33% seen at five years (Chen et al. 2009). Throughout all time points of cosmetic assessment, the percentage of good to excellent scores never fell below 95%.

No statistical difference was noted in the incidence/severity of any toxicity or cosmetic outcome with the following parameters: tamoxifen, type of brachytherapy (LDR vs. HDR), and tumor size (T1 vs. T2) (Pearson's chi square analysis). However, the incidence of breast erythema at two and five years and the incidence of delayed infections were higher for those patients receiving chemotherapy (p = 0.015, 0.016, and 0.003, respectively) (Chen et al. 2006).

12.5 Future Directions

Patients undergoing HDR interstitial brachytherapy for APBI have been done with a fixed rigid template system with interstitial needles in place. Beaumont has now transitioned (since 2005) to replacing the rigid needle system with flexible afterloading silastic catheters. Although the advantage of the template-based needle system was that a library of dosimetric plans could be quickly calculated for each patient, the flexible catheter system should allow for more individualization of the implanted volume such that the goal of such a multicatheter system would be more optimal dosimetric coverage of the target volume while sparing normal surrounding tissues that need not be in the high-dose volume.

Additionally, the brachytherapy interstitial implantation technique is operator dependent in that the skill required for such implant placement can be a technically demanding clinical challenge. Thus, less complex systems that yield the same dosimetric dose coverage include 3D conformal external-beam radiotherapy (3D CRT), delivered in five days or within in ten days (Baglan et al. 2003; Vicini et al. 2003; Formenti et al. 2002, 2004). Such new conformal technology has been investigated by the RTOG in a Phase I/II trial (RTOG 0319) on partial breast irradiation using 3D CRT, which completed accrual in late April 2004. Another means of brachytherapy that is technically less demanding than that of the multicatheter/needle technique is the MammoSite RTS applicator. Approved by the US Food and Drug Administration (FDA) in May 2002, this allows dosimetric coverage of the target volume of interest via a balloon catheter system that can be placed in either an open or a closed cavity setting (Keisch et al. 2003) Other balloon catheter systems such as the Contura MLB system have been developed with multiple offset lumens to allow for customized dosimetry in order to minimize the dose to the overlying skin as well as the underlying chestwall/ribs.

Although the MammoSite RTS applicator and 3D CRT are now available, the experience of Beaumont Hospital would suggest that not all patients would qualify for each of these latter two newer techniques. Depending on the cavity location, cavity configuration, cavity to skin distance, and the relationship of the cavity to the chest wall, there will still be patients who will benefit from the more customized/individualized dosimetry afforded

by multicatheter/multineedle-type interstitial implantations. Thus, although the operator independence of the newer techniques including the MammoSite and 3D CRT treatments is quite appealing, we at Beaumont believe that there is still a role for the multicatheter system based on an individualized case-by-case assessment.

Currently, our policy is that any patient who is eligible for partial breast irradiation is considered for entry into the randomized Phase III clinical trial sponsored jointly by the National Surgical Adjuvant Breast Project and RTOG (NSABP B-39/RTOG 0413 trial) to provide definitive Class I evidence as to the efficacy of APBI compared with that of whole breast irradiation, with the realization that accrual has been closed as of 18 April 2007 to low-risk patients, including patients ≥50 y/o with DCIS regardless of hormone receptor status and patients with invasive breast cancer meeting all of the following criteria: ≥50 y/o, node negative and hormone receptor positive. Thus, high-risk patients, including those with up to three positive axillary nodes, continue to be considered for entry into this randomized clinical study (RTOG 2007). Each patient considered for partial breast irradiation is simulated with virtual CT to assess the most feasible means of delivering APBI. If not eligible for the RTOG 0413/NSABP B-39 trial, assessment is made for the possible placement of a balloon catheter applicator (either the MammoSite RTS applicator or the Contura device) or for treatment via 3D conformal external-beam irradiation via 4–5 noncoplanar fields as per the guidelines set forth by either the American Brachytherapy Society (ABS) (Arthur et al. 2003) or those of the American Society of Breast Surgeons (American Society of Breast Surgeons 2005; http://www.breastsurgeons.org/apbi.shtml).

In conclusion, many single-institutional series employing various PBI techniques including interstitial multicatheter techniques and one published randomized trial from Hungary have demonstrated the efficacy and safety of PBI. These selected patients, treated with PBI in accelerated fractionation schemes, have shown control rates equal to or exceeding those of conventional external beam tangential irradiation delivered over 6.5 weeks. The latest technologies in both brachytherapy and external beam (3DCRT, IGRT) offer the tools to achieve PBI. Several Phase III trials, including the NSABP B-39/RTOG 0413 protocol, are in progress to provide definitive randomized Phase III evidence for the efficacy of PBI compared with whole breast therapy. Beyond clinical efficacy, genetic clonality studies will enable more definitive molecular fingerprinting of failure patterns of PBI (Vicini et al. 2005).

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Brachytherapy Techniques: The Arizona Approach

13

Robert R. Kuske

13.1 Introduction: A 17-Year Historical Perspective on the Evolution of Accelerated Partial Breast Irradiation

"If only you listen to your patients, new ideas will emerge" (Bernard Aron, MD, 1984). In October 1991, a woman from Venezuela with a stage T2 N0 M0 ductal carcinoma of the right supra-areolar breast presented before the multidisciplinary Conference and Clinic at the Ochsner Clinic in New Orleans. Aware that there were alternatives to mastectomy, and that there were no linear accelerators in her home country at the time within 8 h of her home, she insisted that her physician consultants come up with an alternative to the standard 6.5 weeks of external-beam breast irradiation. The surgical oncologist at the Clinic, John Bolton, MD, suggested that we consider offering her wide-volume brachytherapy, similar to how we had been treating soft tissue sarcomas. He noted that the published local control rates with single-plane implants covering the surgical bed with generous margins were excellent, allowing limb preservation (Brennan et al. 1987). Our soft tissue sarcoma brachytherapy results in New Orleans mirrored those published in this series. The low dose rate (LDR) brachytherapy was designed to deliver a radiation dose capable of sterilizing microscopic extensions of sarcoma beyond the surgical margin, which was microscopically clear. An inherently hotter central dose inside the peripheral envelope offers a built-in boost dose to the surface area at the greatest risk for tumor cells after surgical excision. There was an added benefit that was particularly attractive to this patient: since the treatment is delivered with LDR iridium seeds within plastic catheters imbedded directly within the tissues that harbored the malignancy, a tumoricidal dose could be given much more quickly, in 3–5 days instead of the conventional 6–7 weeks of external-beam whole breast irradiation.

Since the margins were not evaluated in Venezuela, Dr. Bolton took her back to surgery for a re-excision in New Orleans, and an axillary dissection for staging was also planned. In the operating room, with the wound open and exposed, multiple brachytherapy catheters

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were inserted, with 1.5 cm between each catheter within a plane and approximately 2.5 cm between the two planes, superficial and deep. The goal was to bracket the lumpectomy cavity between two planes of catheters and extend them peripherally 2 cm beyond the surgical edge in all directions, except superficially and deep, where the skin and pectoralis major fascia provide anatomic limits to coverage.

The prescription dose was 45 Gy in three days with LDR seeds. The seeds were loaded 1 cm deep to the skin surface on both the proximal and distal sides of the implant. This is in contrast to modern three-dimensional treatment planning, where the seed positions in the *z*-plane are placed from each edge of the target volume. The seed strength was 1 mCi per seed, and the dose was delivered in three days as an inpatient with shielding and radiation precautions. On day 4, the patient was on a plane back to Venezuela, her family, and her business. Photos of her breast immediately after catheter removal and at the time of her ten-year follow-up are shown in Fig. 13.1.

The breast team at the Ochsner Clinic was encouraged by the results in this patient, the first patient treated with early-stage (T2 N0) breast cancer, negative surgical margins, and wide-volume breast brachytherapy alone in the modern era. Her breast maintained its softness over time, in contrast to the woody induration seen with brachytherapy as a boost. The cosmetic outcome was favorable.

We submitted a Phase II trial to the Institutional Review Board (IRB). Initially, 50 patients were to be treated by interstitial brachytherapy, followed by a two-year hiatus to

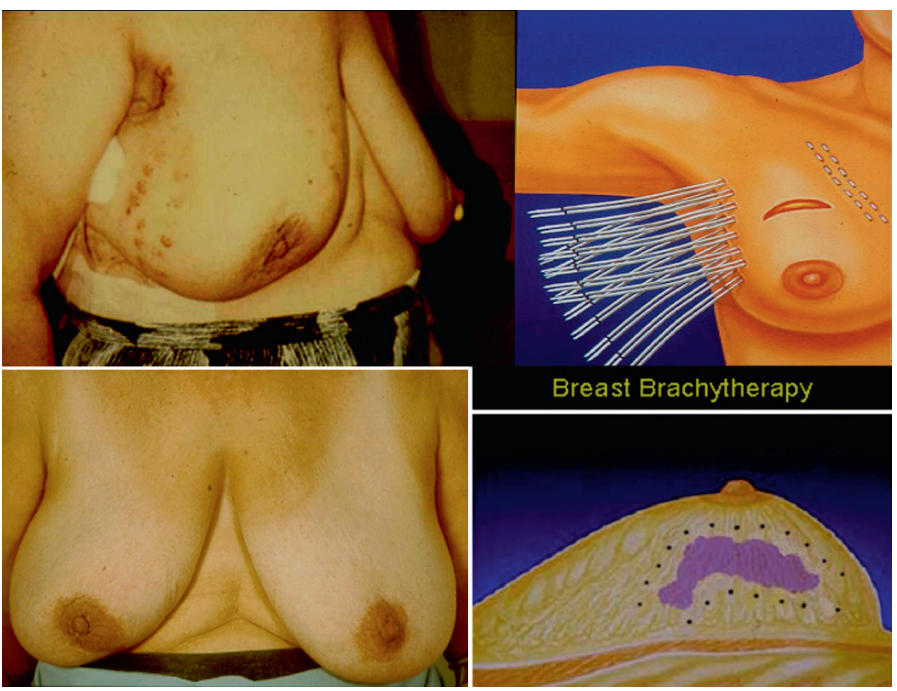

Fig. 13.1 The first APBI patient in the modern era: freehand catheter insertion with the wound open at the time of re-excision and axillary dissection

evaluate acute and subacute toxicity and cosmesis. The study was then extended to 163 patients after a favorable review of the initial data. Selection criteria included pathologic tumor size ≤4 cm, excision with negative margins (no ink on tumor), and negative nodes or 1–3 positive without extracapsular extension. There were no age restrictions, DCIS and lobular histologies were allowed as long as the pathologic extent was ≤4 cm, and an extensive intraductal component to an invasive cancer was allowed. We treated women with LDR or HDR brachytherapy in alternating blocks of ten patients each to avoid selection bias. The HDR dose (32 Gy in eight fractions over four days, or 34 Gy in ten fractions over five days) was independently calculated by prominent biologists/physicists to be equivalent to the LDR regimen for tumor control probability and late tissue effects. The published results for the first 50 patients were presented as a matched pair analysis comparing study brachytherapy patients to whole breast irradiation patients treated by the same selection criteria and the same physicians, and with similar stage, age, and follow-up intervals (King et al. 2000). Tumor control, toxicity, and cosmesis were similar between the matched pairs. There was no significant difference between low and high dose rate results, so the subsequent study extension was primarily HDR.

After IRB review, the trial was extended to 163 patients, including 19 DCIS, 116 invasive ductal, seven invasive ductal with EIC, 11 lobular, six tubular, and four mucinous histologies. Twenty-four patients were node-positive. Overall, 71% of the patients were treated with HDR brachytherapy. Five patients (3%) had breast, four nodal (2.5%), and seven distant (4.3%) recurrences at a median follow-up of 65 months (Kuske et al. 2004a).

The New Orleans excellent outcomes were mirrored by the William Beaumont Hospital (Baglan et al. 2001), providing impetus toward Radiation Therapy Oncology Group (RTOG) Trial 95-17. RTOG 95-17 is the first cooperative group Phase II trial of partial breast irradiation. This trial accrued 100 patients (99 eligible) from ten institutions. It should be remembered that this trial was written in 1994, so there were no CT-based three-dimensional treatment plans and the brachytherapy was primitive compared to modern standards. Dosimetry was planned from orthogonal films with dummy seed strands placed within the catheters. In the *z*-plane, the dose was delivered from skin-to-skin, in contrast to the proximal-to-distal target volume coverage performed today. The implants tended to be one or two planes rather than current volume implants. Despite this low-technology brachytherapy, and inclusion of radiation oncology centers without the experience of the original pioneers, the results were quite impressive. At over six years of follow-up, the ipsilateral breast recurrence rate is 6% actuarial at five years, the same as the contralateral new primary cancer rate. There were no regional nodal failures despite over 20% of patients being initially node positive (Kuske et al. 2004b; Arthur et al. 2008).

Research into accelerated partial breast irradiation is blossoming, with at least five international randomized trials ongoing and numerous single-institution publications. Investigations into APBI have followed an ideal path, from a single patient giving us the concept, to prospective IRB-approved single-institution trials at two hospitals, to a national Phase II cooperative group trial, to multiple international Phase III trials. Soon, we will have direct comparisons between conventional six-week whole breast irradiation and five-day partial breast irradiation. The NSABP-RTOG B-39 North American randomized trial with 4,300 enrolled patients is projected to finish December 2010.

13.2 A New Hypothesis and a Potential Paradigm Shift

There has been a 110-year tradition of treating the entire breast in all breast cancers, no matter at what stage or how early they were detected. Sir William Halstead proposed the original hypothesis that the entire organ needed to be treated as well as all possible extensions of the malignancy, including nodal regions.

In the early 1980s, the Halstead hypothesis was challenged, but only to the extent that comprehensive breast irradiation rather than the scalpel could treat the entire breast.

Attempts at partial breast surgery without whole breast irradiation were failures, with local recurrence rates in the range of 30–40% (Morrow and Harris 2000).

A principle of radiation oncology is: when treating large volumes or entire organs, a lower dose per fraction improves tolerance by decreasing the late effects (e.g., fibrosis, microvessel damage, telangiectasia, and necrosis) of irradiation. Considering the goal of optimizing cosmetic outcome in the treatment of early-stage breast cancer with breast-preserving approaches, the original pioneers of breast conservation therapy chose to treat the ipsilateral breast with daily doses of irradiation in the range of 180–200 cGy per fraction. The whole breast was treated to 4,500–5,000 cGy, usually followed by a boost to the excision site plus a margin to 6,000–6,600 cGy over 6–7 weeks.

The breast team at the Ochsner Clinic in New Orleans hypothesized in 1991 that:

1. In select breast cancers, true biologically significant multicentricity is rare, and more recent improvements in breast imaging (e.g., breast MRI) and pathology (e.g., meticulous margin assessment of an oriented lumpectomy specimen) may further reduce the risk of disconnected multiquadrant disease
2. Virtually extending the surgical margins by eliminating contiguous breast cancer extensions beyond the surgical edge with focused dose-intense radiation might lower the true local recurrence rate
3. Since the radiation source is immediately in the vicinity of the tissue at risk, brachytherapy can be given in a shorter time period, accelerating the treatment time, potentially making breast-conservation radiotherapy more accessible to eligible women
4. As a result of the physics of brachytherapy, the dose falls off rapidly away from the source dwell positions, decreasing normal tissue exposure to radiation, potentially preventing sequelae to the heart, lung, chest wall, skin, lymphatic, and uninvolved breast irradiation
5. The shorter overall treatment duration allows all the local therapy for breast cancer to be given upfront, with systemic therapy to follow without delay, potentially maximizing local and systemic control of the malignancy
6. Partial breast irradiation may allow more options for salvage therapy in the event of local relapse

APBI represents a potential paradigm shift. The existing paradigm assumes that the entire breast needs to be treated by either surgery or limited surgery followed by whole breast

irradiation. APBI introduces the concept that in appropriately selected breast cancers, only the affected portion of the breast needs to be treated. Since the treatment volume is limited, the treatment can be dramatically shortened from six weeks to 4–5 days.

13.3 The Target Volume

In the year 1991, we chose our target volume based upon published pathological and clinical analysis of the extent of breast cancer beyond the primary tumor. We also evaluated where sites of recurrence were found after breast-conserving surgery, with or without whole breast irradiation. We decided to embark upon initial clinical trials treating 2 cm beyond the surgical edge, unless the skin or pectoralis fascia intervened.

Later, after the advent of the balloon intracavitary catheter, considerable discussion and thoughtful analysis ensued about whether 1 cm might be sufficient in carefully selected patients. Some comfort in a tighter 1 cm margin was offered by the concept of tissue compression by the expanded balloon. An analysis by Vicini et al. (2002) put forth a hypothesis that a 1 cm margin may be sufficient in carefully selected patients.

Currently, the choice of appropriate margin of irradiation is hotly debated, and may vary with the age of the patient and the aggressiveness of the tumor. It is clear that 0 cm, or no radiation at all, results in unacceptably high local breast recurrence rates in the range of 30–40%, even with negative surgical margins (Morrow and Harris 2000). The local recurrence rates when an additional 2 cm are treated are 4% at seven years in the New Orleans prospective clinical trials and 6% at five years on the RTOG 95-17 multi-institutional prospective cooperative group Phase II trial. Preliminary short-term local recurrence rates with the balloon intracavitary catheter are acceptable, and we will see in the next few years if the seven- and ten-year outcomes match interstitial results.

For the Phase III trial, considerable thought and discussion went into choosing the ultimate criterion of treating 1.5 cm beyond the lumpectomy cavity edge for interstitial brachytherapy, 1.0 cm out for balloon intracavitary brachytherapy, and 2.5 cm out for the 3D conformal option on this study. We rationalized that if the expanded balloon stretches and compresses breast tissue by approximately 0.5 cm, then the breast tissue treated may be 1.5 cm beyond the surgical edge, which would match that achieved with interstitial brachytherapy. With 3D conformal PBI, we had to take breathing motion and set-up uncertainty into account, resulting in a generous extra 1 cm (total 2.5 cm) treatment margin around the lumpectomy cavity with this technique.

Research in the field of PBI is currently very active, so it is anticipated that determination of the appropriate radiation margin around the excision cavity will be clearer in the future. Perhaps the margin will vary from patient to patient in the future, depending on tumor and patient characteristics. As seen in specimen radiographs, the tumor is frequently eccentrically located within a specimen, with a generous margin on one side and a close margin on another. It is conceivable that in the future the radiation margin may vary geometrically, based upon accurate and reliable pathological determination of surgical margin width in three dimensions.

13.4 Irradiating the Target Volume

Once the decision about the amount of tissue surrounding the lumpectomy edge that needs to be irradiated is made, there are many different means to deliver the radiation dose:

1. *Interstitial brachytherapy*. This is actually the oldest radiation delivery method, used shortly after Madame Curie discovered radium. Geoffrey Keynes applied interstitial brachytherapy to a wide variety of breast cancers in the 1920s, long before the first linear accelerators or even ^{60}Co units were brought into clinical use (Keynes 1937). The first modern day partial breast irradiation technique was developed at the Ochsner Clinic (King et al. 2000). Initial studies there and at the William Beaumont Hospital provide data with long follow-up, providing evidence-based support for the use of APBI (Baglan et al. 2001). Balloon intracavitary and especially 3D conformal or IMRT PBI techniques have less mature data supporting their use. Interstitial brachytherapy can cover any shape or size lumpectomy cavity, and the radiation margin is freely controllable. Interstitial brachytherapy provides the ultimate conformal radiation delivery with the best dose homogeneity. Finally, radiation exposure to surrounding normal tissues is minimized by this technique, since the dose falls off very rapidly just beyond the catheters.
2. *Balloon intracavitary brachytherapy (MammoSite)*. This is the simplest method of APBI, with one catheter centered inside a spherical or elliptical balloon, and usually one dwell position or a limited number of linear dwell positions. Insertion and physics calculations are much easier than with interstitial brachytherapy. Because of the limitations of a single dwell position (or linear array), the dose can be prescribed only 1 cm beyond the surface of the balloon, and symmetrically around the central catheter. Even with tissue compression, the dose does not reach out as far as with interstitial, and narrow skin separations (<7 mm), irregular shaped cavities, or air/fluid loculations pose significant difficulties with this technique and frequently preclude treatment with MammoSite. For carefully selected patients and cavities, however, the simplest solution may be the best solution.
3. *Three-dimensional conformal external beam PBI*. This is the newest technique, with the least data to support it (Vicini et al. 2003). It was introduced to make APBI available at institutions whose physicians were uncomfortable with and unable to perform brachytherapy. Breathing motion and set-up uncertainty pose technical challenges. The prescribed dose must be greater with this technique (385 cGy per fraction), because the hotter central dose inherent to brachytherapy is not seen with the relatively homogeneous dose distribution of 3D conformal. Exit dose to other parts of the body is possible. In our experience, acute skin reactions and late fibrosis can be quite symptomatic with this technique. It is, however, a popular APBI method because radiation oncologists and their physicists are comfortable with their linear accelerators. This technique requires a substantial investment in physics and dosimetry time in order to meet all the dose constraints and normal tissue limits.
4. *Electron beam*. The only published study with PBI using electron beam is a negative study with high local recurrence rates, especially for lobular carcinomas (Ribeiro et al. 1990).

Covering a defined target volume with quality assurance and documentation is a significant challenge. An Italian trial and various institutions in the US are investigating single-dose intraoperative electrons (Veronesi et al. 2008). The radiobiology of a single large fraction such 21 Gy may be suboptimal, but the convenience is undeniable. The patient's local therapy is done when she wakes up from anesthesia, providing the surgical margins prove to be negative and nodal stipulations are not exceeded when the final pathology report becomes available a few days later. It is very difficult to discern how much breast tissue is treated with what margin using this technique. It probably varies from patient to patient and surgeon to surgeon.

5. *Soft X-rays (Intrabeam)*. This intraoperative technique treats approximately 2 mm of breast tissue surrounding the cavity to a very low dose. Most experts consider this to be a homeopathic dose. Quality control with respect to tissue conformance to the metal ball, air/seroma pockets, and target volume coverage seem to be lacking. If the pathology report 2–3 days later is unfavorable (e.g., ≥4 (+) nodes, margins (+), or tumor size ≥3 cm), the dose has already been delivered and you cannot take it away.
6. *Whole breast tangential fields*. One might view conventional radiation delivery as reliably and generously covering the target volume. In reviewing cases on the NSABP/RTOG Phase III trial, however, we find many peripheral tumor locations that result in the cavity being very close to the edge of tangential treatment fields. It is not surprising with far lateral, superior, inferior, or parasternal cavities to find that the target volume is actually covered better by APBI techniques.

13.5 Brachytherapy Techniques

13.5.1 Open Freehand Interstitial Catheter Insertion

The open freehand technique depends upon the skill of the brachytherapist to insert catheters or needles in an array that covers the target volume and provides a spacing that will ensure a homogeneous dose distribution. It was the original method of breast brachytherapy, used by Geoffrey Keynes from England in the 1920s as the original breast conservation therapy (Keynes 1937), Samuel Hellman, MD, from the Joint Center for Radiotherapy in the late 1970s and early 1980s as a boost, and myself in the early 1990s as the first modern-day accelerated partial breast irradiation technique. With newer image-guided template techniques, freehand catheter insertion is now reserved for very small breasts, or to supplement coldspots found upon evaluating template insertions.

At the time of a lumpectomy or re-excision, the radiation oncologist goes to the operating room with the surgeon. With the skin incision open, the extent of the surgical excision can be determined by probing the cavity with an index finger. A sterile magic marker delineates the edges of the cavity onto the skin surface. A single-, double-, or rarely triple-plane implant is then designed by marking the planned needle entry and exit sites on the skin (Fig. 13.1).

Keep in mind that brachytherapy catheter insertion at the time of surgery can be problematic because the pathology report will not be available for 2–3 days after surgery and

catheter insertion. Documenting surgical margins and nodal status is essential before delivering the first brachytherapy dose! One must be prepared to pull the catheters, or to use them as a boost only. Patients should be forewarned of this possibility before the procedure. For this reason, most experienced brachytherapists now prefer image-guided insertions as a separate procedure 2–6 weeks after breast-conserving surgery and sentinel node mapping.

A single-plane implant is indicated if the thickness of the tissue to be covered is 1.0 cm or less. This typically is the case for very medial lesions near the parasternal breast tissue or in very small breasts or augmented breasts. It is appropriate to design a single-plane implant for one side of the target volume where it is thin, and broaden it out into two planes (in a "Y" pattern) where the breast becomes thicker, such as under the nipple. A double plane is necessary if the tissue thickness is greater than 1.0 cm but less than 2.5 cm. A third plane is added when the target tissue exceeds or equals 2.5 cm.

The spacing between needles within a plane varies with the size of the implant. Smaller volumes require closer spacing, and larger volumes should be covered with wider spacing. For example, when using a single-plane implant, the needle spacing is typically 1.0–1.2 cm. For double-plane implants, the spacing is 1.2–1.5 cm. For multiplane implants with three or more planes (routine with modern volume implants), the separation between planes is 1.5–2 cm, and intercatheter separation within each plane is usually 1.5 cm. Closer catheters in volume implants result in an extraordinary total number of catheters, and are not necessary.

In high-risk superficial areas such as directly under the lumpectomy scar, smoother dose distributions are desirable. To avoid scalloping in of the dose under the skin, extra catheters should be added 0.7–1.0 cm deep to the surface between your original superficial catheters. By adding these extra catheters, called the "gauntlet under the skin," you can feather the dose under the skin by varying the dwell times without overdosing the skin surface and running the late risk of telangiectasia.

General principles of freehand technique include: (1) when in doubt about coverage, add an extra catheter in the OR, because you can always pull it or not use it if the dose distribution is acceptable without it, whereas it is harder (but not impossible!) to add it later after the patient has awoken; (2) catheter entry and exit locations should be selected at least 1 cm away from the target volume, or a source dwell will need to be in the skin, guaranteeing a telangiectatic spot; (3) ideally, the needles are perfectly straight and parallel to each other; (4) at the ends of the implant, placing an extra catheter in-between the two planes will prevent bowing in of the isodose curves; and (5) crossing needles in a perpendicular orientation near the catheter entry and exit sites can be helpful in contouring the dose at these ends of the target volume. One or two catheters placed 1 cm below the skin surface along the original catheter entry/exit sites will prevent a scalloping in of the dose at the ends of a line source (Fig. 13.2).

Clearly, freehand techniques require skill and experience from the brachytherapist. For this reason, as well as for the pathology report issue described above, this technique is less commonly used than the other image-guided techniques shown in this chapter. This technique is still frequently used with augmentation mammoplasty at the time of the lumpectomy with the wound open. The silicone surface can be seen as you guide each needle across the target volume. Direct visualization is helpful to avoid augmentation implant puncture and subsequent rupture. Because the peripheral edges of the target

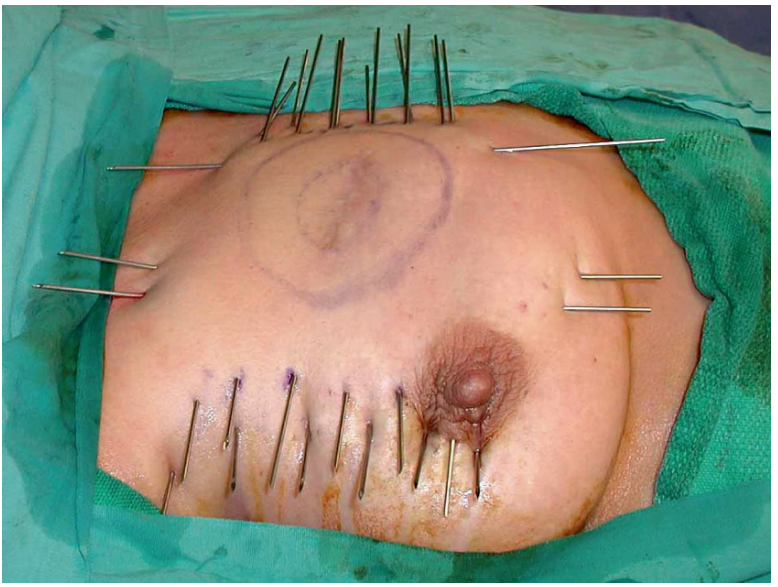

Fig. 13.2 When the target volume is close to the entry site of your needle, crossing needles can prevent scalloping in of the dose under the skin, so you do not need to load the radioactive source close to the skin surface

volume are not visible through the open wound on the right and left sides, it is much safer to have intraoperative ultrasound in order to avoid puncture. Better yet, "pinch-view" catheter insertion with the template and CT guidance provides the safest and most reliable technique in augmented women (Kuske 2008).

13.5.2 Ultrasound-Guided Supine Catheter Insertion

Ultrasound can be very helpful in guiding needle insertion in a closed lumpectomy cavity. The junction between water (seroma) and breast tissue (fat) is clearly seen for the first 5–7 weeks after lumpectomy, unless for some reason the surgeon sutures the cavity shut. In the presence of a seroma, the surgical excision cavity is readily seen by ultrasound for the first 4–6 weeks after lumpectomy or re-excision. Using real-time ultrasound, it is feasible to guide each brachytherapy needle millimeter by millimeter across the breast at a chosen depth (Fig. 13.3a,b). The deep plane is inserted either along the surface of the pectoralis major muscle or 5 mm deep to the lumpectomy cavity. The superficial plane is inserted at a depth of 0.75–1.0 cm from the skin surface. A middle plane is added when the separation between the two planes, easily measured by the ultrasound device, exceeds 2.5–3 cm, or at the ends of the implant to prevent bowing in of the isodose curves as described above.

Choose needles that are easily seen by the ultrasound transducer. The challenge is to make each needle go straight and parallel to the others while looking at the ultrasound

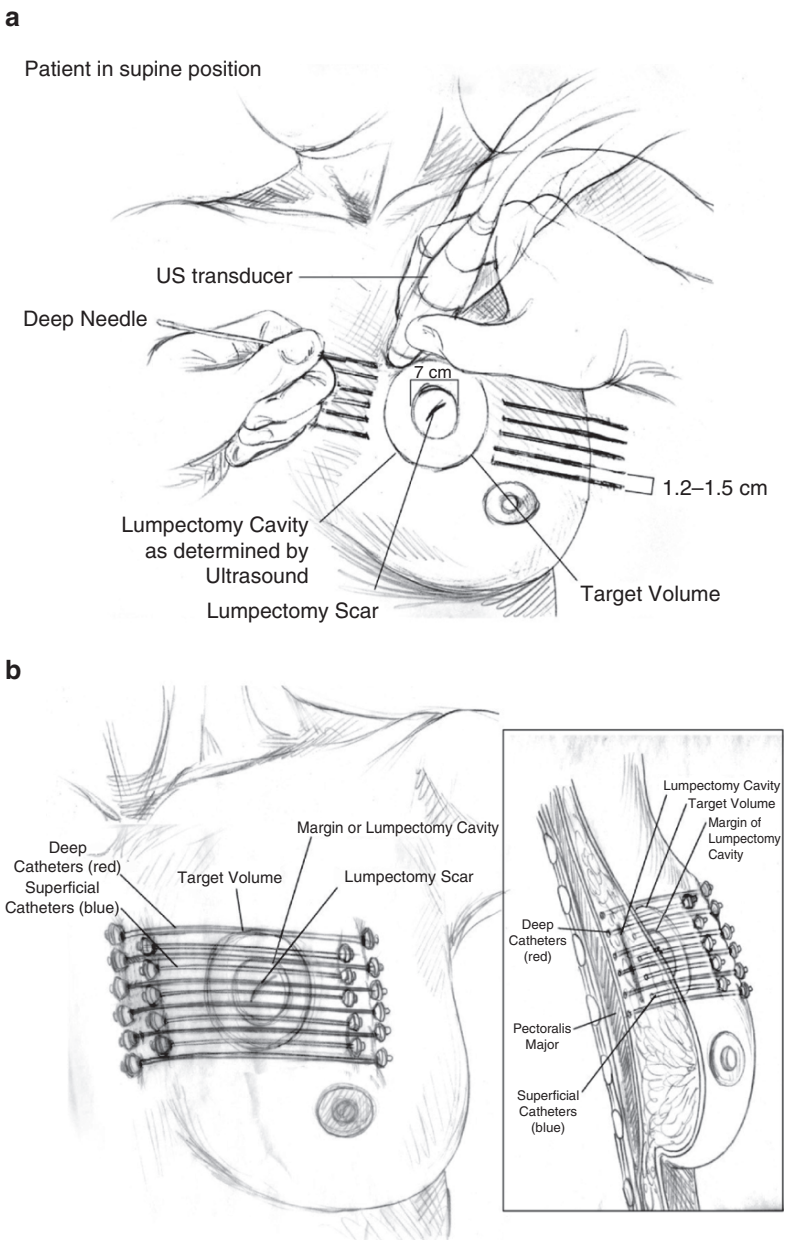

Fig. 13.3 **a** Ultrasound-guided brachytherapy. **b** Watching the US monitor while also checking that the needles are parallel, needle insertion is guided millimeter-by-millimeter across the breast tissue

monitor for proper depth. Some brachytherapists will have a diagnostic radiologist present to hold the transducer and monitor depth and target volume coverage, while others will use their dominant hand for needle insertion and the other hand to hold the transducer.

This technique is also skill dependent, since it is still a freehand technique without a template to ensure a geometrical array of catheters across the target volume. It can be done under local anesthesia with analgesia, or under conscious sedation. Unless you are performing the implant at the time of axillary or breast surgery, general anesthesia is not required. In the presence of augmentation, keep in mind that a 25- or 27-gauge local anesthetic needle is more likely to pierce the augmentation implant than a 19-gauge brachytherapy needle.

Ultrasound catheter insertion in the supine position usually requires fewer catheters than the template-guided insertions below, because the breast flattens out in the supine position and there is no compression to elongate the lumpectomy cavity and subsequent target volume. This fact makes hooking up to the HDR ^{192}Ir remote afterloading machine a simpler task (Fig. 13.4).

13.5.3 Image-Guided Prone Catheter Insertion with a Special Breast Template

This technique in the prone position on a stereotactic core needle breast biopsy table was described in the first edition of this textbook. Since then, we have abandoned this technique, so it will not be described herein. The prone method of catheter insertion was advantageous because it was reproducible and guaranteed three-dimensional coverage of the target vol-

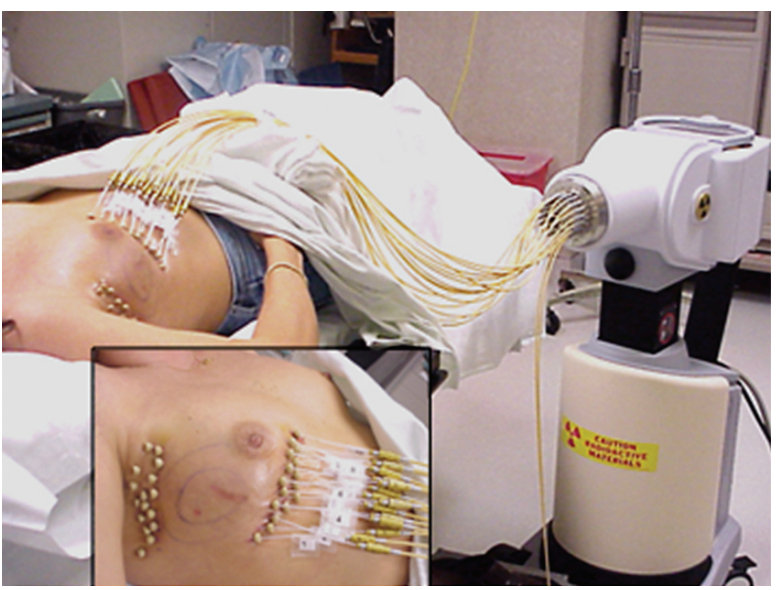

Fig. 13.4 Breast catheters are connected to yellow transfer tubes that are attached to the high dose rate remote afterloader, which positions the ^{192}Ir source at precise locations inside the breast to deliver the prescribed dose

ume. Gravity pulls the breast away from the chest wall, facilitating catheter insertion without fear of a pneumothorax (Figs. 13.5 and 13.6). However, mammographic visualization of the lumpectomy cavity usually requires contrast injection, and the tables are not generally available to radiation oncologists or surgeons, so we now prefer CT-guided brachytherapy catheter insertion. CT scanners are now available to almost all radiation oncologists, which means that this procedure is potentially available to centers all over the USA.

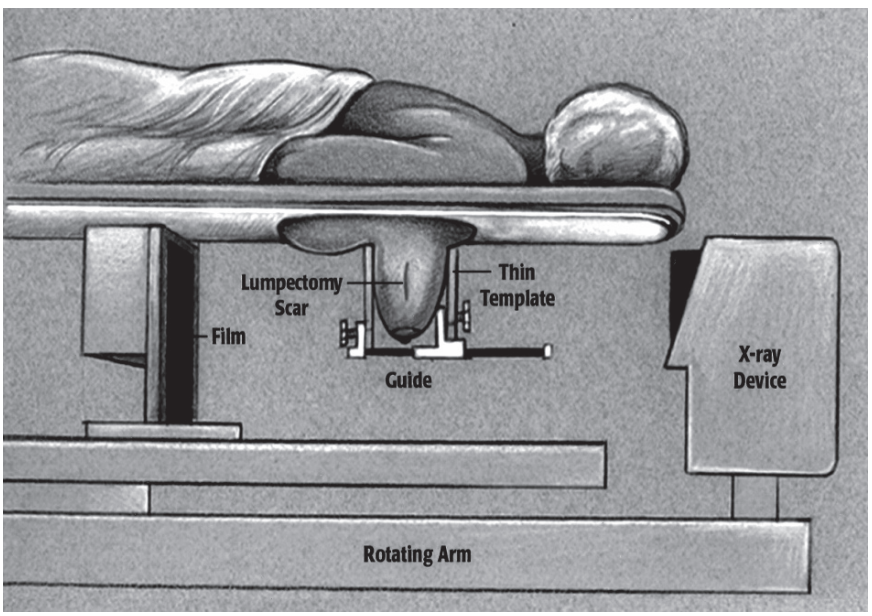

Fig. 13.5 1998 development of the prone technique on the stereotactic breast biopsy table with nonionic contrast in the cavity and a template to guide catheter insertion

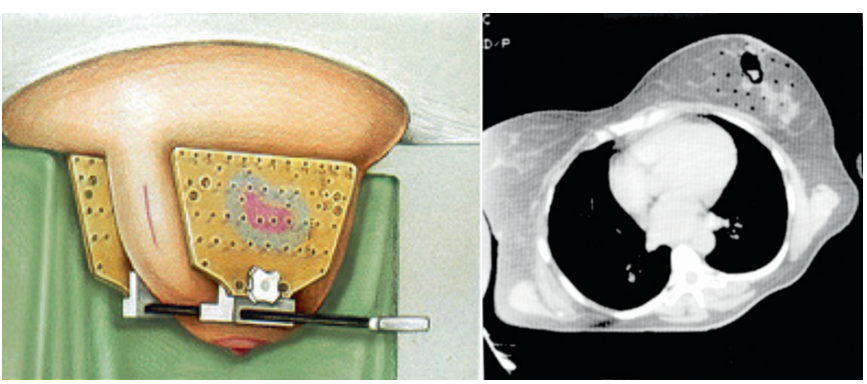

Fig. 13.6 Breast brachytherapy template attached to a hanging breast on a prone stereotactic table with the cavity shown in red and the target volume in gray showing the template coordinates for needle insertion. On the right is a typical CT of the breast after brachytherapy. Note the excellent deep coverage along the pectoralis fascia and the 2 cm margin around the lumpectomy cavity

13.5.4 CT-Guided Supine Catheter Insertion with a Special Breast Template

The procedure can be performed on the radiation oncologist's or surgeon's own time on his or her own treatment planning CT scanner. Furthermore, the patient rests in a supine position, which is much more comfortable than being prone for a 1–2 h procedure (Table 13.1).

A typical procedure would proceed as follows: The patient or a nurse applies topical lidocaine cream (EMLA) to the involved breast 1–2 h before the start time. One hour before start time, the patient takes 5/325 mg Percocet and 5 mg Valium. The patient is taken to the ultrasound suite, where the seroma is identified. Using a straw to make an impression on the patient's skin, the projection of the cavity onto the skin can be mapped. This step is helpful for centering the template on the cavity and choosing template orientation. In 90+% of cases, the cavity is readily seen on CT, and contrast is not necessary. In these cases, proceed directly to the CT scanner without the next step.

If the cavity is old and not readily seen on CT, or the breast is dense, nonionic contrast injection into the cavity can help define to the target. We do this procedure ourselves, but a diagnostic radiologist can provide this service. An ultrasound-compatible needle enters the skin at least 2 cm away from the seroma, to avoid leakage of contrast later, after a small amount of local anesthetic has been injected to raise a skin wheal and along the planned path of the needle. The needle is positioned in the middle of the seroma using ultrasound guidance, and approximately 80% of the seroma fluid is aspirated into a syringe. This decreases the target volume. Then 3 cc nonionic contrast and 2 cc air are injected directly into the cavity. The needle is withdrawn.

Table 13.1 Advantages of supine CT image-guided needle/catheter insertion

1. The lumpectomy cavity is frequently readily discernable by CT. If the breast is dense, or the cavity is old, just 3 cc nonionic contrast (e.g., Omnipaque) can be injected directly into the lumpectomy cavity along with 2 cc air using ultrasound guidance. This extra step highlights the seroma as well as the crevices and outpouchings of the lumpectomy cavity.
2. By manually lifting the breast off the chest wall while attaching a special template with predrilled holes, deep coverage to the pectoralis muscle can be achieved.
3. Using modern, CT-based, three-dimensional treatment planning software (available in most radiation oncology departments), the rendered image of the breast can be viewed with the template attached. The view can be rotated on the computer until the front and back template holes are perfectly aligned.
4. Once the cavity is contoured on each CT slice, the target volume is increased by 1.5–2 cm. The holes needed to cover the target volume are readily apparent in the "beam's eye view." Reliable and reproducible coverage of the target volume by an array of thin plastic catheters is assured.
5. Any margin around the lumpectomy cavity can be chosen (e.g., 1, 1.5, 2.0, 2.5 cm, etc.), and theoretically one could have broader coverage on one side of the cavity, where the margin is perhaps tighter, and a smaller margin on the other side where the surgical margin is generous.
6. The procedure can be performed totally under local anesthesia with analgesia.
7. The resultant catheter distribution is a volume implant, rather than one or two planes, allowing much more flexibility for dosimetry and coverage of odd cavity shapes.
8. Assuming the template is attached in the same way, a radiation oncologist in a different state, or even a resident in training, would perform exactly the same implant as a very experienced brachytherapist would.

The patient is taken to the radiation oncology CT scanner. The table is draped in sterile fashion. The patient's breast is prepped with Betadine or a similar solution. The lumpectomy site is palpated and correlated with the straw marks on the skin outlining the cavity. Tincture of benzoin, Mastisol, or the equivalent is applied to the skin before the template is attached to prevent slippage. The template is positioned on the breast so that the surgical scar is between the two plates and visible to the physician. The surgical scar should not be up against one of the plates because you want the catheters to be parallel to the skin under the lumpectomy scar, not perpendicular, for dosimetry reasons.

The breast is vigorously lifted up and off the chest wall as the template is attached with moderate compression. The base of the template is positioned tightly up against the chest wall while the breast is being lifted so that adequate deep coverage is guaranteed (Fig. 13.7). Immediately, to prevent template slippage, three CT-compatible needles are inserted around the lumpectomy site in a triangle to anchor the template (Fig. 13.8). These marker needles will also provide fiduciary markers to facilitate orientation on CT and the treatment planning renderings. A 27-gauge needle is used to inject 0.5% buffered lidocaine with epinephrine under the skin at each entry site (Figs. 13.9 and 13.10). A 25-gauge needle is used to inject 0.1% buffered lidocaine with epinephrine deeper along the planned pathway of each brachytherapy needle. We use Lactated Ringer's Solution to dilute the local anesthetic, as it causes less stinging when injected into tissue. The template is covered with a sterile towel, and a CT of the breast is obtained (Fig. 13.11). The images are electronically transferred to the treatment planning computer.

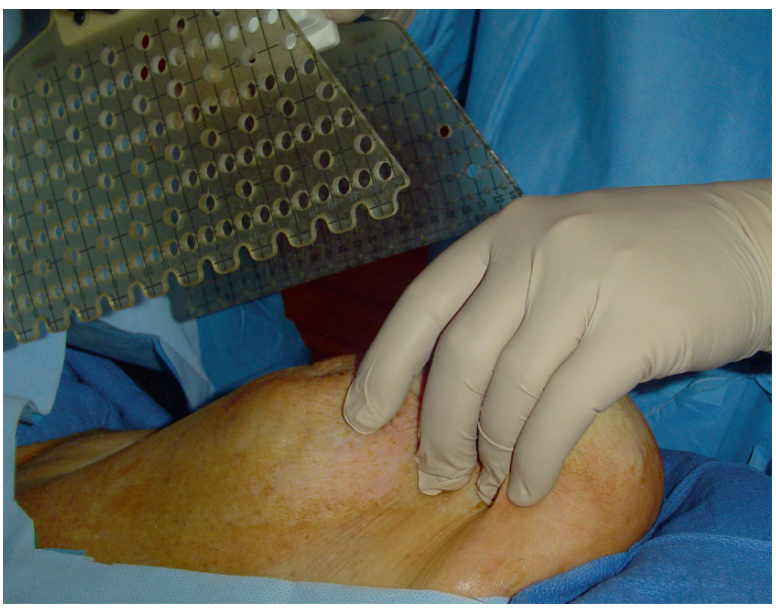

Fig. 13.7 In the supine CT-guided technique with the special template, the breast is grasped and pulled up and away from the chest wall while the two plates are squeezed to apply moderate compression

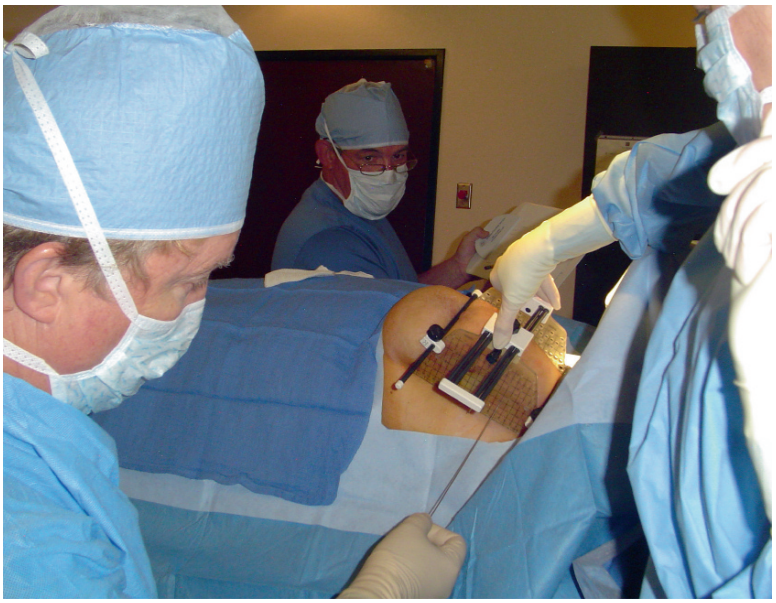

Fig. 13.8 With the nurse stabilizing the template so that it does not slip, the first of three anchoring needle are inserted; these also provide fiduciary markers of three coordinate holes for subsequent 3D planning

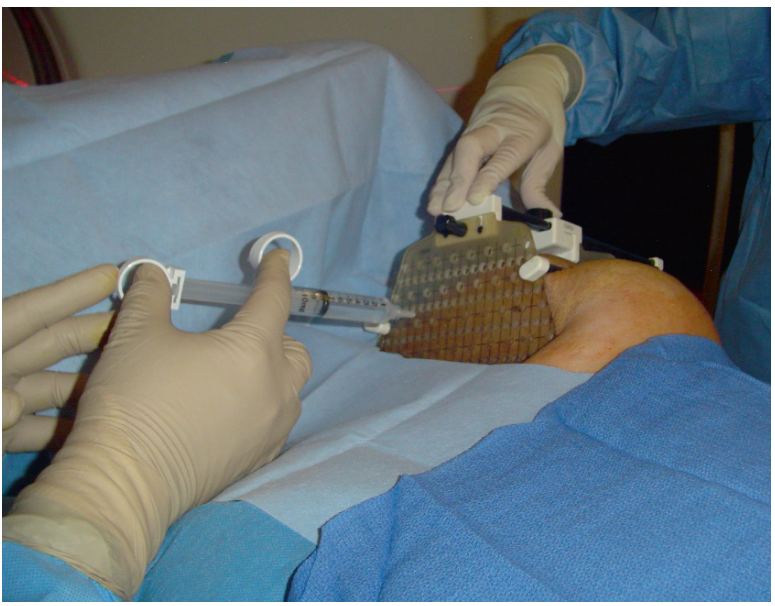

Fig. 13.9 Half %-buffered "skin wheal" lidocaine with epinephrine is injected into the skin at each entry and exit site, and 0.1% "tumescent" is injected deep into the parenchyma of the breast along the future path of each needle

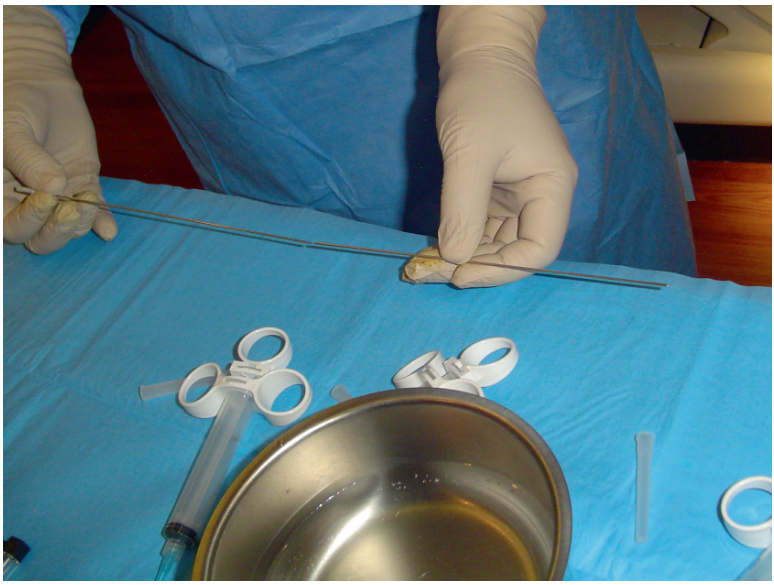

Fig. 13.10 Each hollow needle has a sharp-point, removable central trocar for ease of insertion

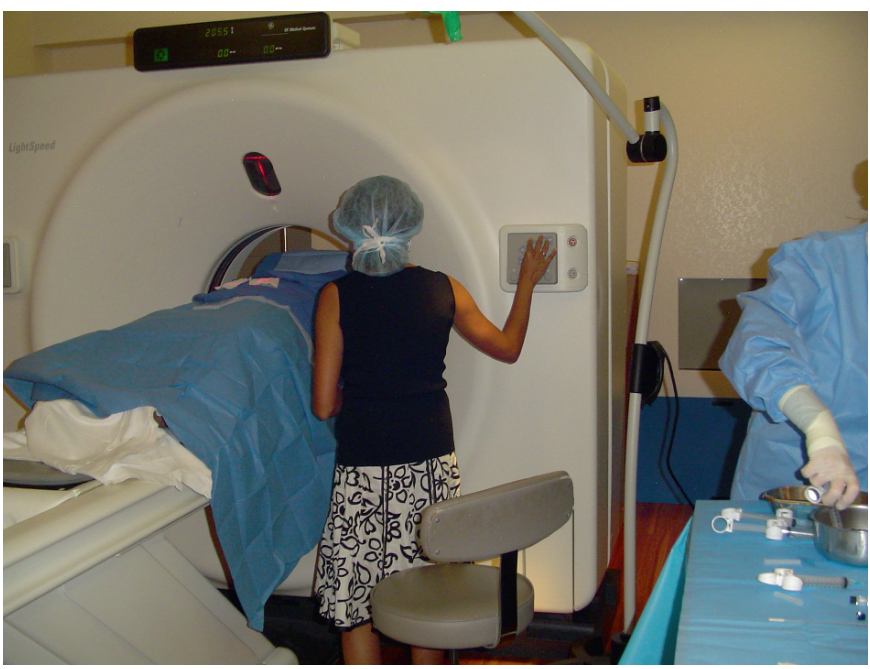

Fig. 13.11 A CT is obtained with the template and three needles in place

The CT images are reviewed on the treatment planning software, and the dosimetrist contours the lumpectomy cavity under the supervision of the radiation oncologist who is sterile gloved and gowned (Fig. 13.12). The planning treatment volume (PTV) represents a 1.5–2 cm growth of the cavity, and is automatically generated by the computer. Using coordinate C12 as a centering location, the front and back template holes are aligned. The lumpectomy cavity and PTV are transparently displayed on a "beam's eye view" with the holes of the front and back templates aligned (Fig. 13.13). The coordinates of template holes required to cover the PTV are then evident, and the computer rendering is printed out. A rule of thumb for any template catheter insertion method is to add a catheter beyond the PTV if the closest hole is inside the PTV. If the template hole is at the edge of the PTV, no additional catheter is necessary.

The radiation oncologist returns to the CT suite with the dosimetrist. Half-strength buffered local anesthetic is injected just under the skin surface to raise a skin wheal, and more dilute tumescent local anesthetic with epinephrine is injected directly down the planned holes of insertion for a relatively painless and bloodless procedure. Allow at least 5 min from local anesthetic injection to brachytherapy catheter insertion for total pain relief, and be sure to inject the skin wheal local on the front and back sides of the template at chosen coordinates to eliminate needle entry and exit pain. A thick guiding template is attached to the thin front template, making sure that the needles are parallel and straight (Fig. 13.14).

Fig. 13.12 The dosimetrist contours the lumpectomy cavity while being supervised by the physician

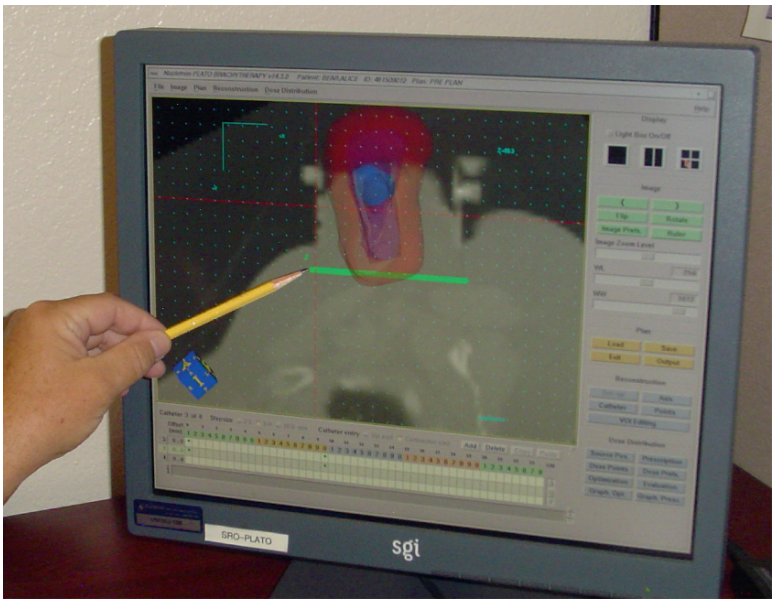

Fig. 13.13 The computer displays a 3D rendition of the cavity and PTV, with the perspective rotated until the front and back template holes are perfectly aligned

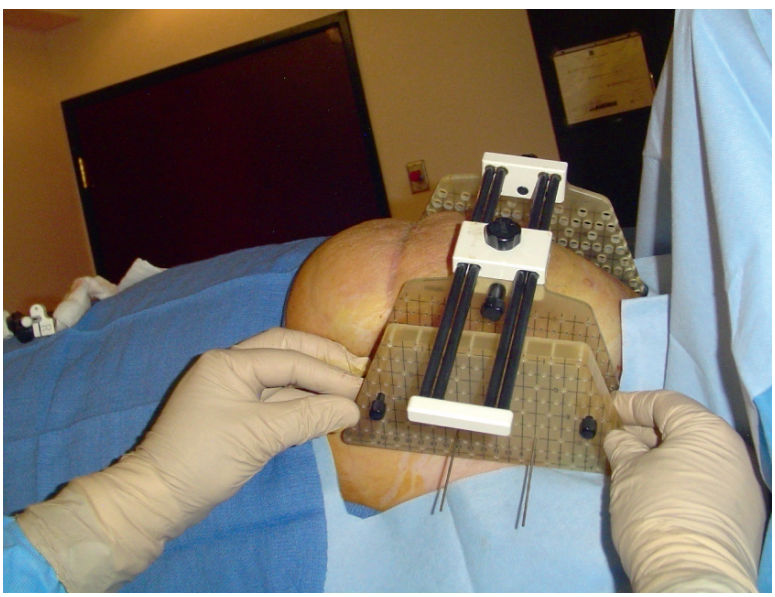

Fig. 13.14 After all required coordinates for target coverage are determined, and each pathway is locally anesthetized, the *thick guiding template* is attached to the front thin template

Since moderate compression is applied by the template, the cavity is somewhat spread out and elongated, causing the use of many more catheters than is usually seen with the old-style one- or two-plane implants. An average of 22 catheters is inserted with this procedure.

This technique provides real-time documentation of coverage of the target volume, and allows immediate adjustments or additional catheters. Deep coverage can be improved by an additional row of deep "sub-A" needles using CT guidance (Figs. 13.15 and 13.16), with you or your nurse lifting the template up and away from the chest wall. By staying parallel to the previous needles and checking the desired additional depth on the CT scan, one can avoid pneumothorax. If in doubt, take a few CT images after the needles are part-way through the breast. All needles are inserted with the same analgesia and tumescent local anesthetic procedure described above.

After the needles are in place, the template is disassembled and removed from the breast, except that the front thin template is left attached temporarily. Plastic Comfort catheters are then inserted inside the distal end of each needle and pulled until the needle is out. Once all of the Comfort catheters have replaced all of the metal needles, the front thin template easily falls off. The catheters are then pulled the rest of the way through the breast until the distal hemispherical buttons touch the skin at the entry position (Figs. 13.17 and 13.18). A button is placed at the other end of each catheter and fixed to the catheter using a heat-flanging device, securing it in place, and the catheter is trimmed to the button.

At the end, it may be advisable to add a few closely spaced superficial (0.7–10 mm below surface) catheters flanking the lumpectomy scar, called the "gauntlet under the

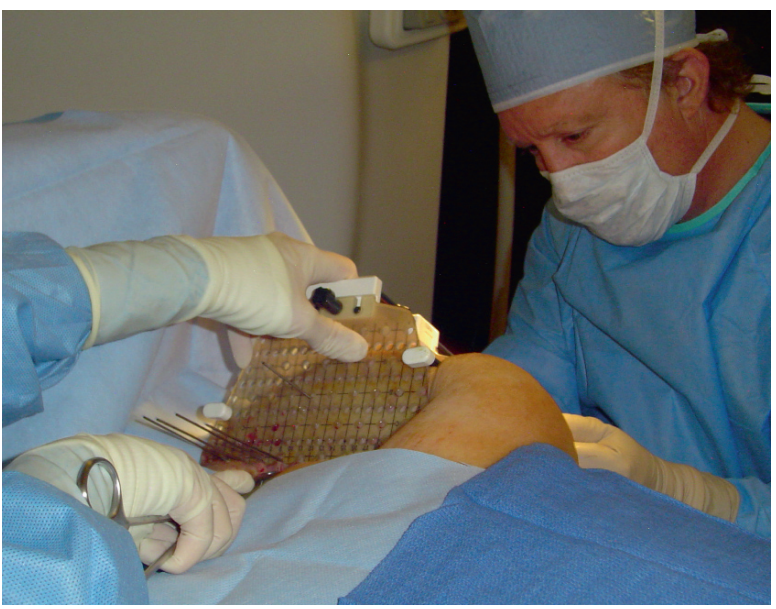

Fig. 13.15 For the deep A and (when needed) sub A rows, the nurse uses O-ring forceps to compress the backside skin down so that the needle tips exit rather than track under the skin

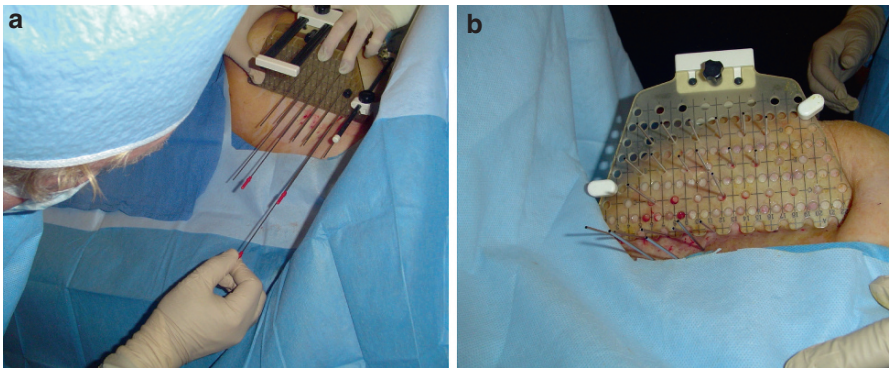

Fig. 13.16 **a** Deep catheters are planned beneath the template for adequate coverage of the PTV along the pectoralis muscle, and the dosimetrist/physicist has mapped a pathway that does not intersect with the pleura. The nurse and physician lift the template off the chest wall while the needles are inserted freehand. **b** On the backside template, the three deep sub-A needles are seen as they exit the skin. The backside template holes are wider since they provide no guidance and simply brace the other side of the breast

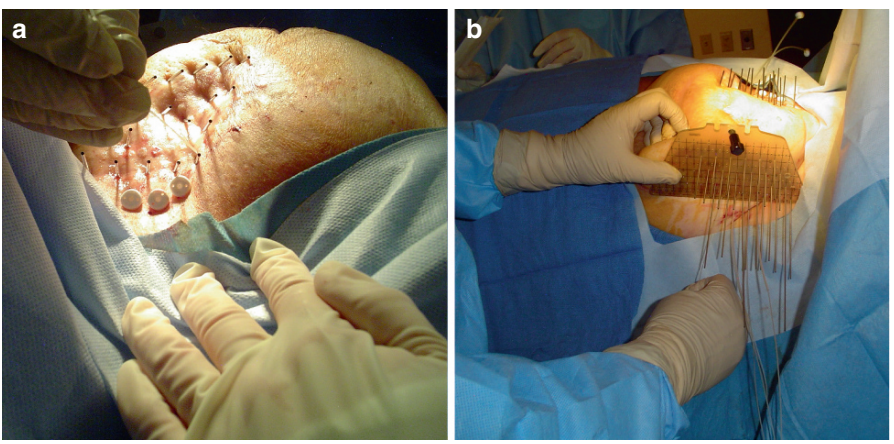

Fig. 13.17 The thin portion of the plastic Comfort catheter is threaded through the backside end of the needle and pulled through the other end until the thick portion hits the front template

skin," ensuring good superficial coverage without the prescription isodose line going beyond the surface (Fig. 13.19). At the end of the procedure, the catheters do not protrude beyond the skin surface (Fig. 13.20), and connection to the HDR remote afterloader is easily accomplished (see Fig. 13.4).

Bacitracin ointment is applied at each entry/exit site, and a Surgi-Bra is used to hold ABD pads in place over the implant so that no tape is necessary.

A treatment planning CT scan is obtained of the involved breast later that day or the next day, after any swelling as subsided. The contrast-enhanced lumpectomy cavity is

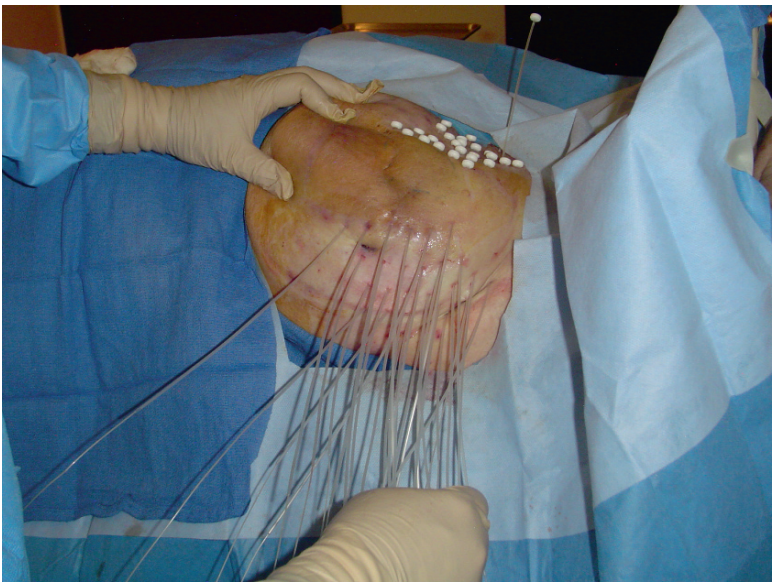

Fig. 13.18 The needle is then removed. After all needles are out, the front thin template falls off easily. The catheters are pulled until the back hemispherical button is flush with the skin

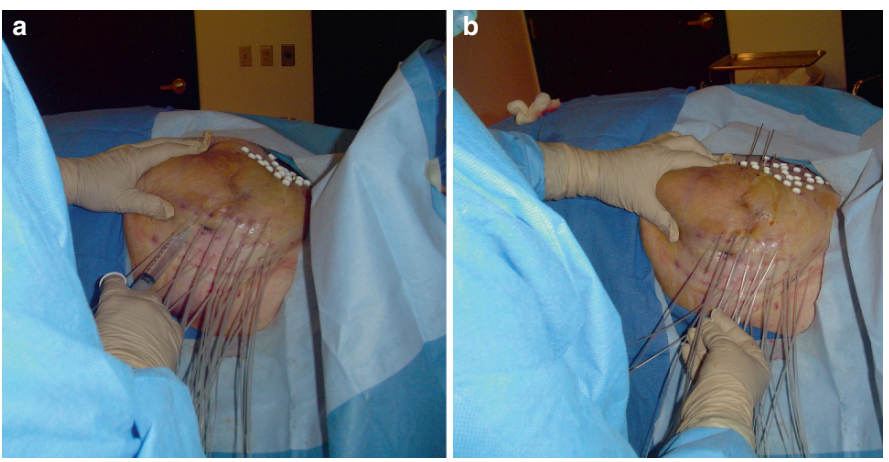

Fig. 13.19 **a** After the template is removed, the physicist/dosimetrist and MD survey the implant, deciding where extra (usually superficial) freehand needles may help cover potential cold spots. As before, skin and tumescent local anesthetic are injected through gaps in the target volume. **b** Needles are inserted freehand along the anesthetized path to fill potential cold spots and prevent scalloping in of the dose underneath the lumpectomy scar

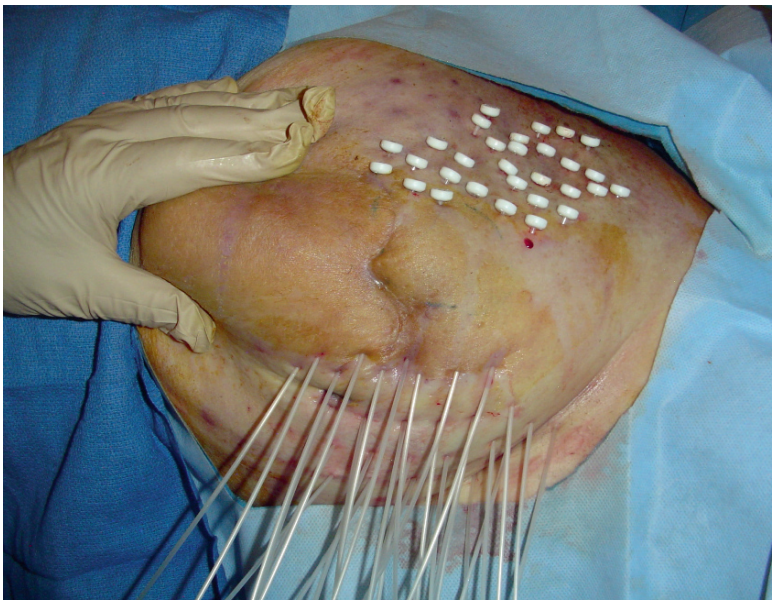

Fig. 13.20 The completed CT-guided multiplanar interstitial volume implant using the special template

contoured on each CT slice, and this volume is expanded by the desired amount (usually 1.5–2 cm) on the computer as the PTV. Within each catheter, dwell times are selected at 0.5 cm intervals so that the prescription isodose line covers the PTV, with an acceptable (>0.75) dose homogeneity index. Treatment systems have dose optimization algorithms that facilitate PTV coverage, but it is important to make sure that none of the 150% isodose curves connect between one catheter and an adjacent one (i.e., contiguous V_{150}s). We also ensure that the prescription line does not reach the skin surface.

13.5.5 Balloon Intracavitary Catheter Insertion

The MammoSite balloon can be inserted at the time of surgery or later as a separate procedure. In the first couple of years after the catheter became available, most of our MammoSites were inserted at the time of surgery for the patient's convenience of having everything done at once. Now, closed wound catheter insertion is preferred because the pathology report is available confirming that the patient is indeed a candidate for APBI or the balloon. We can also perform a preimplant ultrasound or CT to check the skin flap thickness and shape of the cavity, maximizing our success rate with balloon insertion. There are fewer aborted procedures, down from approximately 20% with intraoperative insertion to 10% with a closed wound. Finally, the sutured lumpectomy wound has fully healed and hemostasis has occurred, which further ensures the success of the balloon and in our opinion provides a better cosmetic outcome.

We insert the MammoSite either with the scar-entry technique (SET) or the lateral trocar tunneling technique. The SET uses a #11 blade to reopen the lumpectomy scar approximately 0.75 cm using local anesthesia. The seroma is rarely more than 1–2 cm deep to the lumpectomy scar, making entry into the seroma easy. After the blade nick, a hemostat or Kelly clamp is inserted under ultrasound guidance into the wound and gently opened, and this process is repeated until you get a gush of seroma fluid emanating out of the hole. Express all of the seroma with the hemostat in place. Immediately upon removal of the hemostat, replace it with the deflated MammoSite catheter, checking its position using the ultrasound. Inflate the balloon while observing the ultrasound image. After the balloon is inflated, place Steri-Strips across the rest of the lumpectomy scar so that the wound does not propagate causing a dehiscence.

There are advantages and disadvantages of the SET technique. SET is an easier technique that avoids the large, sharp, threatening trocar. Since the ends of a line source are relatively cold, the anisotropy of the isodose curves helps to pull the dose away from the skin, which is usually the biggest problem with MammoSite, and the chest wall. An additional cosmetically detrimental scar on the breast is avoided. On the other hand, some surgeons sometimes object on basic surgical principles to reopening and entering through the same wound. The catheter enters normal to the skin, which can produce bandaging and patient comfort issues. In a worst-case scenario, which usually happens if the insertion is performed too early for wound healing, the lumpectomy scar can propagate after you have put in the MammoSite, causing a wound dehiscence.

The lateral trocar tunneling method is simpler if done at the time of lumpectomy or re-excision, but intraoperative insertions are plagued with the issues noted above. This procedure can be performed with a closed wound using ultrasound guidance. Since breast tissue tends to collapse after a lateral dissection, the large trocar is necessary to provide a path for the catheter into the lumpectomy cavity. This trocar results in a larger scar on the breast, typically 2 cm or larger.

With either technique, good tissue conformance to the balloon surface must be checked. Separations of the breast tissue you wish to treat from the prescription isodose curve, by air gaps or seroma/hematoma fluid collections, are to be avoided.

13.5.6 SAVI or Contura Insertions

The SAVI is a “strut adjustable volume implant” device, designed to be a hybrid between interstitial brachytherapy with multiple catheters and the single-entry simplicity of the balloon catheter. SAVI consists of six, eight, or ten individual catheters that open after positioning within the lumpectomy cavity using a screwing mechanism (Fig. 13.21). Air and seroma tend to enter the open central part of the device, allowing the struts to be in direct contact with the cavity walls. If the skin is less than 1.0 cm from the cavity, this device allows the dosimetrist to sculpt the dose away from the skin, protecting the skin from radiation overdosage. Similarly, the device can protect the chest wall, lung, and heart for left breast cancers.

The surgeon or the radiation oncologist can perform insertion of the SAVI. Preplanning can be helpful in order to position the device along the long axis of the cavity, since the

Fig. 13.21 The single-entry multicatheter SAVI device

device is "football shaped." We obtain a 3 mm CT scan before device insertion, and contour the lumpectomy cavity on each slice. The radiation physicist can perform 3D planning, choosing the optimal entry site and angle in order to optimize SAVI positioning within the cavity. Obviously, real-time ultrasound may achieve the same result, but the two together may ensure implant success.

The Contura is a balloon device that has offset (by 5 mm) internal catheters that can allow skin protection. The insertion technique mirrors that of MammoSite balloon catheter insertion. One word of advice: quality assurance is mandatory to ensure that the balloon has not rotated! If you are using the offset catheters to lower the skin dose, and the balloon has spun to a different angle, you may be underdosing the tumor and overdosing the skin.

13.6 Judgment: Selecting the Optimal Technique for a Particular Patient

The major decision trees are:

1. When to offer external-beam PBI techniques or breast brachytherapy
2. If you have decided that breast brachytherapy is preferable, do you select balloon intracavitary, SAVI, or interstitial breast brachytherapy techniques?

For the issues and concerns highlighted in the summary section of this chapter, most of the author's patients will receive brachytherapy over external-beam PBI. Please note that

these are theoretical concerns, and more data will be required before one can apply these selection criteria uniformly. The Phase III trial does not ask participants to choose patients in the same way that the author selects patients in his clinic; otherwise selection bias would preclude meaningful data analysis to see if these issues withstand the test of randomized scrutiny.

In the author's clinic, those patients who are offered external-beam PBI are usually women with large breasts or subareolar primaries, and favorable tumor factors such as older age, generous surgical margins >0.5 cm, and smaller tumors lacking EIC or lymphovascular invasion.

Similarly, patients who are offered balloon intracavitary brachytherapy have more favorable tumors in breasts that have a thick skin-cavity separation as determined by pretreatment ultrasound. The prescription point for the balloon catheter is only one centimeter beyond the balloon surface, in contrast to the prescription point for interstitial brachytherapy at 2 cm or whatever distance the radiation oncologist and physics team choose. Despite claims that breast tissue is compressible, and that the balloon can treat as much as 1.6 cm of breast tissue beyond the surgical margin (Edmundson et al. 2002), there are data from the University of Wisconsin indicating that interstitial consistently treats more breast tissue than the balloon catheter (Patel 2005). Furthermore, the compressibility of breast tissue varies between premenopausal dense breasts and postmenopausal fatty breasts.

Because of the physics of balloon intracavitary brachytherapy, prescribing beyond 1 cm results in extraordinary high doses in the breast tissue touching the balloon, so this is strictly forbidden. Interstitial brachytherapy is only limited by the number of catheters inserted, and is determined by geographic coverage. By its nature, interstitial brachytherapy can cover any size or shape cavity, so it is much more dose controllable than the balloon catheter. As a result, most patients who cannot be treated by the balloon (because it does not fit the cavity or has too narrow a skin separation) can have the balloon pulled, and can be treated with interstitial breast brachytherapy.

To decide between balloon intracavitary and interstitial breast brachytherapy, ultrasound is performed in the radiation oncology clinic or radiology after excision with negative margins. In our experience, if the thinnest skin separation at this time is less than 1.0 cm, it is rare that the balloon will fit with a minimum of 7 mm skin separation, given the tissue compression after the balloon is expanded. Potential exceptions would be (1) a good separation in every place except one focal location, and the SET technique is performed to insert the balloon catheter through that thin spot, or; (2) a breast surgeon who is willing to go back in and resects an ellipse of skin over the thin section to widen the skin flap, realizing that this maneuver could adversely affect the cosmetic outcome.

An attempt will be made to insert a balloon catheter, and breast CT evaluation the next day will indicate whether it will work or not. If the skin and pleura separations are at least 10 mm, the treatment can proceed; if the separations are 7–10 mm, you are in the gray zone; if the separations are less than 7 mm, it is recommended that the balloon procedure should be abandoned and that you should proceed to interstitial or 3D conformal techniques.

SAVI or Contura can potentially overcome these skin separation issues.

In all cases, a thorough discussion with the breast surgeon, preferably in a

multidisciplinary breast oncology clinic/conference, is important. As a team, you must decide if you will offer the balloon or 3D external techniques to young women (e.g., <45 years of age), or EIC- or LVI-positive patients, or surgical margins less than 2–5 mm. You may decide, as we have, to offer interstitial brachytherapy to such higher-risk patients and balloon or 3D techniques to the favorable patients with acceptable skin separations or 3D locations.

The clinical judgment and decision-making offered above represents the experience and theoretical concerns of the author and his breast oncology team. Ongoing clinical trials should shed light in the future on appropriate selection criteria for each technique and indeed breast PBI in general.

13.7 Summary

This chapter has reviewed six techniques of covering the target volume with brachytherapy. Each has its advantages and disadvantages, and *a strong recommendation* is for the radiation oncology/surgical team to have many, if not all, techniques of delivering partial breast irradiation in their armamentarium. If a patient who is otherwise a candidate for partial breast irradiation is unable to receive it by one technique, it is far preferable to be able to take care of her by another technique than to resort back to six weeks of whole breast external-beam radiotherapy. For the ongoing Phase III clinical trials, it is critically important to keep the patient on the appropriate arm of the study, even if technical issues make one PBI technique problematic.

There are theoretical reasons why brachytherapy may result in better outcomes than external-beam PBI techniques, such as 3D conformal or intensity-modulated radiotherapy. First, brachytherapy is prescribed to the periphery of the target volume, with all tissue inside this envelope receiving a significantly higher dose of radiation. We call this the inherent "boost" provided by the dose inhomogeneity that is part and parcel of brachytherapy. Indeed, the radiation dose immediately adjacent to a source dwell position within a catheter can be very high. The central higher radiation dose obtained with brachytherapy can improve local control, but can also result in possible fat necrosis, fibrosis, telangiectasia, or other late effects of irradiation. Second, the rapid decrease in the dose with distance from the catheter(s) should reduce the exposure of normal tissue to radiation. External-beam PBI techniques can traverse significant amounts of normal tissue to get to the target, such as the thyroid gland, opposite breast, lung, heart, chest wall, uninvolved breast tissue, skin, or other organs that simply get in the way of the beam. Low doses of irradiation may be even more carcinogenic than therapeutic doses, so long-term effects must be watched for the next 10–25 years on these organs. Third, the typically homogeneous dose distribution obtained with external-beam PBI has inspired the experts in the field to recommend higher prescribed doses than with brachytherapy; 385 cGy per fraction in contrast to 340 cGy per fraction, for example. The net effect is a higher total prescribed dose, a higher dose per fraction, and more normal tissue exposure to radiation with external-beam PBI techniques. There is little or no long-term data with PBI at these doses per fraction, and a formal radiobiological review of the potential effect on late tissue effects and tumor

control probability has not been published. Only the clinical trials will shed ultimate light on the impact that these theoretical concerns will have on outcomes.

One issue that has not been resolved involves our current practice of uniformly treating a certain margin (1–2 cm) around the lumpectomy cavity, regardless of where the tumor is centered or where the pathologic margin is closest.

When viewing specimen radiograms, it is rare that the lesion is centered within the fat, like a sunny-side-up egg. Instead, the visible lesion tends to be eccentrically located near one aspect of the specimen, with a large area of uninvolved fat or normal breast tissue at one end and the tumor approximating the edge on the other end. Ideally, one would want to generously treat the breast tissue adjacent to the close margin and minimize treatment to the breast tissue on the side that has generous surgical margins. Practically, however, contouring partial breast irradiation in this manner has technical challenges, and it is easier to simply treat all margins to a given distance.

The future of breast brachytherapy is promising, with many techniques for accomplishing target volume coverage, and more innovations to come as industry interest in this expanding technology blossoms. Meticulous attention to detail in selecting patients and covering the target volume is key to future success. Learning the above techniques is essential to serving your patients and participating in the ongoing clinical trials. Avenues for learning these techniques include studying this textbook, visiting the clinics of experienced breast brachytherapists, formal schools offered by societies and equipment manufacturers, and of course building your own clinical experience.

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The MammoSite Technique for Accelerated Partial Breast Irradiation

14

Martin Keisch and Frank A. Vicini

The MammoSite RTS (Hologic, Inc.) is an inflatable balloon breast brachytherapy applicator. The introduction of the MammoSite RTS has overcome some of the perceived technical barriers of the multicatheter approach, such as the steep learning curve and challenging quality assurance (Arthur 2003). The device fills the surgical cavity, giving a dose of radiation that is highest on the surface and falls off rapidly, covering the immediately surrounding 1 cm of breast tissue (Edmundson et al. 2002). Since FDA approval of the MammoSite, the device has become the most frequently employed method of partial breast irradiation, with over 4,000 physicians in greater than 1,000 centers trained in its use. More than 40,000 patients are estimated to have been treated using the device.

The original device is a dual-lumen spherical balloon catheter inflatable to 4–5 cm with a central lumen for the high dose rate (HDR) iridium-192 (^{192}Ir) source. The catheter is a silicone balloon and shaft approximately 6 mm in diameter and 15 cm in length (see Fig. 14.1). The shaft contains a small inflation channel and a larger central "treatment" channel for passage of the HDR source. A needleless injection port is attached to the inflation channel, and a Luer fitting is attached to the treatment channel. An adapter is provided separately to connect with any brand of commercially available HDR remote afterloading device. Two additional sized and shaped MammoSite devices are available and will be addressed below. The applicator is placed into the lumpectomy cavity, inflated to fill the cavity, and used to treat the lumpectomy margin.

14.1 History of the Applicator

The MammoSite was developed as a sister product to an inflatable balloon brain brachytherapy applicator, the GliaSite (Dempsey et al. 1998). After modifying the liquid ^{125}I design for HDR and developing the concept into a functional device, animal testing was performed both

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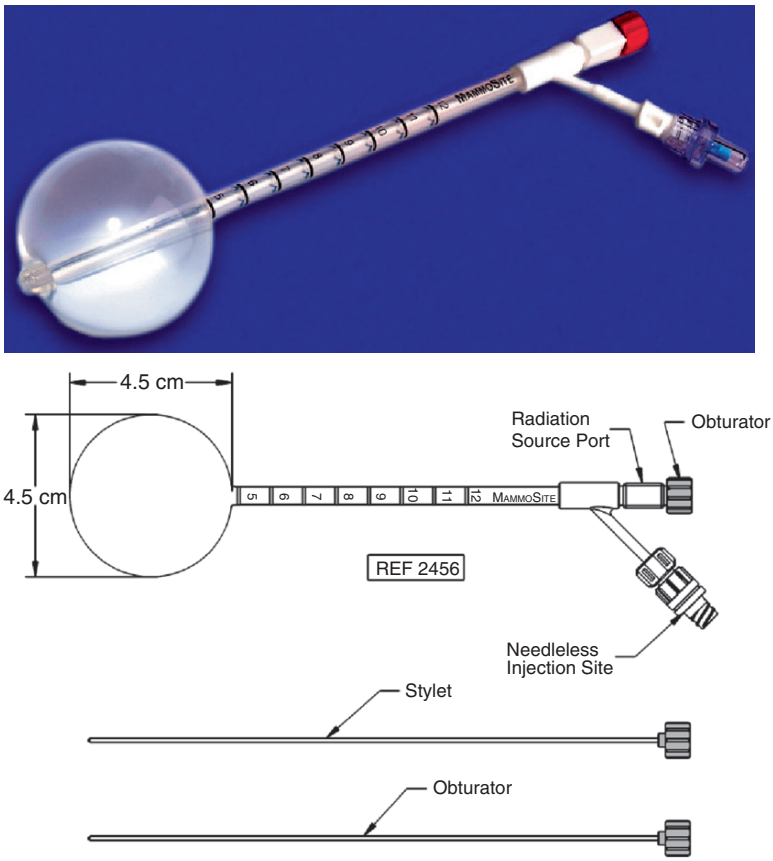

Fig. 14.1 MammoSite dual-lumen breast brachytherapy catheter (reproduced with the permission of Hologic, Inc.)

to determine functionality and to begin understanding the tissue effects of radiation delivered in this novel approach (Spurlock et al. 2000). After completing animal studies, a human Phase I/II trial was performed (Keisch et al. 2003).

14.2 MammoSite and the FDA Trial

Between May 2000 and October 2001, 70 patients were enrolled in a multi-institution Investigational Review Board (IRB)-approved prospective Phase I/II trial designed to test the MammoSite device's safety and performance in preparation for attempted FDA

approval as either the sole modality of irradiation (PBI) or a boost dose after whole breast irradiation (Keisch 2005). However, all patients entered on the trial were enrolled in the PBI arm based on the treating physician's choice.

Eligibility requirements included: age ≥45 years, tumor ≤2 cm, invasive ductal histology, negative nodal status, negative marginal status (National Surgical Adjuvant Breast and Bowel Project definition), applicator placement within ten weeks of final lumpectomy procedure, and a cavity postlumpectomy with one dimension of at least 3.0 cm. Ineligibility criteria included: an extensive intraductal component, pure intraductal cancers, lobular histology, or collagen vascular disease. Additionally, patients were deemed ineligible for technical issues including inadequate balloon–skin distance, excessive cavity size, or poor balloon–cavity conformance. Patients could be enrolled prior to final lumpectomy to allow device placement in an open fashion during that procedure; other patients were enrolled postlumpectomy and implanted using a closed technique (typically under ultrasound guidance).

Final determination of suitability for HDR brachytherapy treatment was made after device placement using computed tomography (CT) imaging in all patients to measure the applicator–skin distance (minimum requirement 5 mm). Conformance was assessed by CT imaging after device placement, and was deemed acceptable if the balloon was in contact with the lumpectomy margin uniformly, without air- or fluid-filled gaps. CT and fluoroscopic simulation were used for treatment planning, both to determine the single dwell position in the center of the balloon and for daily confirmation of balloon diameter. Acceptable diameters ranged from 4 to 5 cm, corresponding to a 35–70 cc fill volume. 34 Gy was delivered in all cases at a point 1 cm from the surface of the balloon in 3.4 Gy fractions (twice daily) over 5–7 elapsed days with various commercially available remote afterloaders. Interfraction separation was a minimum of 6 h.

Seventy patients were enrolled, 54 patients were implanted, and 43 patients were ultimately eligible for and received brachytherapy as the sole radiation modality after lumpectomy. Figure 14.2 shows the distribution of patients from enrollment through to treatment and the reasons for not being implanted or treated. Most of the patients who were not treated were not accepted for treatment due to either technical or pathologic features. Patients implanted after lumpectomy were more likely to be treated than those implanted at the time of lumpectomy, due to knowledge regarding final pathology. The patients tolerated therapy well. The most commonly reported radiation effects were limited to mild or moderate erythema without desquamation. In addition, other less common but significant events included moist desquamation in three patients, two infections including an abscess requiring drainage, and three seromas requiring drainage due to patient discomfort. No definite serious device-related events were reported. In four cases, serious adverse events were noted that were potentially related to the device; these were the previously mentioned abscess and seromas. The trial led to the United States FDA's clearance of the device in May 2002 (Keisch et al. 2003). The final publication from this trial with five-year follow-up showed no local recurrences (Benitez and Keisch 2007).

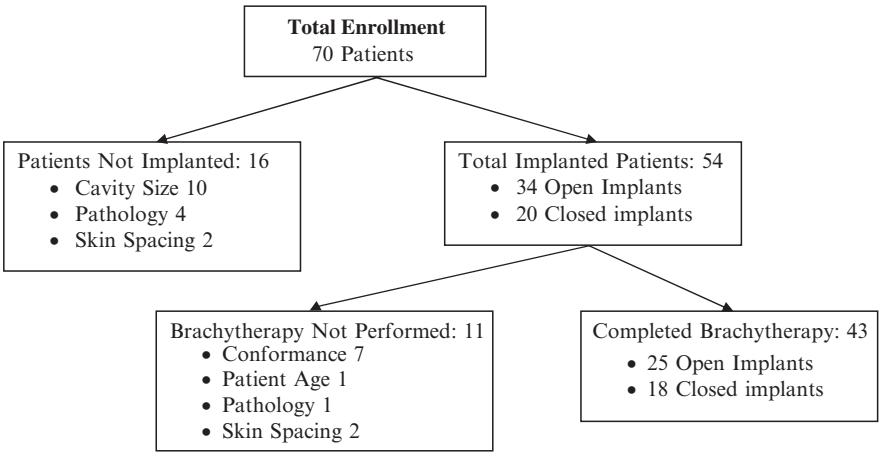

Fig. 14.2 FDA trial patients (Keisch et al. 2003)

14.3 Physics of the MammoSite

14.3.1 General

The 4–5 cm spherical device has been characterized extensively in the literature. It was originally used with a single dwell position in the center of the balloon. The FDA trial used a prescription point 1 cm from the balloon surface at the equator. The depth dose profile is such that the 4 cm diameter volume (35 cc) has a balloon surface dose of 225% when prescribed to 1 cm. Due to the inverse square law, the balloon surface dose is lower with increasing fill volumes. Additionally, the total volume receiving the prescription dose increases with increasing fill volumes and balloon diameter. Figure 14.3 shows the percent depth dose (PDD) curves around the spherical balloon normalized to the prescription point for inflation diameters of 4, 5, and 6 cm.

Data exist comparing the dosimetry of the MammoSite to that of traditional interstitial catheter-based implants (Edmundson et al. 2002). This study confirms that coverage of the target (D_{90}) is generally equal to or superior to older catheter implant techniques. The dose homogeneity with the MammoSite seen across all balloon fill volumes appears to be acceptable when compared to criteria understood to be important in avoiding soft tissue complications. Dose homogeneity, as measured by the dose homogeneity index (DHI), is not as uniform as with a modern CT planned multicatheter implant. The volume receiving over 200% of the prescription is negligible, and the volume receiving 150% falls below the volume found by Wazer et al. (2001) to correlate with a higher incidence of fat necrosis. Dosimetric studies by Edmundson et al. (2002) and Dickler et al. (2004) both demonstrate that the effective treatment depth is often higher than 1 cm due to stretching and/or compression of the breast tissue forming the cavity wall. The depth can be over 1.5 cm quite frequently, depending on the lumpectomy cavity size and the balloon inflation volume.

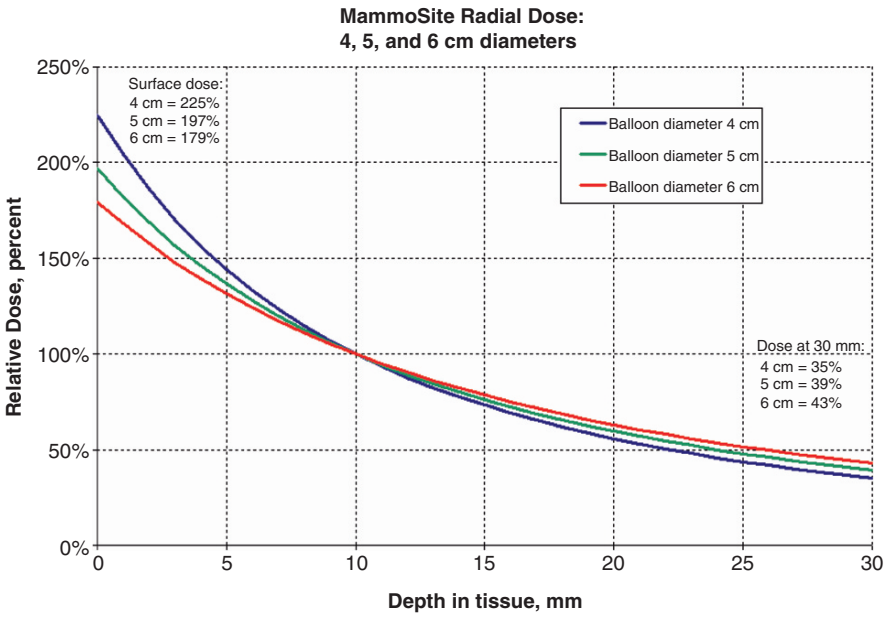

Fig. 14.3 Radial dose distribution around various diameter spherical balloon applicators (reproduced courtesy of G. Edmundson)

The actual volume of the tissue receiving the prescription dose is comparable to that of a catheter-based implant (Edmundson et al. 2002; Major and Niehoff 2006).

14.4 Single Dwell vs. Multidwell

As noted above, the device was designed for a single dwell position in the center of the balloon. When treated and prescribed in this fashion, the dose nearly matches the shape of the balloon in all directions. After the FDA trial, patients were treated with multiple dwell positions, optimized by a variety of methods (Dickler et al. 2004; Astrahan et al. 2004). Physicians were motivated to optimize using multiple dwell positions in order to improve coverage of the PTV, to decrease skin dose, and to attempt to recover implants with less than perfect balloon geometries. Although studies show that optimizing multiple dwell positions can improve coverage and other dosimetric challenges, it is generally at some cost, whether over- or underdosing some breast tissue (Fig. 14.4). An example of a setting in which to consider multiple dwell optimization would be in a patient with the device in proximity to the chest wall or skin. Another setting potentially benefiting from an optimized plan would be a patient with an air- or fluid-filled cavity. In the authors' experience, a combination of preplanning the angle of approach during device placement and optimizing multiple dwell positions with either the elliptical or spherical balloon offers the most flexibility in anatomically challenging situations. However, with an ideal implant geometry and anatomy, a single dwell position may offer the best dosimetric solution.

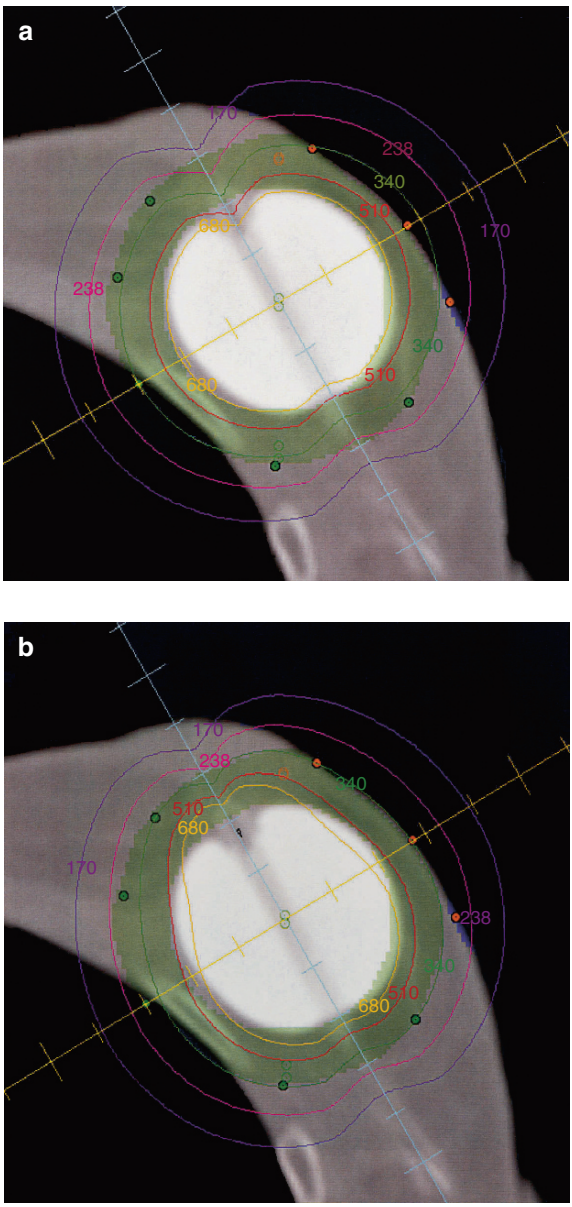

Fig. 14.4 Single dwell position (**a**), and Optimized multiple dwell positions (**b**) demonstrating sparing of skin and deep tissues at the expense of increased inhomogeniety within the PTV. (Astrahan et al 2004)

14.5 Elliptical MammoSite

The elliptical balloon measures 4 × 6 cm and requires multiple dwell positions for appropriate dosimetry. It was designed to improve the filling of the sometimes irregularly shaped lumpectomy cavity. The standard weighting of five dwell positions loaded 50:66:100:66:50 approximately matches the 200% isodose to the balloon surface. Depending on the angle of balloon entry, the weightings can be optimized to potentially spare superficial or deep structures such as the skin or chest wall, while still providing good coverage of the PTV. Unlike the spherical balloons, there is a limited fill range of 60–65 cc inflation, requiring care when determining its appropriateness as an applicator. Additionally, the elliptical balloon must be oriented nearly along the long axis of the cavity, making the surgical approach more limited. Nevertheless, the device can be useful in some clinical situations. According to the manufacturer, the elliptical balloon is employed approximately 5% of the time.

14.6 Contrast Effect

The recommended mixture for filling the balloon is an approximately 5–10% mixture of contrast-to-saline, allowing visualization of the balloon on plain radiographs without significant artifacts on CT imaging. It has been reported that excessive concentrations of contrast can lead to significant underdosing due to absorption in the contrast solution (Cheng and Mitra 2005; Kirk and Hsi 2004).

Clinically, this problem should not arise, as excessive concentrations of contrast material would degrade the CT image to a degree such that determination of appropriateness for treatment would be difficult.

14.7 Implantation Techniques

Three general placement methods exist: the lateral techniques (either open or closed), and the scar entry or SET technique. The guidelines are summarized as follows.

For balloon placement at the time of removal of the breast tumor (open lateral technique), the device should be inserted lateral to the lumpectomy cavity opening using a small skin incision and a trocar-created pathway while the wound is still open. The trocar is then removed and the deflated balloon is inserted through the pathway. The MammoSite balloon is then inflated with a mixture of contrast agent and saline (approximately 5–10%) to approximate the inside of the lumpectomy cavity to the balloon surface. The cavity and balloon are inspected visually for good conformance and the lumpectomy opening is closed using the standard technique with the exception of an additional deep layer closer in the breast tissue to ensure adequate skin spacing (Fig. 14.5). No suturing of the external portion of the MammoSite to the skin surface is recommended.

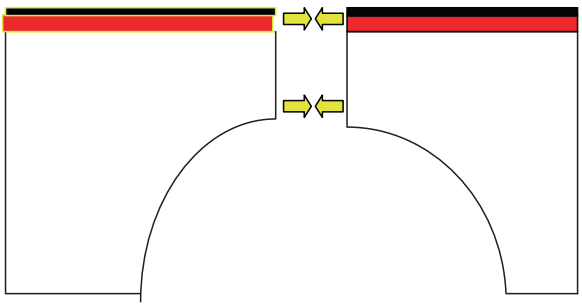

Fig. 14.5 Schematic drawing showing both subcuticular closure and deep closure within breast tissue employed to improve skin spacing

For implants performed after the tumor has already been removed, the balloon can be placed using one of two techniques. An 8 mm trocar is guided into the center of the cavity using ultrasound imaging (with proper local anesthesia). The trocar is then replaced with the deflated MammoSite. The seroma is allowed to drain. The MammoSite is expanded using the saline/contrast agent mixture in a 5–10% ratio. No external suture is required to hold the balloon in place. The external portion of the MammoSite is then dressed. Alternatively, the device can also be implanted postlumpectomy surgery through the surgical scar. The procedure is referred to as the scar entry technique or SET method. It is accomplished under local anesthesia by opening the surgical scar and carefully dissecting down to the lumpectomy cavity. Once the lumpectomy cavity is penetrated, the seroma fluid in the cavity is drained. The MammoSite is then inserted through this opening. The MammoSite is inflated with fluid to fill the cavity. Stitches on either side of MammoSite along the surgical scar are placed to prevent propagation of the wound opening.

For closed placement, the cavity should still be closed at the time of lumpectomy with a superficial and deep closure to improve the likelihood of a successful placement. A typical placement takes less than 15 min whether performed at the time of lumpectomy or as a closed procedure. The patient is then imaged with CT to determine appropriateness for treatment.

The device is simple, but with simplicity comes a degree of limitation. An appropriate cavity is necessary. The configuration of the cavity is determined by direct inspection or by using a disposable sizing device (Cavity Evaluation Device or CED, Hologic, Inc) at the time of lumpectomy, or by CT or ultrasound prior to a delayed placement. The cavity must have an appropriate size, configuration and depth to assure a favorable dosimetry. Surgeons are trained to close the cavity subcutaneously to improve results by improving the depth to the balloon surface, thus reducing skin dose. Balloon orientation can also improve dosimetry by taking advantage of the source anisotropy, if placed directly through the point of minimal skin thickness (Edmundson et al. 2002). Placement in this fashion can reduce the skin dose significantly if the entry angle and placement site are carefully chosen (Fig. 14.6).

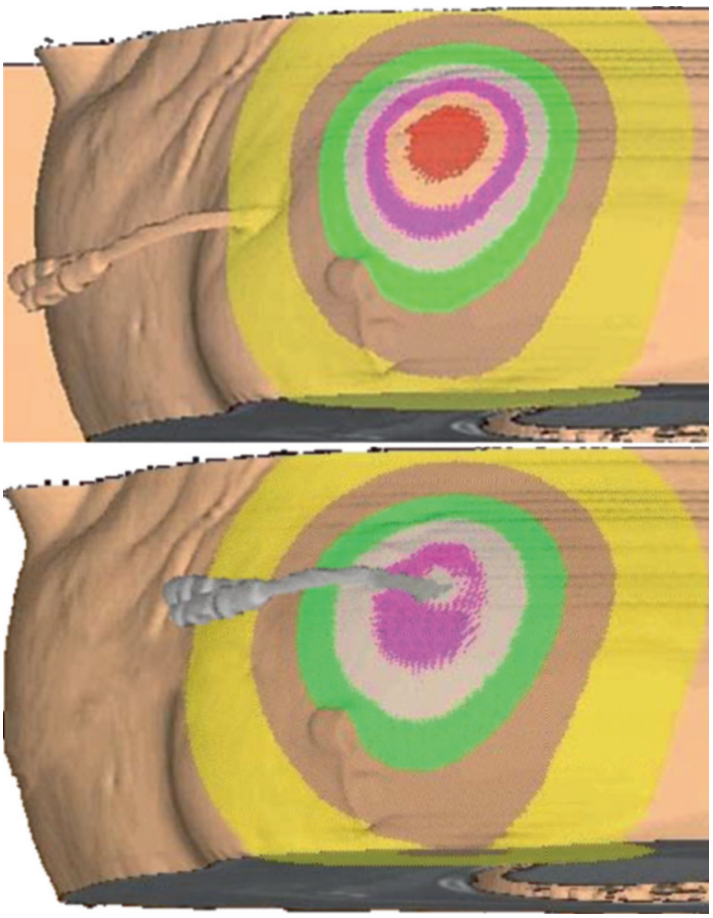

Fig. 14.6 Demonstration of the relative reduction in skin dose due to placement approach to take advantage of the anisotropy of the source. (Edmundson et al. 2002)

14.8 Other Considerations

The balloon occasionally ruptures due to balloon abrasion by needles, surgical clips, or perhaps friction with fibrous tissue. Some early experiences have had significant rupture rates, while others have had low rates (Keisch et al. 2003; Harper and Jenrette 2005; Dickler and Kirk 2005). When rupture occurs, the balloon must be replaced, reimaged and replanned, and treatment continues. A second-generation urethane-based spherical balloon has been cleared by the FDA and appears to be more resistant to rupture. Since the original device was released, the manufacturer has developed and released two additional devices, a 5–6 cm variable volume sphere and a 4 × 6 cm elliptical balloon with a single volume.

The new devices are also approved by the FDA. The larger balloon allows larger cavities to be filled completely, improving conformance after larger lumpectomies (Richards et al. 2004; Keisch et al. 2005). The elliptical balloon provides additional flexibility for irregularly shaped or unusually located lumpectomy cavities. The elliptical balloon requires multiple dwell positions for routine treatment, adding a slightly higher level of complexity to the treatment planning, but also additional flexibility in dosimetric coverage by allowing variable treatment depths along the long axis of the ellipse.

14.9 Appropriateness for Treatment

Final determination of suitability for HDR brachytherapy treatment is made after the device is placed using CT imaging in all patients to measure the applicator–skin distance, assess conformance, and check balloon symmetry. Skin spacing is an approximate surrogate for skin dose. With a distance of 5 mm from the balloon surface to the skin, the dose ranges from a maximum of 145% for a 4 cm sphere to 130% for a 6 cm sphere, not accounting for any dose reduction due to the potential effects of anisotropy, or increases due to the optimization of multiple dwell positions. The conformance describes the degree to which the balloon is in direct contact with the lumpectomy margin, and as such relates to the degree of uniform coverage of the PTV. The recommended minimally accepted conformance is that which results in a D_{90} of 90%. Two methods exist for determining acceptable conformance. First, the air- or fluid-filled spaces around the balloon can be contoured and measured. The resulting volume must be less than 10% of the volume of the PTV as determined by expanding the balloon by 1 cm and subtracting the balloon volume (Fig. 14.7). The second method is performed by contouring a 1 cm rim of tissue in all directions around

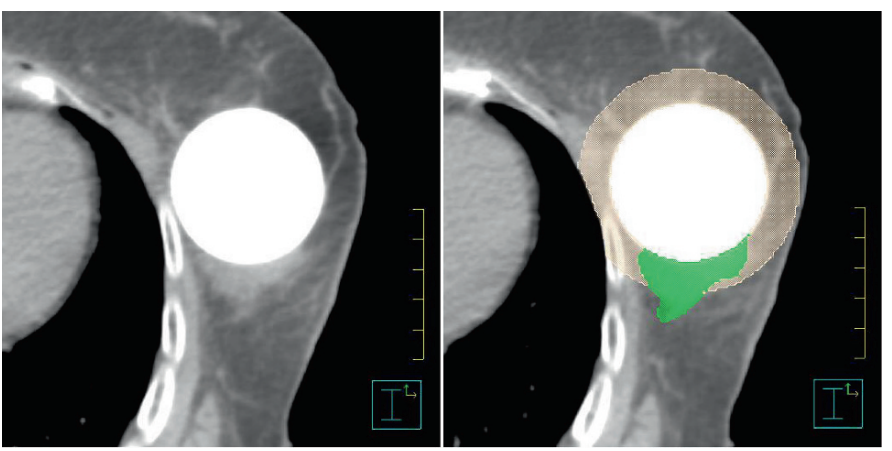

Fig. 14.7 CT scan for determining suitability for treatment due to a small seroma. In this case the seroma measured less than 10% of the PTV and the implant was acceptable for treatment

the balloon, planning the dose to a prescription point 1 cm from the balloon surface at the equator, and directly measuring the D_{90} from a DVH. The latter method is more accurate and allows assessment of the ability of volume optimization calculations to improve coverage. The asymmetry of the balloon can be subtle and inconsequential, such as in the case of local deformation due to the surrounding tissue impinging on the applicator (Fig. 14.8), or it can be due to central lumen deviation from tissue and cavity entry effects, leading to a significant variation in dose from one side of the balloon to the other (Fig. 14.9). A central lumen deviation of 2 mm or less results in a variability in dose of 15% or less, and is deemed clinically acceptable.

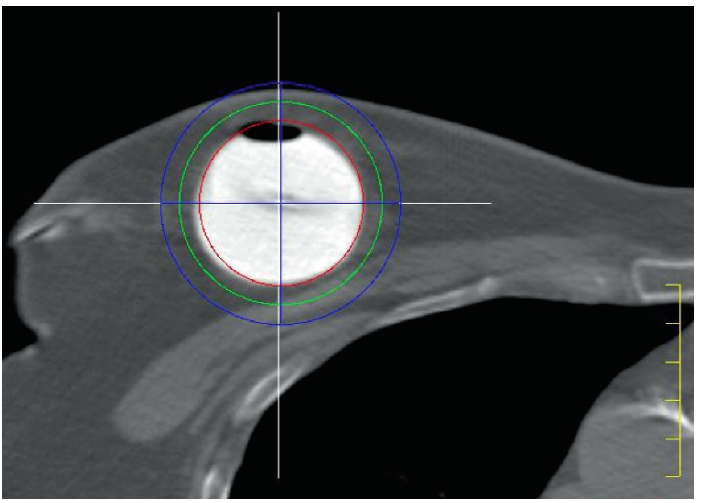

Fig. 14.8 Minimal asymmetry of little dosimetric consequence

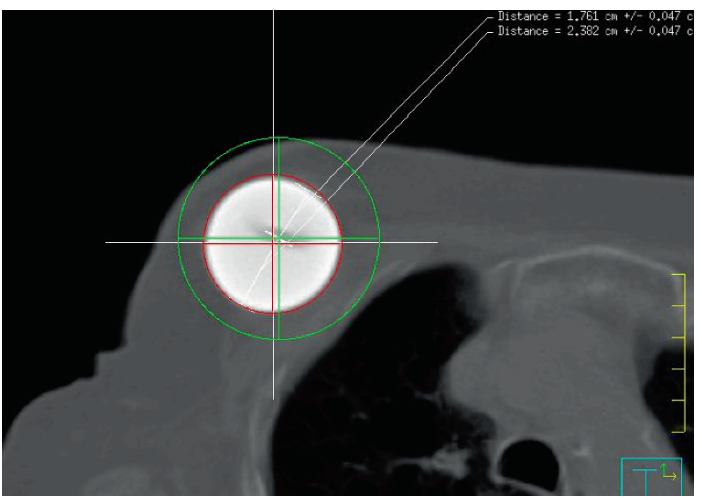

Fig. 14.9 Central lumen deviation of 3mm in a 42 mm diameter balloon

14.10 Clinical Results

The FDA study patients have completed five years of follow-up, and data are published on local control, toxicity, and cosmetic endpoints. Thirty-six of the initial 43 patients are evaluable at five years. Sixty-six month median follow-up information has shown little change over time from previous reports, in regards to both toxicity and local control. Tolerance and cosmesis remain excellent. No local failures have occurred. Eighty-three percent of patients were reported to have good/excellent cosmetic results (Benitez and Keisch 2007). A correlation exists between rated cosmetic outcome and skin spacing, a surrogate measure of skin dose. At last update, skin spacing is associated with a statistically significant improved cosmetic result at cutoffs of 7 and 8 mm in separate 2 × 2 analyses (p = 0.05 and p = 0.005, respectively). Examining skin spacing vs. cosmesis as a continuous variable, a Wilcoxon rank-sum test was highly significant (p value = 0.0051). In all 41 patients, cosmetic results in patients with skin spacings greater than or equal to 7 mm vs. 5–6 mm were excellent/good in 91% and 57% of the patients, respectively. In patients with skin spacings greater than or equal to 8 mm vs. 5–7 mm, cosmetic results were excellent/good in 97% and 58% of the patients, respectively. Although some concern has been expressed over the relatively high incidence of telangiectasias (at 39 months = 34%), it should be noted that these occur over an area typically limited to a 3 cm × 3 cm area or smaller (Richards et al. 2004). Fourteen patients (34%) had local telangiectasias, and 14 patients had localized fibrosis (34%). Fibrosis was not associated with any variable examined. Telangiectasias occurred more frequently in patients that had skin spacing of 5–7 mm (7/12 = 58%) vs. greater than 7 mm (7/22 = 32%) (p = 0.03). The median skin spacings of patients with and without telangiectasias were 0.75 cm and 1.28 cm, respectively (p = 0.001). Local breast tissue retraction was noted in five patients in whom the median skin spacing was 0.72 mm vs. 1.15 mm in those patients not developing retraction (p = 0.04). Skin spacing as a continuous variable was statistically significant, with a spacing of 5–7 mm being more frequently associated with local breast tissue retraction (3/12 = 25%) than >7 mm of skin spacing (2/29 = 7%) (p = 0.05). Fat necrosis occurred in 9.3% of patients; none of these were symptomatic or required treatment (radiographic findings only). No patient has developed adverse sequelae requiring surgical correction or chronic analgesics. Patient satisfaction was rated excellent or good 100% of the time.

Since the FDA approval, additional MammoSite clinical research has continued. Several single-institution series are ongoing, and a large multi-institution registry trial has accrued 1,449 patients and is maturing (Vicini et al. 2005; Beitsch and Vicini 2008). A combined study of results in 11 single institution trials and the FDA trial is underway (Cuttino and Keisch 2008). Many additional studies are summarized in Table 14.1. To date, all of the studies support the initial FDA Trial results.

The manufacturer initiated a registry trial in 2002 after FDA approval for the device was obtained. The American Society of Breast Surgeons (ASBrS) has assumed full responsibility for the trial, including all accrual registration, data collection, analysis, and quality assurance. Eighty-seven institutions and over three hundred investigators participated. The trial closed to accrual in August 2004. All currently available information from this data

Table 14.1 Current MammoSite literature. Prestidge et al. (2006)

Institution	No. cases	Follow-up (months)	% Local recurrence
FDA trial	43	66	0
University of Wisconsin	26	48.5	3[a]
ASBS Registry Trial	1,449	51	2.6
MUSC	99	46	3.1
Rush	70	26	6
WBH	80	24	2.9
VCU	483	24	1.2
Texas Cancer Center	234	21	0.8
Tufts/VCU/NEMC	28	19	0
Totals	*2,512*	*2–66*	*0–6*

[a] High-risk patients

set supports the acceptability of the treatment in regards to tolerance and cosmesis (Vicini et al. 2005). The trial has dramatically increased our knowledge regarding the clinical use of the balloon brachytherapy applicator, and despite the limitations of a registry study it still represents the largest published population of APBI patients. The four-year data on 1,449 patients with a median follow-up of 42 months shows an ipsilateral breast actuarial four-year recurrence rate of 2.5% (Beitsch and Vicini 2008). Additionally, a similar relationship between skin spacing and cosmetic outcome to that in the FDA trial has been noted. Infection can impact cosmesis. The infection rate was 9.5% overall. The registry trial data are the first to clarify the relationship of chemotherapy to recall reactions and cosmetic outcome. An interval of less than three weeks from completion of brachytherapy to the start of chemotherapy is associated with an increased incidence of radiation recall and decreased good to excellent cosmetic outcome (Haffty and Vicini 2008). Furthermore, over time, more patients were implanted in the closed setting, leading to a lower explantation rate due to adverse pathology (Vicini et al. 2005). The ASBrS trial also demonstrated an association between open placement of the balloon and an increased incidence of seroma formation. The pathophysiology of the association is unknown.

The registry trial also has the largest published experience with APBI in the treatment of women with ductal carcinoma in situ (DCIS). The 194 DCIS cases treated in the trial now have a median follow-up of 40 months. The actuarial four-year recurrence rate in the treated breast is 2.09%, nearly identical to the contralateral failure rate 1.5% (Keisch and Vicini 2009).

In September 2004, 12 institutions, representing a combined experience of 483 patients with a median follow-up of 24 months, met at an independent meeting sponsored by Virginia Commonwealth University to review their combined experience. The data continue to support the safety and utility of the device. Infection rates and other adverse events were well within acceptable limits. The infection rate was approximately 7%. The two-year actuarial local recurrence rate was 1.2%. The institutions included several that have already published their initial experiences (Vicini et al. 2005).

Toxicity is an important endpoint and is traditionally broken down into acute and chronic and/or delayed toxicity. Several acute side effects are common with the MammoSite RTS, including erythema and subsequent hyperpigmentation of the skin overlying the implant, seroma formation, and breast tenderness (Keisch et al. 2003). Less frequently seen are the side effects of moist desquamation, delayed healing and infection. Chronic or delayed toxicities include fat necrosis, skin atrophy, telangiectasias, and fibrosis (Keisch et al. 2005). From the data available, incidences are similar to interstitial multicatheter-based brachytherapy for the common and self-limited side effects of erythema, hyperpigmentation and breast tenderness (Beitsch and Vicini 2008). These symptoms affect small volumes of tissue and resolve quickly. Seroma formation is common (10–76%) when assessed by imaging such as ultrasound, but symptomatic seromas are relatively rare (Richards et al. 2004; Keisch et al. 2005; Vicini et al. 2005). The series from Tufts–Brown shows the highest seroma rate with patients being implanted at the time of lumpectomy. The series appears to be an outlier (Evans and Kaufman 2006). Of interest is the incidence of persistent seromas in patients not undergoing MammoSite balloon-based brachytherapy, which is as high as 30% at six months postlumpectomy (Dowlatshahi et al. 2004). Management of seromas should be conservative. Although they can be aspirated, caution is advised due to the potential increased risk of infection. When dealing with an indwelling catheter, proper measures to avoid infection are an important consideration. Published infection rates vary from 5% to 16% (Keisch et al. 2003; Harper and Jenrette 2005; Richards et al. 2004; Zannis et al. 2003). The VCU meeting pooled data showing an infection rate of 9% of the 483 patients treated by experienced physicians. Infection occurred in only 4.8% of patients placed in the postlumpectomy setting (Cuttino and Keisch 2008). It should be noted that some of these patients are included in multiple data sets, including the FDA trial, the MUSC study, the St. Vincent's study and the ASBrS registry trial. The strength of the VCU data lies in the experience level of the treating physicians. All in attendance felt that infection rates are directly related to the level of catheter site care, which should include strict dressing changes and keeping the site dry. The use of prophylactic antibiotics is considered controversial but may be helpful (Cuttino and Keisch 2008). Very few complications requiring surgical intervention have been documented; however, it should be noted that some alarming case reports exist, including flap necrosis and persistent infections requiring drainage. The most common intervention is aspiration of seromas, whether for symptoms or for diagnostic evaluation. The incidence is not clear, but from the authors' experience is approximately 5–10% in the community, though far less at high-volume centers. Fat necrosis is an important delayed toxicity that can cause tender induration in a limited local area at the site of brachytherapy and patient alarm (Wazer et al. 2001). Both asymptomatic and symptomatic fat necrosis occurs, with many more asymptomatic events noted. Overall, fat necrosis is rare, with symptomatic events recorded in less than 5% of cases (Keisch et al. 2005; Vicini et al. 2005; Cuttino and Keisch 2008), comparing favorably to multicatheter brachytherapy (Keisch 2005; Wazer et al. 2001). Regardless, it appears to be most commonly a temporary, self-limited toxicity that may occur and resolve 1–2 years after treatment. Rarely, fat necrosis may cause significant symptoms, requiring intervention. Surgical removal of the necrotic tissue typically allows the symptoms to resolve. Overlying skin changes can occur and may have a lasting impact on cosmesis, as noted above. The changes include both telangiectasias and atrophy, which are located focally at the

brachytherapy site. When evaluating the patients with the longest follow-up, the FDA trial patients (with follow-up out to over four years), these skin changes appear to stabilize after two years.

14.11 Conclusions

MammoSite RTS devices are the most commonly employed method of PBI. The device has reported experiences with follow-up periods as long as five years and patient numbers as high as 1,449. It is the most readily available form of PBI at the current time. The technique requires close interaction between the surgeon and the radiation oncologist for optimum use. Compared to multicatheter-based brachytherapy, the device placement, dosimetry, and physics are relatively simple, and at the same time somewhat less flexible. The resultant dose distribution is less homogeneous but more conformal than both external-beam and multicatheter-based approaches. MammoSite is currently one of three forms of PBI employed on the National Cancer Institute-sponsored Phase III trial randomizing between whole and partial breast irradiation.

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Permanent Breast Seed Implants

15

Jean-Philippe Pignol and Brian M. Keller

15.1 Introduction

Since the first report of retropubic iodine seed implants in 1972 by Whitmore (Whitmore et al. 1972), prostate brachytherapy has evolved to become the sophisticated technique it is today (Woolsey et al. 2003). Seed implants are finding increasing use in low-risk prostate cancer patients because they can be implanted in an outpatient procedure in just 1 h, and they are associated with excellent local control rates and good tolerance (Hall et al. 2003; Zelefsky et al. 1999). Permanent seed implants could, in theory, be applied to any cancer site where the target volume is limited, including early-stage breast cancers eligible for partial breast irradiation. However, there are a number of theoretical limitations on their application to breast cancer. The first concern is the insertion of radioactivity at a shallow depth in the body, resulting in the potential exposure of the patient's partner and the general public to radiation; the second is the need for accurate seed insertion in a soft and mobile organ; and the third is the possible degradation of treatment quality due to seed motion during the course of radioactive decay.

The purpose of this chapter is to present technical solutions to these issues, to describe the permanent breast seed implantation (PBSI) technique, to report the tolerance and efficiency from a prospective cohort study, and to discuss the advantages and disadvantages of the permanent breast seed implant (PBSI) compared to other partial breast irradiation techniques.

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15.2 PBSI Challenges and Solutions

15.2.1 Radioprotection

A general equation has been developed in order to estimate the effective dose received by the patient's partner over the course of her treatment (Keller et al. 2005). On the one hand, this equation accounts for the exposure rate at one meter, which can be modeled provided the radioisotope, the size of the implanted volume (which determines the total activity needed), and the depth of the implant below the skin surface are known; on the other hand, the equation accounts for the length of time the partner spends in the vicinity of the patient. This time is estimated for a "worst-case scenario" where every 24 h the partner spends 8 h sleeping at a distance of 30 cm from the implanted breast. For the rest of the day, the partner is likely to stay more than a meter away, so the additional dose is negligible. The acceptable dose was set at 5 mSv per year following the recommendation of the National Council on Radiation Protection and Measurements Commentary #11 (NCRP 1995). Comparing ^{103}Pd seeds (average photon energy of 21 keV, half-life of 17 days) with ^{125}I seeds (average photon energy of 27.4 keV, half-life of 59 days), we found that the partner's effective dose was consistently below 2.6 mSv for ^{103}Pd, but ranged from 5 to 20 mSv in the majority of cases for ^{125}I. The increased exposure upon using ^{125}I can be reduced by using a bra covered with a thin layer of lead shielding; however, the facts that (i) this protective garment must be worn for several months and (ii) this is an active instead of a passive form of radioprotection make ^{103}Pd seeds more suitable for PBSI.

These estimates for the exposure rate at one meter and the partner's dose were validated prospectively on a cohort of 67 patients treated with PBSI (Keller et al. 2008). The exposure rate at one meter was recorded immediately after the implantation, and the patient's partner was asked to wear a radiation badge for a period of one month. Again, ^{103}Pd was found to be safe for the public.

Nevertheless, radiation safety recommendations are given to the patient at time of the first consultation and repeated after the implantation at the time of patient release. These recommendations include: avoiding close contact with pregnant women or young children for two months; ensuring at least six months of strict birth control; and discontinuing breastfeeding.

15.2.2 Accuracy of the Seed Implant

^{103}Pd has a lower photon energy than other isotopes, and is thus less forgiving in cases of seed misplacement (Nath et al. 2000). The quality of the implant must be ideal because, in contrast to HDR brachytherapy, there is no possibility of optimizing the dose or correcting for a suboptimal implant. Achieving ideal quality is a particularly challenging task in the case of the breast, because the seeds are implanted in an excessively mobile target volume situated in a soft organ.

Immobilizing the whole breast was not found to be helpful, as this does not immobilize the target volume. A special PBSI implantation device was designed that aims to immobilize the target volume (Pignol et al. 2006). It involves placing a fiducial needle in the center of the seroma under ultrasound (US) guidance. This needle is attached to a template. It is a 17-gauge brachytherapy needle that is sanded to better immobilize the target volume and to improve ultrasound visualization. The template is a piece of steam-sterilizable PEEK plastic (polyetheretherketone, Quadrant Engineering Plastic, Reading, PA, USA). A hole drilled in the center is used to attach the fiducial needle using a screw locking mechanism (Fig. 15.1).

There are three benefits of using a fiducial needle and template: (1) it allows the target volume to be immobilized; (2) it guides the insertion of the seed-loaded needles; (3) it ensures that the seeds are released at the appropriate depth. The seed placement accuracies obtained when using either the PBSI device or an US-guided freehand technique were compared experimentally. The comparison was made on 14 gel breast phantoms with a target volume made of a mixture of iron dust and silicon gel for improved US and X-ray visualization. The needle spacing was adequate in both techniques, with only small needle divergences from their expected position: 1.07 mm ± 0.78 mm for the freehand technique and 1.11 mm ± 0.98 mm for the PBSI device (p = 0.488). However, using the freehand

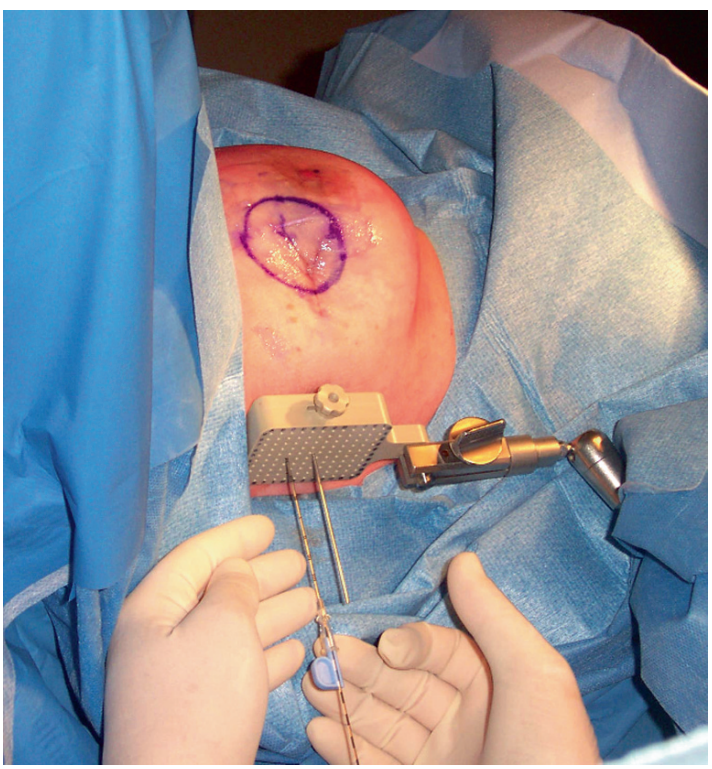

Fig. 15.1 PBSI implantation device and technique

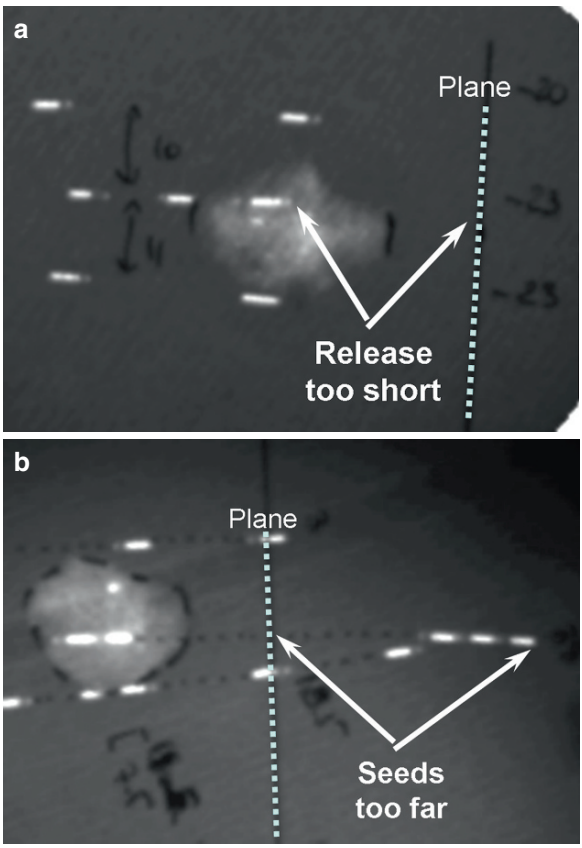

Fig. 15.2a–b X-ray imaging of breast gel phantom after implantation of seeds using the US-guided freehand technique. Seeds are released too far from their planned position (either before—see **a**, or beyond the planned position)

technique, the seeds were frequently released too far from their expected positions (either before or beyond the planned positions, see Fig. 15.2a, b), with an average error of 11.3 mm for the freehand technique compared to 3.3 mm for the PBSI technique ($p = 0.01$). Using the freehand technique, the seeds were released at a distance of more than 5 mm from their planned positions (generally beyond their expected positions) in 71% of the cases. In comparison, the seeds were released within 5 mm or less of the planned positions in 80% of the cases using the PBSI technique. The issue with the freehand technique is a lack of an accurate reference regarding the depth at which the needle is implanted; this reference is provided by the fiducial needle and the template.

15.2.3 Seed Motion

Another concern for PBSI was the possible risk of seed motion inside the breast, since a fluid cavity is generally present after lumpectomy, or outside the breast. This could potentially translate into hotspots or coldspots in the implanted volume, increasing the risk of local recurrence and/or side effects. Though it is hard to track each individual seed after an implant, it is possible to compare the quality of an implant immediately after the procedure

and then two months after by performing postimplant CT. These two planning CT scans were realized as part of the quality assurance in our prospective cohort study of PBSI. The seeds were identified and counted, and the postimplant dose distribution was generated. Dose–volume histograms (DVH) are generated to calculate the amount of the target volume receiving at least 100% (V_{100}) or 200% (V_{200}) of the prescribed dose. No seed was missing. The V_{100} and the V_{200} were better at two months rather than immediately after implantation (Pignol et al. 2008). Reviewing our plans one by one, we found that the seeds tend to coalesce over time (Fig. 15.3). This is most likely due to the reduction of postimplant edema over time (Waterman et al. 1998). Although this translates into hotter implants, this finding is reassuring because the seed motion improves the V_{100}, and thus there is no increase in the risk of local recurrence.

We have adopted three measures to prevent seed motion or to limit its consequences. First, we are using seeds stranded into Vicryl suture, which is an efficient technique for preventing seed migration (Butler and Merrick 1996). Second, we are excluding patients who have large fluid cavities on planning US. One publication has addressed the issue of surgical cavity evolution over time using CT and US imaging techniques (Smitt et al. 2001).

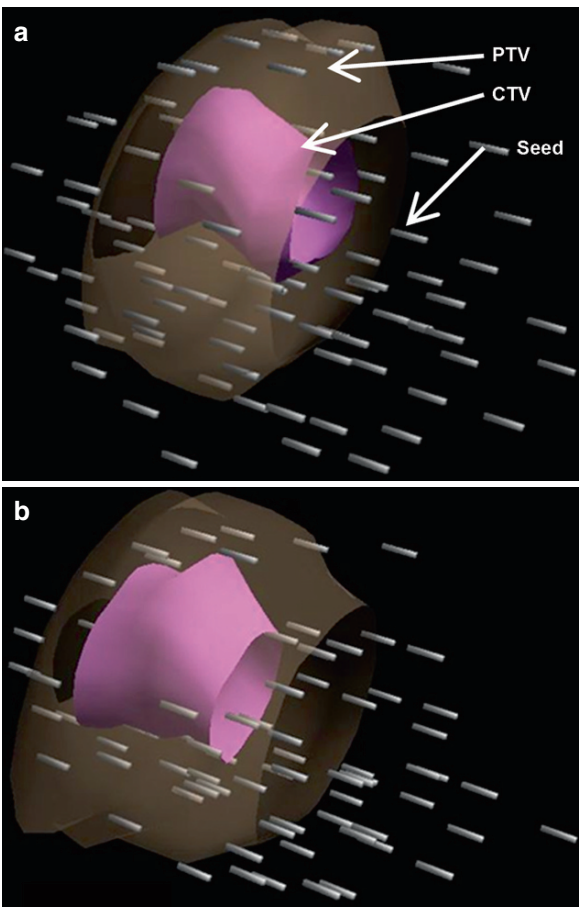

Fig. 15.3a–b Typical 3D CT images taken immediately (**a**) and two months (**b**) postimplantation. The seeds show limited motion, and coalesce. As a result, the implants get hotter but the target coverage is improved

This publication shows that the surgical cavity volume shrinks during the two months following the surgery, then plateaus to a value of 8 cc (~2.5 cm in diameter). Therefore, we are limiting implants to patients that have fluid cavities with maximum diameters of 2.5 cm. Finally, at the time of preimplant dosimetry, seeds are evenly placed within the planning target volume (PTV). This creates a hotter implant, which is acceptable since the center of the PTV is where the microscopic disease would be after breast-conserving surgery. To limit this hotspot, a seed-loading algorithm inspired by the Manchester system (Bloedorn 1956) was adopted. It utilizes constant seed activity, but the seed spacing is modified (see Sect. 15.3.3).

15.3 PBSI Preimplant Planning

15.3.1 Planning and Target Volume Segmentation

PBSI treatment planning includes breast US and CT simulation. The breast US is performed first to assess the size of the fluid cavity, and to evaluate its distance to the skin surface. The CT simulation is performed supine with the arm lifted above the head as if the patient is to receive external beam radiotherapy; this means that no time will be lost if PBSI is not feasible after planning evaluation. The clinical target volume (CTV) is defined as the surgical cavity and the surrounding fibrosis. The PTV corresponds to the CTV plus a margin of 1.5 cm modified to be 5 mm from the skin surface and the fascia pectoralis (Vicini et al. 2007; Weed et al. 2005). An important planning step is the selection of the fiducial needle insertion angle, which must be tangential to the chest wall and minimize the risk of lung or skin perforation. Images are resliced perpendicular to the fiducial needle axis and spaced evenly each 5 mm. These images are transferred to the treatment planning system for seed placement optimization.

When planning, the patient is declined PBSI if a fluid cavity >2.5 cm in diameter is found on US, if the surgical cavity is not clearly identified on the CT images, or if the distance to the skin is too close such that the 85% isodose crosses the skin surface. Patients with PTV volumes >100 cc are also excluded, since these volumes would require the implantation of an excessive amount of radioactivity (Keller et al. 2005).

15.3.2 Dose Prescription

A dose delivered using a low dose rate is not directly proportional to a dose delivered using external-beam radiation using 2 Gy daily fractions. The biological equivalent dose can be calculated from several radiobiological models of tissue response. The oldest method of calculating dose prescription equivalence in regards to normal tissue tolerance is to use the time, dose, and fractionation (TDF) factor derived by Orton and Ellis (Orton and Ellis 1973; Orton and Webber 1977). The TDF factor of an external beam radiotherapy dose of 50 Gy provided in 25 fractions with five treatments per week is 82. For permanent implants, the total dose in cGy and TDF are related by:

$$\text{TDF} = 3.53 \times 10^{-3} \times \lambda^{0.35} \times (\text{Total Dose})^{1.35},$$

such that

$$\text{Total Dose} = \left(\frac{\text{TDF}}{3.53 \times 10^{-3} \lambda^{0.35}} \right)^{0.7407}$$

where $\lambda(h^{-1})$ is the decay constant. For ^{103}Pd, the half-life is 17 days or 408 h, and $\lambda = 1.699 \times 10^{-3} h^{-1}$. A PBSI dose of 90 Gy is equivalent to external-beam radiotherapy delivering 50 Gy in 25 fractions.

The biological effective dose (BED) is a radiobiological index that takes into account specific clinical endpoints (Fowler 1989; Ling and Chui 1993; Rosenstein et al. 2004). The BED calculated for an α/β value of 3 Gy, which corresponds to late-responding tissues, is 76 for 50 Gy external-beam radiotherapy in 25 fractions, 71.5 for 34 Gy using ten high dose rate (HDR) brachytherapy fractions over five days, and 75 for 90 Gy PBSI, demonstrating the equivalence of these regimens. For α/β values of 10 Gy, corresponding to an acute reaction, the BED is 52 for external-beam radiotherapy, 44.5 for HDR, and 71 for PBSI, suggesting a higher risk of acute reactions for PBSI.

15.3.3 Seed Dosimetry Protocol

Using the image at the center of the PTV, a grid of implantation needles is created, with the needles spaced a centimeter apart in a square or a triangular pattern, whichever fits better. Preimplant plans are created by loading seeds of typically 2.5 U (range 1.59–2.7 U) into the needles. For the most peripheral needles, the seeds are spaced a centimeter apart using spacers. For the central needles that are surrounded by other needles, the seeds are spaced 1.5 cm apart using spacers. Also, seeds from two nearby needles are shifted by 0.5 cm to reduce hotspots (Fig. 15.3).

The plan is optimized by changing the seed activity and if necessary by adding or removing seeds. The constraints for the optimization of dosimetry are as follows: the 100% isodose line must ideally cover the PTV and the 85% isodose line must not bulge through the skin surface; the proportion of the PTV that receives at least 100% of the prescribed dose (V_{100}) is above 95%, and the V_{200} remains below 35%.

Two different needle implantation methods are used depending on the localization of the PTV in the breast:

- For laterally situated tumors, the fiducial needle is inserted up to 5 mm, passing the boundaries of the PTV, and the plane perpendicular to the tip of this needle defines the "zero plane." All of the seed-loaded needles are implanted up to this zero plane, and when necessary additional spacers are placed at the end of the seed strand to compensate for the absence of needle retraction (Fig. 15.4a).
- For medially situated tumors, a needle retraction method is used in order to avoid skin or chest wall perforation if the needle is inserted up to the zero plane (Fig. 15.4b).

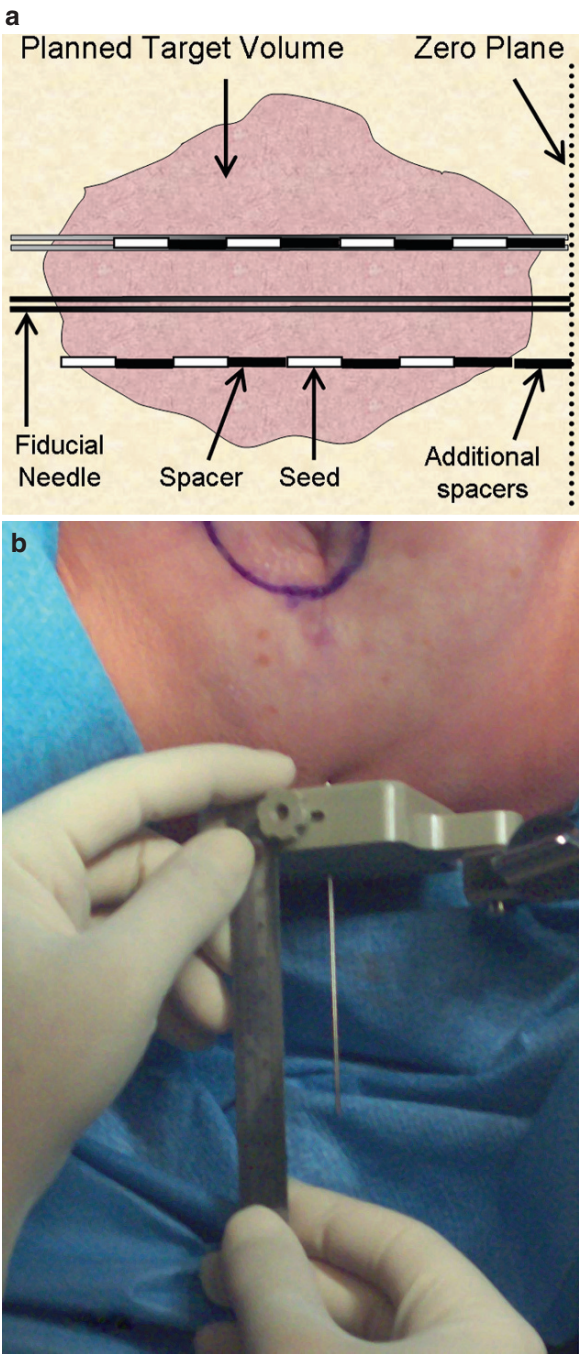

Fig. 15.4a–b For laterally situated tumors, the seeds are loaded into the needles such that they can all be implanted at a plane perpendicular to the tip of the fiducial needle **a**. For a medially situated tumor, needle retraction is necessary is and measured from the bottom of the fiducial needle **b**

15.4 PBSI Procedure

15.4.1 Anesthesia

Patients are placed on a liquid diet from the evening before the implantation, and any blood thinners must be stopped two weeks prior to the implantation. The anesthesia protocol includes:

- Ketoprofen 200 mg PO BID for two days starting on the day of implant, and PRN for 15 days
- Neuroleptanalgesia with fentanyl 100 µg and midazolam 0.3 mg kg^{-1} IV; or propofol
- Local freezing using a maximum of 30 ml of Bupivacaine HCL 0.5% and targeting the skin area where the needles will be inserted, as well as the retroareolar complex if needed

This protocol provided adequate pain control for all patients treated in our cohort study.

15.4.2 Patient Preparation

Patients are placed supine on the surgical bed and the arm is abducted and immobilized at 90°. The breast skin is rigorously sterilized using chlorexhidine 0.5% and the patient is draped sterile. The projected PTV and the surgical cavity are outlined on the skin surface using a sterile pen with the help of 3D reconstruction printouts from the CT planning. Skin tattoos and the nipple are used as skin references and starting points for the drawing. The skin drawing is carefully verified using ultrasound, ensuring that the surgical cavity is well covered by the PTV boundaries, and potentially modified.

15.4.3 Implantation

After local freezing, the fiducial needle is inserted into the middle of the surgical cavity under US guidance. The needle position relative to the surgical cavity laterally and to the skin and chest wall vertically is verified using US. The needle direction and depth of penetration is verified visually using the skin projections and a ruler. When the fiducial needle position is accurate, the template is attached firmly to it using the screw locking mechanism. The whole apparatus is immobilized on the patient's side using a medical articulated arm attached to the couch (Fig. 15.1).

The seed-loaded needles are inserted under US guidance, starting with the deepest row closest to the chest wall. For the first few rows, the needle placement relative to the fiducial needle is carefully verified using distance measurements from US. When the needle position is correct to within 1–2 mm, the seeds are released by firmly holding the trocard and pulling out the needle. When the implantation is finished, the skin is thoroughly cleansed with chlorexhidine 0.5%, and the skin is massaged to prevent strand expulsion.

After the implant, the patient is brought to the recovery room and the exposure rate at one meter is measured in all directions. It is typically on the order of 2.5 mR h^{-1}, and must remain below 5 mR h^{-1} before the patient can be released without additional radioprotection measures including breast shielding (Keller et al. 2007). Two months after the implant, a planning CT is performed for treatment quality assurance purposes. The CTV and evaluation PTV are contoured with the help of the preimplant CT images. Dose–volume histograms (DVH) are generated to calculate the evaluation V_{100} and V_{200}, and the maximum isodose crossing the skin surface is recorded over an area of 1 cm^2 or more.

15.5 Results

15.5.1 Patient Cohort

From May 2004 to March 2007, 67 patients referred to Sunnybrook Health Sciences Centre for adjuvant radiotherapy after breast-conserving surgery were included in a prospective Phase I/II trial and treated with PBSI. Eligible women included individuals aged 40 years or over who presented with an infiltrating ductal carcinoma measuring ≤3 cm, treated with breast conserving surgery, with surgical margins ≥2 mm and negative lymph nodes on axillary dissection or sentinel lymph node biopsy. Women with lobular carcinoma features, extensive in situ carcinoma or evidence of lymphovascular infiltration were excluded. In addition, women with a tumor bed that was localized too far in the inner quadrant of the breast or who exhibited evidence of postsurgery infection were excluded. Finally, at the time of dosimetry, patients that had a PTV larger than 100 cc or a fluid cavity diameter larger than 2.5 cm were also excluded.

15.5.2 Dosimetry Outcomes

In our prospective cohort study, a median of 71 seeds (range 33–102 seeds) were implanted per patient, using a median of 16 needles (range 9–27 needles). Since we excluded patients with a preimplant PTV of >100 cc, the median evaluation PTV in our series was small, 35 cc (range 14.7–66.6 cc). The median and the mean V_{100} at two months postimplant were, respectively, 89.2 and 88.2%, and the median and mean V_{200} were, respectively, 48.7 and 47.7%.

15.5.3 Clinical Outcomes

The PBSI procedure was well tolerated, with less than 5% of the patients experiencing significant pain during the procedure. Pain was more frequent the week following the implant, with up to 17% of patients experiencing significant pain the second day after the implant. This pain was related to the bruising and could be controlled with ketoprofen. The pain frequency dropped to below 5% by two months postimplant (Pignol et al. 2009).

Acute skin reactions to radiation were limited in intensity and peaked at 19.4% between the sixth and the eighth week after the seed implant, when patients were reviewed in FU appointments and had their postimplant CT scans performed. These acute reactions included bruising, induration, redness and moist desquamation. The moist desquamation rate in our series was 10.4%, which is better than that for external-beam breast radiotherapy, for which rates ranging from 38 to 48% have been reported (Freedman et al. 2006; Pignol et al. 2008), but this rate is worse than that for HDR brachytherapy, for which rates of 4–6% have been reported (Cuttino et al. 2008; Kuske et al. 2006).

Delayed side effects occurring between six months and two years postimplant are rare. In our series, 15% of the patients presented only grade I delayed side effects. These included induration, pigmentation and telangiectasia. The maximum dose to the skin surface was the only predictive factor for delayed side effects according to univariate ($p = 0.03$) or multivariate ($p = 0.02$) analyses. When the 85% isodose crossed the skin surface over an area of 1 cm^2 or more, the risk of delayed symptoms at six months was 65%; it was 28% when the skin was not crossed by the 85% isodose ($p = 0.004$). The rates of grade I telangiectasia (corresponding to a small area of red vessels seen under the skin) remained low: 7% and 14% measured at one and two years, respectively. This compares favorably with the rates of telangiectasia grade I or II at two years of 17% and 23% for, respectively, HDR brachytherapy and 3DCRT (Cuttino et al. 2008; Vicini et al. 2007; Chen et al. 2006), and with the rate of 31% reported after standard whole breast radiotherapy (Lilla et al. 2007).

We have not noticed any serious adverse events to date, suggesting that the technique is safe. The rate of breast infection was 1.5%, which is lower than the rates reported for breast HDR, ranging from 4.6% in the Mammosite Registry to 12% in RTOG 97-17 (Cuttino et al. 2008; Kuske et al. 2006; Chen et al. 2006; Benitez et al. 2007). This may be related to the fact that permanent seed implantation was performed under strict asepsis, whereas the catheters are left in the skin for several days in HDR techniques.

At the time of editing this chapter, and after a median follow-up of 43.3 months (range 22.7 – 60.7 months), no patient in our series had developed a breast recurrence. One patient died of cardiac failure nine months after the PBSI treatment, and this death was not related to the procedure.

15.6 Discussion and Conclusion

There have been previous reports on the use of radioactive seeds for breast cancer. Clarke reported the first use of temporary implants with ^{125}I seeds as a substitute for ^{192}Ir for breast brachytherapy (Clarke et al. 1989). ^{125}I was found to be more advantageous in terms of

dose distribution as well as patient and personnel radioprotection. Later Vicini reported the outcomes of 86 patients treated with temporary ^{125}I seed implants as a boost after external-beam radiotherapy. There was no difference in terms of local control, but there was a nonsignificant trend towards better cosmetic outcome for the ^{125}I boost compared to ^{192}Ir, electrons or photons (Vicini et al. 1993). More recently, the possibility of utilizing the permanent implantation of ^{125}I seeds as a boost after whole breast radiotherapy was reported by Jansen on 15 patients (Jansen et al. 2007).

This chapter refers to the permanent implantation of seeds as the sole adjuvant radiation treatment for early stage breast cancer. The advantage to patients and staff of using PBSI is the increased convenience of the technique; it is realized in a single 1 h procedure under light sedation. Patients receive their treatments while living their normal lives. The clinical data available to date suggest that this technique is safe and efficient.

Based on our experience, PBSI appears feasible for early-stage breast cancer patients presenting with a small and deeply situated surgical cavity. However, 45% of the 122 patients that were eligible based on pathology did not receive PBSI. In 35% of the cases, a large fluid cavity was found during the planning US such that the seed implantation was deemed unsafe. Such patients are ideal candidates for HDR brachytherapy using the Mammosite balloon catheter. In 29% of the cases, the patients were declined PBSI because the CTV was deemed too large and so the implantation of a large amount of radioactivity would have been necessary. These patients would have been better treated with catheter HDR brachytherapy. Finally for 36% of the patients, PBSI was found to be challenging, since the CTV was either too close to the skin or was too far inside the upper-inner breast quadrant. Such patients are ideal candidates for 3D conformal partial breast irradiation. All of these partial breast irradiation techniques appear to be complementary, each one having specific advantages that make it the best choice for a particular patient.

Future PBSI technical development will very likely benefit from research done on permanent prostate seed implants, and this could make the technique even safer. These developments include better image guidance for implantation and intraoperative real-time dosimetry. A multicenter Phase IV clinical trial is currently being developed in order to capture possible serious adverse events that cannot be detected in a small prospective cohort study.

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3D Conformal External-Beam Technique

16

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Three-dimensional conformal external-beam accelerated partial breast irradiation (3D conformal APBI) permits the noninvasive delivery of hypofractionated adjuvant radiation treatment to the region of the breast at highest risk of developing a local recurrence after lumpectomy. The potential advantages of a 3D conformal radiation therapy approach to accelerated partial breast irradiation (APBI) compared to brachytherapy include improved dose homogeneity within the target volume, and thus likely a better cosmetic outcome. In addition, the elimination of an additional surgical procedure may reduce complication rates and cost. While brachytherapy requires additional training, most radiation facilities already have the technological tools and experience required to deliver 3D conformal APBI treatment. The primary disadvantage is that the breast represents a moving target, and so potentially larger volumes of normal breast tissue may need to be irradiated to avoid a geographic miss, which has uncertain effects on cosmetic outcome and toxicities.

In developing a 3D conformal partial breast technique, specific objectives include: (1) defining an appropriate clinical target volume (CTV); (2) defining dose–volume constraints for the entire ipsilateral breast, contralateral breast, lung, heart, and skin to assist in treatment plan optimization; (3) developing a relatively standardized beam arrangement (within the geometric couch and gantry angle limitations for the linear accelerator) that can be readily adapted to a majority of patients and that optimizes target coverage and minimizes dose to normal structures; (4) defining an appropriate CTV-to-PTV (planning target volume) margin that accounts for the geometric uncertainty in the CTV location as a result of respiratory motion and daily patient set-up error; (5) verifying accurate dose delivery, and; (6) assessing patient tolerance (Baglan et al. 2003). At the present time, the two ways of delivering 3D conformal partial breast irradiation differ primarily by patient positioning: either supine or prone. The major studies of 3D conformal accelerated partial breast irradiation (Table 16.1), the technique of treatment delivery, and the potential challenges of this approach are discussed in this chapter.

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Table 16.1 Initial experience in accelerated partial breast irradiation: EBRT studies (Rosenstein et al. 2004)

Series	Patients (*n*)	Age (y)	Tumor size (cm)	Dose fractionation	Median follow-up (mo)	Technique	Field arrangement	Tumor bed definition (CTV)	Margin (cm)	Ipsilateral breast recurrence rate (%)
Christie Hospital	353	<70	<4	5 Gy × 8 in 10 days	96	Supine, 10 MeV electrons	Single electron beam	Tumor bed at surgery	0	6 (21/355)
NYU	47	Post-menopausal	<2	6 Gy × 5 in 10 days	17	Prone, 6 MV photons	2 Coplanar minitangents	Architectural distortion on CT	1.5–2	0
WBH	31	50	<3	3.4 Gy × 10 in 5 days or 3.85 Gy × 10 in 5 days	10	Supine, 6, 18 MV photons	3–5 Noncoplanar beams	Architectural distortion and surgical clips on CT	1–1.5	–

EBRT, external beam radiotherapy; *NYU*, New York University; *WBH*, William Beaumont Hospital

16.1 History

16.1.1 Rationale for External-Beam APBI

Data supporting the concept of APBI result from major randomized studies that have evaluated the role of adjuvant radiation therapy in breast conservation (Veronesi et al. 2001; Liljegren et al. 1994; Clark et al. 1996). These studies have been reviewed elsewhere in this textbook, but they basically demonstrate that ipsilateral breast recurrences (IBTRs) largely occur at the original area of the tumor bed and that the ipsilateral breast elsewhere failure rate is similar to the contralateral breast new primary rate (1.5–4% at 13 years) (Vicini et al. 2004; Perera et al. 1995). Based on these data, the partial breast target volume comprising the lumpectomy cavity with a margin may be adequate for reducing the risk of local recurrence in women with small, adequately resected tumors. With hypofractionated radiation therapy, reducing the target volume from the whole breast to the cavity with a margin is intended to reduce late toxicity including telangiectasias and fibrosis, which may be more prominent when the whole breast is treated with a hypofractionated schedule. APBI is now a potential adjuvant treatment option for patients with early-stage breast cancer who, due to comorbid conditions and/or age and/or logistics, are not suitable candidates for 6–7 weeks of daily radiation therapy but would benefit from adjuvant treatment based on life expectancy. However, some patients who are candidates for APBI may not be appropriate candidates for brachytherapy applicators such as the MammoSite balloon or interstitial needles (due to the location of the lumpectomy cavity, its size, shape, or the ratio of breast/cavity volumes), or they may simply request a noninvasive treatment approach. In such patients, 3D conformal APBI may be most applicable.

16.1.2 Prospective Randomized Data Comparing APBI and External-Beam APBI to Whole Breast Radiation Therapy

Polgar et al. reported the five-year results of a Phase I–II study and the initial findings of a randomized Phase III trial assessing adjuvant brachytherapy alone following breast-conserving therapy for stage I breast cancer (Polgar et al. 2002). Initially, 45 patients with stage I breast cancer were prospectively selected to undergo adjuvant tumor bed radiotherapy (TBRT) via interstitial HDR implants that were used to deliver either 4.33 Gy × seven fractions or 5.2 Gy × seven fractions. With a median follow up of 57 months, 4.4% local, 6.7% axillary, and 6.7% distant failures and 4.4% deaths due to breast cancer were observed. The five-year probabilities of cancer-specific, relapse-free and local recurrence-free survival were 90%, 85.9%, and 95.6%, respectively. Cosmetic results were excellent in 97.8% of patients, and no toxicity greater than grade 2 was observed. Based on the technical feasibility and results of the study, a phase III study was initiated, and 258 further patients were

randomized to receive 50 Gy WBRT ($n = 130$) or TBRT ($n = 128$) alone consisting of interstitial HDR brachytherapy delivering 5.2 Gy in seven fractions ($n = 88$) or electron beam irradiation that was used to deliver 50 Gy ($n = 40$) (Polgar et al. 2007). At a mean follow-up of 66 months, the five-year actuarial rate of local recurrence was similar in both arms; specifically, 4.7% and 3.4% in the TBRT and WBRT arms, respectively ($p = 0.5$). The five-year probabilities of overall survival (95% vs. 92%), cancer-specific survival (98% vs. 96%) and disease-free survival (88% vs. 90%) were similar in both arms as well. Furthermore, the rate of good to excellent cosmetic outcomes was higher in the TBRT group (78% vs. 63%, respectively, $p = 0.009$). When comparing the external-beam technique to HDR brachytherapy for TBRT, the latter appeared to result in a better cosmetic outcome (70% vs. 81% good to excellent cosmetic results, respectively). Thus, for carefully selected early-stage breast cancer patients, the five-year results of this study demonstrate that TBRT achieves similar results with respect to disease control to those achieved with WBRT, and likely with better cosmetic outcome. To our knowledge, this study represents one of only two Phase III trials that have utilized external-beam radiotherapy to deliver APBI.

The only other Phase III prospective randomized trial comparing external-beam APBI to whole breast irradiation (WBI) was conducted at the Christie Hospital, Manchester, United Kingdom (Ribeiro et al. 1990; Ribeiro et al. 1993). The study included 708 patients with clinically palpable breast carcinomas (invasive ductal or lobular) measuring 4 cm or less with no palpable axillary adenopathy. Following lumpectomy (with no sentinel or axillary node dissection), the patients were randomized to receive either limited-field (LF) partial breast irradiation including the tumor bed, or wide-field (WF) radiation including the whole breast and regional lymph nodes. Although microscopic margin status was not reported, the primary tumor was reported as being grossly completely excised in 80% of cases, incompletely excised in 10% of cases, and could not be assessed in 10% of cases. In the LF group, 40–42.5 Gy was delivered in eight fractions over ten days, using 8–14 MeV electrons prescribed to the 100% isodose line (IDL). The average field size was 8 × 6 cm. Patients in the WF arm were treated via an opposed tangential field arrangement using 4 MV photons to deliver 40 Gy in 15 fractions over 21 days. The anterior supraclavicular/axillary nodal region was treated with a separate field using 4 MV photons.

At six years from the first randomization, 96% of the WF group and 92% of the LF group were free of breast recurrence. The actuarial breast recurrence-free survivals at five years were 94% and 87% for the WF and LF groups, respectively. In the eight-year update, overall survival rates were similar between the groups (73% and 71% for the LF and WF groups, respectively). The actuarial breast recurrence rates were 20% and 11% in the LF and WF arms, respectively ($P = 0.0008$). However, when histology was factored into the analysis, invasive lobular histology appeared to account for a significant proportion of the local recurrences in the LF group compared to the WF group (34% and 8%, respectively). The local recurrence with invasive ductal carcinomas was similar in both arms (15% with LF, and 11% with WF). Extensive intraductal carcinoma in situ was associated with higher recurrence rates in both arms, 21% for the LF arm and 14% for the WF arm, with salvage surgery possible in 86% and 90% of the patients in each arm, respectively. It is worth noting that the marginal miss/true recurrence (outside the treated field) of invasive ductal carcinoma in the LF arm was 5.5%. The rate of fibrosis and telangiectasias was higher in the LF arm, and cosmetic outcome was worse. However, unlike

contemporary 3D conformal APBI, PBI was delivered by electron beams, which not unexpectedly result in a higher skin dose and therefore a less optimal cosmetic outcome.

Further differences between patient management in this study and the care provided today include a lack of sentinel lymph node biopsy or axillary node dissection, systemic treatment, and evaluation of microscopic margins. Also, most patients did not have pre- or postoperative mammography, and therefore multicentric disease could not be excluded. Furthermore, tumor size was unknown in 42% of patients, extensive ductal carcinoma in situ was not excluded, and all histologies were allowed. The simulation and treatment delivery did not have quality assurance criteria, CT scan evaluation or planning, 3D treatment planning, localization of the lumpectomy cavity borders or depth, daily verification of treatment field, or DVH analysis. Although the authors conclude that limited-field irradiation results in a higher recurrence rate, with the current standard of care and the fact that the rate of recurrence with invasive ductal carcinoma was similar between the two arms, 3D conformal APBI appears to have a significant role to play in the adjuvant treatment of early-stage breast cancer.

16.2 Physics and Techniques

16.2.1 Prone 3D Conformal APBI

Patients who may benefit from the displacement of the lumpectomy cavity away from the chest wall, and thus the heart and lungs, with the prone treatment technique are those who are physically able to tolerate lying prone during simulation and treatment. Patient positioning during treatment delivery is geared toward optimizing daily reproducibility, limiting normal surrounding tissue dose, and ensuring appropriate dose coverage to the target structure. In the case of partial breast irradiation, the respiratory and cardiac motion may potentially result in the movement of breast tissues and thus the target area during treatment delivery. The prone treatment position has been used to reduce breast tissue motion resulting from cardiac systole and respiratory movement (el Fallah et al. 1997). In such a position, excursion of the chest wall can be reduced to 5 mm (Jozsef et al. 2000), minimizing breast tissue motion and therefore target motion. Also, if the breast is allowed to hang through an opening in the table, this may allow the cavity to fall away from the chest wall due to gravity (Formenti 2005) (Fig. 16.1), and may result in the exclusion of the heart and lung from the treatment field (Griem et al. 2003).

16.2.2 Dose Fractionation Scheme for Postoperative Supine and Prone External-Beam APBI

Baillet et al. completed a prospective study of 230 elderly patients who were randomized to receive hypofractionated postoperative whole breast radiation therapy to 23 Gy in four fractions over 17 days versus 45 Gy in 25 fractions over 33 days, which resulted in equivalent

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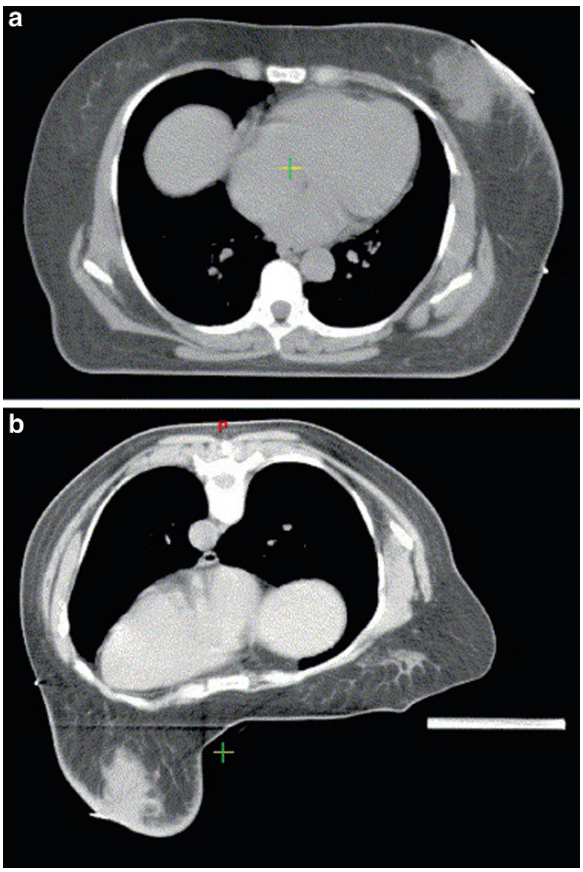

Fig. 16.1a–b Supine **a** and prone **b** patient positioning (Formenti 2005)

local control at four years (7% vs 5%, respectively), although the cosmetic outcome was inferior in the hypofractionated treatment arm (Baillet et al. 1990). The fibrosis rate was 18% in the group randomized to hypofractionated radiation treatment compared to 9% in the standard fractionation group. As surrounding normal structures, like heart and lung, do not significantly restrict the target volume coverage for patients treated in the prone position, hypofractionated partial breast irradiation doses were safely explored. The linear–quadratic cell survival model with an alpha–beta value of 4 for breast carcinoma was used to develop fractionation schedules including a dose of 30 Gy in five fractions over ten days, which is biologically equivalent to delivering 50 Gy in 25 fractions of 2 Gy over five weeks (Barendsen 1982; Steel et al. 1987; Yamada et al. 1999). With respect to cosmesis, the late tissue complications were similar to those observed with five weeks of standard whole breast irradiation followed by a boost to 60 Gy to the tumor bed, which results in acceptable cosmetic outcome (Archambeau et al. 1995; de la Rochefordière et al. 1992).

Biologically equivalent doses of different fractionation schemes are listed in Table 16.2.

Table 16.2 Biologically equivalent doses of different fractionation schemes (Formenti 2005)

Endpoint	α/β	50 Gy/25 fx	30 Gy/5 fx	60 Gy/30 fx	34 Gy/10 fx
Erythema	8[b]	$63\,Gy_{8}$	$53\,Gy_{8}$	$75\,Gy_{8}$	$48\,Gy_{8}$
Desquamation	11[b]	$59\,Gy_{11}$	$6\,Gy_{11}$	$71\,Gy_{11}$	$45\,Gy_{11}$
Telangiectasia	4[b]	$75\,Gy_{4}$	$75\,Gy_{4}$	$90\,Gy_{4}$	$63\,Gy_{4}$
Fibrosis	2[b]	$100\,Gy_{2}$	$120\,Gy_{2}$	$120\,Gy_{2}$	$92\,Gy_{2}$
Tumor control	4	$75\,Gy_{4}$	$75\,Gy_{4}$	$90\,Gy_{4}$	$63\,Gy_{4}$
Tumor control[a]	4	$72\,Gy_{4}$	$75\,Gy_{4}$	$86\,Gy_{4}$	$63\,Gy_{4}$

[a] Taking into account cell proliferation during the course of treatment (Barendsen 1982 162 /id; Steel et al. 1987; Yamada et al. 1999)
[b] Data from Archambeau et al. (1995)

16.2.3 Novel Treatment Delivery Techniques for 3D Conformal APBI

Recent investigations studying intensity-modulated radiation therapy (IMRT) and tomotherapy have shown at least equivalent, if not improved, normal tissue sparing and target volume homogeneity compared to 3D conformal EB APBI (McIntosh et al. 2008; Oliver et al. 2007). In the treatment planning study by Oliver et al., WB irradiation was compared to APBI plans using small-field rectangle tangents (ST), a two-field conformal radiation therapy technique (CRT2), a four-field conformal technique (CRT4), two-field IMRT (IMRT2), four-field IMRT (IMRT4), and tomotherapy (TOMO). The average radiation conformity indices (RCI) for all of the APBI techniques were significantly superior to the RCI values for WB tangents. Homogeneity indices were significantly superior for IMRT2, IMRT4, and TOMO. For the APBI techniques, all doses to organs at risk were significantly lower than the WB values except for the mean dose to the contralateral lung and contralateral breast, which were not significantly different. Not surprisingly, the choice of the important parameters has a direct impact on the dose to the organs at risk. Also, IMRT may require accounting for respiratory motion to reduce the likelihood of a geographic miss, especially in cases where the cavity extends to the skin and the PTV_{EVAL} is limited to 5 mm from the skin surface. While active breathing control or gating may allow reductions in PTV margins that are used to account for breathing, some data suggest that greater errors likely result from interfraction set-up variation than from intrafraction breathing motion (Kron et al. 2004). Further studies employing IMRT will determine its clinical utility.

Finally, proton therapy has recently been studied in the delivery of APBI. A dosimetric comparison of proton and mixed photon–electron 3D conformal APBI revealed acceptable PTV coverage with both techniques and excellent dose homogeneity (Kozak et al. 2006a, b). Furthermore, proton therapy resulted in a mean 36% reduction in the volume of the non-target breast volume receiving 50% of the prescribed dose, which was independent of tumor location, breast size, PTV size, or PTV/breast ratio. Recent investigations using proton therapy to deliver APBI in 20 patients demonstrated excellent disease control (100%) with a short follow-up of 12 months (Kozak et al. 2006b). While six- and 12-month physician-rated cosmetic outcomes were good to excellent in 89% and 100%, respectively,

and patient-rated breast global breast cosmesis was 100% and 100%, respectively, proton 3D conformal APBI produced high rates of acute skin toxicity. At 3–4 weeks, 79% of patients experienced moderate to severe skin color changes, and at 6–8 weeks, 22% of patients experienced moderate to severe moist desquamation. Telangiectasia, rib tenderness, and rib fracture were noted in three, three, and one patient respectively. Another report by Massachusetts General Hospital describes excellent PTV coverage and normal tissue sparing, with the exception of when a single proton beam was used and led to severe moist desquamation (Taghian et al. 2006). The cost analysis in the report describes proton therapy as being modestly more expensive (by 25%) than standard WB RT. Thus, while proton therapy may provide an interesting opportunity for some normal tissue sparing, further investigations are needed to ensure feasibility, improved skin toxicity and appropriate cost when using this modality for the delivery of APBI.

16.3 Clinical Results

16.3.1 Pilot Phase I Dose-Escalation Trial

Formenti et al. initially conducted a study at the University of Southern California using two "radiosurgical" approaches that were originally intended as substitutes for surgical excision in patients with breast cancers ≤5 mm (Jozsef et al. 2000; Formenti 2005). The treatment techniques used included using 4 MV photons to deliver 15, 18, and 20 Gy (with a 32 mm diameter collimator) via (Baglan et al. 2003) seven fixed horizontal beams or (Veronesi et al. 2001) six 45° arcs and a 90° sagittal arc, with minimum target doses at 83% and 86% of the dose maximum, respectively. Post-treatment target area excisions of the first three patients demonstrated a viable tumor 8–10 weeks after therapy. Therefore, the research focus was modified to treat the postlumpectomy cavity with margin.

Subsequently, Formenti et al. conducted a pilot dose escalation study to evaluate the feasibility of hypofractionated conformal PBI therapy in the prone position (Formenti et al. 2002). Eligibility criteria included postmenopausal status, nonpalpable pT1 invasive breast cancer, estrogen receptor positive tumors, lack of extensive intraductal component, negative surgical margins by at least 2 mm, and patient refusal to undergo six weeks of radiation therapy. All nine patients who underwent treatment received five fractions over ten days, with total doses ranging from 25 to 30 Gy. Patients were treated in the prone position on a table with an aperture with variable diameter settings. The daily set-up was based upon external markings on the patient's skin and also radiopaque markers in the lumpectomy cavity (clips) if present. Set-up accuracy was verified with orthogonal post-films prior to each fraction, and at least two fields were ported as well. Target definition was accomplished by CT contours of the lumpectomy cavity and a 2 cm margin. The prescription dose was defined as the minimum dose encompassing 95% of the PTV. The maximum dose was not to exceed the prescription dose by more than 10% (Fig. 16.2). In most cases, the treatment fields were 5–7 horizontal fixed beams in a coronal plane (Fig. 16.3). Out of a total of nine randomized and treated patients, three received

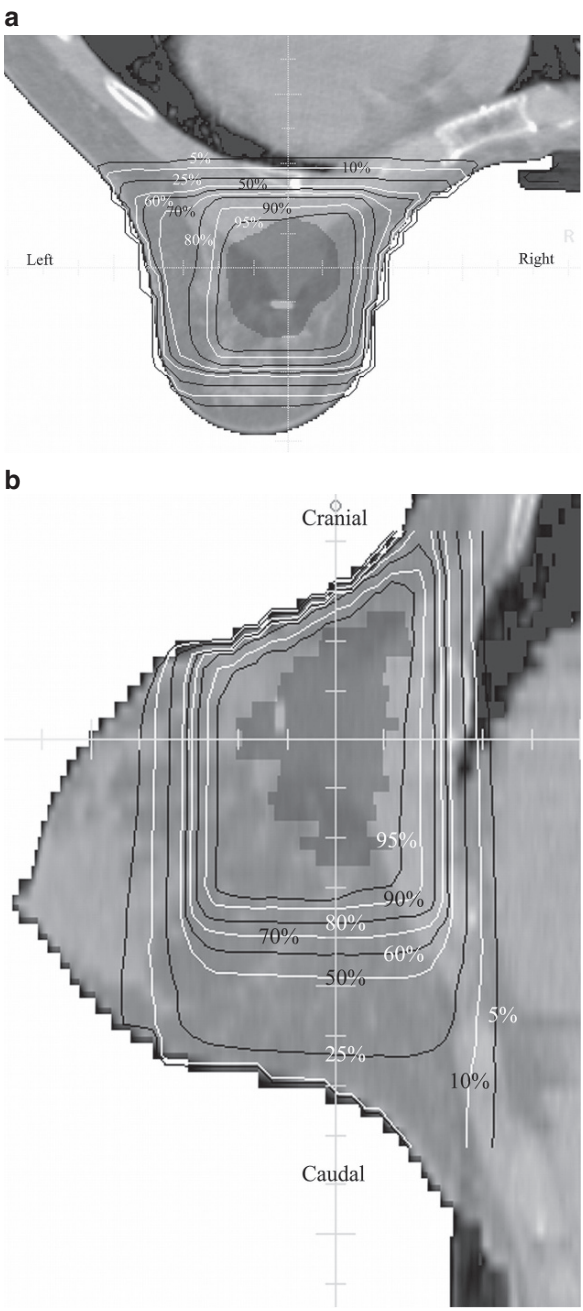

Fig. 16.2 **a** Planning target volume and isodose distributions (*left–right*): NYU (Formenti et al. 2002). **b** Planning target volume and isodose distributions (*cranial–caudal*): NYU (Formenti et al. 2002)

5 Gy per fraction, four received 5.5 Gy per fraction, and two received 6 Gy per fraction. Two of the nine patients did not undergo lymph node sampling. Follow-up ranged from 36 to 53 months, and cosmetic results were good to excellent for all patients.

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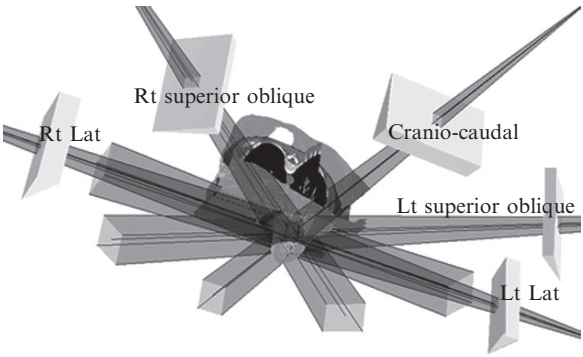

Fig. 16.3 Three-dimensional graphic reconstruction of five beam-eye views for prone 3D conformal APBI (Formenti et al. 2002)

16.3.2 Phase I/II Trial of Prone 3D Conformal APBI: New York University

On the basis of the results of the pilot study, Formenti et al. conducted a study of 47 postmenopausal women with stage I T1N0 breast cancer who refused to undergo six weeks of whole breast radiation treatment. These women were treated to 30 Gy in five 6 Gy fractions over ten days (on Monday, Wednesday, Friday, Monday, and Wednesday) (Formenti et al. 2004). Other eligibility criteria included negative margins by at least 5 mm. The patients were treated in the prone position and the PTV was defined as the lumpectomy cavity with a 1.5 cm margin, limited anteriorly by the skin and posteriorly by the chest wall. CT-defined target volumes were treated with opposed minitangents with wedges (Fig. 16.4). The dose was normalized to 100% at the isocenter before an isodose was selected that encompassed the PTV, 95% isodose line. Dose inhomogeneity was less than 110%. Fifty percent of the ipsilateral breast volume received less than 50% of the prescribed dose (Fig. 16.5). The contralateral breast and ipsilateral heart and lung were avoided completely in the beam arrangement. Forty-seven patients entered treatment and 46 completed. Most of the patients were treated in the prone position (four were treated supine due to patient intolerance of the prone position or because the lumpectomy cavity was located in the axillary tail). The median follow-up was 18 months. The most common acute toxicity was grade 1–2 toxicity, which was seen in 60% of patients. Late toxicity, totaling 21 in 14 patients, was primarily grade 1, and cosmetic results were mostly good to excellent. Only two patients had fair cosmetic results, and no patients had a worse score after radiation when compared to their postoperative baseline score. At this short follow-up, no patients had local recurrence. The mean and median lumpectomy cavity or CTV were 52 cc and 34 cc (range 7–379 cc), respectively. The mean and median PTV were 228 cc and 192 cc (range 57–1,118 cc), respectively. The mean and median ipsilateral breast volumes were 1,102 cc and 1,006 cc (range 258–346 cc) respectively. The coverage of the PTV by the 30 Gy isodose line was 100% (both mean and median). The ipsilateral breast volume receiving 100% of the prescribed dose ranged from 10 to 45% (mean and median 26 and 27%, respectively). In 25% of

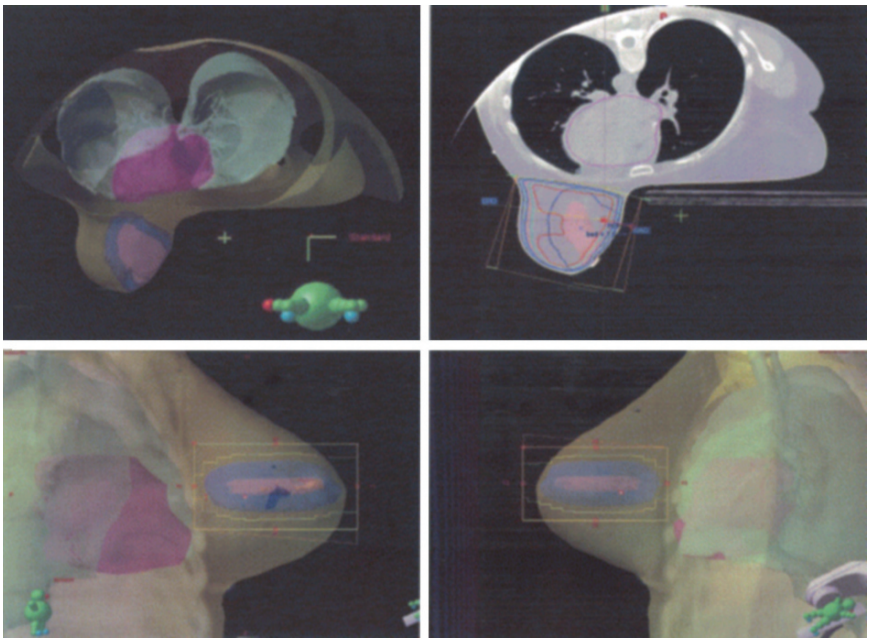

Fig. 16.4 Example of the relationship of the tumor bed to the planning target volume (PTV) (*upper*); tumor bed in *red* wash, PTV in *blue*, heart in *pink*, and lung in *light green*. PTV represents a 1.5 cm margin on the tumor bed. *Lower*: digitally reconstructed radiographs, right anterior oblique and left posterior oblique portals for left-sided breast cancer (Formenti et al. 2004)

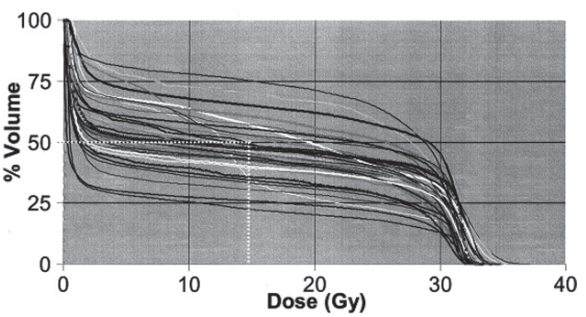

Fig. 16.5 Dose–volume histogram of ipsilateral breasts of 47 patients (Formenti et al. 2004)

patients, >50% of the ipsilateral breast volume was treated to >50% of the prescribed dose in order to cover the PTV adequately (Table 16.3). The mean percentages of lung volume and heart volume receiving 20, 10, and 5 Gy were 0% and 0%, respectively, in the patients treated in the prone position. In the four patients treated in the supine position, the median doses to the lung receiving 20, 10, and 5 Gy were 2%, 4%, and 6%, respectively.

Table 16.3 Dosimetric findings: CTV, PTV, and ipsilateral breast volume (IBV): NYU (Formenti et al. 2004)

Dosimetric characteristics	Mean value	Median value	Range
IBV (cm^3)	1102	1006	258–3468
CTV (cm^3)	52	34	7–379
PTV (cm^3)	228	192	57–1118
Maximal dose (% of PD)	110	108	105–117
PTV coverage by 95% iso-dose surface (%)	100	100	–
Ispilateral breast coverage (% IBV encompassed by % of PD)			
100% of PD	26	27	10–45
75% of PD	41	40	20–68
50% of PD	47	46	23–75
25% of PD	53	53	27–82
CTV/IBV (%)	5	4	1–22
PTV/IBV (%)	22	20	10–55
CTV/PTV (%)	20	20	6–46

16.3.3 The William Beaumont Hospital Experience: 3D Conformal APBI in the Supine Position

Initial clinical experience at William Beaumont Hospital in utilizing 3D conformal radiation therapy to deliver APBI in patients with early-stage breast cancer treated with breast-conserving therapy supported the technical feasibility of such treatment delivery (Baglan et al. 2003; Vicini et al. 2003a, b). In this Phase I/II study, 23 patients were prospectively enrolled between August 2000 and December 2002. An additional five patients were treated according to the guidelines of the protocol for compassionate purposes. Eligibility for the protocol included patient age ≥ 50, tumor size ≤ 3 cm, invasive ductal histology, lumpectomy with negative surgical margins by at least 2 mm, negative axillary lymph nodes with a minimum of six sampled (or negative sentinel lymph node biopsy), no extensive intraductal component or skin involvement, and no Paget's disease of the nipple. The details of the simulation and treatment planning are as follows. All patients initially underwent virtual CT breast simulation with alpha-cradle immobilization and delineation of the breast borders with physician-placed radiopaque catheters. The CTV was defined as the lumpectomy cavity uniformly expanded by 10–15 mm, and limited to 5 mm from the skin surface and lung–chest wall interface. The PTV was defined by adding 5 mm to the CTV for breathing motion and another 5 mm for set-up error. The beam arrangement included three, four, five, or seven noncoplanar beams with 6 MV photons alone in 21 patients, combined 6 and 18 MV photons in four patients, a combination of photons and electrons in two patients, and electrons alone in one patient. Field arrangements were designed with the isocenter placed in the center of the PTV, and approximated breast tangents with a 10–20° steeper gantry angle for the medial beams for maximal breast tissue sparing and a couch angle of 15–70°.

The procedure used to set up the four-field technique, consisting of a left anterior superior-to-inferior oblique (Lt ASIO), a left anterior inferior-to-superior oblique (Lt AISO), a right anterior inferior-to-superior oblique (Rt AISO), and a right posterior superior-to-inferior oblique (Rt PSIO) for a right breast lesion, is described as follows (Fig. 16.6). First, three medial tangents (couch angle of 0° for two and 180° for one of the beams) and one lateral tangent (couch angle of 0°) are constructed. Typically, the medial tangents have a 10–20° steeper gantry angle than whole breast tangents to spare more breast tissue. The lateral tangent may also have a slightly shallower gantry angle to spare breast tissue, provided that it does not exit through the contralateral breast. Next, couch angles were applied to each beam. Typical couch angles for the three anterior oblique fields were 35–45° from a transverse plane. However, for the Rt AISO beam, particular care was taken to ensure that the field exited superior to the heart. The couch angle used for the posterior oblique field was usually only 10–20° to avoid entering through the ipsilateral arm and collision problems with the gantry head and treatment couch.

The five-field technique was initially used for left-sided lesions and consisted of Rt ASIO, Rt Lateral, Rt AISO, Lt PSIO, and Lt PISO beams. The primary difference that made this technique better suited for left-sided lesions was the elimination of the Lt AISO beam that would exit through the heart. The tradeoff was a larger volume of normal breast tissue irradiated (Fig. 16.7). With additional experience, only three- and four-beam combinations were employed. It should be noted that these beam arrangements may not be possible with linear accelerators that have larger gantry heads than the Elekta SL20. Each field had a universal 60° wedge in place for part of the treatment time. The heel of the wedge was directed anteriorly for all fields, and its direction was manually optimized if necessary.

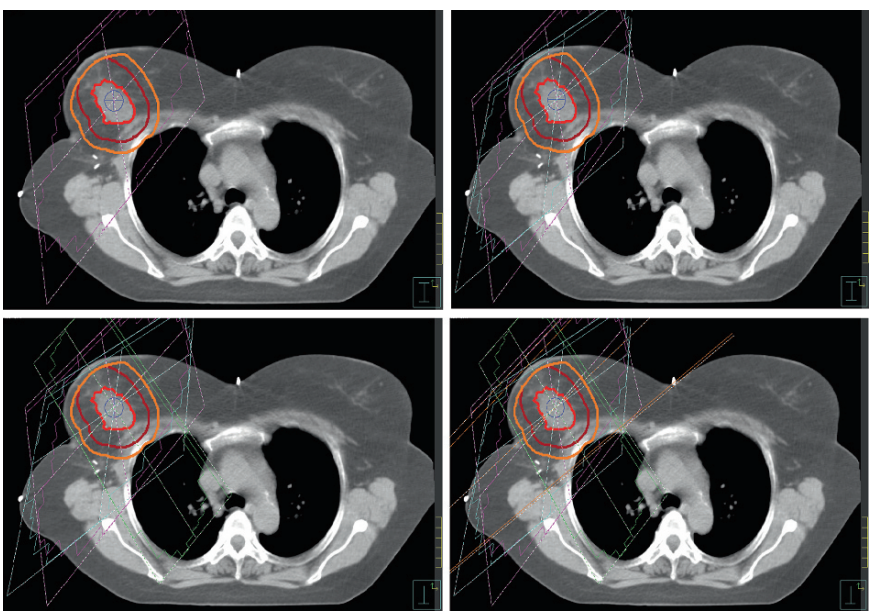

Fig. 16.6 Consecutive addition of LASIO, LAISO, RAISO, RPO beams (WBH)

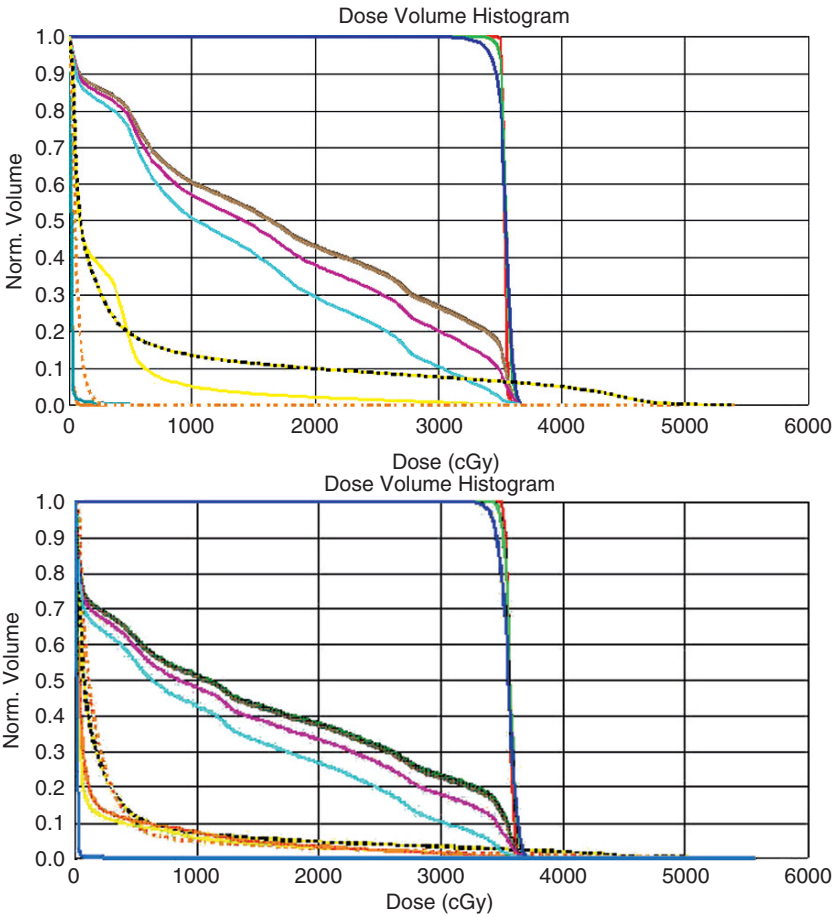

Fig. 16.7 Dose–volume histogram: WBH; four-field technique (*top*), five-field technique (*bottom*)

The field edge was 5–7 mm beyond the PTV to account for penumbra. Beam weights were manually optimized such that the CTV was completely encompassed by the 100% isodose line (IDL) and the PTV by the 95% IDL, while maintaining a hotspot of < 110%. The initial dose-fractionation schedule was 34 Gy delivered in ten fractions of 3.4 Gy, administered twice daily over five consecutive days with at least a 6 h interfraction interval, which is identical to the RTOG 95-17 brachytherapy dose schedule. After treating six patients, the fraction size was increased to 3.85 Gy, giving a total dose to 38.5 Gy. This corresponds to a radiobiological dose of approximately 45 Gy given in 25 fractions using WBI and assuming an α/β ratio of 10.

Additional normal tissue dose guidelines were used during beam weight optimization. These included limiting 50–60% of the ipsilateral breast volume to ≤ 50% of the prescribed dose and 25–35% of the ipsilateral breast volume to ≤ 100% of the prescribed dose. In addition, the heart and lung dose–volume histograms (DVHs) were below those for

whole breast tangents for left-sided lesions. In all patients, a comparison was made in terms of the doses delivered to normal tissues between the 3D conformal APBI plan and standard tangents. The goal was to accept plans that matched or preferably reduced doses to the heart and lung. Mean and median values (as well as ranges) for doses to the CTV, PTV, heart, and lung with the 3D conformal APBI plans were calculated on the protocol patients only. It should be noted also that serial CT scans were performed to determine the lumpectomy cavity changes over time in 18 patients. In 72% of the patients, the cavity decreased by a mean of 49% and a median of 45%, with mean and median times between CT scans of 7 and 11 days, respectively. In 22% of patients, the cavity increased in volume by a mean of 61% and median of 50% (range of 27–116%). The mean and median times between the CT scans were 22 and 17 days, respectively. Dosimetric findings are given in Table 16.4.

The mean and median sizes of the lumpectomy cavity at the time of dosimetric treatment planning were 22 cc and 14 cc, respectively (range 3–70 cc). The mean and median volume of the CTV was 118 cc and 112 cc, respectively (range 28–231 cc). The mean and median coverages of the CTV by the 100% isodose line (IDL) were 97 and 100%, respectively. Coverage of the CTV by the 95% IDL had a mean and median of 100%. The mean and median coverages of the PTV by the 95% IDL were 100%. The mean and median volumes of the ipsilateral breast receiving 100% of the prescribed dose were 23% and 21%, respectively. The mean and median volumes receiving 50% of the prescribed dose were 47% and 46%, respectively. The mean and median volumes of the heart receiving 10, 20 and 30% of the PD were compared for the 3D conformal APBI technique and standard WBI, and are presented in Table 16.5. For all of the parameters examined, unnecessary doses to the heart delivered with the APBI technique were less than or equal to those delivered with standard WBI. Likewise, the mean and median volumes of the lung receiving 5, 10, and 20% of the prescribed dose were compared for the 3D conformal APBI technique and standard WBI, and are also presented in Table 16.5. Again, for all of the parameters

Table 16.4 Dosimetric findings: CTV, PTV, and ipsilateral breast (protocol patients, $n = 26$): WBH (Vicini 2003b)

Dosimetric characteristics	Mean value (%)	Median value (%)	Range (%)
Maximum dose (% of PD)	109	109	100–112
CTV coverage			
100% IDL	98	100	54–100
95% IDL	100	100	99–100
PTV coverage			
95% IDL	100	100	97–100
Ipsilateral breast coverage			
100% IDL	23	21	14–39
75% IDL	36	35	26–53
50% IDL	47	46	34–60
25% IDL	60	60	39–92
PTV/total breast volume	17	17	11–22

CTV clinical target volume; **PTV** planning target volume; **PD** prescribed dose; **IDL** isodose line

Table 16.5 Dosimetric findings and normal tissue doses (n = 26): Tangents versus APBI–WBH (Vicini 2003b)

Dosimetric characteristics	Mean values		Median values		Range	
	Tangents (%)	PBI (%)	Tangents (%)	PBI (%)	Tangents (%)	PBI (%)
Cardiac doses						
V30	1	0	0	0	0–9	0–1
V20	2	0	0	0	0–12	0–3
V10	2	0	0	0	0–16	0–7
Lung doses						
V20	10	4	11	4	2–19	0–8
V10	14	9	14	9	4–23	0–34
V5	18	16	19	16	8–30	0–37

examined, unnecessary doses to the lung delivered with the PBI technique were less than or equal to those delivered with standard WBI.

Patients were initially seen at follow-up 4–6 weeks after completing treatment and then at three-month intervals. The median follow-up duration was eight months (range 1–24 months), and cosmetic results and acute toxicity were assessed for protocol patients only. Of the 28 patients, 19 (68%) experienced grade 1 toxicity and 11% (three patients) had grade 2 toxicity in the first six weeks of follow up. Cosmetic results were rated as good/excellent in all evaluable patients at six months (n = 2), 12 months (n = 3), 18 months (n = 4), and in the three evaluable patients at >18 months after treatment. Six-month follow-up mammograms were negative in all evaluable patients (n = 12).

16.3.4 William Beaumont Hospital Experience

The initial experience at William Beaumont Hospital was reported by Vicini et al. regarding thirty-one patients treated with 3D conformal APBI (Vicini et al. 2003a, b). Of these 31 patients, 94% had surgical clips outlining the lumpectomy cavity (mean: six clips). The CTV consisted of the lumpectomy cavity plus a 10 mm margin in nine patients and a 15-mm margin in 22 (median 15 mm). The PTV consisted of the CTV plus a 10 mm margin for breathing motion and treatment set-up uncertainties. The prescribed dose was 34 or 38.5 Gy (six patients and 25 patients, respectively) in ten fractions twice daily, with fractions separated by 6 h and delivered over five consecutive days. Patients were treated in the supine position with 3–5 beams (mean: four) that were designed to irradiate the CTV with <10% inhomogeneity and a comparable or lower dose to the heart, lung, and contralateral breast compared with standard whole breast tangents. The mean coverage of the CTV by the 100% IDL was 98% (range 54–100%, median 100%) and by the 95% IDL was 100% (range 99–100%). The mean coverage of the planning target volume by the 95% IDL was 100% (range 97–100%). The mean percentage of the breast receiving 100% of the PD was 23% (range 14–39%). The mean percentage of the breast receiving 50% of the PD was 47% (range 34–60%). The data are summarized in Table 16.4.

The median follow-up duration was ten months (range 1–30 months). Four patients were followed for >2 years, six for >1.5 years, and five for >1 year. The remaining 16 patients have been followed <12 months. While all patients had none to minimal skin changes during treatment, at the initial six-week follow-up, 61% had grade 1 toxicity and 10% had grade 2 toxicity. The remaining 29% of patients had no observable side effects and no grade 3 toxicities were observed. Cosmetic results were rated as good/excellent in all evaluable patients at six months ($n = 3$), 12 months ($n = 5$), 18 months ($n = 6$), and in the four evaluable patients at >2 years after treatment. Based on these results, further studies were conducted, including RTOG 0319.

16.3.5 Two-and Three-Year Clinical Experience (William Beaumont Hospital)

While 3D conformal PBI remains a relatively new form of APBI, data appear to indicate acceptable cosmetic results and side effects with median follow-ups of two and three years (Vicini et al. 2007; Gustafson et al. 2008). As most recently reported by William Beaumont Hospital, in 96 patients with low-risk features (tumor size < 2.0 cm in 89% of cases, margins of >2 mm in 93% of patients, and 99% node negative) and a median age of 62, one local recurrence developed at 18 months, for a three- and five-year actuarial rate of 1%. Cosmetic results were rated as good/excellent in 90% of evaluable patients at three years ($n = 10$). Grade I and II rates of erythema, hyperpigmentation, breast edema, breast pain, telangiectasias, fibrosis and fat necrosis with a minimum follow-up of three years were 0%, 7%, 0%, 0%, 7%, 21% and 7%, respectively. Only two patients (3%) developed grade III toxicity (breast pain), which resolved with time. While the cosmetic outcome and chronic toxicity appear acceptable, further follow-up will be needed to assess long-term efficacy.

16.3.6 RTOG 0319

Activated in August of 2003, the RTOG 0319 Phase I/II technical feasibility study was based upon the initial William Beaumont Hospital experience. The same eligibility criteria and treatment technique, doses and fractionation schedule as used in RTOG 95-13 were employed in this study. The accrual goal was 42 patients and a total of 58 enrolled (with seven patients excluded). The analysis was based on the first 42 of 51 evaluable patients from 17 different institutions treated by April 2004. Only four of the first 42 evaluable treatments were scored as unacceptable due to normal tissue DVHs exceeding 5% of the specified limit. Thirty-two cases of minor variations in the treatment plans were noted, with 16 related to normal tissue DVH exceeding the limits by ≤5%, six related to suboptimal coverage of the PTV, and ten related to both. Of the 51 evaluable patients, one additional major and five minor variations in the treatment plans were detected. As the study was designed to demonstrate reproducibility if fewer than five cases among the first 42 evaluable patients were scored as unacceptable, 3D conformal APBI was considered to be technically feasible in this study (Vicini et al. 2005).

16.3.7 Massachusetts General Hospital Experience

The initial clinical data acquired from the first 22 patients who underwent treatment reported by Taghian et al. at 1–6 months follow-up supports the feasibility and minimal acute toxicity of 3D conformal APBI demonstrated in other studies. The eligibility criteria included histology of invasive ductal carcinoma ≤2 cm, negative lymph nodes, negative margins by at least 2 mm, and no lymphovascular space invasion or extensive intraductal component. The prescribed dose was 32 Gy in eight fractions twice daily, separated by 6 h and delivered over 4–5 days. The PTV consisted of the lumpectomy cavity with a 15–20 mm margin. The dose inhomogeneity was less than 10% across the PTV. The patients were treated in the supine position with three or four beams of mostly mixed photons and electrons (one patient was treated with only photons). The mean and median tumor sizes were 0.86 cm and 0.9 cm, respectively, with mean and median lumpectomy volumes of 42.9 cc and 34.0 cc, respectively. The mean and median PTVs were 178.1 cc and 151 cc, respectively. The mean doses received by 20% (V20), 10% (V10), and 5% (V5) of the ipsilateral lung volume were 2.3 Gy, 4.5 Gy and 6.7 Gy, respectively. The mean V20, V10, and V5 of the heart for left-sided lesions were 1.5 Gy, 2.2 Gy, and 3.2 Gy, respectively. For the nontarget breast volume, 50% was an average of 6.7 Gy. At the initial follow-up, 41% of patients had mild erythema and 9% had moderate erythema, with no patients having moist desquamation. Cosmetic results were good to excellent in all patients.

16.4 Challenges and Limiting Factors in the Application of 3D Conformal APBI

A primary potential disadvantage of 3D conformal APBI relates to organ motion effects and patient set-up, which can necessitate a larger target volume in order to avoid a geographic miss. Based on previously published data (Frazier et al. 2004), a 5 mm CTV to PTV expansion should account for normal breathing (Baglan et al. 2003), and the use of 10 mm CTV–PTV margin also accounts for random and systematic components of set-up error. The final component of geometric uncertainty is the potential for the lumpectomy cavity to change shape and/or position independently of the surrounding breast tissue. A potential method of accounting for this motion involves on-line image guidance, which may employ the use of surgical clips to serve as a surrogate for the lumpectomy cavity during the abbreviated course of treatment (Weed et al. 2004). Studies have demonstrated that using either surgical clips or the breast surface for alignment results in improved localization over traditional alignment with lasers on stable anatomical structures such as bony anatomy (Hasan et al. 2008; Bert et al. 2006). A recent study by Gierga et al. compared four methods of target localization: standard laser-based set-up; kilovolt imaging of the chest wall; kilovolt imaging of the surgical clips; and 3D imaging of the breast (Gierga et al. 2008). In this study, target registration errors (TRE) for each modality were calculated assuming that the clip alignment was the gold standard. The TRE for surface imaging when using a reference surface captured directly with 3D video and gated imaging and the TRE for clip-based

registration were within 1 mm (3.2 mm vs. 2.4 mm, respectively). The importance of gating for surface imaging in this study was reflected in the TRE of about 5 mm when using surface imaging from a free-breathing CT scan or chest wall imaging.

The William Beaumont Hospital data were analyzed to determine if certain variables that predict whether a patient is technically suitable for the 3D conformal quadrant technique could be identified (Vicini et al. 2003). Based on previously published PBI brachytherapy data, a "borderline acceptable" plan was determined to have >50–60% of the breast volume covered by the 50% IDL. Based on this endpoint, several factors were analyzed for their association with the probability of a particular case being appropriate for 3D conformal APBI, including cavity volume, CTV volume, PTV volume, breast volume (BV), CTV:BV ratio, PTV:BV ratio (Table 16.6), tumor location, etc. The factor that was found to have the highest correlation with the ability to meet the dose–volume constraints was the PTV:BV ratio, with ratios of >0.2 being unlikely to meet the requirements of the protocol. As described previously, surgical clips have been used to delineate the lumpectomy cavity, and this may be assessed at some institutions via CT scanning.

Finally, as with the delivery of any form of irradiation, the issue of verification of treatment delivery, when the uncertainty factors have been accounted for during planning, must also be addressed. This is especially important during EB-APBI, as small inaccuracies may be more clinically significant, resulting in a potential geographic miss.

In order to study such potential target underdosage and/or overdosage of normal tissue, recent investigations to reconstruct dose delivery during EB-APBI by incorporating set-up errors and deformable registration have been conducted at William Beaumont Hospital (Hasan et al. 2007).

Sixteen patients with early-stage breast cancer treated with postlumpectomy EB APBI (CTV-to-PTV margin of 10 mm) prospectively underwent cone-beam CT (CBCT) prior to each fraction (ten scans per patient) and daily helical CT (HCT) (five scans per patient). Patients were set up on the treatment couch using laser localization of skin tattoos. CBCT images obtained prior to each fraction were automatically registered with the planning CT to determine translation/rotation set-up errors. Daily HCTs were imported into the planning system in treatment positions specified by CBCTs. The cavity was contoured and

Table 16.6 Dosimetric comparison of 3D conformal APBI techniques (Rosenstein et al. 2004)

				Ipsilateral breast coverage			
Series		PTV (cm^3)	PTV/TBV[a] (%)	100%	75%	50%	25%
NYU	Median	192	22	27	40	46	53
	Range	57–118	10–55	10–45	20–68	23–75	27–82
WBH	Median	240	17	21	35	46	60
	Range	82–482	11–22	14–39	26–53	34–60	39–92

[a] Planning target volume/total breast volume

dose per fraction was calculated in the HCTs. For 12 patients, an in-house image intensity-based deformable registration program was used to register the HCTs with the planning CT and generate the cumulative dose in the planning CT. The treatment schedule was 38.5 Gy in ten fractions BID over five days. EB APBI dose constraints from the NSABP-B39 protocol were used to compare the cumulative reconstruction and initial plan for each patient, specifically, PTV_{EVAL} V90, ipsilateral breast V50 and V100, lung V30, heart V5, and MaxDose. The mean set-up error magnitude based on CBCT registration was 9 ± 5 mm. The mean percentage change in cavity volume between the planning CT and treatment day 1 was −31 ± 35% (1 SD) over a median of 23 days (range 7–40), with ten (88%) patients showing a volume decrease. Between the first and last treatment day (relative to the planning CT volume), the mean percentage change in cavity volume was 1 ± 21%, with 7/16 patients showing increasing cavity volume. DVH analysis showed one patient (8%) with a decrease in CTV V90 of 8%. All other patients demonstrated adequate target coverage with a reduction in CTV V90 ≤ 1%. PTV_{EVAL} V90 was on average 3% (range 0–16%) less than planned. For the ipsilateral breast, four patients had an increase in V50 (max. 1% increase) and three patients had an increase in V100 (max. 9% increase), though only one showed an increase > 5%. Four patients had an increase in ipsilateral lung V30 (max. 3%). One of nine patients had an increase in heart V5 (1%). Four patients had an increase in MaxDose (max. increase of 89 cGy). Thus, according to this study, the current CTV-to-PTV margin of 10 mm appears to be sufficient for Ð92% of patients treated with EB APBI. While expansion of the population's PTV margin to 14 mm would provide a Ð97% confidence level, on-line image guidance may be a more favorable alternative that may potentially allow CTV-to PTV margin reduction and improve normal tissue sparing. CBCT used for on-line image guidance has been shown in other independent studies to also result in at least a modest decrease in systematic errors when using a bony anatomy or skin-mark set-up (Fatunase et al. 2008; White et al. 2007).

16.5 Future Directions

To determine whether APBI limited to the region of the tumor bed following lumpectomy provides equivalent local tumor control in the breast compared to conventional whole breast irradiation in the local management of early-stage breast cancer, the first Phase III randomized study of conventional whole breast irradiation versus APBI opened in March 2005. This study originally included patients with stage 0, I, or II breast cancer resected by lumpectomy with tumor size ≤ 3 cm and no more than three histologically positive axillary lymph nodes. Due to the rapid enrollment of a greater than expected proportion of low-risk patients, the accrual was increased by 1,300 (4,300 total) and, as of 1 January 2007, the eligibility criteria excluded low-risk patients (i.e., excluded patients ≥ 50 years of age with DCIS, and women with invasive cancer with all of the following features: ≥ 50 years of age with lymph nodes uninvolved, and/or ER-positive status). The stratification of patients is based upon disease stage (DCIS only; invasive and node negative; invasive with 1–3 lymph nodes involved), menopausal status, hormone receptor status, and intention to receive chemotherapy. Randomization is completed after the patient is identified as being

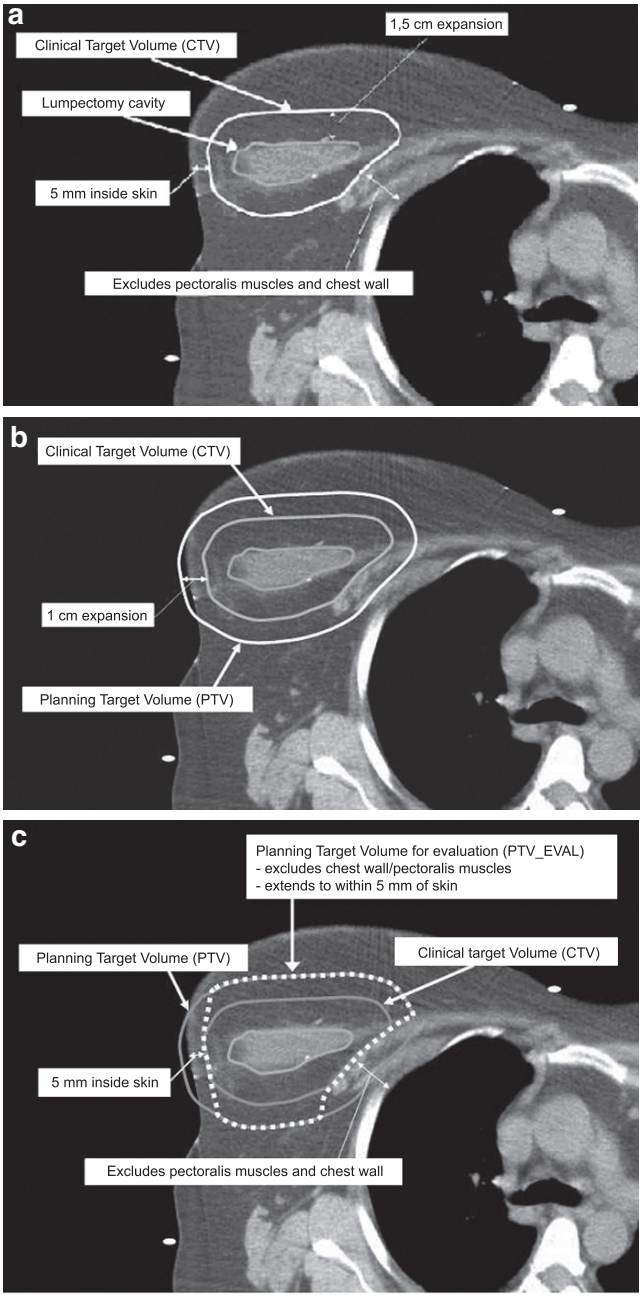

Fig. 16.8 **a** Phase III NSABP-B39/RTOG 0413 3D conformal APBI (cavity and CTV). **b** Phase III NSABP-B39/RTOG 0413 3D conformal APBI (cavity, CTV, and PTV) **c** Phase III NSABP-B39/RTOG 0413 3D conformal APBI (cavity, CTV, PTV, and PTV_EVAL)

an appropriate candidate for possible APBI based on CT criteria including lumpectomy cavity shape, absolute volume, volume in reference to the whole breast volume, location, and distance from the skin surface. If the patient is found to be appropriate candidate, randomization places her into either Group 1 (WBI) or Group 2 (PBI). WBI involves the delivery of 45–50 Gy in 25 fractions of 1.8–2.0 Gy per fraction to the whole breast, followed by an optional boost to ≥60 Gy. If the patient is randomized to Group 2, she will receive (as determined by her physicians in addition to patient preference) APBI via one of three modalities. The first two methods involve the delivery of 34 Gy in 3.4 Gy fractions twice daily over 5–10 days using multicatheter brachytherapy or the MammoSite balloon applicator. The third method of APBI delivery is via 3D conformal external-beam irradiation in which 38.5 Gy is delivered twice daily over 5–10 days in 3.85 Gy fractions. The interfraction time for all treatments is at least 6 h (Fig. 16.8). It should be noted that, perhaps due to ease of delivery and/or patient preference for noninvasive treatment, over 70% of patients enrolled into Arm 2 of the study, receiving APBI via the external-beam technique. Thus, it will be particularly interesting to see results regarding this particular mode of APBI when data are mature.

Furthermore, a recent Phase III trial from Canada randomized patients to either 3D conformal APBI only (Arm 1) or conventional whole breast irradiation of 42.5 Gy in 16 fractions (Arm 2), with either followed by an optional 10 Gy boost. The results of this study will provide further information regarding EB APBI specifically, and will also provide comparison data from hypofractionated (three weeks) whole breast irradiation.

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External-Beam Partial Breast Irradiation: The New York University Prone Technique

17

Silvia Formenti and Stella Lymberis

17.1 External-Beam Partial Breast Irradiation

External-beam radiotherapy has many advantages over other techniques of partial breast irradiation (PBI) (Formenti 2005, 2007). First and foremost, treatment is given after lumpectomy, when complete pathologic information is available on the original tumor and the status of the resection margins. Second, it spares the patient from the need for a second surgical procedure, since simulation and treatment are performed using a noninvasive method that does not require anesthesia. Third, the technique of external-beam PBI is more likely to be easily reproducible across different radiation oncology centers, since treatment outcomes are less likely to depend on the experience and operative skills of individual oncologists, unlike interstitial brachytherapy or MammoSite treatment techniques. External-beam PBI also generates better dose homogeneity, which may result in improved cosmetic outcome as compared to brachytherapy techniques. Finally, external-beam PBI is more cost-effective and less expensive than brachytherapy techniques (Suh 2005; Ellerin 2004). Considering these theoretical advantages, we developed a partial breast irradiation program that uses prone positioning, originally at the University of Southern California (Jozsef et al. 2000). Over the past eight years, this approach has been studied and defined further at New York University (Formenti 2004). In parallel, a series of different prone boards or prone tables were developed, with the intention of converging daily reproducibility with patient comfort (Fig. 17.1).

17.2 Selection of a Dose Fractionation Scheme for Postoperative Prone EB-PBI

The ease of target coverage in the prone position, without exposure to the heart or lung, together with the treatment of a partial volume of the breast with PBI created the ideal conditions to safely explore an accelerated hypofractionated regimen. By applying the

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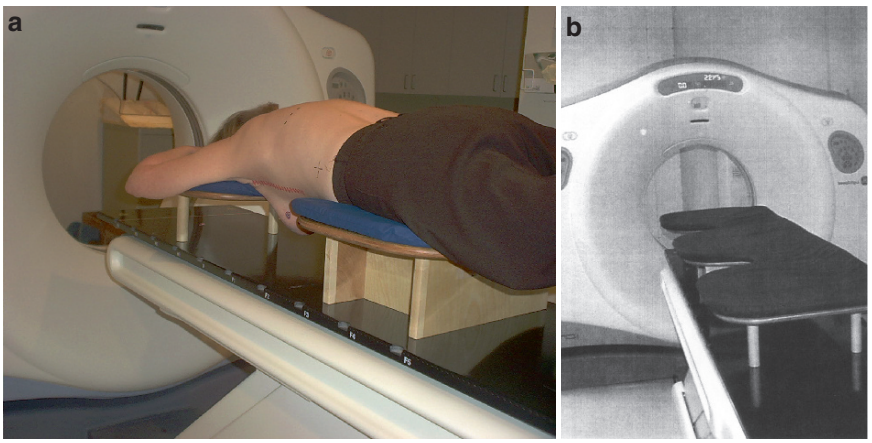


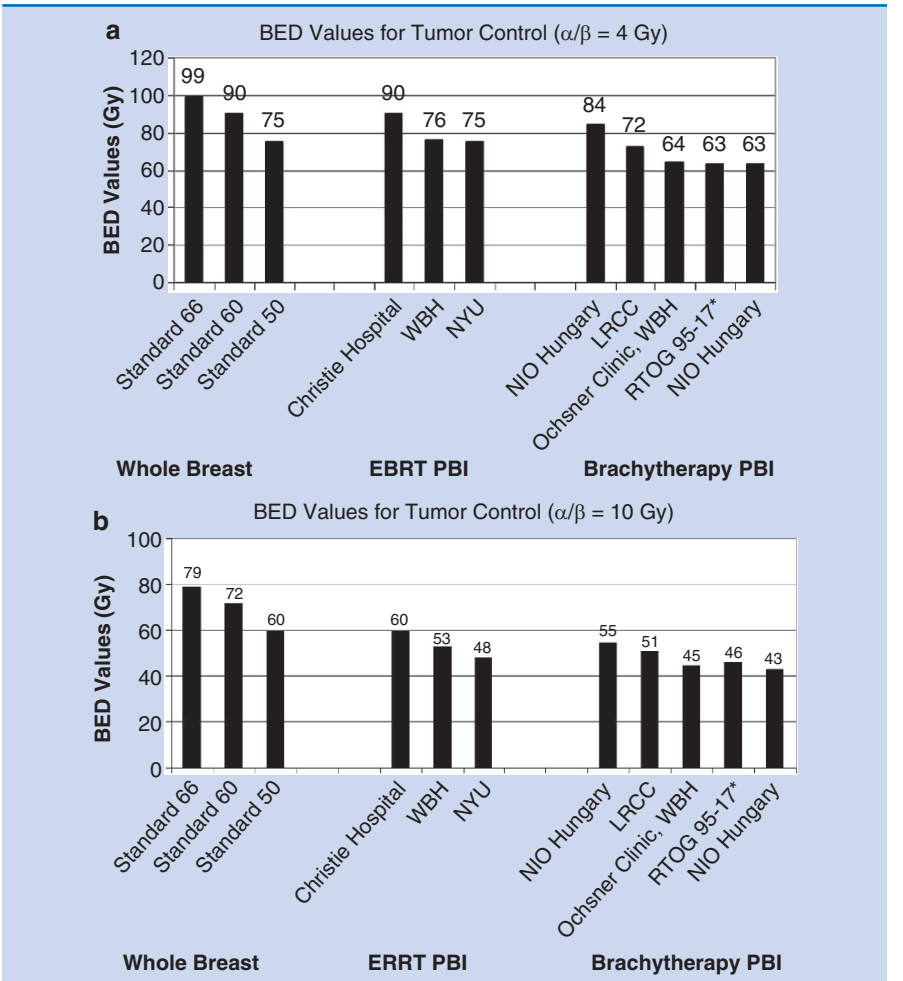
Fig. 17.1a–b Example of a prone breast table developed at NYU

linear–quadratic cell survival model with an α/β value for breast carcinoma of 4 (Barendsen 1982; Steel 1987; el-Fallah et al. 1997), a dose of 30 Gy given in five fractions of 6 Gy over ten days was found to be radiobiologically equivalent in tumor control to a dose of 50 Gy given in 25 fractions of 2 Gy over five weeks, as used in most breast cancer studies of the National Surgical Adjuvant Breast and Bowel Project (Fisher 2002). At the time of the original trial design, the question of the appropriate α/β value for breast cancer was the focus of lively debate within the breast cancer radiotherapy research community, with many supporting the adoption of an α/β of 10 for breast cancer. Based on available preclinical and clinical indications, in 2004 we conducted an analysis of the biologically equivalent doses of different fractionation schemes (Table 17.1a and b) (Rosenstein et al. 2004). Recently, the results from the randomized UK START A trail confirmed in a larger series of patients that the α/β value of 4 for breast cancer was a prescient and accurate estimate by confirming in the clinic what we had originally predicted based on preclinical models (Bentzen 2008).

17.3 Rationale for Patient Selection Criteria for Postoperative Prone EB-PBI

The ongoing randomized trial sponsored by the National Surgical Adjuvant Breast and Bowel Project and Radiation Therapy Oncology Group, NSABP-39/RTOG 0413, compares partial breast to whole breast radiation. Eligible for this trial are women with Stage 0, I, and II breast cancers under 3 cm in size and with less than three axillary lymph node metastases. Results from this trial that will allow the optimal selection of patients for whom partial breast treatment is most appropriate are not yet available. Moreover, in the absence of proven equivalence at an adequate long-term follow-up, partial breast irradiation remains investigational and should be made available only in the context of a clinical trial.

Table 17.1 Biologically effective dose calculations



Biologically effective dose calculations using an α/β value of 4 (Table 17.1a) and 10 (Table 17.1b) for tumor control comparing different approaches to partial breast radiotherapy treatment as compared to standard fractionation schedules used for whole breast radiotherapy. Reprinted from (Rosenstein et al. 2004) with permission from Elsevier

Our approach to testing PBI has been to design trials for the subset of breast cancer patients for whom partial breast irradiation is most likely to be the least risky: postmenopausal women with small tumors, mammographically detected (i.e., nonpalpable), surgically excised with negative margins, and found at pathology to be hormone receptor positive and with negative nodes. These patients have five- and ten-year survival rates of 95% and 85%, respectively (Kerner 2001), and the lowest risk of local recurrence. While at least two large prospective randomized studies have provided evidence that, in the absence of radiotherapy, the local recurrence rate in these patients is quite low, it was

significantly affected by the addition of standard radiotherapy in both studies (Fisher 2002; Fyles et al. 2001).

Note that a recent trial attempted to identify a subset of patients who could safely forgo adjuvant radiotherapy after breast-conservation surgery (BCS), by selecting women estimated to carry the lowest predictable risk of local recurrence and testing the feasibility of omitting radiotherapy. The trial required early closure because an excess of breast cancer recurrences were detected. The authors concluded that with the possible exception of elderly women with severe comorbid conditions, adjuvant radiotherapy after BCS remains the standard treatment (Lim 2006). Consequently, an accelerated approach of PBI delivered in five fractions appears to be an appealing compromise, particularly among the elderly (Joslyn 1999; Hebert-Croteau 1999).

In summary, hypofractionated EB-PBI is a cost-effective, noninvasive method which could best satisfy the needs of specific patient populations, since it is likely to impact on the risk of most local recurrences (at the tumor bed) while allowing for a condensed regimen with fewer trips to the radiation facility.

17.4 Rationale for Prone Patient Positioning

Positioning patients in the prone position has many advantages over standard supine positioning for breast treatment. Prone positioning leverages gravity to displace the tissue of the index breast away from the chest, often enhancing the distance between the tumor bed and the lung and heart. Using the simple technique of opposed tangent fields, one can target the whole or the partial breast while excluding the lungs and heart from the radiation field. At NYU, to achieve a reproducible prone breast position, a special mattress with an opening (Fig. 17.2a) that allows the breast tissue to fall away from the chest wall (Fig. 17.2b) is used. Figure 17.3 demonstrates a patient with a cancer of the right breast

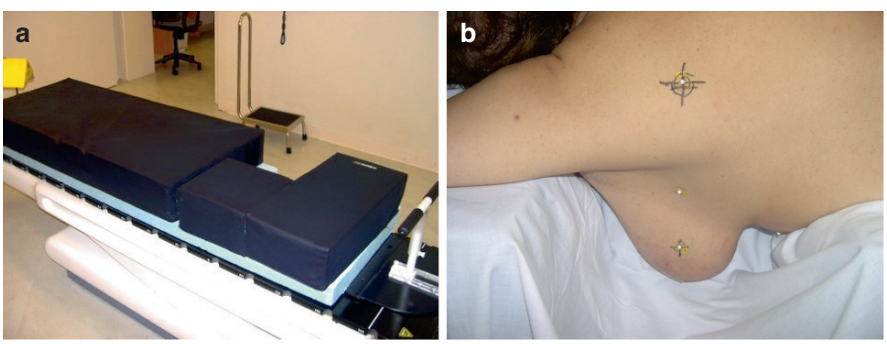


Fig. 17.2a–b A special mattress with an opening **a** that allows the breast tissue to fall away from the chest wall **b** is used to position the patient in a reproducible prone breast position. The mattress consists of three distinct elements that can be connected to create an opening, either on the right or left, for selective prone positioning of the index breast

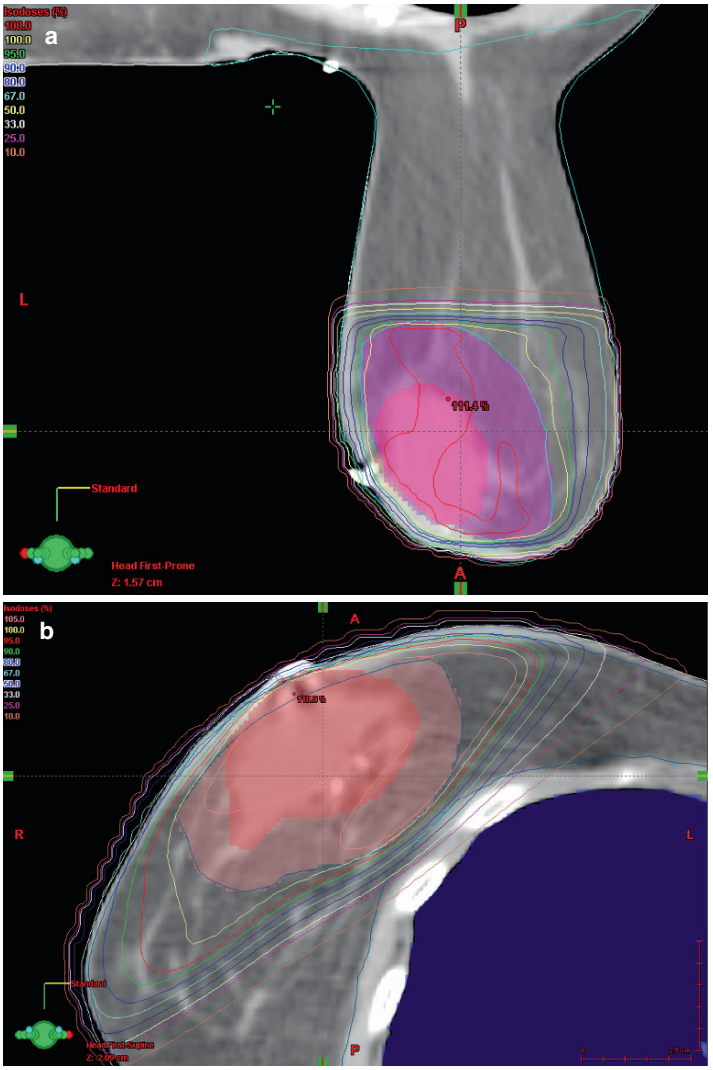


Fig. 17.3a–b A patient with cancer in the right breast positioned in both the prone **a** and supine **b** positions. When prone, the cavity moves away from the chest wall by gravity, allowing the inclusion of the cavity plus a margin by opposed tangent fields and maximal sparing of the lungs

positioned in both the prone (Fig. 17.3a) and supine (Fig. 17.3b) positions. When prone, the cavity moves away from the chest wall by gravity, allowing the inclusion of the cavity plus a margin by opposed tangent fields, and moves the maximal distance from the chest wall, leading to optimal dose sparing of the lungs (and heart for patients with cancer of the left breast). This sparing of heart and lungs is relevant, particularly considering recent evidence from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) that

traditional radiotherapy, delivered with the patient in the supine position, increases both cardiac morbidity and the incidence of lung cancer (Clarke 2005).

Additionally, positioning patients prone considerably reduces the breast tissue motion associated both with cardiac systole and respiration (el-Fallah et al. 1997). Using CINE imaging to capture patient positioning during treatment, over 4,000 EPID images were evaluated for motion for ten patients treated over 15 fractions. This analysis demonstrated that in the prone position intrafraction movement was limited to a mean value of 0.13 cm, with a 95% confidence interval of 0.12–0.15 cm (DeWyngaert et al. 2006). Similar results for women in the prone position were found by Morrow et al. (Morrow 2007) and Becker et al. (Becker and Mackie 2006) using 4D-CT analysis. Both authors showed reduced motion in the prone position compared to the supine position.

17.5 Phase I Trial Using the Prone Position (University of Southern California)

Prone EB-PBI was initiated at the University of Southern California, Los Angeles, funded by the California Breast Cancer Research Program. Our team initially studied the physical and dosimetric aspects of multiple noncoplanar fields aimed at the tumor bed in the prone patient and developed the first generation of dedicated tables for prone partial breast irradiation therapy treatment (Jozsef et al. 2000).

From January 1997 to June 1998, a pilot dose-escalation study of hypofractionated conformal external-beam PBI to the tumor bed in selected postmenopausal women with T1 breast cancers seen consecutively at the University of Southern California was the first to test prone EB-PBI (Formenti 2002). All patients were required to be postmenopausal, with nonpalpable, mammographically detected tumors measuring less than 1 cm in diameter that were excised with negative margins, and with pathologically negative axillary lymph nodes. The study randomly assigned cohorts of three patients each to three dose levels (five fractions of 5, 5.5, or 6 Gy each, respectively, delivered over ten days). Treatment was found to be feasible in nine of the ten consecutive patients; the only excluded patient had a tumor cavity that was extremely lateral (in the tail of Spence) and it was determined that she was best treated supine. After waiting for a minimum follow-up of three years to demonstrate the initial feasibility and safety of the approach, defined as no recurrences and "good or excellent" cosmetic results in all treated patients, a Phase I–II trial was designed and proposed to the Breast Cancer Research Program of the Department of Defense.

17.6 Results of the Subsequent Phase I/II Protocol NYU 00-23 (New York University)

In 2000, funded by an IDEA grant from the Department of Defense, a Phase I–II trial was started at New York University to determine the feasibility and efficacy of prone partial breast conformal RT to the tumor bed. Eligibility for the trial was limited to postmenopausal women with T1N0M0 breast cancer who had undergone segmental mastectomy and had refused standard postoperative whole breast RT. The treatment regimen was five fractions

of 6 Gy, delivered over ten days, for a total dose of 30 Gy. CT planning was carried out with patients in the prone position on a dedicated table with the intent to include ≤ 25% of breast tissue in the PBI field. Field arrangements were designed to completely avoid the contralateral breast, the lungs bilaterally, the heart, and the thyroid. The postsurgical cavity was defined as the clinical target volume (CTV). A 1.5 cm margin was added to generate the planning target volume (PTV). A treatment plan using opposed tangential fields fitted to the PTV with a 0.7 cm field edge margin was designed using 3D conformal treatment planning and wedges, if necessary, to achieve homogeneity in the target.

Results for the first 47 patients entered were reported in 2004 (Formenti 2004). The mean volume of the ipsilateral breast receiving 100% of the prescribed dose was 26% (range 10–45%). The heart and lung were consistently spared.

The preliminary cosmetic outcomes of the first 78 patients were reported in 2006, at a median follow-up of 28 months (range 1–71 months) (Wernicke et al. 2006). The median age of this cohort of women was 67.5 years (range 52–88 years), with median tumor size of 0.9 cm (range 0.1–1.9 cm). Thirty-five patients with a follow-up of at least 28 months were assessed for late toxicity by medical professionals not involved in the original treatment using the LENT/SOMA inventory: twenty (57%) had no detectable toxicity, six (17%) had residual asymmetry related to surgery, and nine (26%) had detectable radiation-related toxicity. Fibrosis was observed in 4/9 patients (grade 1 = 2/4 and grade 2 = 2/4), retraction in 2/9 (grade 1), telangiectasia in 3/9 (grade1 = 1/3 and grade 2 = 2/3), and hyperpigmentation in 1/9 (grade 2). Cosmesis was evaluated by each patient. Patients described their cosmetic results as excellent in 16/35 (46%), good/excellent in 9/35 (26%), good in 7/35 (20%), and fair in 3/35 (8%).

The trial recently completed the planned accrual of 99 patients and closed in 2008. At this time, the median follow-up of patients is 42.5 months, and a manuscript reporting the results for the entire cohort of 99 patients is in preparation.

17.7 Preliminary Results of PBI Using Cone-Beam Imaging: NYU Protocol 07-582

Upon the completion of accrual for NYU Protocol 00-23, a new trial of prone PBI using image guidance for target definition opened in 2007. NYU 07-582 is an IRB-approved protocol testing the use of cone beam computed tomography (CBCT) image guidance in the treatment of breast cancer patients with partial breast radiation therapy. Eligibility for this protocol is similar to that for the preceding studies of prone partial breast radiotherapy, and includes the following patient and tumor criteria: postmenopausal women with a pT1N0M0, stage I breast cancer, excised with negative margins (at least 5 mm), and with negative sentinel node or axillary dissection. Exclusion criteria include previous radiation therapy to the ipsilateral breast and presence of an extensive intraductal component (EIC). The main differences between the current NYU partial breast protocol 07-582 and the ongoing RTOG/NSABP trial are shown in Table 17.2. This protocol was designed to test the feasibility of CBCT for prone PBI and to determine whether CBCT improves set-up accuracy over portal imaging. A second aim of this protocol is to test a regimen of 6 Gy × 5

Table 17.2 Differences between NSABP-39/RTOG 0413 and NYU trials

	Supine external-beam and NYU prone PBI	
	NSABP external-beam PBI	NYU prone PBI
Eligibility	Stage 0, I, or II T < 3 cm, N < 3 axillary	T1N0M0, stage I
Treatment planning	CTV = TB + 1.5 cm PTV = CTV + 1.0 cm	CTV = TB PTV = CTV + 1.5 cm
Beam arrangement	Supine 3–5 Noncoplanar beams	Prone Mini-tangents

fractions over five consecutive days instead of the original regimen of five fractions over ten days used in the previous protocols of prone partial breast irradiation.

17.7.1 NYU 07-582: Dose Specification and Planning

NYU 07-582 allows the beam arrangement used for partial breast treatment to be either 3D conformal or intensity modulated ratiation therapy (IMRT) with a typical arrangement of mini-tangent fields. Using CT treatment planning along with correlated preoperative imaging (including mammography, sonography and/or MRI imaging), the tumor cavity is identified and contouring of the tumor bed is performed (CTV). Subsequently, the planning target volume is created as the CTV + 1.5 cm margin (PTV). The dose prescribed to the PTV is 600 cGy in five consecutive fractions over one week, with the dosimetric constraint that 100% of the volume receives >95% of the prescription dose. In addition, there is a constraint on the dose that the breast will receive, namely that 60% of the breast volume must receive less than 50% of the prescription dose of 30 Gy (i.e., 15 Gy). A mini-tangent field arrangement is typically used, unless there is obvious advantage to the use of a different field arrangement or if the breast volume criteria are not satisfied. In these instances noncoplanar 3D or IMRT field arrangements are utilized. If the extension of the CTV to obtain the PTV extends outside of the breast tissue, which can happen in the case of a tumor bed close to the chest wall or the surface of the breast, a PTV-EVAL is generated that is restricted to the breast tissue and is used in the dose volume histogram (DVH) evaluation of the plan. The original PTV is still used to design the field shapes using beam's eye view (BEV) editing of the multi-leaf collimator (MLC) leaf positions. As the skin and scar are not considered a target, there are no general energy restrictions on the choice of X-ray beam, although 6 MV X-rays are the standard choice for most clinical situations.

17.7.2 Cone-Beam Imaging for PBI

Despite adherence to the protocol described above to correctly position the patients at each fraction, the daily set-up process is inevitably associated with uncertainty. The planning target volume (PTV) includes a margin around the cavity to account for inter- and intrafraction

motion. Accurate alignment with the target is even more important for PBI treatment because the volume is smaller, there are fewer fractions, and each fraction is three times larger than the usual dose of 2 Gy used in standard fractionation of breast radiotherapy. As stated previously, the intrafraction component of target positioning uncertainty has been reported to be negligible for prone breast treatments. We can therefore focus on the interfraction accuracy and reproducibility through a method that aids in the alignment of the patient on a daily basis, without concerning ourselves with motion artifacts during the time assigned for dose delivery. On-board cone-beam CT (CBCT) obtained using the Varian OBI system provides three-dimensional (3D) soft tissue and bony anatomic information. Early reports of cone-beam imaging PBI have demonstrated the feasibility and potential usefulness of this approach (Fatunase 2008; White 2007; Kim et al. 2007; Chen and Vicini 2007).

17.7.3 Preliminary Clinical Results of NYU Protocol 07-582: Image Guidance for Prone PBI

The first 23 patients participating in 07-582 were analyzed to assess the interfraction reproducibility of the original set-up. After the initial placement of radiopaque skin marks and patient alignment, MV portal imaging of the tangent beam's eye view was used to optimize the set-up. CBCTs were performed prior to all fractions with the Varian On-Board Imager kV imaging system with a 35 cm field of view and a 2.5 mm slice thickness. The CBCTs were overlaid with the planning CT and shifted in the lateral, longitudinal, and anterior/posterior directions to achieve the best possible match. Depending on the location of the tumor bed, either the chest wall or the outer breast contour was registered using the visualized seroma cavity. The shift was recorded as the residual error after portal images. Rotational changes seen on CBCT were also analyzed but not implemented, since rotational yaw and pitch adjustments cannot be made on a standard couch.

After initial skin mark set-up and alignment, MV portal imaging with shifting using the tangent beam's eye view was used to optimize the set-up for the first six patients (Group I). Figure 17.4 shows an example of a portal film obtained in a patient with an upper outer quadrant cancer. For all daily fractions, CBCT was performed prior to treatment. An example of a cone-beam CT image of a patient with a lower inner quadrant tumor is provided in Fig. 17.5. CBCT was compared with the planning CT to shift the patient and evaluate the residual error in the set-up. The residual error from the CBCT set-up after optimal portal imaging was recorded for each patient. For the subsequent 17 patients (Group II), portal imaging was performed without shifting in order to calculate the residual error from the CBCT set-up representing skin mark set-up.

For the 23 patients that have currently completed the course of treatment (five treatment fractions), only minimal interfraction changes were detected in each individual five-fraction set. The values of residual error detected after cone-beam CT for Group I (after skin mark set-up and portal imaging) and for Group II (after skin mark set-up alone) are compared and shown in Table 17.3. These preliminary results for a small number of patients demonstrate that the residual error was found to be minimal, approximately 2 mm.

In summary, preliminary CBCT data suggest that the residual shift detected by CBCT imaging of patients immobilized on our customized mattress is minimal. Similar reports from investigators exploring supine partial breast irradiation have also demonstrated

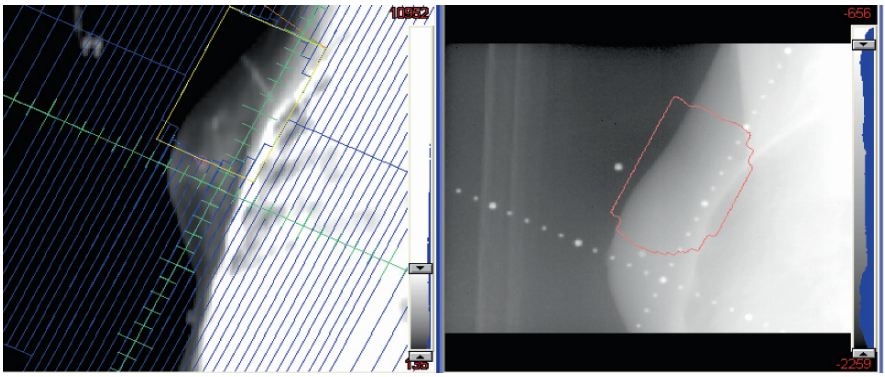


Fig. 17.4 Portal film of the radiation field treating the upper breast

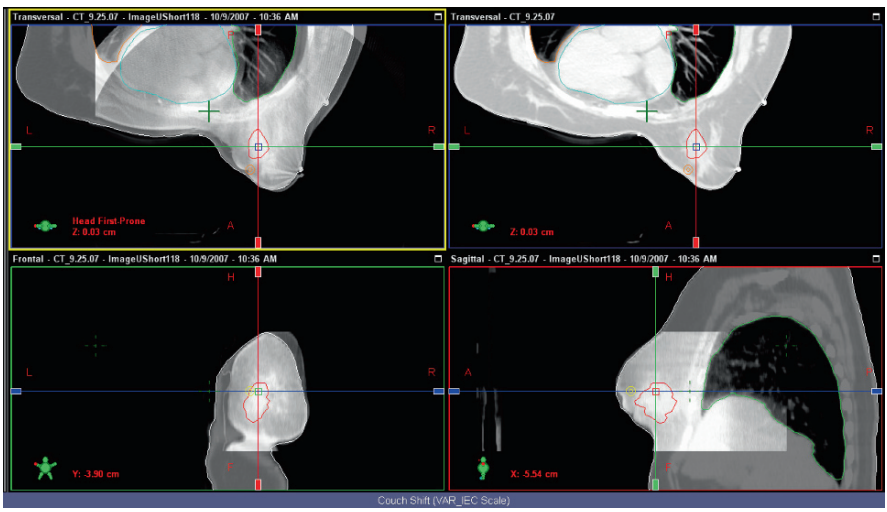


Fig. 17.5 Cone-beam image of a patient with a lower inner quadrant tumor

minimal errors (Morrow 2007; Fatunase 2008; White 2007; Kim et al. 2007). Given the very small residual error detected, clinicians should be wary of the indiscriminant use of CBCT for PBI. Cautionary reports of increased rates of secondary cancers from low-dose radiation exposure remind us of the potential impact on secondary cancer risks (Sachs 2007; Brenner and Hall 2007; Brenner and Sachs 2006).

Although image guidance can localize the cavity in partial breast radiotherapy, it should be performed as part of the research protocol. Concerns over contralateral breast dose and carcinogenic risk should limit the routine use of CBCT imaging for breast radiotherapy unless larger studies demonstrate improved accuracy of treatment delivery with CBCT.

Table 17.3 Preliminary experience acquired with cone-beam image-guided radiation therapy for prone partial breast radiation

	Residual error	
	Group I (skin mark set-up and portal imaging)	Group II (skin mark set-up only
Number of patients	6	17
RMS vert. (mm)	1.6	2.5
RMS long. (mm)	1.0	1.4
RMS lat. (mm)	1.9	1.8
Random error (RMS of all SDs; mm)	1.7	2.0
Mean vector sum (mm)	1.5 ± 0.5	1.9 ± 0.9

17.8 Conclusions

Accelerated prone EB-PBI has maintained the clinical and technical promise that was identified 15 years ago, when our group initially committed to the development of this approach. Modern technology has provided us with the appropriate tools (CINE and cone-beam CT) to demonstrate limited intrafraction and interfraction changes, thus confirming the technical feasibility and accurate reproducibility of this approach.

While it remains confined to the setting of a clinical trial, with results from the RTOG/NSABP Phase III trial awaited, the prone EB-PBI approach for partial breast radiotherapy is rapidly gaining in popularity internationally, with multiple investigators visiting NYU to acquire "hands-on" experience in this technique.

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APBI 3D Conformal External Beam: The MGH Technique

18

Shannon M. MacDonald, David P. Gierga, Brian Napolitano, and Alphonse G. Taghian

18.1 Introduction

External-beam accelerated partial breast irradiation (APBI) represents one of the most modern and popular delivery techniques for the administration of ABPI. There are several potential benefits to the use of external-beam radiation therapy (EBRT) for APBI, including the ability to evaluate all pathological data prior to radiation, decreased invasiveness, decreased risk of infection, availability, and attainment of a homogeneous dose distribution (Formenti 2005; Taghian et al. 2006a; Arthur and Vicini 2005; Macdonald and Taghian 2007; Baglan et al. 2003; Swanson and Vicini 2008). EBRT is a widely accessible technique that is offered in nearly all radiation centers and requires little additional specialized training. It has been thus far the most commonly chosen technique for APBI in the NSABP B-39/RTOG 0413 Phase III randomized trial comparing standard whole breast irradiation to APBI. Several external-beam techniques exist for the planning and delivery of APBI. It is our opinion that the Massachusetts General Hospital's (MGH) photon/electron technique represents a relatively simple method that provides a homogeneous dose to the target breast tissue while sparing uninvolved breast tissue and other normal tissues. Another external beam modality available for delivery of APBI is proton radiation. Although proton radiation is currently limited to a handful of centers, a number of proton facilities are planned to open in the coming years. The properties of protons enable increased conformality while maintaining all of the advantages of EBRT.

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18.2 MGH External-Beam Technique in APBI

The majority of patients treated with APBI at the MGH have received treatment based on an in-house protocol evaluating feasibility as well as optimal dose for APBI. The preferred method of treatment planning and delivery is to use a combination of photons (two mini-tangents) and electrons (en face). All patients undergo computed tomography (CT) scanning in the supine position on a dedicated breast board with both arms above their head if possible. The physician places a small wire around the extent of the palpable breast tissue, which helps with the contouring of the whole breast tissue volume. A small wire placed over the incision site demarcates the resection scar. Axial images of 1.5–3 mm slice thickness are obtained from the level of the mandible to just inferior to the lung bases. The resection cavity is then contoured on axial CT images and confirmed on coronal and sagittal planes. The resection cavity includes the seroma, clips placed in the cavity at the time of surgery, and any noted soft tissue changes attributed to the surgical resection. Radiographic studies including mammogram and magnetic resonance imaging (MRI) of the breast are often used to assist in defining this volume. Comparison to the soft tissue of the contralateral breast tissue may also be useful to detect parenchymal changes in the breast tissue. The placement of radiopaque clips within the resection cavity became standard policy after some patients were considered poor candidates for APBI based on an inability to define the cavity with accuracy. Our breast surgeons now routinely place clips (around six clips; one in each side) in the resection cavity at the time of surgery. We have found that clips are essential for delineating the resection cavity for patients without a seroma or clear parenchymal changes, and are valuable in verifying correct patient position, as described in detail later in this chapter.

Each individual surgical clip is contoured, in addition to normal structures such as the heart (until the bifurcation of pulmonary arteries), lungs, ribs within the radiation field, and the breast tissue. The planning target volume (PTV) is generated with a 1.5–2.0 cm volumetric expansion of the resection site. The uninvolved breast tissue is defined as the breast tissue minus this PTV expansion. We usually maintain the ratio PTV/total ipsilateral breast tissue at < 25%. If this ratio exceeds 25%, the patient's CT simulation is postponed for 2–3 weeks to give the seroma a chance to decrease in size. The PTV expansion does not extend outside of the extent of ipsilateral breast tissue (i.e., into the lung, contralateral breast, outside of the patient, beyond the latissimus dorsi). The expansion is limited to 0.5 cm inside of the patient's skin surface, unless the resection cavity extends to the skin subcutaneous tissue superficially.

Treatment planning is performed with Xio treatment planning software (CMS Inc., St. Louis, MO, USA). Usually, two mini-tangent photon fields and one en-face electron field (similar to a boost field) are designed. The photon fields are set up using a source-to-axis distance (SAD) technique. The photon isocenter is placed at the estimated center of the resection cavity at the time of CT simulation to avoid unnecessary shifts. Isocenter placement is optimized to try to limit the divergence of the photon beams into the lung (and heart for left-sided cavities). The photon field gantry angles are designed to diminish the treatment of uninvolved breast tissue as well as organs at risk. The photon fields can be

parallel opposed, but this is not an absolute necessity, and at times noncoplanar fields are advantageous. The electron field is placed using a source-to-skin distance (SSD) technique, usually at 100 cm from the radiation source. The electron set-up point is positioned such that the beam center will traverse the photon isocenter at the gantry angle of choice. The electron field gantry angle is designed such that the beam entry is generally en face with the breast tissue; but again, this is not essential. A margin of 0.7 cm to the block edge is utilized to account for penumbra. The treatment machine's multileaf collimators (MLCs) shape the aperture for the photon fields, while a Cerrobend block is used to define the electron field. Wedge filters are usually necessary in the photon fields to ensure adequate isodose coverage of the PTV. Tissue equivalent bolus is rarely used in cases of superficial resection cavities to avoid telangiectasia. Figure 18.1 demonstrates a typical field arrangement with two mini-tangents and en-face electron field(s).

Usually 80% of the dose is delivered through the photon fields and the remaining 20% is delivered with electrons. The preferred photon energy is 6 MV, but higher energy photons may be necessary to ensure adequate PTV coverage. The electron energy selection is based on the depth of the seroma and should limit the dose to underlying normal tissues (ribs, lung, heart) whenever possible and avoid a full dose to the skin unless the tumor cavity is superficial. We usually prescribe the dose on the 95% isodose line, which should

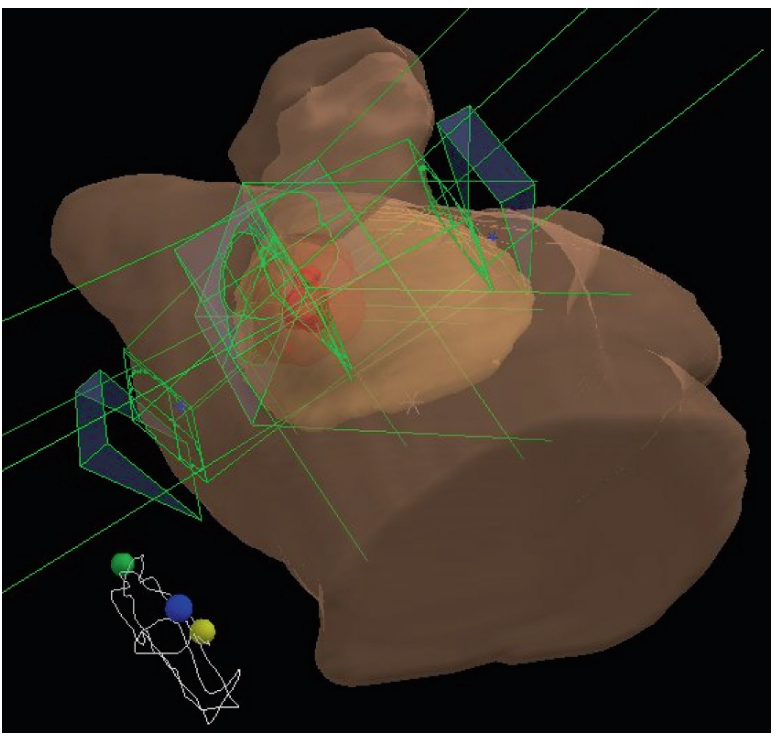

Fig. 18.1 Field arrangement used for mixed photon/electron PBI. Two mini-tangents delivering approximately 80% of the prescription dose are combined with one, or for certain cases two, en-face electron fields delivering approximately 20% of the prescription dose

cover at least 98% of the PTV. Dose inhomogeneity is usually on the order of a few to five percent. The PTV-to-breast tissue ratio should be ≤ 25% and the nontarget breast tissue receiving 50% of the prescription dose should be less than 50%. The total ipsilateral breast tissue receiving 50% of the prescription dose should be less than 60%. The ipsilateral lung volumes receiving 20 Gy, 10 Gy, and 5 Gy should not exceed 3%, 10%, and 20%, respectively. The contralateral lung volumes receiving 20 Gy, 10 Gy, and 5 Gy should not exceed 1%, 2%, and 3%, respectively. Lung constraints are based on recent reports of radiation pneumonitis reported by Recht et al. (where an en face photon field was used) (Recht 2008). These lung constraints are easily met with our mixed photon/electron technique. The use of an en-face photon field is strongly discouraged, as dose limits for organs at risk can be difficult to achieve, and also the risk for radiation pneumonitis increases (Recht 2008). The dose to the heart is kept as low as possible, with every effort made to completely avoid cardiac structures.

Treatment of APBI cases can present challenges based on anatomical limitations. We have found that lesions that are located in the extreme medial or lateral extent of the breast prove to be technically challenging. Although the vast majority of APBI cases treated at the MGH involve the use of coplanar beams of differing photon and electron modalities, we do find that there are select cases where the use of noncoplanar beams, similar to the technique described by Vicini et al. in conjunction with an electron field, can be beneficial (Baglan et al. 2003). In Fig. 18.2, the medial location of the resection cavity presents several challenges. The left-sided medial lesion sits in close proximity to the lung and heart. While treatment of standard coplanar beams would include a significant portion of the contralateral breast, the use of photon beams with noncoplanar geometries avoids the contralateral breast while achieving our normal tissue constraints. This inclusion of noncoplanar beams does present a new set of physical limitations for treatment delivery, and careful pretreatment simulation is an essential tool in determining whether the radiation dose can be delivered as planned.

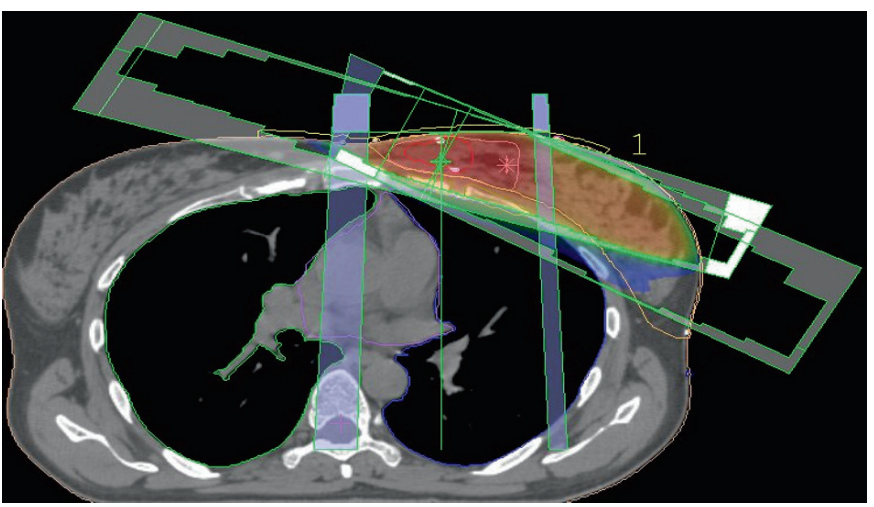

Fig. 18.2 Medial tumor bed. This axial CT image at the level of the tumor bed demonstrates the use of a noncoplanar field arrangement for mixed photon/electron PBI

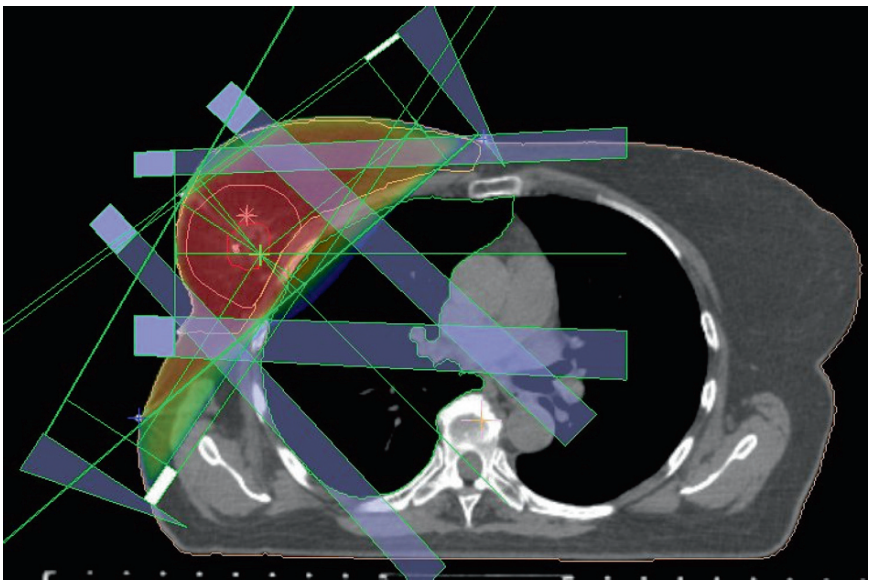

Fig. 18.3 Lateral tumor bed. This axial CT image at the level of the tumor bed shows the use of multiple electron fields in combination with mini-tangent photon fields

Lateral resection cavities also present technical challenges for treatment planning. Figure 18.3 demonstrates the introduction of a fourth field in a patient treated with APBI for a right-sided lateral resection cavity. The lateral location of this cavity necessitated the use of an additional field in order to meet our normal breast tissue constraint. The second electron field produced a tighter isodose distribution around our planning target volume, giving greater sparing to the normal breast tissue within our constraints. The addition of this field also limits the amount of normal tissue lateral and posterior to the breast that receives a substantial percentage of the prescription dose. As with medial resection cavities, there are treatment delivery considerations. With the inclusion of a second electron field, there is the creation of a second electron set-up point on the patient's skin surface, again making pretreatment verification imperative.

18.3 Position Verification

The proper delivery of ABPI with external-beam modalities is dependent upon accurate and reproducible treatment set-up. Standard verification of position for EBRT consists of laser alignment, films (often of suboptimal quality), and reliance on bony radiopaque structures as opposed to soft tissues such as the breast itself. Surface imaging and kilovolt imaging of fiducial clips implanted in the resection site are under investigation as image guidance methods for PBI (Bert et al. 2006; Gierga et al. 2008). Gierga et al. examined the alignment errors associated with different image guidance techniques for PBI, including

laser alignment, chest wall/bony anatomy alignment, surface imaging, and kilovolt imaging of implanted fiducial clips. The results showed that neither laser alignment nor chest wall alignment were ideal for the precision required for PBI. The errors for clip imaging and surface imaging were smaller, on the order of 2–3 mm, and both methods have been utilized to position patients for PBI at MGH.

PBI patients are currently treated on a Varian iX linear accelerator equipped with a kilovolt X-ray on-board imaging device (OBI). The AlignRT system (VisionRT, London, UK) is used for surface imaging. The workflow for patient set-up for the first treatment begins with standard laser alignment followed by orthogonal X-ray imaging. The clip orientation in the daily kilovolt X-rays are manually matched to the digital reconstructed radiograph (DRR) from CT simulation in order precisely position the target, and the couch is automatically shifted based on the clip match. Couch corrections are made using only translational shifts; no couch rotations are utilized. The X-ray images are manually gated at exhale to minimize variations in clip position caused by patient respiration. If the couch shifts are greater than or equal to 5 mm in any one direction, the patient is imaged again with orthogonal X-rays in order to confirm that the realignment is correct. Once the patient has been positioned based on clip configuration, a reference surface image is obtained for use in subsequent treatment fractions. The use of a reference surface image using a surface generated from the CT simulation scan is the subject of ongoing research and can likely be utilized for as a positioning reference.

The image guidance workflow is slightly modified for subsequent fractions, as outlined in Fig. 18.4, in order to minimize the number of X-ray images and to better monitor the patient during treatment. The patient is initially positioned on the table using lasers, and using the patient monitoring mode of AlignRT, which calculates real-time couch shifts, the patient position is interactively corrected based on surface imaging. Again, only translational corrections are made, although real-time rotations are calculated and displayed by the software. If large rotations exist, then the patient set-up is reassessed before continuing with the remainder of the set-up and treatment procedure. A follow-up image is taken to confirm the results of the real-time positioning and fully document the patient position. The patient position is corrected if the calculated shifts are greater than or equal to 3 mm.

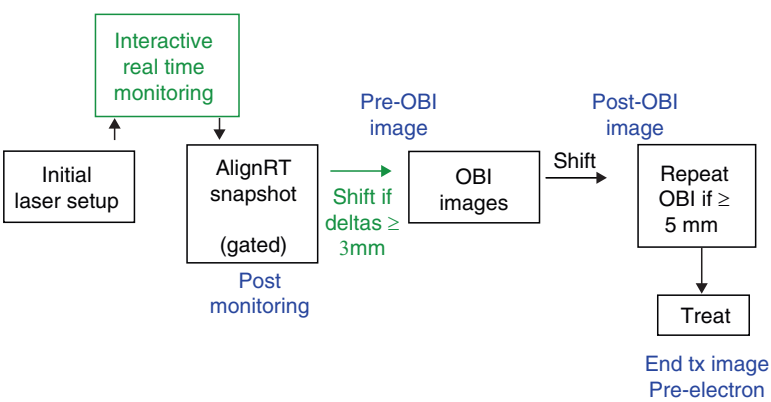

Fig. 18.4 Image guidance workflow for PBI patients for fractions 2–10

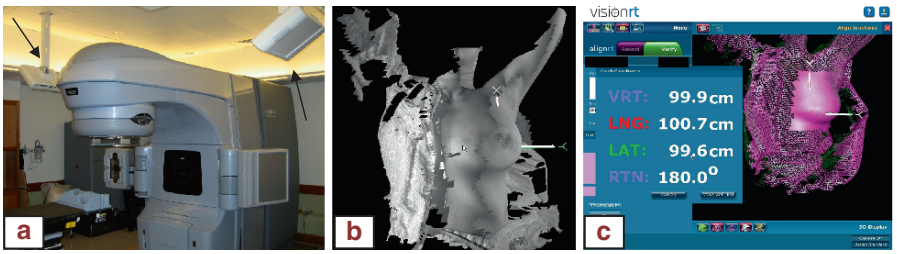

Fig. 18.5 Align RT. **a** Digital images are obtained from cameras mounted on the ceiling (*arrows*) of the treatment room. **b** Surface images are obtained (shown here with optional texture information). **c** Daily surface images are compared with the reference surface image and shifts are calculated and displayed

All images in AlignRT are taken using gated capture, which allows an exhale image to be extracted from the patient's breathing cycle. Figure 18.5 depicts a sample surface image, alignment with the reference surface image, and instructions for realignment. Orthogonal X-rays follow surface imaging alignment using the OBI, and any adjustments to the patient's position are made based on registering the daily clip position to the DRR clip position. Since surface imaging is used prior to X-ray imaging, the couch shifts determined from clip imaging are generally small, and reimaging using X-rays to confirm large shifts is rarely necessary. Surface images are typically taken immediately before and after the OBI X-rays to provide additional assurance that the patient position is stable. End-of-treatment surface images (prior to any shifts for the electron field) are also taken to monitor any patient motion during treatment. Continuous surface monitoring can also be employed. One obvious advantage of surface imaging over other image guidance modalities is the avoidance of any additional radiation exposure to the patient. An additional advantage is the ability to assess more subtle changes in breast or arm positioning. Although the great majority of patients enrolled on the PBI protocol at the MGH currently have clips placed in the target prior to radiation therapy, the use of surface imaging for image guidance in patients without clips is the subject of current research.

18.4 Initial Results of the MGH Protocol

Early outcomes and the feasibility of the experience with EB-APBI at the MGH have been reported along with results from Beth Israel Medical Center and Boston University on a Phase I/II protocol open at these institutions (Kozak et al. 2006c). This is a dose-escalation study where three dose levels are evaluated: 32 Gy in eight fractions BID over four days, 36 Gy in nine fractions BID over four and a half days, and 40 Gy in ten fractions BID over five days. Each dose level includes 100 patients. Eligibility criteria included T1N0 invasive breast cancers and unifocal DCIS, grades 1 and 2, less than 2 cm in size. Patients with invasive lobular cancer, extensive intraductal component, lymphovascular space invasion, collagen vascular disease, or a known BRCA1 or BRCA2 mutation were excluded.

In addition, patients with prior breast surgery or breast implants were excluded. Initial protocol eligibility required sentinel lymph node biopsy or axillary lymph node dissection. This was later revised to allow for patients ≥ 70 to be enrolled without pathological sampling of the axilla if clinically node negative. Treatment was initiated within 12 weeks following surgery or, if chemotherapy was initiated, within six weeks following chemotherapy. PTV was defined as the tumor cavity plus a 1.5–2.0 cm expansion. Nontarget breast volume was defined as breast tissue minus the PTV. Only the first dose level (32 Gy in eight fractions BID, with fractions separated by a minimum of 6 h) has been reported. A combination of photons and electrons was used for 85% of patients, which is the preferred technique at MGH. A three-field technique using two photon fields and one en-face electron field was used in 70% of patients; 15% of patients were treated with four fields, three photon fields and one electron field. Fifteen percent of patients were treated with photons alone. The median contribution of electrons for patients treated with a combination of photons and electrons was 20%. Excellent PTV coverage and homogeneity were achieved with this technique. Dose inhomogeneity exceeded 10% in only seven patients.

18.5 External-Beam APBI Dosimetric Comparison

Kozak and colleagues at the Massachusetts General Hospital performed a comparison between the multifield photon technique, as described by Vicini et al., and a mixed photon–electron technique, as described by Taghian et al. (Taghian et al. 2006a; Kozak et al. 2006a). Similar PTV coverage was obtained with an average of 4.1 fields for photon plans and 3.1 fields for mixed photon–electron plans. No difference in volumes of heart and lung receiving > 5 Gy were seen. Photon-only plans delivered an increased dose to uninvolved breast tissue, while mixed photon–electron plans delivered low-dose radiation to a greater volume of lung and heart.

18.6 APBI with Protons

Protons are charged particles that enter tissue and deliver a small and relatively constant dose until near the end of the proton range (where the majority of dose is delivered) and beyond; no dose is deposited after this (Bussiere and Adams 2003). They have a defined depth in tissue that is proportional to the energy of the proton beam that is chosen for treatment and allows for complete sparing of normal tissues beyond this chosen depth. The dosimetric advantage of protons over photons in their ability to spare more normal tissue has been well demonstrated, and its use is well established for many malignancies (MacDonald et al. 2006; St Clair et al. 2004; Hug 2004). However, the experience for the use of proton radiation for breast cancer is modest and limited to mainly dosimetric comparisons (Lomax et al. 2003; Bjork-Eriksson and Glimelius 2005; Schwab 2004; MacDonald and Taghian 2007). There are currently a limited number of proton facilities, but several treatment sites are currently in their planning or construction phases in both the

academic and private sectors. Increased capacity will enable additional malignancies to be treated, including breast cancer. To date, there are limited data regarding clinical experience using protons for the treatment of breast cancer, but this is an area of active research. The clinical experience that exists is for the use of proton radiation for APBI (Kozak et al. 2006c; Bush et al. 2007).

The rationale for the use of protons for APBI is to spare more uninvolved breast tissue. External-beam radiation represents a noninvasive technique that requires little additional specialized training and has minimal technical limitations. One disadvantage of photon EBRT compared to brachytherapy techniques is the increased volume of uninvolved breast tissue receiving radiation. Intracavitary or interstitial brachytherapy delivers half of the prescribed dose to 25% or less of the uninvolved breast tissue; for photon EBRT the amount of uninvolved breast tissue receiving half of the prescription dose is much higher, on average near 40% (Kozak et al. 2006a; Formenti et al. 2004; Vicini et al. 2005). Proton radiation represents an external-beam modality with the advantages of such (aside from wide accessibility at this time), and the added dosimetric advantage of increased sparing of nontarget tissues, in particular nontarget breast tissue.

In our MGH in-house APBI protocol described above, proton radiation was allowed, giving us the opportunity to explore the feasibility as well as potential risks and benefits of its use for APBI. Clinical experience and dosimetric data for patients treated with proton beam accelerated partial breast irradiation were obtained and reported (Taghian et al. 2006a, b). Twenty-five patients were treated on protocol with APBI using proton beam therapy at the Francis H. Burr Proton Center (Taghian et al. 2006a). One to three proton fields were used to achieve adequate coverage of the tumor volume. The majority of patients (72%) were treated with a two-field plan. A solitary field was used for three patients (12%); four patients (16%) required three fields.

One of the main dosimetric goals for the use of proton radiation was to show improved dose conformity and increased sparing of nontarget breast tissue. For the purpose of the dosimetric comparison, mixed-modality 3D photon–electron plans were generated for twenty-four of the twenty-five patients planned and treated with partial breast proton irradiation (Kozak et al. 2006b). An optimal 3D photon–electron plan could not be generated for one patient (due to an inability to abduct her arm), so this patient was excluded from the analysis. Both plans were reviewed and approved by the treating radiation oncologist. Dose–volume histograms were generated and compared. Figure 18.6 shows isodose distributions for a representative proton plan and mixed-modality 3D photon–electron plan for the same patient. Both of these techniques provided adequate and homogeneous coverage of the target volume. The use of proton therapy provided substantial sparing of nontarget breast tissue. The volume receiving half of the prescribed dose was reduced by 40–45% with proton therapy as compared to mixed-beam therapy. Proton therapy also provided small but significant reductions in dose to the heart and ipsilateral lung. Failure to produce a satisfactory 3D photon–electron plan for a patient who was unable to tolerate the standard treatment position demonstrates the potential for protons to deliver adequate treatment despite limitations in patient positioning.

An increase in acute moist desquamation was noted for patients treated with a solitary field. This was almost certainly a result of the increased skin dose associated with the formation of a “spread-out Bragg peak” (SOBP) in conventional 3D proton irradiation. For most standard proton treatments, skin or entrance doses are higher than in photon

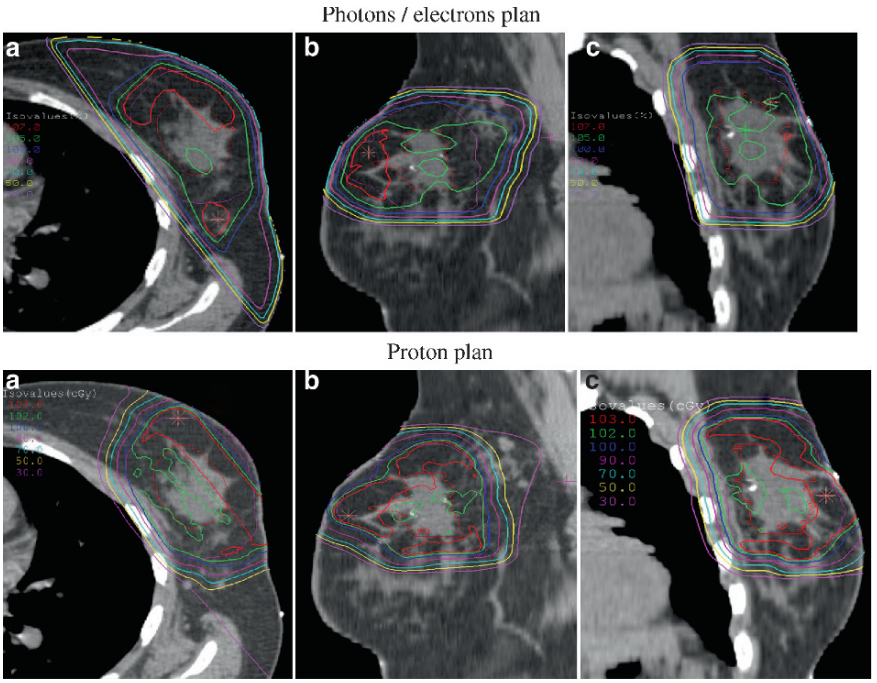

Fig. 18.6 Representative dosimetry for a three-field, mixed-modality, partial breast irradiation treatment plan (*upper panel*) compared with a proton partial breast irradiation treatment plan (*lower panel*) for the same patient with axial **a**, sagittal **b**, and coronal **c** views. The use of proton partial breast irradiation reduced the volume of nontarget breast tissue receiving 50% of the prescribed dose by an average of 36%. Reproduced with permission from Kozak KR, Katz A, Adams J, et al. Dosimetric comparison of proton and photon three-dimensional, conformal, external beam accelerated partial breast irradiation techniques. Int J Radiat Oncol Biol Phys 65: 1572–8

treatments. To achieve the full dose to a target >1 cm in size in the path of the beam, multiple individual proton beams (Bragg peaks) of different energies are stacked to form what is referred to as a spread-out Bragg peak (SOBP). Adding individual proton beams increases the entrance dose (i.e., the skin dose), and so skin dose is higher for larger target volumes in the path of the beam. This increases the entrance dose or skin dose, but still allows full sparing of all tissues distal to the tumor volume and a decreased dose proximal to the target (other than at the point of entrance). Because of the increase in skin dose, we recommend using caution when evaluating the skin dose for proton plans, and strongly encourage multiple fields for each treatment, all treated in the same fraction. Another potential approach to reducing the skin dose for APBI with protons is to use intensity-modulated proton therapy (IMPT). Although some intensity modulation is intrinsic to the use of protons, IMPT (similar to IMRT) uses several inhomogeneous pencil beams to achieve a homogeneous dose distribution in the target volume. This allows for increased conformality, not only at the distal edge of the target volume but also at the proximal target volume, allowing for a decreased skin dose for most target volumes (Oelfke and Bortfeld 2003). Research is currently being performed to evaluate the benefit of IMPT for APBI.

18.7 Conclusions

PBI has yet to be proven as an equivalent to or improvement over whole breast irradiation. Despite this, it has rapidly gained the interest of both researchers and the public. The RTOG and NSABP are rapidly adding patients to a Phase III randomized trial comparing whole breast irradiation to APBI. It is likely that APBI will be proven an equivalent treatment with the benefit of increased convenience for at least a subset of patients with early-stage breast cancer. If APBI is established as an acceptable standard for some patients, the use of APBI is likely to increase exponentially. Many techniques for APBI have been explored. It seems unlikely that one technique will be appropriate for all patients. We believe that the MGH technique offers a relatively simple and widely applicable technique that can be utilized by most radiation centers.

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APBI with 50 kV Photons: Targeted Intraoperative Radiotherapy (TARGIT)

19

Jayant S. Vaidya

19.1 Individualizing Local Treatment for Breast Cancer

It took the mammoth effort of the 26,000 women in 36 randomized trials that were meta-analyzed in the Oxford overview (Early Breast Cancer Trialists' Collaborative Group 1995, 2000) to make the move from the radical mastectomy described by William Halsted more than 100 years ago (Halsted 1894) to breast-conserving therapy that is considered the norm today. Standing on the shoulders of these giants, the next step—the real paradigm shift to a local therapy truly localized to the tumor and its environs in selected patients may be an easier one.

In this chapter, I will provide a synopsis of its rationale followed by details about the intraoperative approach to delivering partial breast radiotherapy.

The dogma of 3–6 weeks of postoperative radiotherapy after breast-conservative surgery for all patients is one of the main obstacles to the widespread utilization of breast-conserving surgery. The radiotherapy schedule is inconvenient for patients and contributes substantially to the unacceptable waiting lists experienced in many oncology departments worldwide. When making decisions about which operation to choose, recurrence, radiation therapy, and quick recovery are the main factors women are concerned about (Katz et al. 2005). Consequently, if radiation can be completed at the time of the surgery, then two large concerns will be taken care of and perhaps fewer women will feel obliged to choose mastectomy just because they live far from a radiotherapy facility (Athas et al. 2000) or to avoid prolonging their treatment.

It has been estimated that the externally delivered boost dose misses the target volume in 24–88% of cases (Sedlmayer et al. 1996; Machtay et al. 1994). Thus a large proportion of local recurrences could be attributed to this "geographical miss." This could be even more important today, in the age of oncoplastic surgery, when there is extensive

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remodeling of the breast in order to achieve a better cosmetic result. In this situation, it is very difficult to delineate the tumor bed, even with markers such as gold seeds. This can result either in completely missing the target or "precautionary" overtreatment achieved by enlarging the boost field. Delivering radiotherapy immediately after tumor excision with the TARGIT approach before remodeling occurs could ensure that the radiotherapy (boost or alone) is delivered to the correct target.

A delay in the delivery of radiotherapy, either because of a long waiting list or because chemotherapy is given first, may jeopardize its effectiveness (Wyatt et al. 2003; Mikeljevic et al. 2004), although this has been difficult to substantiate. The really important delay may however be the one that occurs immediately after surgery. We have found that the tumor bed is a rich microenvironment that promotes proliferation, migration and invasion (Massarut et al. 2006; Baldassarre et al. 2007). Targeting this microenvironment at the right time could be crucially important. I would like to call missing this window of opportunity a "temporal miss," analogous to its spatial counterpart. Finally, whole breast irradiation carries the risks of acute and long-term complications such as erythema, fatigue, prolonged discomfort, radiation pneumonitis, rib fracture, cardiovascular effects and carcinogenesis, which could compromise the long-term benefit of postoperative radiotherapy (Rutqvist and Johansson 1990; Early Breast Cancer Trialists' Collaborative Group 2000).

Recent data suggest that local recurrence may be facilitated by a local field defect. The morphologically normal cells surrounding the breast cancer demonstrate a loss of heterozygosity that is often identical to that of the primary tumor (Deng et al. 1996). In addition, aromatase activity in the index quadrant is higher than in other quadrants (O'Neill et al. 1988), and has the potential via estrogen to stimulate mutagenesis, growth and angiogenesis (Nakamura et al. 1996; Lu et al. 1996). Patients with ipsilateral breast tumor recurrence (IBTR) have an increased risk of carrying the mutant p53 gene (23% vs. 1%) (Turner et al. 2000), and young patients (<40 years) with IBTR have a disproportionately increased risk (40%) of carrying a deleterious BRCA1/2 gene mutation (Turner et al. 1999). This suggests that local recurrence is probably related more to background genetic instability than to a different tumor biology at a younger age. It appears that a dynamic interaction between the local factors (such as aromatase) present in the breast parenchyma, the systemic hormonal milieu and genetic instability will determine the risk of local recurrence, in addition to the biology of the excised primary tumor.

The location of recurrence in the breast with respect to site of the primary tumor shows an interesting distribution. Between 80 and 100% of early breast recurrences occur in the quadrant that harbored the primary tumor. This is in contrast to the findings of 3D analysis of mastectomy specimens (Vaidya et al. 1996), which reveal that 63% of breasts harbor occult cancer foci, and 80% of these are situated remote from the index quadrant. It therefore appears that these widespread and occult multifocal/multicentric cancers in other quadrants of the breast remain dormant for a long time and have a low risk of causing clinical tumors. This is corroborated by the fact that although there is a high frequency—20% in young (median age 39) women and 33% in women between 50 and 55—of tumors found in breasts when analyzed in autopsy studies (Nielsen et al. 1987), the frequency of clinical breast cancer in the population is considerably lower.

Arguably, in the EORTC study (Bartelink et al. 2001), only 56% of local recurrences are reported to have occurred in the original tumor bed. In fact, a further 27% recurred diffusely throughout the breast including the tumor bed, leaving 29% recurrences outside the index quadrant. However, patients in this study received intensive mammographic follow-up, which might have unearthed subclinical occult tumors in other quadrants of unproven clinical significance.

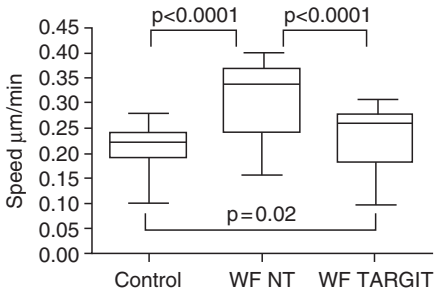
19.2 Radiotherapy Has a Dual Benefit: On the Seed and On the Soil!

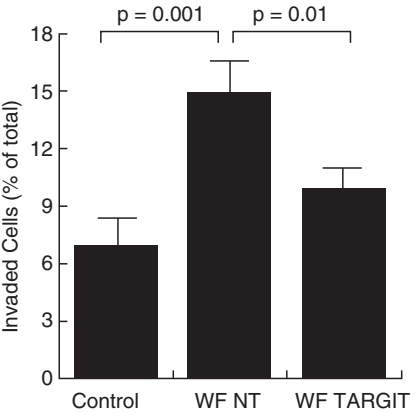
It appears that local recurrence occurs in the index quadrant, whether or not radiotherapy is given (Clark et al. 1982, 1992; McCulloch and MacIntyre 1993) and irrespective of clear margins. Of the breast-conserving trials that have tested the effect of radiotherapy, patients in the NSABP-B06 (Fisher et al. 1995), Ontario (Clark et al. 1996), Swedish (Liljegren et al. 1999) and Scottish (Forrest et al. 1996) trials had less extensive surgery compared with the Milan III trial (Veronesi et al. 1993). The recurrence rate in the control arm of the Milan III trial, in which the tumors were smaller and excision was considerably wider, was low (8.8% vs. 24–27% in other trials), albeit at the cost of cosmesis. Nevertheless, radiotherapy reduced it even further and at the same proportional rate as in other trials. If local recurrences were caused by residual disease only, then radiotherapy should have effected a much larger proportional reduction in those patients with positive margins or less extensive surgery; but radiotherapy is as effective in patients with negative margins, suggesting that radiotherapy may have an effect on the soil rather than the seed (Vaidya et al. 2004b).

Thus, radiotherapy may have a dual effect of inhibiting the growth of genetically unstable cells around the primary tumor and of making the breast tissue less conducive to growth (Vaidya et al. 2004b). This idea has been vindicated by translational research during intraoperative radiotherapy. This study, performed at the Centro di Riferimento di Oncologia, Aviano, Italy (Belletti et al. 2008), demonstrated for the first time that radiotherapy could exert its beneficial effects by affecting the tumor microenvironment. We found that the wound fluid collected in the 24 hours following surgical wide local excision of cancer stimulates breast cancer cell lines to proliferate, migrate and invade Matrigel. On the other hand, the fluid collected from wounds that had received targeted intraoperative radiotherapy did not have such an effect (Fig. 19.1). Thus, if radiotherapy is delivered immediately after the operation using TARGIT, it could be superior to conventional radiotherapy that suffers from a “temporal miss.”

Systemic therapies such as aromatase inhibitors or ovarian suppression may achieve a similar effect on the microenvironment by reducing the estrogen concentration in the breast, and may have a synergistic effect with radiotherapy (Azria et al. 2005). Thus, with the increasing use of systemic therapy, intraoperative radiotherapy to the tissues surrounding the primary tumor might be all that is necessary, and such an approach may solve many of the problems of postoperative radiotherapy discussed earlier and may allow many more women with breast cancer to conserve their breast.

19





Decreased by TARGIT	Increased by TARGIT
Angiogenin	AgRP
Flt-3 ligand	EFGR
IL-10	FAS/TNFRSF6
IL-6	FGF-4
IL-7	G-CSF
Leptin	IFGBP-6
MCP-1	IL-13
MCP-2	IL-4
RANTES	IL-5
PDGF-BB	Mip-1d
GRO	
HGF	
IL-8	
Mip-1a	
sTNFR-II	
sTNFR-I	
uPAR	
VEGF-R3	
Tie-1	
Tie-2	

Fig. 19.1 TARGIT treatment impairs the WF-induced cancer cell migration and invasion, and changes the tumor microenvironment. Mammary carcinoma-derived cell lines MDA-MB 231 and MDA-MB 453 were tested in a Transwell-based chemotaxis assay and via video endoscopy for their ability to migrate toward the indicated treatment. Preoperative serum (PS) and wound fluid (WF) pools were used at 2.5% in serum-free medium (SFM). The *figure on the left* shows the single-cell speed of MDA-MB 453 immersed in a three-dimensional collagen I matrix and treated as indicated (*NT*, surgery only; *IORT*, surgery + TARGIT). The *figure on the right* shows the percentage of MDA-MB 231 cells invading a three-dimensional Matrigel in a Transwell-based chemotaxis assay in response to the indicated WF, used at a concentration of 2.5%. The box lists the results of the proteomic assay, showing the factors in the wound fluid that are modified by intraoperative radiotherapy (TARGIT). Modified from Belletti et al. (2008)

19.3 Radiobiology of Intraoperative Radiotherapy

The main basis of intraoperative radiotherapy is that a single dose of IORT could have a biological effect on tissue that is equivalent to a full course of fractionated external-beam radiotherapy (EBRT). This is therefore being tested in randomized trials. There is already some evidence suggesting the safety and effectiveness of a single dose of radiotherapy in achieving tumor cell kill (Vaidya et al. 2004b, 2005b, 2006a, 2008). The theoretical basis for calculating the biological effects of a given dose of radiation is the linear–quadratic model. This model is based on the different shapes of cell survival curves of acute and late-reacting tissues. It is assumed that large single doses of radiation are more effective on late-responding tissues as compared to acute reacting tissues. However, the LQ model is reliable for single doses up to 6–8 Gy only, and may therefore not be appropriate for modeling the effects of the high single doses (~20 Gy) that are used in IORT or radiosurgery. There is now abundant clinical information about the effects and side effects of high single doses on a variety of cancers. Radiosurgery doses of 20–25 Gy are sufficient to sterilize macroscopic brain metastases with a very low risk of causing brain necrosis or functional damage when the dose is given to a small volume (Flickinger et al. 1995, 2003; Wenz et al. 1998). Long-term follow-up of large Swedish (Swedish Rectal Cancer Trial 1997) and Dutch (Kapiteijn et al. 2001) rectal cancer trials in which 25 Gy, given in five fractions, was prescribed to the pelvis has not shown unacceptable toxicity. Thus, severe long-term side effects would not be expected after administration of 5 Gy to 1 cm of breast tissue surrounding an excision cavity, although caution should be exercised when giving high single doses to skin and ribs (Reitsamer et al. 2004).

A detailed analysis of the radiobiological aspects specific to the Intrabeam system requires consideration of the increased relative biologic efficiency (RBE) of the low-energy X-rays, the steep dose-dependency of RBE, and the rate of damage repair during radiotherapy delivery (30–50 min). Brenner et al. (1999) have estimated an RBE of about 1.5 for this type of low-energy X-rays. To achieve a complete model of RBE, the introduction of the Lea–Catchside time factor (Herskind et al. 2004) is important. Using this equation, RBEs of 1.0 at the applicator surface, of 1.5 at 10 mm, and about 2.0 at 25 mm can be estimated, with the exact value depending on the size of the applicator. The risk of side effects can also calculated, although there are insufficient data as to the impact of the volume of treatment to include this as a factor. (However, since the treatment volume is small for IORT, the risk of side effects will probably be lower than that calculated from this model.) Since the $TD_{50/5}$ for pneumonitis is about 9–10 Gy, the thickness of the chest wall should ensure that virtually no risk of pneumonitis is expected. The same is true for the heart. Since the dose to the heart and lungs during IORT is almost negligible, the mortality from cardiac ischemia that has been observed in some trials using conventional radiation therapy (Rutqvist and Johansson 1990; Lind et al. 1997; Bates and Evans 1995; Meinardi et al. 2001) should not be seen. The $TD_{50/5}$ for subcutaneous fibrosis is in the range of 13 Gy. The risk of fibrosis shows a steep decrease with increasing distance from the applicator, reaching nearly zero at about 5 mm tissue depth. The calculated low risk of toxicity is in good agreement with the available clinical data from patients treated with

TARGIT (Vaidya et al. 2003, 2006a; Kraus-Tiefenbacher et al. 2006a, b; Joseph et al. 2004). The single dose of radiation is administered using Intrabeam over 25–35 min. Since normal tissues can repair their DNA within a few minutes, a large proportion of radiation-induced DNA damage is repaired in normal tissues during this long duration of IORT. On the other hand, cancer cells or precancerous cells with poor DNA-repair machinery are unable to do so. Thus, radiation administered using Intrabeam over 25–35 min would have a high therapeutic index, and would induce lesser normal tissue damage than similar doses given over 2–3 min (Herskind et al. 2005, 2006), as used when electrons are employed (ELIOT trial).

We have developed a mathematical model (Enderling et al. 2006, 2007) to estimate the effect of a single dose of radiotherapy as given with Intrabeam in the TARGIT trial. We hypothesize that the therapeutic effectiveness or not of radiotherapy is influenced by the fact that breast cancers are surrounded by morphologically normal cells that already show a loss of heterozygosity in critical genes (Deng et al. 1994, 1996). These cells would be able to repair their DNA in response to fractionated radiotherapy, just like normal cells. Continuing survival and subsequent transformation of these cells may be a large factor in the development of local recurrence. This mathematical model (which can be accessed at https://www.cvit.org/spotlight/RT_applet/) is the first to offer an explanation for the observation that conventional radiotherapy is effective in only two-thirds of cases of early breast cancers. This proportional reduction in recurrence by conventional radiotherapy (of 66%) is constant across tumor sizes and excision extents. However, when a subjected to a single large dose of radiotherapy (as in TARGIT), these cells would succumb and thus the source of local recurrence would be eliminated. Furthermore, the radiobiological effect of a single fraction of radiotherapy may actually be paradoxically higher at greater depth (Astor et al. 2000). This idea gained recent support from the results of the START trials (Bentzen et al. 2008a, b), which suggested that the breast cancer tissue may be more sensitive to fraction size, and delivery in a small number of larger fractions could be a valid option. Thus, the tissues immediately next to the applicator would have a high physical dose with low therapeutic ratio, while those away from the applicator would have a lower physical dose but a high therapeutic ratio. This is an advantage of Intrabeam over the systems that use electrons to deliver a uniform dose or radiation, because its high (physical) dose region is small and it is expected that this would increase acute tumor effects while reducing normal tissue damage and long-term toxicity.

The radiation produced by Intrabeam (the X-ray source is called PRS: Photon Radiosurgery System) is found to induce both necrotic and apoptotic cell death in addition to rapid cell death through nonapoptotic pathways (Kurita et al. 2000). Animal experiments have demonstrated that PRS can induce well-demarcated ablation in canine liver and kidney (Chan et al. 2000; Koniaris et al. 2000; Solomon et al. 2001). As a demonstration of its efficacy at ablating tumor tissue, a series of three breast cancer patients (T = 1–2.5 cm) have been treated with a PRS 400 (bare probe only; i.e., without the applicators, but with the same Intrabeam machine that is used for intraoperative radiotherapy, as shown in the left lower part of Fig. 19.3). These patients were too frail to have surgery. The tumor was localized on the Mammotest, a digital stereotactic prone mammography

table. The tip of the probe was placed in the center of the tumor and radiation was delivered in about 6–12 min. The tumors, ranging in size from 1 to 2.5 cm, were ablated with a single dose of radiotherapy, as demonstrated on biopsy and serial contrast-enhanced MRI (Vaidya et al. 2002c).

Another radiobiologic question of importance is whether the tolerable dose is sufficient to prevent local recurrence. We have previously discussed the comparison of how a single IORT treatment of 20 Gy compares to a course of fractionated external-beam radiotherapy (EBRT) of about 50 Gy (Vaidya et al. 2004a). One advantage of IORT is that there is no delay between tumor excision and treatment, so there is no loss of efficacy due to tumor-cell proliferation before starting EBRT or during the EBRT course. The RBE of low-energy X-rays for early-reacting tissues and tumor cells (α/β ratio of 3 Gy) is higher than for late-reacting tissues (α/β ratio of 10 Gy). As noted above, the RBE increases with distance from the applicator (Herskind et al. 2004). Thus, the surviving fraction of tumor cells at the applicator surface will be 10^{-12}; 99% of the tumor cells 10 mm from the applicator surface should be sterilized. The tissues immediately next to the applicator would thus receive a high physical dose (with a low therapeutic ratio), and those further away from the applicator would receive a lower physical dose, but with a high therapeutic ratio (Astor et al. 2000). This is an advantage of Intrabeam over the systems using electrons to deliver a uniform dose or radiation, because its small high (physical) dose region would be expected to increase tumor cell death while reducing normal tissue damage and long-term toxicity. In contrast, EBRT has a homogeneous dose distribution, and therefore the spatial distribution of the risk of recurrence depends only on the tumor cell density (which is highest close to the excision cavity). One may therefore expect that there is a "sphere of equivalence" (Herskind et al. 2008 and Vaidya et al. 2009) around the excision cavity in which the risk of recurrence for IORT is equivalent to that obtained by EBRT (Early Breast Cancer Trialists' Collaborative Group 2000). The radius of this sphere depends on the applicator size and is about 15 mm for the applicators used most often.

As yet, there is no firmly established standardized IORT dose or dose rate for use in early breast cancer. IORT doses investigated for use in early breast cancer have ranged from 5 to 22 Gy using a variety of different IORT systems. The Intrabeam IORT system delivers a physical dose of 18–20 Gy administered to the tumor bed and about 5–7 Gy at a distance of 1.0 cm from the breast tumor cavity for a period of 20–25 min. Using their Novac7 IORT technology, Veronesi et al. have estimated that an external-beam dose of 60 Gy delivered in 30 fractions at 2 Gy/fraction is equivalent to a single IORT fraction of 20–22 Gy (using an α/β ratio at 10 Gy, typical for tumors and acute reacting tissues). The doses delivered by other methods of partial breast irradiation such as intraoperative systems such as Novac7 have been criticized as being large (Pawlik and Kuerer 2005), and while that dose is uniform, the dose distribution delivered using the TARGIT approach theoretically approximates the geographic distribution of risk of recurrence within the breast.

There has been some discussion about the gap between the IORT and EBRT when TARGIT is delivered as a boost. From the long-term data, it appears that it is safe (Kraus-Tiefenbacher et al. 2006b) and effective (Vaidya et al. 2008). It also appears that the gap is

necessary to avoid late toxicity (Wenz et al. 2008), and we believe at least a five- to six-week gap could be ideal.

19.4 Intraoperative Radiotherapy: An Elegant Method of Partial Breast Irradiation

Modern intraoperative radiotherapy devices derive benefit from miniaturization technology. No longer do we need to transport the patient to the purpose-built radiotherapy suite; the (mini) radiotherapy suite comes to the patient right in the operating room! The first device to be used for IORT was the Intrabeam (Photoelectron Corporation, Lexington, MA, USA) (Vaidya et al. 1999, 2001), which is now manufactured by Carl Zeiss AG (Oberkochen, Germany) (Fig. 19.2). The two other systems of mobile linear accelerators are the Mobetron System (Oncology Care Systems Group of Siemens Medical Systems, Intraop Medical Inc., Santa Clara, CA, USA) and the Novac7 System (Hitesys SPA, Italy). Some of the characteristics of these machines are given in Table 19.1 (taken from Vaidya et al. 2004b).

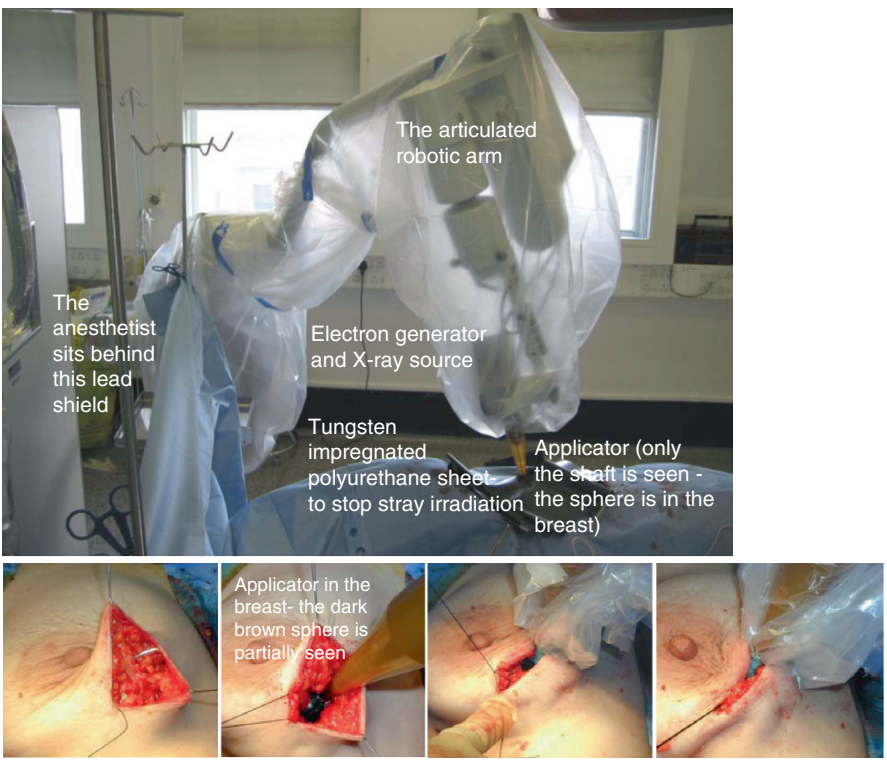


Fig. 19.2 The Intrabeam system (with the X-ray source in the breast wound) and the electron generator and accelerator held by the articulated arm. The figures below demonstrate how the target breast tissue wraps around the applicator, giving true conformal brachytherapy. Modified from Vaidya et al. 2004b.

Table 19.1 Some characteristics of intraoperative radiotherapy systems

Device	Company	Radiation type	Dose	Weight (kg)	Modification of operating room
Intrabeam	Carl Zeiss AG, Germany	Soft X-rays at 50 kV	Physical dose of 20 Gy next to the applicator (with a quick attenuation) over 25–30 min. Setting-up time is about 10–12 min	1.8	Not usually required
Mobitron	Intraop Medical Inc., USA	Electrons at 4–12 MeV	20 Gy physical dose in 3–5 min. Setting-up time is about 20 min	1,275	Necessary
Novac7	Hitesys SPA, Italy	Electrons at 4–12 MeV	20 Gy physical dose in 3–5 min. Setting-up time is about 20 min	650	Necessary

19.5 The Intrabeam Machine and Surgical Technique

The Intrabeam machine contains a miniature electron gun and electron accelerator contained in an X-ray tube powered by a 12 V power supply. "Soft" X-rays (50 kVp) are emitted from the point source. Tissue is kept at a distance from the source by spherical applicators in order to give a uniform dose. Various sizes of applicator spheres are available to suit the size of the surgical cavity. The precise dose rate depends on the diameter of the applicator and the energy of the beam, both of which may be varied to optimize the radiation treatment. For example, a dose of 18–20 Gy at the applicator surface (i.e., the tumor bed) can be delivered in about 25–35 min with a 3.5 cm applicator. The quick attenuation of the radiation minimizes the need for radiation protection to the operating personnel. Usually the operating team leaves the room, but the anesthetist (and anyone else interested in observing the procedure) sits behind a mobile lead shield that prevents exposure. The technique has been previously described in detail (Vaidya et al. 2002a), and an operative video is available from the authors via the Internet.

In the operating room, wide local excision of the primary tumor is carried out in the usual manner, with a margin of normal breast tissue. After the lumpectomy, it is important to achieve complete hemostasis, because even a small amount of bleeding in the 20–25 min during which radiotherapy is being delivered can distort the cavity enough to considerably change the dosimetry. Applicators of different sizes are tried until one is found that fits snugly within the cavity. A purse string suture needs to be skillfully placed: it must pass through the breast parenchyma and appose it to the applicator surface; but at the same time it must not bring the dermis too close to the applicator surface. It is important to protect the

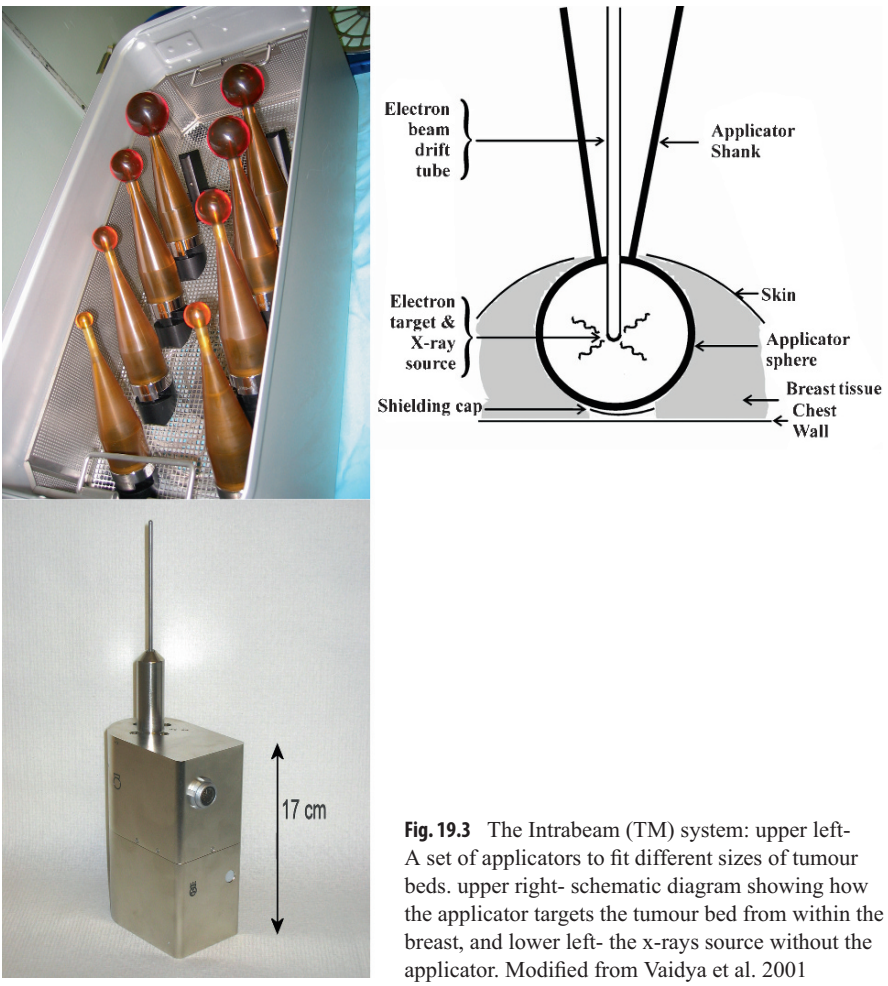


Fig. 19.3 The Intrabeam (TM) system: upper left- A set of applicators to fit different sizes of tumour beds. upper right- schematic diagram showing how the applicator targets the tumour bed from within the breast, and lower left- the x-rays source without the applicator. Modified from Vaidya et al. 2001

dermis, which should not be brought to within 1 cm of the applicator surface. Fine prolene sutures can be used to slightly retract the skin edge away from the applicator. However, complete eversion of the skin or the use of self-retaining retractors will increase the separation from the applicator so much that it would jeopardize the radiation dose and risk under treatment. For skin further away from the edge that cannot be effectively retracted for fear of reducing the dose to target tissues, a customized piece of surgical gauze soaked in saline, 0.5–0.9 cm thick, can be inserted deep to the skin. This allows the dermis to be lifted off the applicator while ensuring that the breast tissue just deep to it still receives radiotherapy. If necessary, the chest wall and skin can be protected by radiopaque tungsten-filled polyurethane material. These thin rubber-like sheets are supplied as caps that fit on

the applicator or can be cut to size from a larger flat sheet on the operating table so as to fit the area of pectoralis muscle that is exposed and does not need to be irradiated. These provide effective (95% shielding) protection to intrathoracic structures. In patients undergoing sentinel node sampling with immediate cytological or histological evaluation (so that complete axillary clearance can be carried out at the same sitting), TARGIT can often be delivered while the surgical team waits for this result without wasting operating room time. With this elegant approach, the pliable breast tissue around the cavity of surgical excision wraps around the radiotherapy source; i.e., the target is "conformed" to the source. This simple, effective technique avoids the unnecessarily complex and sophisticated techniques of using interstitial implantation of radioactive wires or the even more complex techniques needed for conformal radiotherapy by external beams with multileaf collimators from a linear accelerator. It eliminates "geographical miss" and delivers radiotherapy at the earliest possible time after surgery. The quick attenuation of the radiation dose protects normal tissues and allows the treatment to be carried out in unmodified operating theaters. Thus, in theory, the biological effect and cosmetic outcome can be improved.

The surgical part of the TARGIT technique is simple and does *not* require extensive dissection around the breast, separating it from the skin anteriorly and the chest wall posteriorly, which is necessary to perform intraoperative radiotherapy with other devices such as the Novac7 used in the ELIOT trial. This means that it can be administered even under local anesthetic (Vaidya et al. 2006b), especially when it is being given as a second procedure a few days after the primary tumor is excised. This latter approach is useful when it is logistically easier and when the primary operation is not performed at a center equipped with the Intrabeam machine. We have found that about 10% of patients get additional EBRT and about 25% of patients are given TARGIT as a second procedure.

19.6 Results of Clinical Trials with the Intrabeam System

Based on the hypothesis that index quadrant irradiation is sufficient, in July 1998 we introduced the technique of targeted intraoperative radiotherapy (TARGIT) (Vaidya et al. 2001, 2002b, 2004b; Vaidya 2002) radiotherapy delivered as a single dose using low-energy X-rays targeted to the peritumoral tissues from within the breast using the Intrabeam device. In patients with small, well-differentiated breast cancers, which are now becoming the majority, this could be the sole radiotherapy treatment.

In pilot studies performed in the United Kingdom, the United States, Australia, Germany, and Italy testing the feasibility and safety of the technique, TARGIT was used as a "boost" dose (Vaidya et al. 2005a, 2006a, 2008) and whole breast EBRT was also given. The median follow-up is 49 months, and the first patient was treated over ten years ago. This was not a low-risk group. A third of the patients were younger than 51 years, 57% of cancers were between 1 and 2 cm (21% > 2 cm), 29% had a grade 3 tumor and 29% were node positive. Amongst these 300 patients, five patients had a local recurrence (five-year actuarial recurrence rate = 1.52%, SE = 0.76%). This compares very favorably with the recurrence rates achieved in recent radiotherapy trials (see Table 19.2)

Table 19.2 Comparison of TARGIT boost with recent clinical trial data

High-risk factors	EORTC boost[8]	START-B trial[9]	TARGIT boost
Young age	37% (< = 50)	21% (<50)	32% (<50)
% >1 cm	75%	86%	78%
% Grade 3	N/A	23%	29%
% Node +ve	21%	23.6%	29%
Recurrence rate at 5 years	4.3%	2.8%	1.52%

despite having a cohort of patients with a worse prognosis. It appears that, given as a boost, TARGIT yields very low recurrence rates.

TARGIT is already used a standard option for the routine tumor bed boost in many centers, and is included in the German radiation oncology guidelines since 2008. While we recognize that a TARGIT boost is at least equivalent to a conventional EBRT boost, we believe that there is pathological, biological (geographical and temporal accuracy), mathematical-modeling, and clinical evidence to suggest that it is likely to be superior. Hence, we have recently launched the TARGIT boost trial that is aimed at ascertaining whether it yields a lower recurrence rate than EBRT in higher-risk (especially young) patients who still suffer a 8–13% local recurrence rate.

During this pilot phase, and for some time later on, a few highly selected patients received TARGIT as the sole modality of radiotherapy (Vaidya et al. 2005b). The updated report on such patients who could not otherwise be given EBRT or entered into the TARGIT trial now includes 78 patients (Keshtgar et al. 2008) with a median follow up of 2–3 years and with excellent local control, giving us reassurance that an inferior result is unlikely.

Over 1,300 patients have been treated with the TARGIT technique. Apart from two patients treated early in these studies, wound healing has been excellent. The cosmetic outcome was assessed formally in available patients treated in the United Kingdom at a median follow-up of 42 months by a surgeon and a nurse not involved in the trial (Vaidya et al. 2003). On a scale of 1–5 (with five being best), mean scores for appearance, texture and comfort of the breast given by these observers were 3.5, 2.7 and 3.7. The corresponding scores given by the patient herself were 4, 3.1 and 3.5.

The multicenter randomized trial of TARGIT (Vaidya et al. 1999, 2002d, 2004b; Vaidya 2002) using the Intrabeam system is now recruiting patients at 23 centers in the United Kingdom, Germany, Italy, Denmark, Poland, Switzerland, the United States, Canada, and Australia. Over 1,600 patients have already been randomized.

In this trial, patients with invasive breast cancer over the age of 45 and suitable for breast-conserving therapy are enrolled prior to tumor excision to receive either IORT or conventional whole breast radiotherapy. Patients with a preoperative diagnosis of invasive lobular carcinoma are excluded because this is indicative of a higher risk of recurrence away from the tumor bed. The pragmatic design of the trial means that if factors such as lobular carcinoma, extensive intraductal component and positive margins are found only postoperatively, then whole breast EBRT can be added safely without jeopardizing the trial analysis. In addition, each center can choose (at the outset) to give additional EBRT in patients in whom they feel it is needed (e.g., those who are found to have multiple lymph

node involvement or extensive lymphovascular invasion). We have found that EBRT was added for 10% of the ~1,600 patients randomized to date. This facility allows pragmatic management of patients with an equipoise that can be decided by each individual center before they start to recruit in the trial. Furthermore, the trial allows the radiotherapy to be delivered at a second procedure, after the final histopathology is available and eligibility criteria are met satisfactorily. Initially at University College London, we were exclusively delivering intraoperative radiotherapy at the time of the primary operation. Our Australian collaborators administered TARGIT as a second procedure for logistic reasons and found that it is indeed safe. In Dundee, Scotland, for example, both approaches are being used, and this allows the recruitment of patients from another hospital that is part of the same NHS trust but is situated some distance away in Perth.

The first patient was randomized in the TARGIT trial in March 2000. Twenty-three centers are now recruiting in this trial. The outcome measures are local recurrence, cosmetic outcome, patient satisfaction and cost analysis, and it is expected that the first results of this trial will be available in 2010/11.

It is well recognized, as in every adjuvant situation, that postoperative whole breast radiotherapy is an overtreatment 60–70% of the time, since only 30–40% of patients will ever get a local recurrence after surgery alone. Our approach to intraoperative radiotherapy intends to refine the treatment of breast cancer patients by introducing a risk-adapted strategy; the elderly patient with a T1G1a tumor should perhaps be treated with a different kind of therapy, such as targeted intraoperative radiotherapy (TARGIT) only, whereas to the young patient with a T2G3 tumor, would have a more accurate boost with TARGIT in addition to whole breast radiotherapy. The TARGIT trial is testing just such a strategy. Hence, the TARGIT trial should not be mistaken for a trial that is solely designed to compare intraoperative with postoperative radiotherapy when actually it is testing two different treatment approaches: the conventional blanket approach versus the new approach of tailored treatment. Endpoints include local recurrence, cosmetic outcome, patient satisfaction and cost analysis.

19.7 Health Economics

Delivering IORT with the Intrabeam prolongs the primary operation by 5–45 min (the shorter extra time when it is performed in conjunction with immediate analysis of the sentinel lymph node). In addition, approximately 1 h of a radiotherapy physicist's time is needed to prepare the device. External-beam radiotherapy requires about nine man-hours of planning, 6 h of radiotherapy-room time, and 30–60 h of patient time. If the cost of conventional radiotherapy was £2,400, using the most conservative estimates, then considering only the 66% saving in man-hours, this novel technique would save £1,800 per patient. If we assume that 25% of the 27,000 breast cancer patients diagnosed every year in the United Kingdom might be treated by BCS and IORT instead of conventional EBRT, the yearly savings for the National Health Service would be £12,150,000. This does not include the substantial saving of expensive time on the linear accelerators, which would allow reduced waiting lists and—most importantly—the saving of time, effort, and inconvenience

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for patients. Thus, unlike most other "new" treatments, this one may be actually be less expensive than the current standard! The results of the START trials (Bentzen et al. 2008a) have now resulted in an increase in the popularity of a three-week course of radiotherapy in the UK, although this has not been widely adapted elsewhere in the world. Reducing the radiotherapy duration would change the magnitude of the economic benefit, but TARGIT will still maintain its potential advantages in terms of avoiding geographical and temporal misses and reducing the duration from 15 to 20 postoperative fractions to a single intraoperative fraction of radiotherapy, while also retaining its promise of significantly improving the accessibility to breast-conserving surgery in remote areas around the world.

As we have reiterated before (Vaidya et al. 2004a, b), mere novelty and the convenience of this new technology should not stand in the way of its proper scientific assessment before it is used for standard care. Randomized clinical trials are essential to test this revolutionary approach. We believe that in the future, local treatment of breast cancer could be tailored to the needs of the patient and the tumor. The patient, the surgeon and the radiation oncologist will be able to choose from several well-tested approaches. This may mean not only a wider availability of breast-conserving therapy, but also that small, incremental benefits from targeted and tailored treatment may reduce morbidity and even mortality.

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APBI Intraoperative Technique with Electrons

20

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20.1 Introduction

Breast-conserving surgery (BCS) consists of the surgical removal of the tumor mass plus a margin, followed by postoperative whole breast irradiation (WBI). This combined treatment is currently considered the standard approach for most women with early-stage breast cancer (Veronesi et al. 2002; Fischer et al. 1995, 2002) because it has shown equivalent results in terms of local control and survival rates to those obtained with mastectomy in women with comparable tumor sizes and stages. Postoperative radiation therapy (RT) consists of the irradiation of the whole breast tissue left by the surgeon up to a dose of 45–50 Gy delivered over 5–6 weeks. In most patients, a boost dose of 10–15 Gy to the tumor bed is added, further prolonging the treatment time by an additional 1–2 weeks (Veronesi et al. 1993).

Radiotherapy significantly reduces local recurrence, 15-year breast cancer mortality and overall mortality, as a meta-analysis of the most relevant recently published randomized trials has shown (Clarke et al. 2005). While these data were ripening, several institutions attempted to revisit the adjuvant radiation treatment settings, changing fractionation, overall treatment time and target volume (Sanders et al. 2007; Walner et al. 2004; Arthur et al. 2003; Ribeiro et al. 1993). The concept of partial breast irradiation (PBI), which consists of the irradiation of the site of surgical excision and adjacent tissues only, is driving the modern evolution of minimum effective treatment in breast radiotherapy. PBI can be performed using different approaches, including brachytherapy (Polgar et al. 2004; Vicini et al. 1999, 2003, 2005; Arthur et al. 2003; Baglan et al. 2001; King et al. 2000; Harpe et al. 2005; Belkacemi et al. 2003; Keisch et al. 2003; Ott et al. 2007; Patel and Das 2006; Chen et al. 2006), intraoperative RT (IORT) (Vaidya et al. 2004; Orecchia et al. 2003; Veronesi et al. 2003a, b), and high-precision external-beam RT (EBRT) (Formenti 2005; Formenti et al. 2004; Kozak et al. 2006; Bovi et al. 2007). With PBI, it is possible to limit

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the irradiation to only the involved quadrant of the breast plus a margin. The resulting drastic reductions in both target volume and nontarget tissue allow the RT course to be changed from 40–50 days to a shorter, more intensive schedule of fractionation (no more than ten fractions). IORT performed with electron beams (IOERT) targeted at the tumor bed pushes the concept of hypofractionation to the limits—right up to a single irradiation performed during the surgical procedure, immediately after the removal of the tumor mass.

20.2 Rationale for the Use of IOERT in Breast Cancer

The key issue in the debate regarding the adequacy of PBI is whether irradiation of the entire breast is required after BCS. The rationale for the use of segmental irradiation in place of WBI can be understood by observing the results of some long-term studies that report that local relapses occur at the original tumor site at a rate of 85% or more after BCS, independent of whether EBRT was additionally performed. In the Milan III trial (Veronesi et al. 2001a, b), which compared quadrantectomy alone vs. quadrantectomy plus conventional WBI, a significant reduction in local failure rate was observed, particularly in patients over 55 years. Furthermore, patients older than 65 have also shown a significantly lower failure rate in other clinical studies, although these differences could be related to the higher percentage of low-risk factors in this age group: better-differentiated tumors, poor extensive intraductal component (EIC), and minimal lymphovascular invasion (Abner et al. 2000; Voogd et al. 1999; Bartelink et al. 2001; Holland et al. 1985).

As yet there are no conclusive data that support the use of IOERT in the routine management of early-stage breast cancer. Clinical outcome can be strongly influenced by patient selection. There are major differences in technical approach, fractionation schedules and skills between difference centers, and so the results for safety and efficacy should be approached with caution. Uncertainties in clinical outcome are mainly due to the short follow-up times of some institutional experiences, often in association with only small numbers of patients treated, and the need for definitive results from several large randomized trials that are still currently ongoing. By shortening the treatment time, IOERT minimizes some of the constraints and setbacks that affect compliance to adjuvant RT. For the majority of patients, and particularly for the elderly, long traveling distances from home to hospital or long waiting times to begin radiation often decrease the number of patients that actually receive the recommended local treatment (Athas et al. 2000; Du et al. 1999). Moreover, just as surgery has shifted from mastectomy to lumpectomy and from axillary dissection to sentinel node biopsy, IOERT is reducing the "intensity" of RT. PBI is an effective way of reducing the volume of nontarget tissue irradiated, and just as in the case of electron intraoperative techniques, it avoids delivering any dose to the skin and subcutaneous tissues. IOERT has the other important advantage of avoiding interactions with systemic therapy that may result in delays in the initiation or the accomplishment of conventional treatment, particularly when chemotherapy with anthracyclin or taxanes is given. The timing of IOERT represents a further potential biological advantage since it could reduce tumor cell repopulation, a possible detrimental effect caused by delays in starting RT, especially in patients with fast-growing tumor cells or with close or positive margins.

IOERT thus lends itself to implementing the treatment philosophy of partial breast irradiation: to treat only the excision site and the adjacent tissues. However, studies that clearly show which patients can be appropriately selected for partial breast irradiation only and which should receive whole breast irradiation as well are not available. The good results obtained with PBI in Phase I and II trials (Kuske et al. 2004; Mussari et al. 2006a, b; Luini et al. 2005; Polgár et al. 2002; Vaidya et al. 2006), when appropriate selection criteria and quality assurance (QA) were used, must be confirmed by comparing them with those obtained with WBI in randomized Phase III trials. At present, two trials has been completed and three are still ongoing (Polgár et al. 2002, 2005, 2006; NSABP B-39, RTOG 0413 2006; Calvo et al. 2006). Therefore, this technique should not be used as a standard treatment. We believe that its use should currently be limited to a subgroup of patients at low risk of local recurrence who have the following characteristics: age older than 45 years, tumor diameter less than 3 cm, infiltrating ductal histology, no mammographic evidence of multifocality, negative resection margins, negative or no more than three positive axillary nodes, and no extensive intraductal component.

20.3 Radiobiology

The initial number of malignant cells influences the probability of tumor control for a given absorbed dose (assuming no differences in cellular radiosensitivity). Poisson statistics correlate the probability of tumor control with the cell survival rate as (Perez and Brady 2008):

$$P_{\text{cure}} = e^{-x} = e^{-(SF.M)},$$

where: P_{cure} is the probability of cure, X is the average number of surviving clonogens per tumor, SF is the fraction of cells surviving, and M is the initial number of cells.

This relationship between probability of cure and initial number of cells show how the probability of tumor control, at the same dose, increases for a decreasing initial number of cells; therefore, the greater the volume of the tumor, the higher the dose required to achieve the same control rate.

From this point of view, IOERT offers an important theoretical advantage over conventional postoperative EBRT and other PBI techniques. In most cases, the interval between the surgical procedure and the start of radiotherapy allows repopulation from the neoplastic clones present in microscopic residual disease. Indeed, after surgery, there can be "accelerated repopulation" of neoplastic clones, which can follow an exponential course in the first phases. Thus, giving IOERT immediately after surgery, either as a boost or as the sole treatment, may avoid this problem.

The dose–response relationship can be analyzed by various mathematical models, but the linear–quadratic (LQ) model is the one most commonly used (although this model is validated mostly for fraction sizes smaller than 8–10 Gy). In fact, the LQ model fits over the low-dose range but does not fit properly in the high-dose range. According to the LQ model, the biological response to irradiation can be expressed in terms of a linear dose coefficient α and a coefficient β for the square of the dose (Lea 1955; Read 1952).

The linear dose coefficient is

$$S = \alpha D,$$

where S is the cellular survival, α is a constant, and D is the dose delivered.

The coefficient α is correlated to the amount of lethal damage caused to a specific histological type.

The quadratic dose coefficient β is

$$S = \beta D^2.$$

The coefficient β is correlated to the amount of potentially lethal damage that actually becomes lethal under specific environmental conditions.

The linear component dominates the response at the low doses that are usually delivered in conventional fractionation (with about 2 Gy per fraction). The quadratic component rules at high doses.

The cell survival fraction is

$$\mathrm{SF} = \mathrm{e}^{-(\alpha D + \beta D 2)}.$$

The α/β ratio defines the dose at which the number of cells killed by the linear and quadratic components are equal:

$$\alpha D = \beta D^2$$
$$\alpha = \beta D^2 / D$$
$$\alpha = \beta D$$
$$D = \alpha / \beta$$

Usually, late-responding tissues have a low α/β ratio, while early-responding tissue have a large α/β ratio.

In conventional fractionated regimens, the time between two dose fractions allows the sublethal damage to be repaired (due to the β component). The greater the interval between fractions, the greater the number of cells repaired. This means that, using a multifractionated regimen, it is necessary to increase the total dose in order to kill the same amount of tumor cells compared to a single fraction. This increase in total dose necessary to achieve the same rate of cell death increases with increasing time between the dose fractions or with the number of fractions. Where large dose fractions are given in a single exposure, as in intraoperative radiation therapy, the cell survival rate is reduced, which means that such an approach requires a lower total dose than that needed in conventional fractionation (Thames et al. 1982; Elkinol and Sutton 1959). IOERT therefore has the radiobiological advantage of eliminating or reducing repopulation by eliminating the interval between surgery and radiotherapy and between radiotherapy fractions, during which tumor cells can proliferate. Moreover, tissues treated during surgery still have rich vascularization and aerobic metabolism, which (because of the oxygen effect) makes them more sensitive to radiation than they are after surgery, when they may become hypoxic due to postoperative changes.

According to the LQ model, the relationship between the biologically equivalent doses in single dose and multiple fractionated dose regimens is

$$D_{\mathrm{IORT}} = (1/2)\{[(\alpha/\beta)^2 + 4D_{2\mathrm{Gy}}(\alpha/\beta + 2)]^{0.5} - \alpha/\beta\}.$$

The doses most commonly used in cases of anticipated boost are 9, 10 or 12 Gy, while 21 Gy is the dose used in the Phase III trial at the European Institute of Oncology (EIO). Assuming that the α/β ratio is equal to 10; 9, 10, 12 and 21 Gy should result in the same local control as conventionally fractionated doses of 17, 20, 26 and 65 Gy, respectively. However, many clinical and experimental studies have shown that increasing the size of the dose fraction increases the severity of late responses. Therefore, in a single-fraction treatment, there may be a higher risk of late effects, such as fibrosis, for late-responding tissue.

20.4 Radiation Technique

Electron-beam accelerators that can be used in the operating room without the need to modify the room itself have greatly facilitated the application of IORT in our clinical practice. "Dedicated accelerators" have been designed that require only limited shielding (15 cm in width) around the operating table. Such accelerators are mobile and can therefore be transported from one operating room to another. They are also articulated, so they can be positioned properly in relation to the operating table and then make precisely controlled, small, incremental motions to facilitate alignment and docking with the applicator.

There are currently only three commercially available mobile IORT systems. The Mobetron (Intraop Medical, Inc., Santa Clara, CA, USA), which is more established in the United States, uses a soft-docking system in which the gantry is optically guided to a position 4 cm above the applicator. The Mobetron system consists of three separate units: the control console, the modulator, and the therapy module. The control console, which operates the accelerator during radiation treatment delivery, is placed outside the operating room so that radiation treatment delivery is controlled remotely. The modulator houses the electronic system of the accelerator and energizes the accelerator to produce the electron beams. The therapy module houses the accelerator guidance and control systems that generate and deliver the radiation. The Mobetron system produces four levels of energy: 4, 6, 9, and 12 MeV, with therapeutic ranges of up to 4 cm. The system is designed to deliver a very large, uniform dose of 10–25 Gy in a single fraction at a dose rate of 10 Gy min^{-1}. Treatments can be delivered using either flat or beveled circular applicators. Eight flat applicators ranging from 3 to 10 cm in diameter in 1 cm increments and four beveled applicators (3, 4, 5, and 6 cm in diameter) are available (Meurk et al. 1997).

The EIO has two other types of dedicated accelerators, which have enormously facilitated the implementation of a broad program of electron intraoperative radiation (ELIOT), allowing the treatment of a large number of patients in this institution. The radiation

therapy department installed the first accelerator, known as Novac7 (Hitesys, Latina, Italy), in 1998. It has a robotic arm with four rotational joints and a motorized base that allows translator movements of the entire structure without modifying the head orientation. Base and arm movements are controlled by an operator through a remote control connected to the mobile unit. Novac7 delivers electron beams (3–9 MeV) at a much higher dose per pulse than conventional accelerators (0.02–0.09 Gy/pulse, depending on the radiation beam energy and applicator size), thus substantially reducing the irradiation time needed during the surgical procedure (1–2 min typically for a prescribed dose of 20 Gy). Novac7 is equipped with cylindrical Perspex applicators of various diameters (4–10 cm), which are flat-ended or beveled (22.5–45°). More recently, at the beginning of 2004, a new dedicated accelerator, the Liac (Info & Tech, Rome, Italy) was also installed. Both the accelerators can easily be moved from one operating room to another. The Liac produces electrons at nominal energies of 4–10 MeV. Applicators with diameters of between 3 and 12 cm are available (flat or 15–30–45° beveled). Very high dose rates, similar to those obtained with Novac7, can be achieved. The nominal source-to-surface distance (SSD) is 80 cm for Novac7 and 60 cm for the Liac (Orecchia et al. 2005). The ELIOT program requires specialized staff and strict attention must be paid to the scheduling of the operating rooms. All procedures and the personnel involved have been explicitly described, as has the training required, with a special emphasis placed on dosimetry. ELIOT requires special dosimetric determinations that are different than those needed for conventional EBRT. The main reason for this is that a single high dose of radiation is delivered to a selectively defined volume of tissue, with an extension and a depth that are directly determined in the operating room. It is also in the operating room that the ELIOT team selects the appropriate diameter of the applicator, the energy of the electron beam, and the proper reference isodose to prescribe the dose. Moreover, the use of specific applicators contributes to the determination of the quality, output, homogeneity, and other physical and geometrical characteristics of the electron beams. These dosimetric data are needed to calculate the monitor units needed to deliver the prescribed dose to the target volume. Up to now, there has been no possibility of using a treatment planning system (TPS), and there is little time to make the dosimetric calculations, so it is necessary to make all of the physical data available, for each combination of applicator and energy, in a format that facilitates rapid consultation and easy use. In particular, the dosimetric data must allow for the calculation in real time of the monitor units (MU) necessary to deliver the prescribed dose to the target volume.

Other differences between ELIOT and EBRT are the use of specific applicators that contribute to the determination of the physical–geometrical characteristics of the electron beams (quality, output, homogeneity, etc.) and the high dose/pulse delivered by Novac7 and Liac. In general, international dosimetric protocols, such as the International Atomic Energy Agency (IAEA) and the American Association of Physicists in Medicine (AAPM) reports, should be used for the accurate determination of the absorbed dose to water. Those dedicated accelerators are characterized by a high dose/pulse, so it is not possible to apply the previously mentioned recommendations for measuring the dose using an ionization chamber due to the uncertainty over the ion recombination inside the gas of the chamber. As a consequence, it has been recommended that a calibrated and traceable detector that is

independent of dose per pulse, such as a Fricke or alanine dosimeter, should be used. Dosimetry under reference conditions should in any case be performed for all of the energies used in the ELIOT treatment. Dosimetry under nonreference conditions, referred to as clinical dosimetry, aims at the dosimetric characterization of the electron beams, mainly in terms of percentage depth dose (PPD) curves measured along the clinical axis of the beam, transversal beam profiles, isodose curves and output factors (Ciocca et al. 2006).

Another device used for intraoperative radiotherapy is the Intrabeam, developed by the Photoelectron Corporation (Lexington, MA, USA) and currently manufactured by Carl Zeiss AG (Oberkochen, Germany). The Intrabeam machine consists of a miniature electron beam-driven X-ray source that provides a point source of low-energy X-rays, 50 kV maximum. The radiation source is surrounded by a conical sheath with a sphere at the tip of various sizes, and can be inserted into the surgical cavity after tumor excision. The radiation dose at various distances from the cavity margin varies due to the rapid dose attenuation. Typical physical doses were 5 Gy at 1 cm, 10 Gy at 0.5 cm or 20 Gy next to the applicator over 21–28 min. The precise dose rate depends on the diameter of the applicator and the energy of the beam (Vaidya et al. 2005).

After a pilot study of 25 patients performed in 1998, a multicenter randomized trial using the Intrabeam system termed "TARGIT" started in March 2000 with an accrual goal of 2,232 patients, and is now recruiting patients in the United Kingdom, Germany, Italy, the United States and Australia. Patients are enrolled before tumor excision and receive either IORT or conventional whole breast radiotherapy. However, each center may decide to perform whole breast radiation in addition to IORT, based on histologic features (Holmes et al. 2007).

20.5 ELIOT After Quadrantectomy

The ELIOT treatment procedure consists of the following steps (Intra et al. 2002, 2006; Veronesi et al. 2003a, b).

20.5.1 Tumor Removal

At the EIO, patients undergo quadrantectomy according to Veronesi's technique, with sentinel node biopsy (SNB). Only patients with positive SNB undergo axillary dissection. Wide breast resection is performed by either radial skin incision centered on the tumor or periareolar incision if the lesion is near to the areola (Fig. 20.1). In cases of clinically nonpalpable tumors, resection guided by a radioisotopic localization with technetium-99m is performed and an X-ray film is obtained to verify the presence and the topography of the lesion. The excision extends deeply, to the fascia of the muscle, with safety margins of at least 1 cm around the tumor. ELIOT requires a special sequence of procedures to facilitate the radiation treatment.

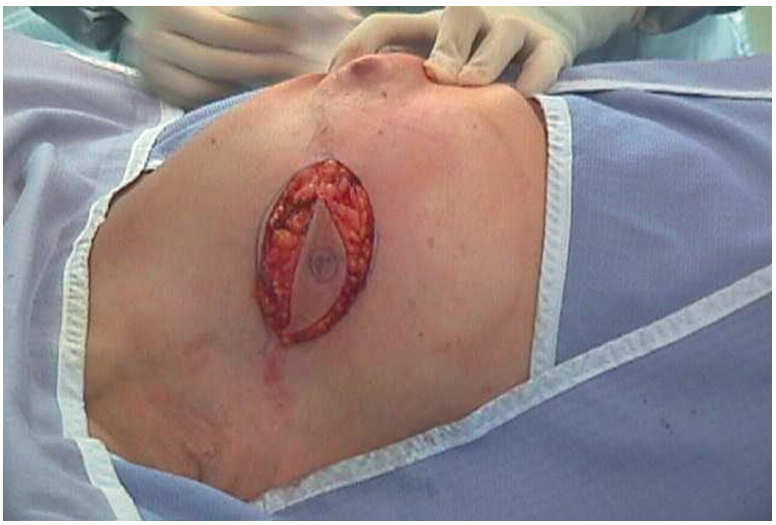

Fig. 20.1 Tumor removal. Radical skin excision centered on the palpable tumor

20.5.2 Breast Mobilization

After tumor removal, the breast gland is prepared by mobilizing the deep face from the fascia of the pectoralis major muscle and separating it superficially from the subcutaneous tissue at the level of the anterior adipose lamina for 4–5 cm in every direction around the remaining portion of the gland, to obtain the optimal exposure of the target to the radiation beam.

20.5.3 Thoracic Wall Protection

Immediately after the breast resection, a dedicated aluminum–lead shielding disk is placed between the gland and the pectoral muscle in order to minimize the irradiation of the thoracic wall (Fig. 20.2). The disk is inserted with the lead facing down and the aluminum up, and is available in various diameters as it must be larger than the collimator used.

20.5.4 Breast Gland Reconstruction

The breast gland must be temporarily reconstructed by suturing the surgical breach resulting from the tumor removal in order to restore the anatomy and the thickness of the gland (Fig. 20.3). The best dose distribution of the electron beam is achieved if the shape of the

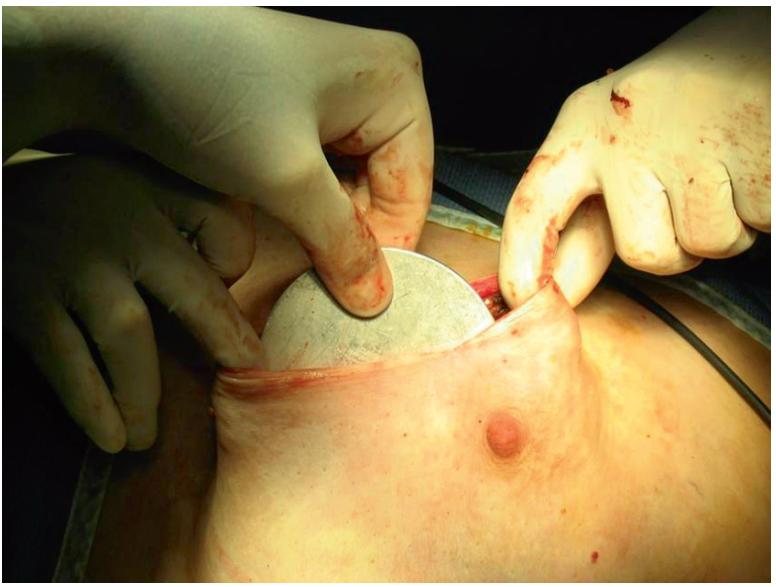

Fig. 20.2 Thoracic wall protection. A dedicated lead and aluminum disk acting as a protective device is placed between the gland and the pectoral muscle

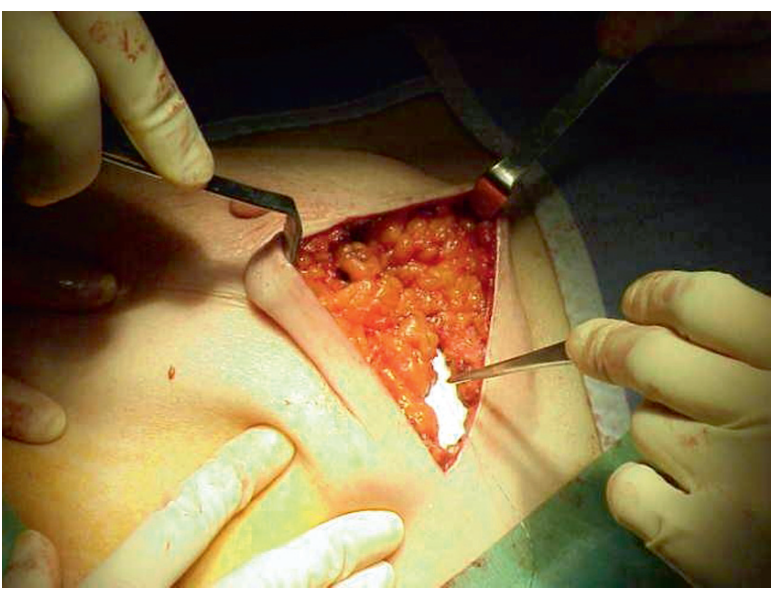

Fig. 20.3 Breast gland reconstruction. The remaining breast tissue is temporarily approximated by sutures in order to expose the correct portion of the gland to radiation beam

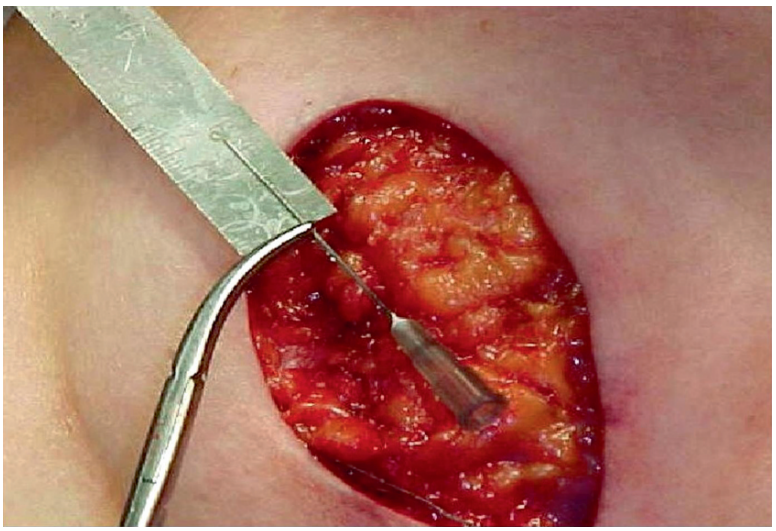

Fig. 20.4 Depth dose prescription. After reconstruction, the gland thickness is measured using a needle inserted perpendicularly through the breast target until the disk surface is reached, in order to select the appropriate electron energy

irradiated gland remains as homogeneous as possible. The gland thickness is then measured using a needle inserted perpendicularly through the reconstructed breast, deep to the disk surface (Fig. 20.4). Based on the thickness measured, the appropriate electron energy is selected.

20.5.5 IORT Collimator Placement and Connection to the Linear Accelerator

The sterile polymethyl methacrylate collimator of the linear accelerator is placed directly in contact with the reconstructed breast gland (Fig. 20.5), focusing on the site where the tumor was located. The portion of the breast that needs to be irradiated is generally an area 4–6 cm in diameter, but the size of the collimator is also selected based on the breast size, cancer site and technical capacity to mobilize the gland. The applicator is then connected to the head of the treatment unit: hard docking (Fig. 20.6).

20.5.6 Radiation Treatment

After the docking, a series of mobile barriers are positioned around the operating table, in order to provide good shielding from the scattered X-rays. After the irradiation, which usually takes from 1.5 to 3 min, the applicator and the aluminum–lead disk used to protect the thoracic wall are removed and the breast reconstruction is completed.

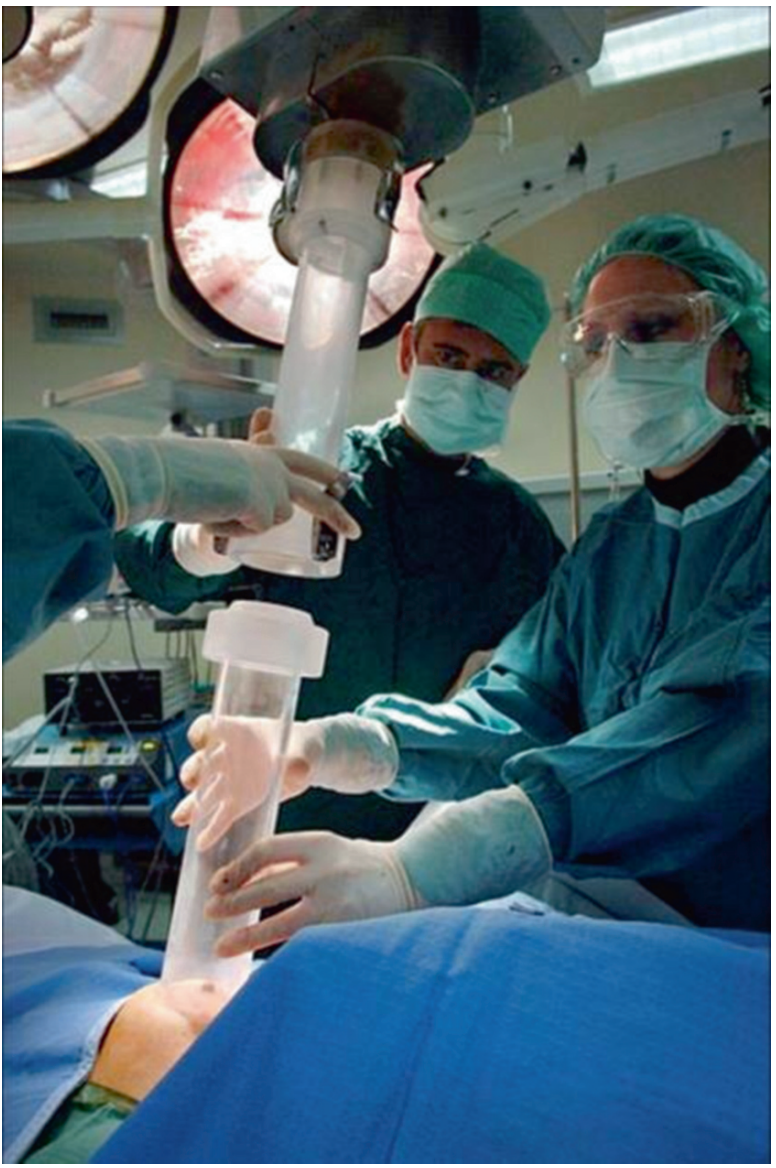

Fig. 20.5 Hard-docking system. The distal part of the applicator is directly connected to the linear accelerator. The remote control produces gentle movements of the linac in every direction

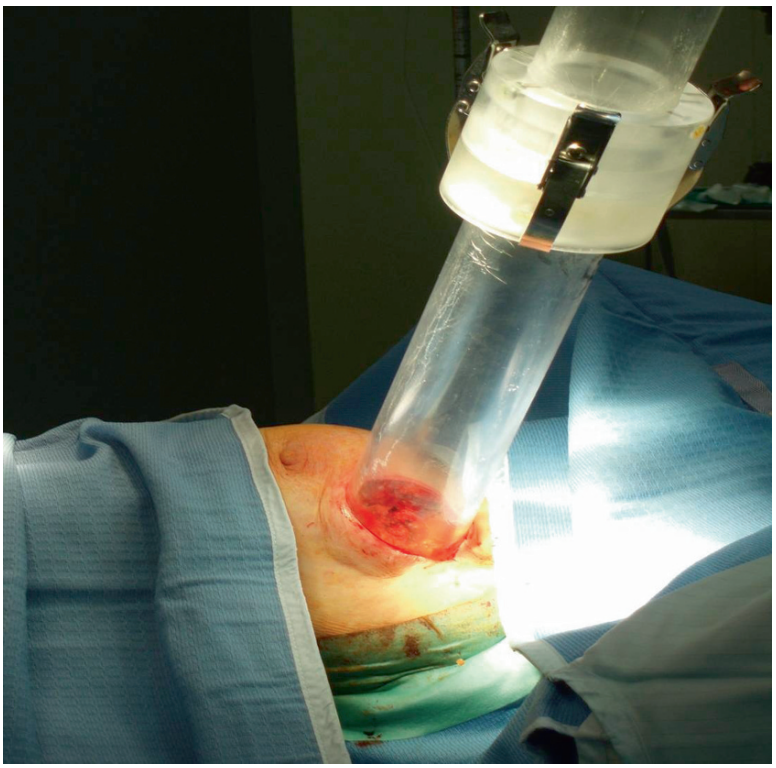

Fig. 20.6 Radiation treatment. The applicator is placed in the correct position in order to guarantee coverage of the entire target volume, which is generally an area 4–6 cm in diameter around the cancer resection site. The whole intraoperative irradiation procedure is completed in 2–4 min

20.6 EIO Experience

20.6.1 Phase I/II Study

Between July 1999 and May 2000 at EIO in Milan, a dose-escalation study was performed in order to define the maximum dose tolerable in a single fraction and to establish equivalence between the single ELIOT dose value attained and the conventional fractionated schedule of external-beam radiotherapy (EBRT). One hundred and one patients with a total of 103 breast carcinomas (two bilateral), underwent conservative surgery, sentinel node biopsy with or without axillary dissection for a T1–2 breast cancer no larger than 2.5 cm. Surgery was followed by ELIOT with or without EBRT. Mean age was 57 years. The most common histology was invasive ductal carcinoma (45 cases, 78%).

Table 20.1 ELIOT dose levels (Luini et al. 2005)

Dose level (Gy)	Aim	No. patients
10	Anticipated boost	10
15	Anticipated boost	7 (1 bilateral)
17	Whole treatment	8 (1 bilateral)
19	Whole treatment	6
21	Whole treatment	70 (46 patients at 90% isodose)

The first ten patients received a single intraoperative dose of 10 Gy as an anticipated boost followed by conventional fractionated EBRT at a total dose of 44 Gy in 22 fractions. Seven patients received 15 Gy followed by EBRT at a total dose of 40 Gy in 20 fractions. The other 84 patients were treated with ELIOT alone at three different dose levels of 17, 19 and 21, as shown in Table 20.1.

In the Phase I study (Veronesi et al. 2001a, b), the dose was prescribed at Dmax, according to ICRU recommendations. The single dose of 21 Gy was calculated to be theoretically equivalent to a full course of conventional EBRT. In fact, based on the linear–quadratic model, when using an α/β ratio of 10 Gy (typical of tumors and early reacting tissue), a dose of 60 Gy delivered at 2 Gy daily—which is the radiation dose required to control the microscopic residual disease after breast resection—is estimated to be equivalent to a single fraction of 21 Gy. Using the same equation, but calculating the tolerance of late-responding tissues (α/β ratio of 3 Gy), this equivalent value rises to at least 110 Gy. This dose was selected for the Phase II trial of ELIOT (Luini et al. 2005), conducted between May and November 2000. In this study, the maximum dose 21 Gy was investigated in order to assess the acute and intermediate toxicity in a larger cohort of patients. Forty-six additional patients were treated. The dose was prescribed not at Dmax but at the 90% isodose. This change brings Dmax to 23.2 Gy, since in the first study slight underdosage of the target in deeply situated tumors of thickness 25 mm or more was observed. At a mean follow-up of 42 months, 16 patients (16%) had developed breast fibrosis that was mild in 15 and severe in one. One of them received ELIOT 10 Gy and three received 15 Gy. EBRT completed the radiation course with 17 Gy for two patients and 19 Gy for one, while the others received 21 Gy ELIOT as the sole treatment. Two patients treated with 21 Gy suffered postsurgical infections, and four developed a liponecrosis of the treated area, consisting of a localized collection of brown fluid with mild skin erythema and no sign of infection that was treated with a few sessions of medical care. Other side effects included mild pain (G2) in the irradiated area (two patients), local hematoma (three patients), and transitory edema (G1 or 2) of the breast tissue (three patients). Three patients treated with ELIOT alone developed ipsilateral recurrences (one patient received 17 Gy and two 19 Gy); only one of these was a true in-field recurrence, detected 36 months after the treatment. Two patients developed contralateral cancer and two distant metastases.

20.6.2 Prospective Randomized Phase III Study of ELIOT

In December 2000 the EIO started a prospective randomized Phase III trial to compare conventional EBRT (50 Gy to the whole breast plus a 10 Gy boost to the tumor bed) with a single dose of 21 Gy of intraoperative radiotherapy with electrons prescribed at the 90% isodose. Patients were older than 48 years and affected by unicentric infiltrating carcinomas of the breast with diameters of less than 2.5 cm. The aim of the study was to evaluate the efficacy of this new approach in terms of local control, regional control, disease-free, distant metastases, and overall survival, cosmetic outcome and costs. Exclusion criteria were previous therapy (including biopsy) performed in other institutions and the presence of comorbidity, like multisystem disease with dermal/soft tissue involvement (lupus, scleroderma, dermatomyositis, and polyarteritis). Patients with tumor locations considered unsuitable for treatment with ELIOT, such as those in the tail of the breast or lesions too close to the skin (less than 5 mm from it), were also excluded. All patients received quadrantectomy followed by sentinel node biopsy and (only when there were positive nodes) axillary dissection. Accrual for the trial was closed in December 2007. Overall, 1,306 patients were recruited, 655 in the external-beam radiotherapy arm and 651 in the ELIOT arm. The primary endpoint for analysis is the rate of local recurrence within a five-year observation period. The statistical hypothesis is the noninferiority of partial breast irradiation (PBI) with respect to whole breast irradiation (WBI) in terms of local recurrence (LR). To calculate the sample size, a difference in LR of 2.5% between the two arms was not considered relevant (e.g., 7.5% after PBI vs. 5% after WBI). This sample size should be able to detect a 2.5% difference in LR rate at five years between the two treatment arms with a statistical power of 90% and a significance level of 5%. The median age of the 1,306 patients enrolled in the ELIOT trial is 60 years. The median pathological tumor size is 1.3 cm (range 0.045–6.5 cm); the same in both arms. Most patients received quadrantectomy with sentinel node biopsy, which was negative in 73% of the patients. In cases of positive sentinel node, patients received complete axillary dissection. The main histological type is ductal carcinoma: lobular carcinoma was found in 8.5% of the cases. The majority of patients had estrogen or progesterone receptor positive disease that do not overexpress HER2. The median collimator diameter needed to cover the tumor bed with a 1–2 cm margin was 4 cm (range 3–8). The median electron energy chosen for the intraoperative treatment was 8 MeV (range 4–10 cm). The median gland thickness was 1.6 cm (range 0.6–3.2 cm) (unpublished data). Patients are currently being actively followed (median follow-up is now 33.8 months) in order to evaluate chronic toxicity, and this should make it possible to determine whether ELIOT can replace conventional radiotherapy in that subgroup of women.

20.6.3 21 Gy as Sole Treatment at EIO

At the same time, patients who either did not completely fulfill the eligibility criteria or refused to enter the ELIOT trial were treated intraoperatively with the same modality of

Table 20.2 Side effects and unfavorable events in 1,246 patients

Side effects	N	%
Severe fibrosis	6	0.5
Mild fibrosis	40	3.2
Lyponecrosis	58	4.7
Skin retraction	15	1.2
Total	119	9.6
Unfavorable events		
Event		
Local recurrence	30	(2.4)
Ipsilateral second breast carcinoma	11	(0.9)
Contralateral carcinoma	11	(0.9)
Axillary lymph node metastases	4	(0.3)
Distant metastases	20	(1.6)
Other primary tumors	13	(1.0)
Total	89	(7.1)
Deaths		
Deaths due to breast cancer	8	(0.6)
Deaths due to other causes	10	(0.8)
Total deaths	18	(1.4)

the randomized trial. From July 1999 to December 2006, 1,246 patients with unicentric primary carcinomas less than 2.5 cm in diameter, mostly over 48 years of age, were treated with ELIOT. One thousand two hundred thirteen received a single dose of 21 Gy; the remaining patients were part of the Phase I/II studies and received various doses ranging from 10 to 19 Gy. After a median follow-up of 26 months (0.3–94.7 months), 30 patients (2.4%) developed local recurrence and 20 distant metastases. Eight patients (0.6%) died due to progression of the primary tumor, and ten (0.8%) due to other causes (Table 20.2). The five-year crude survival rate was 96.5%. Six patients (0.5%) developed severe breast fibrosis. Forty patients suffered from mild fibrosis. Cosmetic results were good (Veronesi et al. 2008).

20.7 21 Gy as Sole Treatment at Santa Chiara Hospital

Between October 2000 and November 2002, 47 early-stage breast cancer patients were enrolled into a Phase I/II study investigating ELIOT as sole radiation treatment after conservative surgery at Santa Chiara Hospital in Trento, Italy (Mussari et al. 2006a, b). Eligibility criteria included age > 45 years old, clinical stage T1N0M0, G1–2, positive hormone receptors, and no intraductal carcinoma at preliminary biopsy. Three different dose levels prescribed at Dmax were used: 20 Gy (seven patients), 22 Gy (20 patients), and 24 Gy (20 patients). After a median follow-up of 48 months, 15 (30%) patients developed

breast fibrosis (14 G2 and one G3). Only one clinical liponecrosis was recorded, but mammographic signs of fat necrosis were observed in 25% of the treated patients. One patient complained of edema and pain in the treated breast. Two patients showed a permanent G3 alteration of the skin with pigmentation change and telangiectasia. No local recurrence was observed. Overall cosmesis was judged good/excellent in 44 (94%) of the 47 treated patients, while a bad score was assigned to only one patient.

20.8 The Experience at the University of North Carolina

Initial experience with in situ intraoperative radiotherapy was investigated in 23 patients at University of North Carolina (Ollila et al. 2007). The authors modified the ELIOT technique of Veronesi: instead of delivering ELIOT after tumor removal and restoration of breast anatomy, they irradiated the tumor and the surrounding tissue intraoperatively prior to excision in order to achieve better target definition with the tumor plus normal tissue margins. The eligibility criteria included patients 55 years or older and a tumor diameter of less than 3 cm, clinically node negative. Intraoperative radiotherapy was delivered using a Mobetron, and the average maximum dose was 15.6 Gy (ranging from 13.54 to 18.50 Gy) to cover 1 cm deep to the posterior edge of the tumor with the 90% isodose. If, on final pathology, specific histologic features such as lobular carcinoma, a tumor diameter greater than 3 cm, or an extensive intraductal component indicated the need for additional treatment, an external radiation course of 46 Gy in 23 fractions was delivered to the whole breast using opposed tangential fields. In these cases, ELIOT was considered a boost. Eighteen of the 23 enrolled patients received ELIOT: ten of them as sole treatment, five as a boost, while three patients completed surgery with mastectomy because of unexpectedly aggressive disease. Preliminary data in terms of feasibility and cosmesis are promising.

20.9 IORT as a Boost

Several studies significantly correlate young age with poor local control and local relapse-free survival rate. EORTC trial 22881/10882 demonstrated that a supplemental dose of irradiation to the tumor bed significantly reduced the rate of local recurrence at five years, with the greatest benefit seen in women younger than 40 (Bartelink et al. 2007). Moreover, most trials have shown that, particularly in premenopausal women, the rate of development of breast tumor outside the area of the initial primary tumor is not negligible (up to 42%), although it is lower than in the immediate vicinity of the lumpectomy site (Poortmans et al. 2004). There are several techniques for delivering the boost in breast radiotherapy. The main constraint is accurately defining the boundaries of the tumor bed after surgery. This can be difficult, particularly when the breast has been reconstructed, when marking clips have not been placed, or when there is no radiological evidence of its location (scarring or a seroma cavity). These inaccuracies could increase the target miss rate, resulting in a higher local recurrence rate. Enlarging the volume of irradiated tissue could reduce

these errors, but this could increase the risk of late tissue reactions or poor cosmetic outcome. Thus, IOERT offers important advantages compared with conventional EBRT. Direct exposure of the operating bed eliminates the possible inaccuracy of tumor-bed localization, permitting the treatment of a more limited volume of breast tissue. Other critical structures adjacent to the tumor bed (heart and lung) can be spared by shielding, and the skin is moved outside the irradiated field, minimizing late sequelae. Moreover, using an electron beam ensures a homogeneous dose distribution of the target volume (Veronesi et al. 2003a, b). Accumulating evidence suggests that the ELIOT boost is well tolerated, with acceptable cosmesis and good local control. This approach has been investigated since 1980 in American and French studies with similar designs. In the first (Merrick et al. 1997), Merrick reported the experiences for 21 women with stage I or II breast cancer undergoing lumpectomy with axillary dissection and intraoperative RT with a single-fraction dose of either 10 Gy (18 patients) or 15 Gy (3 patients) between 1984 and 1996. All patients postoperatively received 45–50 Gy EBRT over 5–6 weeks using 6 MV photons to the whole breast. Cosmesis was generally excellent. After a median follow-up of 71 months, two patients developed a symptomatic but palpable fibrosis of the lumpectomy site and no evidence of recurrence was observed. For the French study, preliminary results were presented by Dubois in 1997 (Dubois et al. 1997), and the long-term follow-up was published in 2006 by Lemanski et al. (2006). Between 1989 and 1999, after breast-conserving surgery, 50 patients with early breast cancer were treated with a 10 Gy intraoperative boost using 9 MeV electron beams followed by whole breast EBRT (50 Gy in 2 Gy fractions). After a median follow-up of 9.1 years (range 5–15 years), two local recurrences (4%) were observed within the primary tumor bed, and six distant metastases (12%). The ten-year overall survival rate was 94%. Of the 42 remaining disease-free patients, six (14%) experienced G2 subcutaneous fibrosis with good/excellent overall cosmesis.

More recently, Reitsamer and his group (Reitsamer et al. 2006) demonstrated that an immediate ELIOT boost yields excellent local control in patients with invasive breast cancer who had been treated with breast-conserving surgery and postoperative RT to the whole breast up to 51–56.1 Gy in 1.7 Gy fractions. The boost to the tumor bed was performed with either a postoperative electron boost of 12 Gy in group 1 (188 patients) or an intraoperative boost (IORT) of 9 Gy in group 2 (190 patients). During median follow-ups of 81 months in group 1 and 51.1 in group 2, local recurrences were observed in 12 of 188 patients (6.4%) in group 1 and no event was observed in group 2. Distant metastases occurred in 15 out of the 188 (7.9%) in group 1 and in two patients out of 190 in group 2 (1.1%). The five-year actuarial rates of recurrence were 4.3 and 0.0% ($p = 0.0018$) and the five-year actuarial rates of distant metastases were 8.6 and 4.2% ($p = 0.08$). The five-year disease-free survival rates were 90.9% in group 1 and 95.8% in group 2 ($p = 0.064$).

20.9.1 EIO Experience

Based on data published on the efficacy of the boost, particularly in younger patients, and with the aim of further reducing the total treatment time, a trial was designed at the European Institute of Oncology in 2004 (Ivaldi et al. 2008). It consists of a nonrandomized

study with ELIOT used as a boost followed by hypofractionated external-beam radiotherapy (HEBRT) to the whole breast in 13 fractions over a period of 2.5 weeks. Eligible patients are premenopausal women below 48 years of age affected by invasive breast cancer cT1–T2, clinically cN0–1, who are candidates for breast-conserving surgery. The treatment provides an initial boost of ELIOT of 12 Gy (prescribed to the 90% isodose) followed, 3–4 weeks later, by hypofractionated whole breast ERT to a total dose of 37.05 Gy. The 13 sessions of 2.85 Gy each are delivered via an isocentric technique using two opposite tangential fields. Correcting for overall treatment time, and assuming that the EQD2 of 37.05 Gy/13 fractions is 39.7 Gy and a recovery factor (*K*) of 0.7 Gy/day, the biological effectiveness of the hypofractionated scheme increases up to about 51 Gy. Available data on the first 211 patients treated showed a high compliance with the treatment: 99.5% of the patients completed the whole treatment schedule including HEBRT. Currently, only acute/intermediate toxicity data are available. Maximum acute side effects were observed at the end of HEBRT, with grade 3 skin toxicity in 3.8% and grade 2 in 29% of patients. At a median follow up of 11 months, six patients complained of symptomatic edema, one patient suffered from grade 3 fibrosis, and one grade 4 event was recorded. Overall, 4.4% of patients experienced liponecrosis of the surgical area within the first month from surgery.

Thus, IOERT as a boost appears to be an effective alternative to conventional EBRT. Giving the boost in a single intraoperative session, when a dedicated IOERT unit is available, only modestly increases the operative time of 15–20 min. This technique reduces the total external treatment time by 1–2 weeks, and results in economic savings and improvements in the general well-being of the patient. Preliminary data are promising, but the median follow-up is still too short to draw conclusions on the efficacy.

20.10 ELIOT After Nipple-Sparing Mastectomy

The present consensus on the surgical treatment of breast cancer is to limit the disfigurement of the patient as much as possible by performing lumpectomy or quadrantectomy if possible. However, a mastectomy is still required in patients with large or multifocal infiltrating tumors, in some cases of local recurrence after conservative treatment, and with diffuse in situ carcinomas. Skin-sparing mastectomy facilitates immediate breast reconstruction, but the removal of the nipple-areola complex (NAC) dramatically increases the feeling of mutilation. To reduce this psychological impact, the NAC could be spared and ELIOT used to treat the remaining glandular tissue behind the areola. Therefore, at the EIO, breast surgeons and radiation oncologists combined subcutaneous mastectomy with ELIOT to the NAC (Petit et al. 2005). The aim of this approach was to maintain the blood supply and the sensitivity of the NAC while reducing the risk of recurrence in the central area of the breast. The skin incision is made over the tumor site. An elliptical skin paddle is removed, the size of which is determined by the distance between the tumor and the dermis, not including the areola, with the incision stopping about 0.5–1 cm from the lateral borders of the areola. A preliminary subcutaneous dissection is performed with a smooth Hegar dilator or with long scissors to avoid any injury to the subdermal vascular network. A 0.5 cm thick parenchymal layer is left attached to the dermis to preserve the blood supply

and the sensitivity of the NAC. This glandular "patch" should extend 1 or 2 cm beyond the lateral borders of the areola. The gland is undermined and separated from the pectoral fascia in the same way as in classical mastectomy. Thus, the only glandular tissue remaining after the specimen has been removed and sent to the pathologist is that behind the NAC. ELIOT is performed only after intraoperative pathological examination of the tissue taken from this thin layer left behind the areola verifies it as being free of cancer. The clinical target volume includes the remaining glandular tissue behind the NAC corresponding to the diameter of the NAC and its periphery. Two protective devices (aluminum–lead disks) are placed between the NAC and the pectoralis muscle to minimize irradiation of the thoracic wall. The sterile collimator of the mobile linear accelerator is placed in contact with the NAC, and a 16 Gy dose is delivered. Breast reconstruction is performed immediately after irradiation with the use of prosthesis or a myocutaneous flap (Petit et al. 2006). A total dose of 16 Gy at 90% isodose is delivered in a single fraction. According to the linear–quadratic model, a single dose of 16 Gy corresponds to a fractionated dose of about 45 Gy for early-responding tissue (tumor cells) and 70–80 Gy for late-responding tissues (fat and vessels). Results for 579 skin-sparing mastectomies (NSM) plus ELIOT performed at EIO in 570 patients from March 2002 and November 2006 (Petit et al. 2009) illustrate that the procedure is feasible and leads to a high level of satisfaction. The rate of local relapse was 0.9% per year: this incidence was consistent with the rate of LR after modified mastectomy. Most relapses were observed near to the primary tumor bed, while no event occurred underneath the preserved NAC. From this experience, we conclude that for large or multicentric tumors and/or diffuse microcalcifications far from the NAC, NSM with ELIOT of the NAC provides good local control and satisfactory cosmetic results.

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Intraoperative Radiation Therapy During Breast-Conserving Surgery; the Memorial Sloan–Kettering Cancer Center Technique

21

Kathryn Beal, Gil'ad N. Cohen, Beryl McCormick, Virgilio Sacchini, and Michael Zelefsky

21.1 Background

IORT is the intraoperative treatment of a surgically exposed area, and may be delivered with either electrons using a linear accelerator or brachytherapy using HDR ^{192}Ir (other source types, such as electronic brachytherapy devices, are being investigated as well). While both methods may be used successfully to treat breast cancer, the electron beam approach presents technical challenges when applied to other treatment sites where the target surface area is large, curved, or in a deep cavity. For this reason, the brachytherapy approach has been the preferred method for IORT at MSKCC; it has recently been applied to the treatment of breast cancer.

Brachytherapy is a form of radiation therapy in which the radiation source is placed inside (or next to) the target volume, thus delivering a very high dose to the target while sparing adjacent tissue. The inherently high therapeutic ratio achieved is the main advantage of brachytherapy. This conformal therapy modality is used in a wide variety of treatments, including the treatment of prostate cancer, head and neck cancers and gynecological cancers. The advantage of HDR brachytherapy is that it can be delivered safely, in a relatively short treatment time, and with no exposure to staff, allowing for efficient treatment.

Many different sources are used to deliver brachytherapy. However, ^{192}Ir has been the isotope of choice for interstitial and intracavitary breast brachytherapy.

An intraoperative applicator used specifically for breast treatments (Mick Radio-Nuclear Instruments, Inc., Mount Vernon, NY, USA) has been used successfully at Memorial Sloan–Kettering for IORT during the lumpectomy procedure.

MSKCC's experience with HDR IORT using the HAM applicator has been documented elsewhere (Harrison 1998; Anderson et al. 1997; Cohen et al. 2005). The breast applicator

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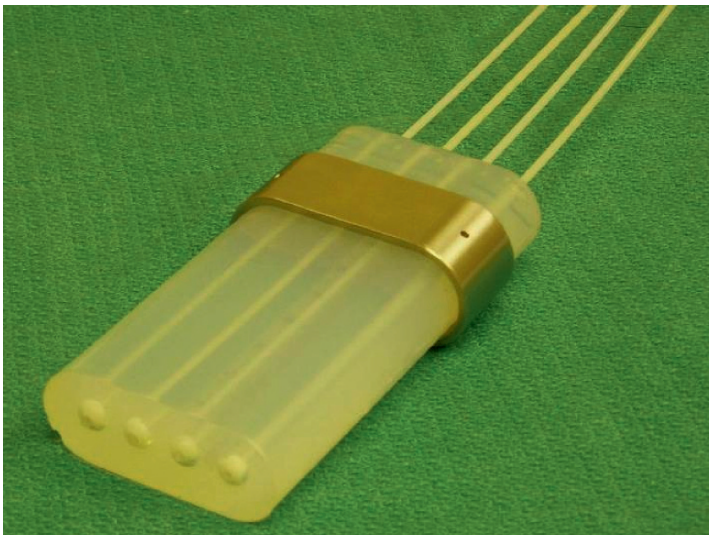

Fig. 21.1 Breast applicator with tungsten skin shield

described here was modeled after the HAM applicator and consists of catheters embedded in Silastic material and a matching tungsten shield to protect the skin at the incision area (see Fig. 21.1). The breast applicator is placed in the surgical cavity and the catheters are attached to a machine that houses the ^{192}Ir HDR radiation source, as shown in Fig. 21.2. The source steps through each catheter to deliver radiation to the target as determined by a custom treatment plan. 20 Gy is prescribed to a depth of 1 cm from the surface of the applicator, and care is taken to keep the skin dose under 10 Gy. A typical brachytherapy plan, demonstrating the isodose curves and dose distribution, is shown in Fig. 21.3.

There have been several small studies of the use of IORT for breast cancer (Fentiman 2000; Clark 1996), but Umberto Veronesi, MD, and colleagues at the European Institute of Oncology in Milan, Italy, have the most extensive experience of using IORT for breast cancer. They first published their experience of using electrons for breast IORT in 2001 (Veronesi 2001). IORT was used initially as a boost at the time of surgery prior to standard whole breast external-beam radiation. Eventually the dose was escalated and electrons to the tumor bed were delivered as the sole modality of radiation. Since their initial publication, the Milan group has shown IORT with electrons to be effective, well tolerated and convenient for a select group of patients. There has been criticism of IORT for breast cancer treatment, just as there has been criticism of all partial breast irradiation techniques (Bartelink 2001), but IORT offers yet another approach to partial breast irradiation that is even more logistically convenient for the patient than other techniques that are delivered postoperatively.

Given the emerging data on the safety and efficacy of partial breast irradiation, and given the early excellent experience of Veronesi's group, Memorial Sloan–Kettering Cancer Center (MSKCC) proposed a pilot study of high dose rate IORT using a modified HAM applicator for early-stage breast cancer.

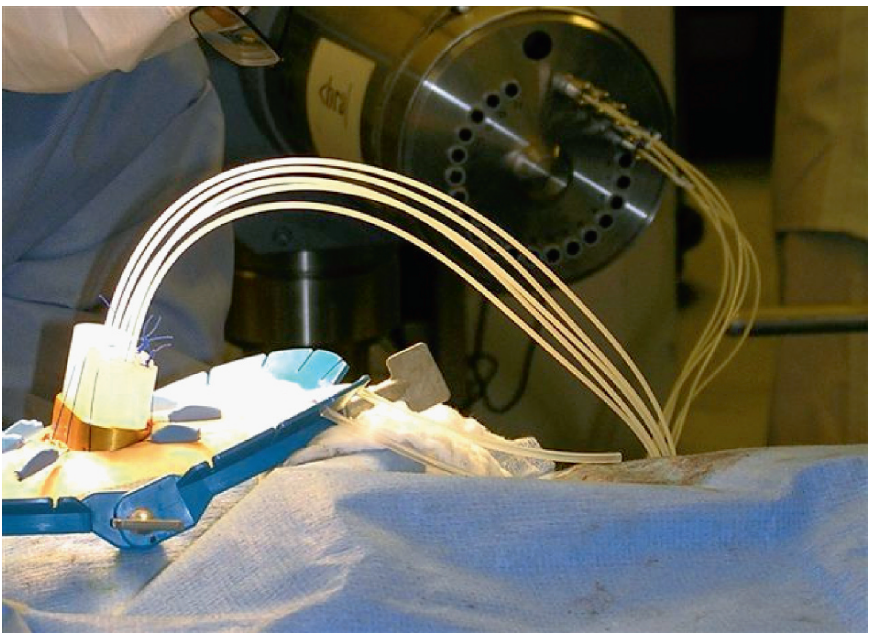

Fig. 21.2 Breast applicator attached to high dose-rate afterloader

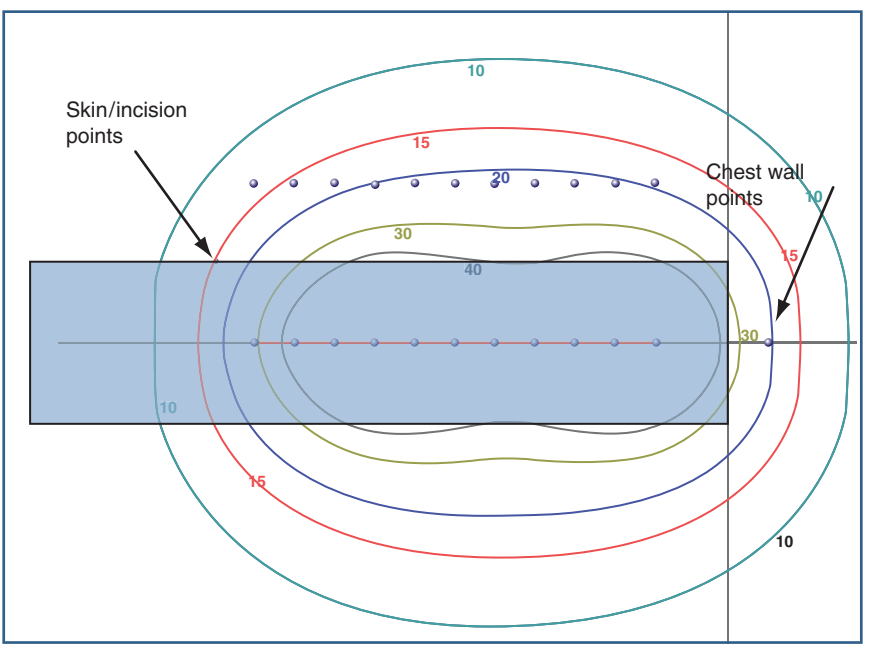

Fig. 21.3 Isodose lines of breast applicator in cross-section

21.2 Patient Selection

In general, the selection criteria for breast IORT should be similar to the selection criteria for any partial breast irradiation technique. Specifically, inclusion criteria for the MSKCC protocol for IORT were designed to select for women at low risk for a local (or distant) recurrence. Only women who were ≥ 60 years old were included. This age criteria was based on both the Milan group's data demonstrating a lower risk of local recurrence in that age group (Veronesi 2002) and the increasing risk of breast cancer in the elderly population. Inclusion criteria also included a core biopsy or open biopsy confirming an invasive ductal carcinoma that was no larger than 2.0 cm on imaging. The patients also had to be clinically node negative, with no evidence of multifocality or multicentricity on imaging or physical examination. Details regarding selection criteria for the Milan technique should be obtained by reviewing their respective publications.

21.3 Technique

The most well-described technique is the Milan electron beam technique, which is briefly reviewed below in contrast to the MSKCC technique, a description of which follows as well.

21.4 The Milan Electron Beam IORT Technique

The EIO trial used the Novac7 (Hitesys S.p.A., Aprilia [LT], Italy), an accelerator with a robotic arm weighing approximately 1,100 pounds and measuring 232 cm in length, 114 cm in width, and 199 in height. This device can be moved easily into an operating room and can deliver electron beams at four different normal energies: 3, 5, 7, and 9 MeV. Radiation beams are collimated by means of a 5 mm thick Perspex tube, known as the "hard docking," which connects the two parts of the applicator during surgery. This ensures maximum precision in alignment, thus providing very high dose reproducibility. The lower portion of this tube, located at the operatory bed, may be 4, 5, 6, 8 or 10 cm in diameter according to the size of the irradiation field.

The accelerator's floor-stand structure, its articulated arm with four rotational joints, and its motorized base allow translator movements of the entire structure without modifying head orientation. The electron beams are delivered perpendicular to the tissue, with the depth of the 80% isodose ranging between 13 mm (3 MeV) and 24 mm (9 MeV). At the 9 MeV energy level, for the 22.5°- and 45°-angled applicators, the depth was decreased to 21 and 17 mm, respectively.

The surgical excision of the tumor in the Milan IORT trial is done in the standard way: quadrantectomy with 1–2 cm grossly free margins, usually including a small lozenge of

skin. The excision extends to the fascia of the pectoral major muscle, which is usually removed with the specimen. Particular attention is paid to the surgical margins. Effort should be made to decrease the risk of positive surgical margins on final pathology, so as to avoid the need for a potentially problematic re-excision. This quadrantectomy procedure is in no way different from that normally performed outside of the clinical trial setting.

The method of IORT administration may change the subsequent surgical technique. Following quadrantectomy, the breast tissue is usually reapproximated in order to close the breast surgical wound. In the case of IORT, which is delivered by a vertical beam perpendicular to the tissue, the breast tissue must be detached from the underlying skin and the skin retracted to avoid skin necrosis secondary to high-dose irradiation. The irradiation tube is inserted past the withdrawn skin, directly to the breast tissue. An aluminum–lead disk is inserted on the surface of the major pectoral muscle as a safety precaution in order to prevent any irradiation of the chest wall. Placement of this disk requires that the residual breast tissue be disconnected from the pectoral major fascia for 3–4 cm. The two breast-tissue flaps, anteriorly disconnected from the skin and posteriorly disconnected from the muscular fascia, are temporarily stitched together above the metal disk. The thickness of these flaps is measured with a needle and ruler at a minimum of three points on the portion of the breast to be irradiated, and the average value of thickness is taken into consideration when determining RT dose. The area of the flaps lying above the metal disk and directly beneath the cathodic tube is then irradiated. The entire irradiation procedure is completed in 2 min.

21.5 The MSKCC High Dose Rate Remote Afterloading IORT Technique

This method is currently in use at MSKCC. The IORT in this case is administered by means of a high dose rate remote afterloading system utilizing an iridium-192 (^{192}Ir) source to deliver high dose rate brachytherapy to the tumor bed. The catheters for the iridium source are contained in a quadrangular Silastic template (2 cm thick × 10 cm L), a "breast applicator." The breast applicator is available in different widths and with a varying number of catheters according to the volume to be irradiated (2–10 catheters at 1 cm spacing). This template is inserted into the cavity with the deep margin resting on the major pectoral muscle. From a surgical point of view, the main difference between this technique and the one described previously is that it is not necessary with this high dose rate remote afterloading technique to detach the breast tissue from the skin and the major pectoral fascia following local wide excision. Radiation distribution occurs along the catheters, diffusing transversely in the breast parenchyma; the skin and the pectoral surface receive minimal radiation (skin dose is kept under 10 Gy). For this reason we prefer to remove only a small lozenge of skin, especially when the tumor is superficial, and the fascia of the major pectoral muscle. This simple procedure is not expected to significantly increase the risk of positive posterior and anterior resection margins, nor is it expected to affect cosmesis.

In an attempt to reduce to whatever degree possible the risk of an involved margin (clear margins are also a criterion for initial case selection), we implemented the following

procedure. The specimen, once removed, is labeled with two stitches, one short superior and one long lateral. In addition, one radiopaque clip will be secured to the short wire (superior margin) and two to the long wire (lateral margin). The specimen is placed on a Plexiglas plate, with the deep margin carefully placed on the platform. An X-ray of the specimen is then obtained. The X-ray of the specimen is useful for identifying the concentricity of the lesion in the specimen. An additional margin is usually removed if the lesion appears to be too close to the margin.

The specimen is then sent to Pathology, where it is grossly analyzed, with particular attention paid to any close margins. In the case of a close margin, the surgeon is advised to perform an immediate additional resection of that margin. If the diagnosis of malignancy was made on cytology only, a histological confirmation is required, as achieved by by performing either a core/open biopsy or a frozen-section analysis.

The breast parenchyma must be flush with the breast Silastic applicator to the greatest extent possible. To achieve this, an applicator of an appropriate size to fill the cavity is chosen, and then it is sometimes secured by 2–3 stitches done with a 1 curved needle running through the breast parenchyma and the Silastic applicator. Figure 21.4 demonstrates the applicator secured in the breast cavity. The breast applicators most typically used range in size from three to nine channels with a 1 cm spacing between channels. Initially hand-placed lead shields were placed at the level of the skin, but custom tungsten shields are now used. The shields slide up and down the applicator to protect the skin depending on the depth of the cavity. After the applicator and shield are carefully positioned in the lumpectomy cavity, the skin is retracted with a LoneStar retractor to further protect the skin. The catheters are then connected to appropriate source-guide tubes.

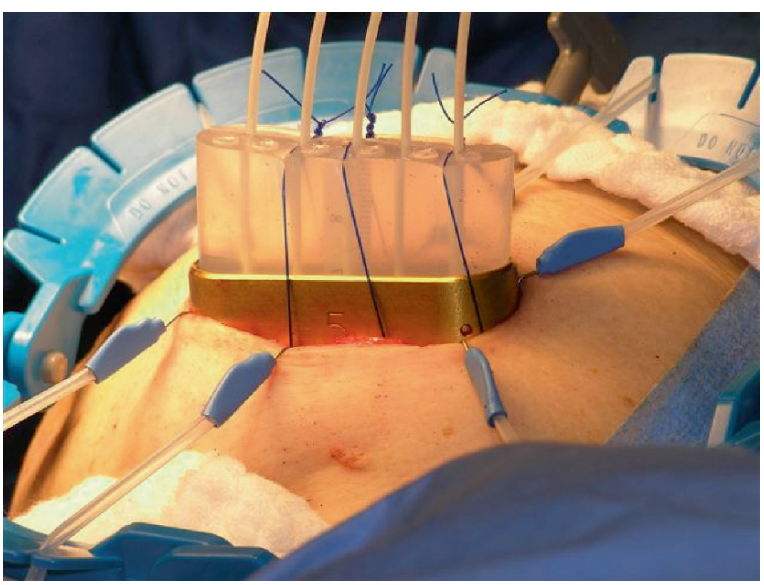

Fig. 21.4 Breast applicator secured in the breast

During this time, computer-based dosimetry is generated to calculate and optimize the isotope dwell times necessary to achieve optimal dose distribution within the cavity. The computer program has the ability to modulate the homogeneity of the radiation as required and specifically define points within the target region which would require intensification or diminution of the dose. The radiation dose is prescribed at 1 cm from the surface of the applicator in all directions except in the deep (distal) direction towards the chest wall, where it is prescribed to 0.5 cm, and the superficial (proximal) direction, where skin points are into the treatment planning system. A dose of 20 Gy is prescribed in all directions except at the lateral edges of the applicator, where the prescribed dose is 18 Gy. The computer plan is then generated in approximately 5 min and evaluated by the radiation oncologist. The computer-optimized dwell times (times for which the radiation source is positioned along the various positions of the catheters within the breast cavity or target volume) are input into the treatment computer operating the afterloading machine. This machine controls the delivery of the source at the predetermined position in the applicator in order to deliver the prescribed radiation dose.

For radiation safety reasons, personnel must leave the room for the entire irradiation period. A special anesthesiology monitoring station is available outside the room. The electrocardiogram (EKG) and all ventilatory parameters are reported on a collimated monitor outside, and special cameras in the operating room are focused on the patient, IV device, and operatory field. When local anesthesia with sedation has been used, the anesthesiologist should check that the patient is properly sedated to avoid gross movement by the patient. The radiation itself takes approximately 20–30 min depending on the size of the cavity or target and the activity of the source.

Once the treatment is complete, the staff re-enter the room, the Silastic breast applicator is removed, the breast parenchyma may be reapproximated, and the breast cavity is closed.

21.6 Patient Management

At MSKCC, the wide local excision surgery and IORT are typically performed as an outpatient procedure. Postoperatively there does not appear to be any increase in complications such as infection, hematoma or seroma formation. During the subacute period there may be mild skin erythema depending on how superficial the target region is and the dose of radiation delivered to the skin. If erythema develops, we recommend the use of standard skin ointments that are typically recommended for patients undergoing external-beam radiation therapy. The patients are seen in follow-up on a typical breast-conserving surgery schedule, usually with an appointment with their surgeon about 1–2 weeks postoperatively, and then by the radiation oncologist and/or surgeon every 3–6 months in the first 2–3 years following the procedure and annually thereafter. Routine follow-up mammography is performed on an annual basis unless there is an indication to proceed otherwise.

As part of the pilot feasibility study at MSKCC, photography to document cosmetic outcome was obtained at baseline (preoperatively) and at six and twelve months postoperatively. The cosmetic results from the pilot study have been published and are summarized below.

21

21.7 Cosmetic Results

As part of the feasibility pilot study of IORT at MSKCC using high dose rate IORT with ^{192}Ir, photographs of each patient were taken at baseline and at six and twelve months postprocedure. Four examiners independently graded the photos for symmetry, edema, discoloration, contour and scarring. The grades were evaluated in relationship to the volume of tissue irradiated, tumor location, and dose at the lateral aspects of the cavity. The median volume of tissue receiving 100% of the prescription dose was 47 cc. Analyses revealed that women with ≤ 47 cc of treated tissue had better cosmetic outcomes and women who received 18 Gy (rather than 20 Gy) at the lateral aspect of the cavity had better outcomes. Cosmetic results at twelve months in comparison to six months were stable for 63% of patients, better for 17% and worse for 20%. However, the cosmetic results appeared to improve with the experience of the treating physician. This is likely due to more purposeful shielding of the skin and careful attention to radiation planning to decrease the dose to the skin when possible. Full details of the cosmetic result study were published by Beal et al. (2007). Examples of good cosmetic results are demonstrated in Fig. 21.5.

Although the information regarding cosmetic results following breast IORT with the MSKCC technique is limited to the above, cosmetic results following other techniques of high dose rate brachytherapy for breast cancer are reportedly quite good (King 2000; Baglan 2001; Benitez 2004; Wazer 2006). Although fractionated high dose rate brachytherapy is a different technique than IORT, it more closely approximates the biologic and thus clinical and cosmetic effects of IORT than other forms of radiation therapy.

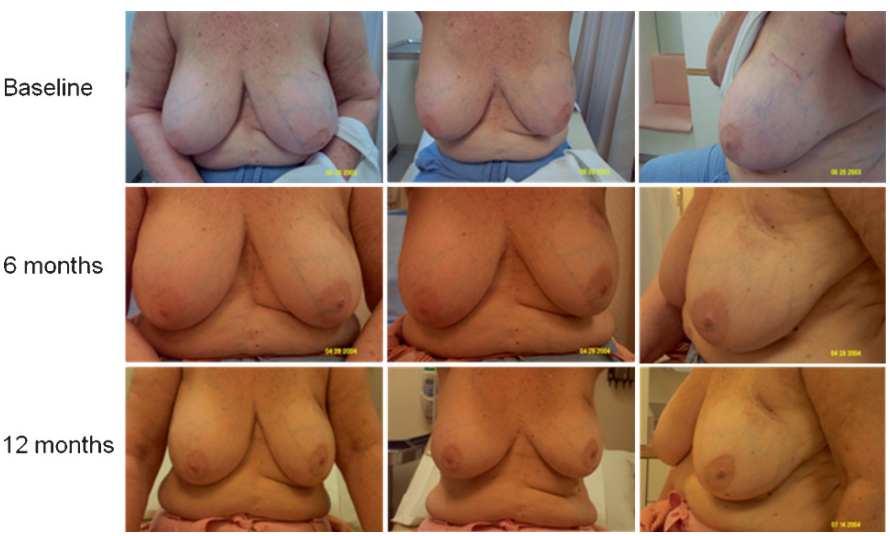

Fig. 21.5 Cosmetic outcome

21.8 Clinical Results

To date, MSKCC has treated approximately 115 (patients 1–50 were on protocol) patients with IORT at the time of breast-conserving surgery in total. With a median follow-up of 42 months for the initial patients treated on protocol, there is only one local failure to date. This patient had invasive ductal carcinoma on the core needle biopsy. However, her final pathology from her surgery yielded invasive lobular carcinoma. She had a suspicious finding on a follow-up mammogram that lead to a biopsy-proven recurrence of her lobular carcinoma. She underwent a modified radical mastectomy that revealed multicentric recurrence and she is now without evidence of disease.

21.9 Complications

The rate of typical acute surgical complications such as infection and wound-healing issues does not appear to be higher in patients treated with IORT for breast-conservation surgery as opposed to surgery alone. Long-term toxicities are related to cosmesis, with the initial patients more likely to have a poor cosmetic result with fibrosis and retraction leading to evolving asymmetry. Several patients have also had persistent seromas requiring multiple drainage procedures. This process appears to be more likely in patients who have thin skin and ptotic breasts. However, the seromas resolved spontaneously with time in all the patients to date.

The rate of cosmetic complications declined with treating physician experience. The vast majority of patients are very satisfied with this procedure and state that they would repeat breast IORT if needed in the future.

21.10 Discussion

IORT with high dose rate ^{192}Ir for early-stage breast cancer is yet another approach to accelerated partial breast irradiation. Like other forms of partial breast irradiation, it is logical and feasible for the appropriately selected patient. The Milan experience with electrons and the MSKCC experience to date have been promising. Although the results are relatively early for the MSKCC approach, the cosmetic results are good for the majority of patients and the clinical results appear to be excellent. Of course, the patients are all highly selected to have disease that is at low risk for local recurrence. Many of the patients treated at MSKCC with IORT are also over 70 years old with hormone receptor positive disease. These women are often advised to take hormonal therapy, and thus would be at very low risk for local recurrence even without adjuvant radiation, as evidenced by the CALGB trial (Hughes 2004). However, the hormonal status and intent to take hormonal therapy is not known at the time of surgery, which is why IORT is administered. Furthermore, many of

these women may elect to proceed with radiation even with hormone receptor positive disease, as they may not be able or want to commit to five years of hormonal therapy, or they may want to proceed with both forms of adjuvant therapy (radiation and hormonal therapy) in order to reduce the chances of recurrence as much as possible.

In summary, breast IORT is a novel, feasible, convenient technique that appears effective and safe when delivered at institutions with well-developed protocols and experience. Further follow-up studies are needed to document the long-term safety and clinical and cosmetic outcomes.

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Normal Tissue Toxicity After Accelerated Partial Breast Irradiation

22

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A number of studies in recent years have detailed the rationale for and the various technical considerations of partial breast irradiation, which is defined as radiation of the site of excision and adjacent breast tissue only (Kuerer et al. 2004). Partial breast irradiation can be delivered with brachytherapy or external modalities. Accelerated partial breast irradiation (APBI) is defined as radiotherapy that employs fractions higher than 1.8–2.0 Gy per day over a period of less than 5–6 weeks and uses any of four techniques: (1) interstitial brachytherapy; (2) intracavity brachytherapy through the use of a variety of balloon or "cage-like" catheter products; (3) highly conformal external beam; (4) intraoperative radiation therapy with photons, electrons, and specialized brachytherapy applicators. Several clinical reports of predominantly nonrandomized treatment groups with prolonged follow-up duration have produced substantial interest in APBI amongst surgeons, radiation oncologists, and patients. Several ongoing prospectively randomized Phase III trials in both Europe and North America are underway to evaluate APBI as an alternative to conventional whole breast irradiation. In the interim, there appears to be mounting evidence that APBI may be considered currently as a practical treatment option for some early breast cancers.

To date, the focus of many APBI studies has been on local control with limited information available on normal tissue toxicity. Further, the studies that provide detailed data pertaining to normal tissue toxicity have been limited mostly to brachytherapy techniques: multiple catheter interstitial and intracavity catheters. Relatively little information has been presented thus far regarding the toxicity associated with APBI delivered by conformal external-beam or intraoperative techniques.

A comprehensive and comparative systemic evaluation of early, intermediate, and late toxicity associated with APBI has not been performed, particularly in relation to the wide variety of clinical and treatment-related technical variables that are inherent in the different treatment modalities. In this chapter, a summary of the current information regarding toxicity after APBI is presented. Where possible, an attempt will be made to distill the currently available data into specific clinical recommendations designed to minimize the risk of normal tissue toxicity.

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22.1 Terminology, Techniques, and Radiation Biology

Any comparison of toxicity for the various methods of APBI is complicated by the distinctive dosimetry and radiation biology inherent in interstitial, intracavity, intraoperative, or external-beam techniques. Table 22.1 summarizes the four most commonly practiced APBI modalities in general terms of commonly employed prescription points, fractionation schemes, total delivered dose, and a simplified comparison of biological effective dose (BED) as calculated at the prescription point (which ignores critical dose gradients). The interpretation of toxicity data can be further complicated when one considers, for example, such "operator-specific" variables as the method of catheter placement for interstitial brachytherapy. Controlling for needle placement technique can be difficult, as complex interstitial breast brachytherapy systems have evolved primarily as institution-specific practices that may entail the use of customized rigid templates (Das et al. 2004; Vicini et al. 1999), specialized devices to guide freehand placement (Wazer et al. 1997), or CT-guided placement (Arthur et al. 2003). There are no clear data to suggest that there are differences in normal tissue toxicity as related to specific interstitial brachytherapy techniques.

It is again important to emphasize that virtually all of the long-term toxicity data currently available for APBI is derived from the use of brachytherapy with either interstitial or intracavity techniques. Early data are becoming available for APBI delivered via conformal external-beam and for single fraction intraoperative applications of electrons or low-energy photons. As such, this chapter will focus primarily on studies of APBI by brachytherapy.

Table 22.1 A comparison of the common APBI modalities for prescription point, total dose, fractionation/dose-rate, and biological effective dose (BED)

APBI technique	Typical prescription point	Total dose	Fractionation or dose rate	BED normal tissue	BED tumor
Interstitial brachytherapy HDR	PTV = tumor bed plus 1.5 cm	34 Gy	10 fractions BID	72.5 Gy	45.6 Gy
Interstitial brachytherapy LDR	PTV = tumor bed plus 2.0 cm	45 Gy	50 cGy h^{-1}	75 Gy	54 Gy
MammoSite	PTV = 1 cm from Balloon surface	34 Gy	10 fractions BID	72.5 Gy	45.6 Gy
3D conformal external beam	PTV = tumor bed plus 2.5 cm	38.5 Gy	10 fractions QD or BID	164.9 Gy	53.3 Gy
Intraoperative electrons	PTV = "operative bed"	21 Gy	Single fraction	168 Gy	65.1 Gy
Intraoperative 50 kV photons	PTV = 1 cm from surface of applicator	5 Gy	Single fraction	13.3 Gy	7.5 Gy

Prior to reviewing the results of clinical studies, it would be useful to briefly explain some terminology that has been employed to describe the dosimetric characteristics of both interstitial and intra-cavity implants. V_{100}, V_{150}, and V_{200} represent the volumes of breast tissue encompassed by the 100, 150, and 200% isodose lines, respectively. The dose homogeneity index (DHI) has been defined as a method for evaluating the dosimetric quality of an implant (Wu et al. 1988). The higher the DHI, the more uniform is the dose distribution within the treatment volume. Numerous methods have been proposed to calculate the DHI, but the formula commonly used in the assessment of APBI brachytherapy (Edmundson et al. 2002) is:

$$\mathrm{DHI} = \frac{V_{100} - V_{150}}{V_{100}}.$$

APBI brachytherapy has been delivered with both low dose-rate (LDR) and high dose-rate (HDR) techniques. Typically, LDR implants have been performed at a dose-rate of 40–60 cGy h^{-1} to a total dose of 45–60 Gy (Kuerer et al. 2004; Arthur et al. 2003; Vicini et al. 1997; Kuske et al. 1998). HDR implants have most commonly been prescribed to a total dose of 32–34 Gy at 3.4–4.0 Gy/fraction delivered BID.

The normal tissue toxicity endpoints commonly evaluated after APBI are early and late changes to skin and subcutaneous tissues. These can be objectively scored using established grading criteria such as those of the RTOG/EORTC (Table 22.2). There is no uniformly accepted scoring system for cosmetic outcome and, as such, there is considerable variability in the criteria applied across studies. In general, a four-tiered grading of excellent, good, fair, and poor has been applied in the majority of studies.

Table 22.2 RTOG/EORTC normal tissue late toxicity scoring criteria

Grade	Description
Skin	
0	No change from baseline
1	Slight atrophy; pigmentation change; some hair loss
2	Patchy atrophy; moderate telangiectasia; total hair loss
3	Marked atrophy; macroscopic telangiectasia
4	Ulceration
Subcutaneous tissues	
0	No change from baseline
1	Slight induration (fibrosis) and loss of subcutaneous fat
2	Moderate fibrosis (asymptomatic); slight field contracture < 10% linear reduction
3	Severe induration and loss of subcutaneous tissue; field contracture> 10% linear measurement
4	Necrosis

22.2 Interstitial Brachytherapy: Toxicity Reports from Select Single - and Multi-institutional Studies

One of the original efforts to explore the role of interstitial brachytherapy APBI was performed under the direction of Dr. Robert Kuske, initially at the Ochsner Clinic in New Orleans and subsequently at the University of Wisconsin. His group first reported on 51 patients (25 LDR, 26 HDR) with a median follow-up of 75 months (King et al. 2000). The interpretation of the late normal tissue effects observed by these authors is limited by the fact that they employed their own three-tiered institution-specific grading scheme where Grade I/II reflected primarily early events and Grade III recorded late events. Nonetheless, they reported Grade I/II and Grade III toxicity in 22 and 8% of patients, respectively. The cosmetic outcome was rated as good/excellent in 75% of cases.

Stimulated in part by these early results, the RTOG launched in 1995 a phase II trial (protocol 95–17) to further investigate the potential role of interstitial brachytherapy APBI in a multi-institutional setting. Enrollment allowed for randomization to two different dose delivery schedules: LDR (45 Gy in 3.5–5 days) or HDR (34 Gy BID in ten fractions). This afforded the first opportunity to directly compare the effect of dose-rate technique on outcome. A toxicity analysis was reported on 99 cases (33 LDR; 66 HDR) after a median follow-up of 29 months (Kuske et al. 2006). The mean DHI for the entire study cohort was 0.82. Major acute toxicity was more commonly seen with LDR as compared to HDR techniques, with grade 3–4 toxicity found in 9 and 3%, respectively. Similarly, late toxicity was found to be more severe with the LDR technique, with a 9% incidence of grade 3–4 skin thickening and a 12% incidence of grade 3–4 subcutaneous fibrosis. This was in contrast to patients treated with HDR, where grade 3–4 skin thickening and subcutaneous fibrosis were seen in 1.5 and 3%, respectively.

Two noteworthy papers describing a detailed analysis of normal tissue effects after interstitial brachytherapy APBI for 199 patients (a mix of LDR and HDR techniques) with follow-up for as long as ten years have been presented by investigators from the William Beaumont Hospital (Benitez et al. 2004; Chen et al. 2006). These studies were the first to clearly document that normal tissue changes after APBI evolve dramatically over time. Further, this time-dependent evolution can be both for the better and the worse. Some endpoint measures significantly improved with time. For example, the cosmetic rating was scored as excellent/good in 95% at a median follow-up of ≤6 months, but improved to 99% after 60 months. Breast pain, present in 27% at ≤ 6 months, decreased to 9% at ≥ 5 years. Similarly, edema and erythema progressively improved over the observation period (Fig. 22.1). In contrast, other measured endpoints clearly worsened with prolonged follow-up. Over time, the incidence of fat necrosis, subcutaneous fibrosis, and telangiectasias all progressively increased (Figs. 22.1 and 22.2). Of particular note, the incidence of fat necrosis rose from 1% at ≤ 6 months to 11% at > 5 years (Fig. 22.2).

More recently, a similar time dependence in the evolution of some late effects after interstitial brachytherapy APBI has been reported from the German–Austrian multicenter trial (Ott et al. 2007). In this study of 274 patients that employed both HDR and pulsed-dose rate (PDR) techniques, there was a progressive increase over five years in the incidence of telangiectasia, fibrosis, and hyperpigmentation.

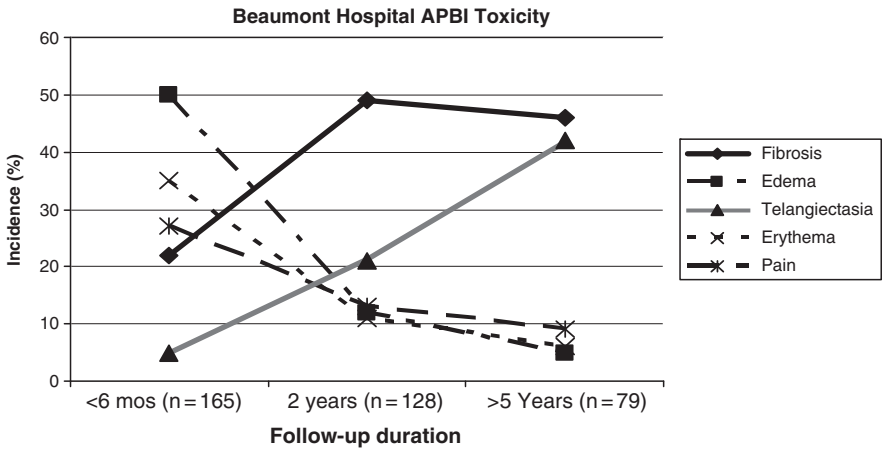

Fig. 22.1 The incidence of normal tissue toxicity as a function of time after interstitial brachytherapy APBI at the William Beaumont Hospital (data plotted from Benitez et al. 2004)

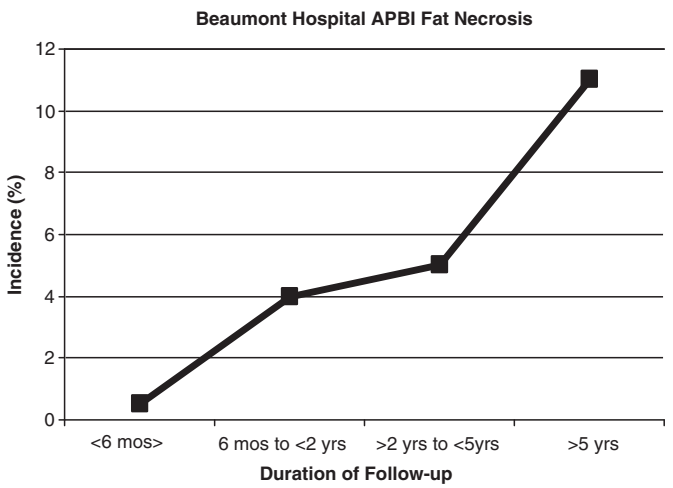

Fig. 22.2 The incidence of fat necrosis as a function of time after interstitial brachytherapy APBI at the William Beaumont Hospital (data plotted from Benitez et al. 2004)

These findings underscore the complexity inherent in the assessment of late normal tissue effects after APBI, as the incidence of any given endpoint will be highly dependent upon when the measurement was obtained. As such, all short follow-up, "snap shot" views

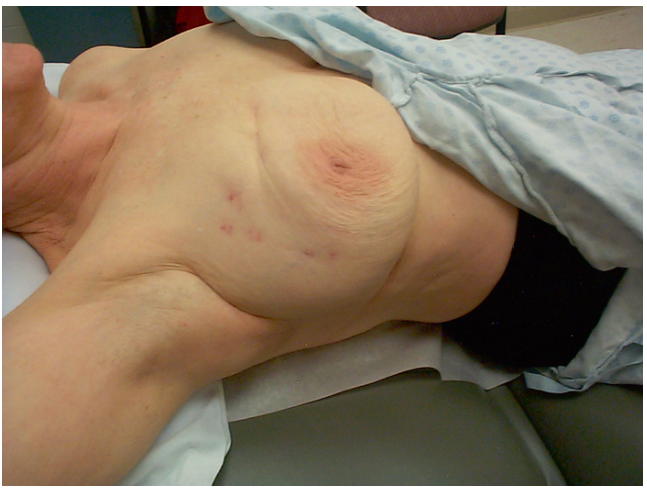

Fig. 22.3 Grade 1 late skin toxicity after interstitial brachytherapy APBI. Note the telangiectasias at the catheter entry sites in the lateral aspect of the breast

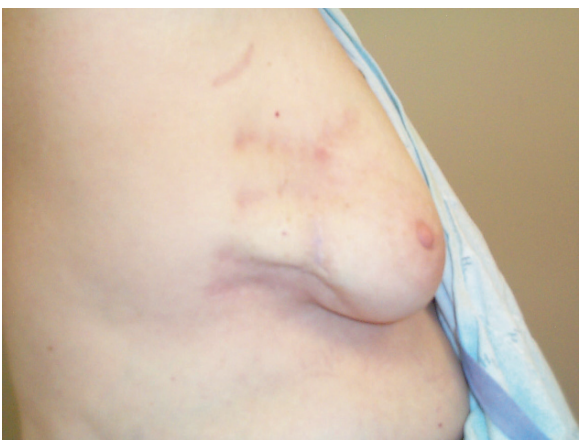

Fig. 22.4 Grade 3 late subcutaneous toxicity after interstitial brachytherapy APBI. Note the fibrotic contracture of tissues within the implant volume

of normal tissue effects (common with many studies of APBI) must be interpreted with caution (Figs. 22.3 and 22.4).

22.2.1 Interstitial Brachytherapy: Dosimetric Variables

The APBI toxicity data reported from the Ochsner Clinic/University of Wisconsin, the RTOG, and the William Beaumont Hospital employed a mix of LDR and HDR techniques. The evaluation of these trials for specific variables that may influence complications is

limited due to the markedly distinct normal tissue radiobiology of LDR vs. HDR. In order to address this concern, more recent studies have focused exclusively on patients treated with either LDR or HDR applications.

As noted above, in the RTOG 9517 trial, LDR implants prescribed to 45 Gy were found to have a greater incidence of clinically significant normal tissue toxicity than HDR implants. In addition, MacDonald et al. (2007) reported on 48 patients enrolled on a Phase I/II dose escalation study of LDR brachytherapy APBI and found a high rate of normal tissue injury. The implants were delivered at 50 cGy h^{-1} to total doses of 50, 55, and 60 Gy. After a median follow-up of 84 months, cosmetic results were rated as good to excellent in 68% of patients. Rates of moderate-to-severe fibrosis and telangiectasia were both 43%. Fat necrosis was reported in 50% of patients and marked atrophy was noted in 7%. No correlations were found between dose or irradiated volume and cosmetic outcome. Unfortunately, apart from dose and volume, there were no other dosimetric data available from this study to correlate outcome with treatment-related variables.

In a subset analysis of the William Beaumont Hospital experience, Baglan et al. (2001) reported on 38 patients treated exclusively with HDR interstitial brachytherapy after a median follow-up of 31 months. APBI was delivered as 32 Gy in eight twice-daily fractions. The median DHI, V_{100}, and V_{150} were 0.878, 216, and 26 cc, respectively. The cosmetic outcome was rated as good or excellent in 100%, and "mild residual fullness" was noted in 9%. No patients were found to have either persistent breast pain or symptomatic fat necrosis.

At the National Institute of Oncology in Budapest, Hungary, a series of trials of APBI have been performed that have predominantly employed HDR interstitial brachytherapy (Polgar et al. 2004; Polgar et al. 2007). The treatment scheme for APBI included HDR interstitial brachytherapy consisting of seven fractions to a total dose of either 30.3 or 36.4 Gy. In this cohort of patients, the mean V_{100} was 50 cc and the mean dose nonuniformity ratio was 0.45. After a median follow-up of seven years, good/excellent cosmetic outcome was seen in 84.4% of cases. Late skin effects were generally mild, with only 4.4% reported as grade 2–3. Grade 2–3 subcutaneous fibrosis was observed in 20% of cases (Polgar et al. 2007). These authors (Lovey et al. 2007) have performed a separate detailed analysis of fat necrosis with a reported incidence rate of 31% for the entire study cohort. No significant difference in the risk of fat necrosis was seen when comparing patients randomized to whole breast radiotherapy vs. interstitial brachytherapy APBI.

In order to more fully understand the clinical and treatment-related variables that could affect normal tissue toxicity, investigators from Tufts University, Brown University, and Virginia Commonwealth University pooled their data for patients treated with HDR interstitial APBI. Patients at all three institutions were treated in an identical manner with respect to selection criteria, implant technique, dosimetric evaluation, and follow-up assessment (Wazer et al. 2006). The cohort consisted of 75 patients with a median follow-up of 73 months and, similar to the RTOG 9517 trial, the "worst toxic event" was recorded for analysis. Clinical variables including patient age, volume of excised tissue, tumor diameter, and a history of diabetes or hypertension were not found to be significantly associated with either cosmetic score or normal tissue toxicity. In contrast, several implant-associated variables could be identified as having a significant influence on the risk of an adverse

Table 22.3 Summary of results from the Tufts/Brown/VCU analysis of variables associated with late normal tissue effects after HDR interstitial brachytherapy APBI

Endpoint measured	Significantly associated variable	
Cosmetic outcome	No. of dwell positions	211 vs. 250 ($p = 0.04$)
E vs. G/F/P	V_{150}	43 cc vs. 59 cc ($p = 0.03$)
	DHI	0.77 vs. 0.73 ($p = 0.05$)
Late skin toxicity	V_{150}	44 cc vs. 62 cc ($p = 0.04$)
Grade 0 vs. grade 1,2	DHI	0.77 vs. 0.71 ($p = 0.009$)
Late subcutaneous toxicity	DHI	0.77 vs. 0.73 ($p = 0.02$)
Grade 0,1 vs. grade 2,3,4		
Clinically evident fat necrosis	V_{150}	44 cc vs. 69 cc ($p = 0.02$)

cosmetic outcome or increased risk of late skin toxicity, late subcutaneous toxicity, and clinically evident fat necrosis (Table 22.3) (Wazer et al. 2006). In general, the volume of the implant, the volume of dose "hotspots" as defined by the V_{150} and V_{200}, and the global dose homogeneity of the implant as described by the DHI were strongly correlated with outcome.

The technical variables associated with the risk of fat necrosis after HDR interstitial brachytherapy have been most thoroughly evaluated by a group at the University of Wisconsin (Patel et al. 2007). They analyzed a cohort of 173 patients who received APBI via HDR multicatheter implants. Of note, in all cases, sophisticated three-dimensional CT-based treatment planning was employed. They found that clinical fat necrosis was significantly correlated with a larger planning target volume (PTV) (168 cc vs. 135 cc; $p = 0.006$) and larger regions of "hot spots" including the V_{150} (45 cc vs. 41 cc; $p = 0.004$), V_{200}, V_{250}, and V_{300}. Factors found not to be associated with the risk of fat necrosis were the number of catheters, V_{100}, and DHI.

These studies have provided valuable specific dosimetric parameters to guide clinicians in defining, at least with respect to late tissue effects, what constitutes an optimal interstitial HDR implant.

22.2.2 Interstitial Brachytherapy for APBI: Toxicity Avoidance Guidelines

As clinical data continues to accumulate, toxicity avoidance guidelines will likely evolve and be subject to future revision. The guidelines that will be put forward are limited to the use of HDR interstitial brachytherapy. To date, the amount and dosimetric specificity of data regarding LDR implants is simply too sparse to make even limited recommendations. With these caveats, current data does suggest the following:

1. Volume matters; that is, keep it as low as practically achievable within the constraints imposed by adequate coverage of the PTV. Less than 60% of the normal whole breast reference volume should receive greater than or equal to 50% of the prescribed dose.

There is some evidence to suggest that the absolute value of the PTV should be no greater than 150 cc.

2. It is important to minimize the volume of dose "hot spots." Dosimetric parameters that appear to be particularly sensitive in this regard are the V_{150} and V_{200}. It appears preferable to strive for values of no greater than 45 and 14 cc, respectively.
3. Maintain a high level of global dose uniformity as defined by the DHI value: at least > 0.75, even better if > 0.85. This is achievable with all of the common currently employed interstitial catheter placement techniques, but does require attention to the detail of catheter position.
4. The dose/volume limits to the skin and chest wall are not defined as yet. In general, the dose delivered to these structures should be less than the prescribed dose. An appropriate rule of thumb is to delineate the PTV such that it is at least 5 mm from the skin and underlying rib.

22.3 Intracavity Brachytherapy

There are now several catheter systems designed to deliver intracavity brachytherapy (reviewed in detail in Chaps. 23 and 24), but the only system that has been extensively employed over several years is the MammoSite catheter. Therefore, this discussion of late normal tissue effects will be limited to data related to this system.

The first and perhaps most critical factor to consider in assessing the risk of normal tissue effects with MammoSite brachytherapy is that, from the perspective of both dosimetry and radiobiology, it is a distinctly different implant from interstitial brachytherapy. As such, one must be cautious in transferring the lessons learned from interstitial brachytherapy APBI, as they likely have limited relevance to this applicator system. As an example of these inherent differences, Shah et al. (2004) reported a series of interstitial and MammoSite implants and found significant differences in critical dosimetric parameters. MammoSite implants are associated with significantly less irradiated tissue and "hotspots" that are smaller in volume as compared to interstitial brachytherapy (for example, V_{150} of 26 cc with MammoSite vs. 40 cc with interstitial technique, $p < 0.0001$). In contrast, the global uniformity as reflected in the calculated DHI is superior with an interstitial implant (DHI of 0.83 with interstitial technique vs. 0.73 with MammoSite, $p < 0.0001$). The relative importance of these variables in predicting for normal tissue toxicity after MammoSite is yet to be fully elucidated but, to date, none of the dosimetric variables related to toxicity for interstitial brachytherapy have been found to be clinical relevant to predicting toxicity after MammoSite brachytherapy.

In addition to the standard toxicity endpoints as described in the RTOG/EORTC rating scale, there are events that are (for the most part) specific to the MammoSite catheter that can result in implant failure. These include:

1. Nonconformance of the applicator to the excision cavity (Fig. 22.5)
2. Hemorrhage (Fig. 22.6)
3. Balloon rupture (Fig. 22.7)

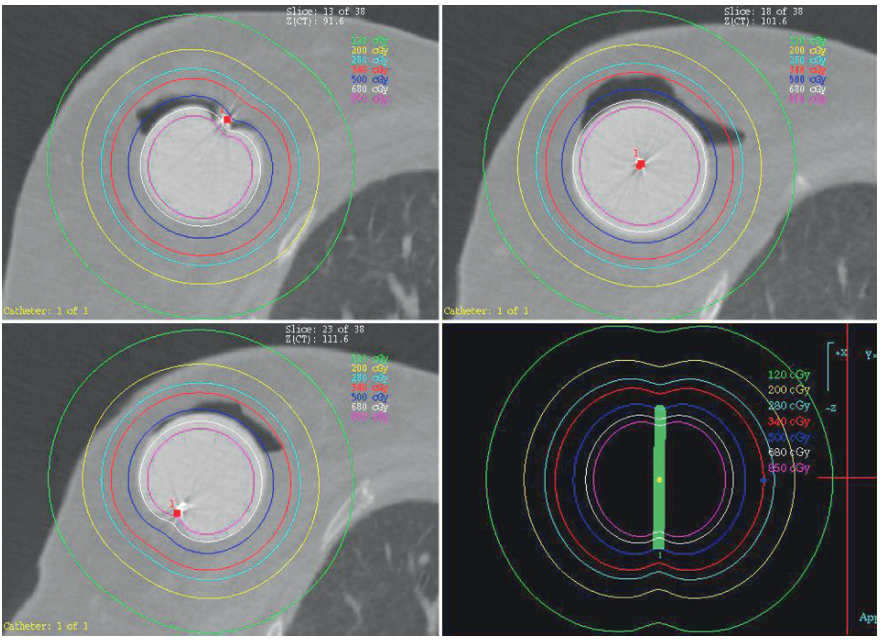

Fig. 22.5 An example of unacceptable nonconformance to target breast tissue of the fully inflated MammoSite catheter

4. Suboptimal balloon-to-skin spacing (Fig. 22.8)
5. Inadequate tumor excision margin or nodal status (for intraoperative placement)

A multi-institutional trial designed to evaluate the safety and performance of the MammoSite catheter was performed by Keisch et al. (2003) as part of the regulatory approval process in the United States. This study of 43 patients initially reported on acute toxicity encountered up to four weeks post-treatment. The most common side effects of the procedure included mild erythema (57.4%), drainage (51.9%), pain (42.6%), ecchymosis (31.5%), seroma (11.1%), and an infection rate of 3.7%.

Postprocedure infections (Fig. 22.9) have been the focus of some controversy in early experience with the MammoSite catheter (Harper et al. 2005). However, it does appear that with meticulous wound care during the 1–2 weeks required to complete irradiation, the infection rate can be kept acceptably low, even when assessed amongst a broad base of users. In a report of the American Society of Breast Surgeons (ASBS) Breast Brachytherapy Registry Trial, the device-related infection rate of 793 patients was only 5.9% (Vicini et al. 2005). There is evidence to suggest that prophylactic antibiotic use may reduce the risk of device-related infections (Harper et al. 2005; Vicini et al. 2005; Cuttino et al. 2008).

MammoSite catheters are currently available in a variety of sizes with balloons that will assume both spherical and ellipsoidal shapes (reviewed in Chap. 14). Nonetheless, the fundamental dosimetry of the catheter system is rather simple and predictable, with a near-symmetric geometrical distribution (Chap. 14). As such, the distance from balloon surface to skin is a critical determinant in normal tissue toxicity. The time period after implantation in which acute skin toxicity can manifest after MammoSite brachytherapy can vary from several days to several weeks (Fig. 22.10). This “delayed acute” skin reaction can

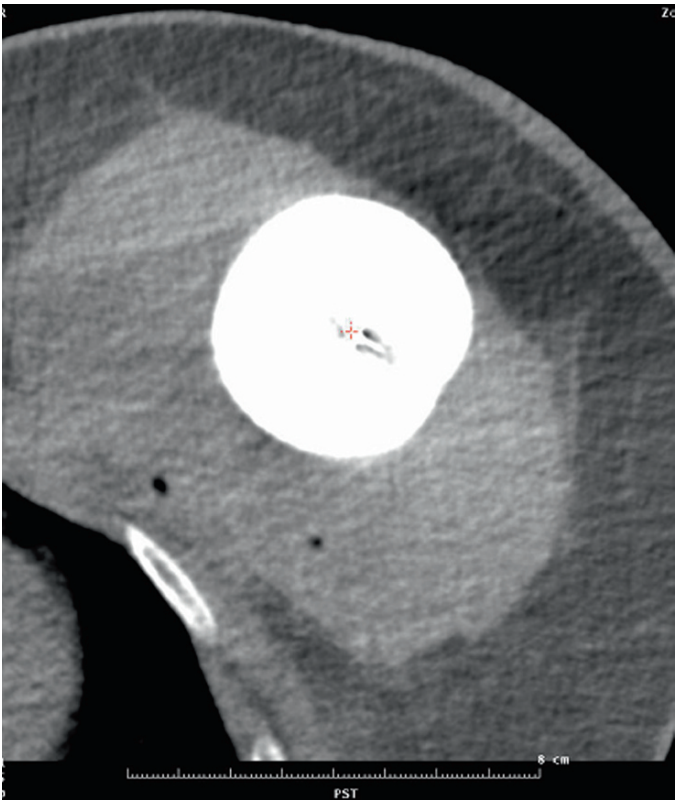

Fig. 22.6 Intracavitary hemorrhage 24 h after intraoperative placement of a MammoSite catheter

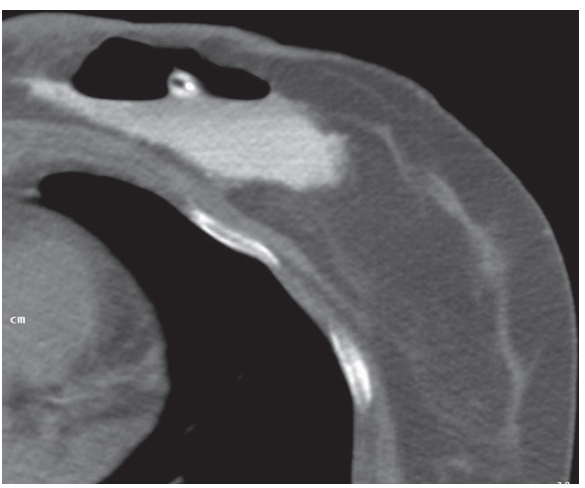

Fig. 22.7 Spontaneous rupture of a MammoSite catheter 48 h after placement results in partial filling of the lumpectomy cavity with dilute contrast material

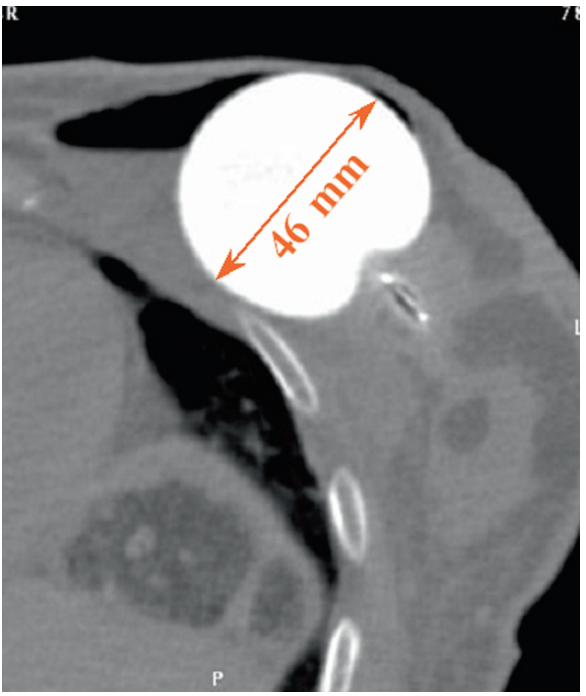

Fig. 22.8 Suboptimal balloon-to-skin spacing after intraoperative MammoSite placement necessitating catheter removal

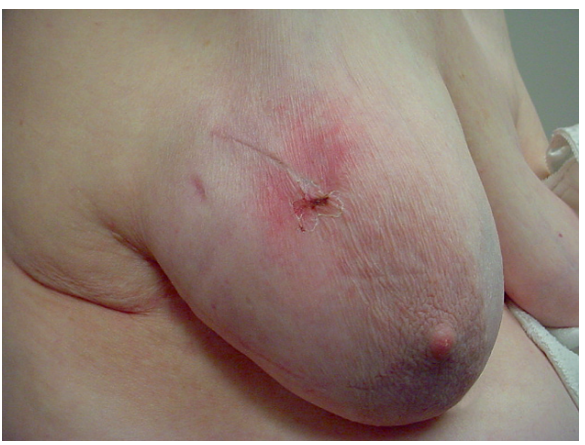

Fig. 22.9 Infection in the operative bed eight weeks after completion of MammoSite brachy-therapy APBI

sometimes be erroneously diagnosed as a device-related infection, and may have confused some of the early observations related to the incidence of infection.

As the MammoSite catheter was approved for clinical use in May 2002 by the United States Food and Drug Administration (FDA), there are now extensive data available that describe intermediate-to-late skin and subcutaneous toxicity. Benitez et al. (2007) have reported on a more extended evaluation of the original patient cohort in the MammoSite

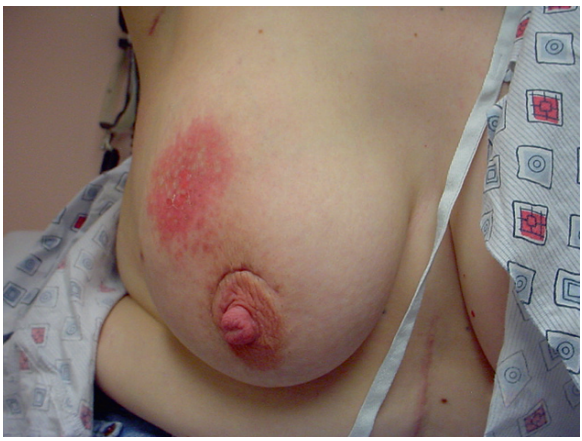

Fig. 22.10 An example of delayed acute skin reaction seen after MammoSite brachytherapy APBI: grade 3 skin reaction five weeks after completion of treatment. The balloon-to-skin distance was > 9 mm

evaluation trial for the FDA. Follow-up for a median of 5.5 years is now available for 36 patients. These data have shown that cosmetic scores are clearly related to balloon-to-skin spacing such that suboptimal results are seen when spacing is ≤ 7 mm. Further, these authors report asymptomatic fat necrosis in 9% and seroma in 33% (12% symptomatic). Additional data regarding intermediate and late effects on normal tissue after MammoSite APBI have been collected through the ASBS MammoSite Registry Trial (Vicini et al. (2005), Vicini et al. (2007a); and reviewed extensively in Chap. 14). The factors found to be significantly associated with favorable cosmetic outcome at two years of follow-up were balloon-to-skin spacing (as a continuous variable), the absence of infection, and the absence of chemotherapy treatment (Vicini et al. 2005, 2007a, b). In the three-year update of this trial, good-to-excellent cosmetic outcome was seen in 93% of patients, and fat necrosis was reported in 1.5% (Vicini et al. 2007a, b).

In order to more thoroughly evaluate the clinical and technical variables related to outcome with the MammoSite catheter, Cuttino et al. (2008) initiated a collaborative study amongst nine institutions designed to achieve a high level of quality control with respect to data gathering and interpretation. The study cohort consisted of 483 patients with a median follow-up of two years. There was a nearly even divide amongst patients who had the catheter placed by an "open" (intraoperative) or "closed" (postoperative) technique. Though spherical balloons designed for a single source dwell position were used in most patients, 21% of cases had multiple source dwell positions in an attempt to minimize skin dose. This study found that infection significantly increased the risk of an adverse cosmetic outcome, and that the risk of infection was markedly reduced through a closed cavity placement technique. Further, a balloon-to-skin spacing of > 6 mm and the use of prophylactic antibiotics significantly reduced the risk of an acute skin reaction. Lastly, dose optimization, even to the limited degree achievable in a spherical balloon with multiple dwell positions, resulted in a significantly lower risk of severe hyperpigmentation.

The incidence of persistent and, in some cases, symptomatic seroma after MammoSite is another area of ongoing study (Fig. 22.11). The acute incidence of 11% reported by

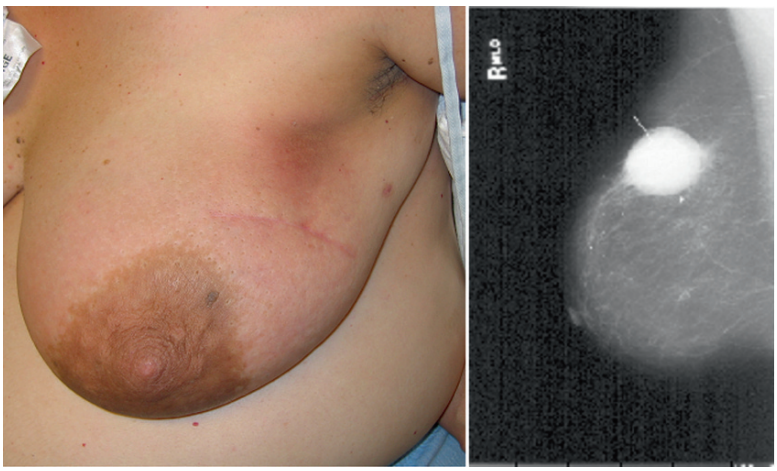

Fig. 22.11 Persistent and painful seroma (with associated mammogram) at the operative bed in the upper outer quadrant nine months after completion of MammoSite brachytherapy APBI

Keisch et al. (2003) appears to underrepresent the frequency of persistent asymptomatic and symptomatic seroma seen after several months of follow-up. Evans et al. (2006) reported the presence of persistent seroma (defined as detectable after more than six months of follow-up) in 68% of patients who had intraoperative MammoSite placement. In 31% of cases, the seroma was associated with some degree of symptoms. Further, the presence of a persistent seroma was significantly associated with an adverse cosmetic outcome. Subsequent reports that included both intraoperative and postoperative MammoSite placement techniques have reported persistent seroma in 21–67% of cases (Vicini et al. 2007a, b; Chao et al. 2007; Haley et al. 2007). The ASBS MammoSite registry trial found that seromas were reported more often after open rather than closed catheter placement (30% vs. 19%), and with the use of larger balloons (Vicini et al. 2007a, b).

22.3.1 MammoSite Brachytherapy for APBI: Toxicity Avoidance Guidelines

As with interstitial brachytherapy, toxicity avoidance guidelines for use of the MammoSite catheter for APBI must be considered preliminary and subject to change with the emergence of longer-term follow-up studies. Nonetheless, based upon currently available information, the following guidelines are offered:

1. It is essential to avoid infection. This is best achieved through the use of prophylactic antibiotics and the placement of the catheter via a “closed” technique performed postoperatively. Meticulous attention to wound care is essential throughout the duration of any intracavity catheter placement. Adherence to wound care instructions should result in a minimal rate (< 5%) of device-related infections.

2. Intraoperative catheter placement is clearly associated with a significantly increased risk of not only infection but also persistent seroma.
3. Under all circumstances, maintain a balloon-to-skin separation of at least 6 mm.
4. Dose optimization will affect outcome. When necessary, use multiple dwell positions, elliptical balloons, or alternative catheter systems to minimize dose to the skin.

22.3.2 Is There an Adverse Interaction Between Brachytherapy APBI and Chemotherapy?

As is the case with chemotherapy administration and conventional whole breast irradiation, the answer is most definitely yes. The first evidence presented in this regard was reported by Kuske et al. (2006) from the RTOG 9517 trial. In their study, grade 3 toxicity was significantly increased with the use of chemotherapy. This was true for both HDR and LDR techniques, but particularly so for LDR implants. Similarly, Arthur et al. (2003) found that APBI with an LDR interstitial technique was associated with a significant decrement in cosmetic outcome when patients also received adriamycin-based chemotherapy. In the combined Tufts/Brown/VCU series (Wazer et al. 2006) of HDR interstitial brachy-therapy, the use of adriamycin-based chemotherapy was associated with an increased risk of clinically evident fat necrosis, grade 1–2 skin toxicity, and suboptimal cosmetic scores. Finally, the ASBS MammoSite Registry Trial (Vicini et al. 2005, 2007a, b) has found that chemotherapy is significantly associated with a less favorable cosmetic outcome.

22.4 3D Conformal External-Beam APBI

The data available to assess normal tissue effects after 3D conformal external beam (3D-CRT) are very limited and conclusions are, at best, preliminary. The specific details related to set-up and techniques are described in Chaps. 16–18. One of the largest experiences to date has been published by the staff of the William Beaumont Hospital (Baglan et al. 2003; Vicini et al. 2003, 2007a, b), who developed the four- to five-field 3D-CRT technique that is used in the NSABP B-39/RTOG 0143 Phase III trial of APBI. They have most recently reported on 91 patients treated with 34 or 38.5 Gy in ten twice-daily fractions. After a median follow-up of 24 months, they report good-to-excellent cosmetic results in 100% at ≥ 6 months, 93% at one year, 91% at two years, and 90% at ≥ 3 years. They found that all late normal tissue toxicity was stabilized within three years of treatment and included Grade I/II telangiectasia, fibrosis, and fat necrosis on 9, 18, and 9%, respectively. The only Grade III toxicity encountered was breast pain, and that was seen in 3% of the cohort.

Formenti and colleagues (Formenti et al. 2004; Wernicke et al. 2006) have used a two-field external-beam partial breast irradiation technique with patients in the prone position. In contrast to the William Beaumont Hospital group, a more extreme hypofractionation scheme was employed, with 30 Gy at 6 Gy per fraction delivered in five fractions over ten days. In a report of 78 patients with a median follow-up of 28 months, radiation-related

normal tissue effects have been found in 26% of patients, including fibrosis, retraction, telangiectasia, and hyperpigmentation.

Kozak et al. (2006) has reported on a Phase I/II trial of three-dimensional conformal proton beam (3D-CPBI) APBI. A preliminary report on 20 patients with short follow-up has shown only minor acute reactions. There are no long-term follow-up data available yet. Similarly, Leonard et al. (2007) have performed a trial of external-beam APBI using intensity-modulated radiation therapy (IMRT). The study enrolled 55 patients and currently has only short-term data to report.

22.4.1 3D Conformal External-Beam APBI: Toxicity Avoidance Guidelines

As noted, the actual clinical toxicity data on 3D conformal external-beam APBI are sparse, and specific dose–volume relationships cannot yet be stated with confidence. Nonetheless, based upon practice at the William Beaumont Hospital (Baglan et al. 2003; Vicini et al. 2007a, b), the following is suggested:

1. Less than 60% of the whole breast normal reference volume should receive greater than or equal to 50% of the prescribed dose; and less than 35% of the whole breast normal reference volume should receive the prescribed dose.
2. The contralateral breast should receive less than 3% of the prescribed dose to any point.
3. Less than 10% of either lung can receive greater than 5% of the prescribed dose.
4. For right-sided lesions, less than 5% of the heart should receive greater than 5% of the prescribed dose. As for left-sided lesions, acceptable dose–volume limits are still uncertain and are subject to further analysis of data accumulated in the Phase II trial of 3D conformal external-beam APBI (RTOG 0319).
5. A maximum point dose to the thyroid should be no more than 3% of the prescribed dose.

22.5 Intraoperative APBI

There are three intraoperative partial breast irradiation techniques currently under investigation (described more fully in Chaps. 19–21). In Milan, Italy, Veronesi et al. (2005) are testing an approach that employs 3–9 MeV electrons to deliver 21 Gy as a single fraction to the excision bed. In a report of 590 patients with a median follow-up of 20 months, the authors report a low rate of complications. They describe mild to severe fibrosis in 3.2% "that resolved in 24 months." Overt fat necrosis was seen in 2.5% of cases within 1–4 weeks after treatment. However, there is evidence to suggest that, as with other APBI modalities, the toxicity of intraoperative therapy will become more pronounced with a longer observation period. Mussari et al. (2006) reported on 47 patients treated with single-fraction intraoperative electrons to dose levels of 20, 22, and 24. At a median follow-up of 48 months, grade 2 or 3 fibrosis was seen in 32 and 4% exhibited grade 3 skin toxicity.

Fat necrosis was described as "clinically relevant" in 2% and was evident in 47% of cases by either mammography or ultrasound examination. In 8% of cases, the mammogram or ultrasound findings associated with fat necrosis required biopsy.

Another intraoperative approach pioneered by Vaidya et al. (2004) uses a device with a spherical tip that is inserted into the open lumpectomy cavity. A 50 kV X-ray beam is generated to deliver a single fraction of 5 Gy prescribed at 1 cm from the surface of the applicator. A prospective randomized trial of this technique has been completed and, to date, no normal tissue toxicity data is available.

A protocol at the Memorial Sloan Kettering Cancer Center (Beal et al. 2007) is testing a single-fraction intraoperative technique for APBI with a modified Harrison–Anderson–Mick HDR brachytherapy applicator. A dose of 20 Gy is prescribed at 1 cm from the surface of the applicator. A total of 50 patients have been enrolled and the follow-up remains very short. No definite conclusions can be reached as yet with respect to normal tissue effects.

22.6 Conclusion

Current techniques of APBI differ markedly in their dosimetric and radiobiologic properties. As such, normal tissue toxicity data must be carefully collected in a prospective fashion for each treatment modality and fractionation scheme. Ongoing assessment of both clinical and treatment-related factors that may contribute to adverse normal tissue effects is required in order to minimize the risk of both early and late toxicity. To date, our most complete understanding of the incidence and variables associated with normal tissue injury after APBI is based upon experience with interstitial brachytherapy and, to a lesser degree, the MammoSite catheter. An important cautionary note in an era of rapidly expanding technological options for APBI is that we cannot say with confidence that of the lessons learned with these older catheter systems will apply to more recently developed APBI modalities.

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Emerging Technologies Part I: New Brachytherapy Catheter Systems

23

Rakesh R. Patel and Adam Dickler

23.1 Introduction

Early outcomes from studies evaluating accelerated partial breast irradiation (APBI) as an alternative adjuvant treatment after breast-conserving surgery for early-stage breast cancer have been promising (Arthur et al. 2004). The method with the longest-standing history and supporting outcome data for APBI is multicatheter interstitial brachytherapy. The advent of a single-channel intracavitary device, the MammoSite balloon, has allowed a more simple and reproducible approach and has in turn led to a significantly increase in the number of patients treated with APBI. More recently, several investigators have attempted to emulate the brachytherapy APBI methods based on the favorable outcomes of the above techniques; there have been several innovative methods of APBI that have been developed in an effort to retain the benefits but overcome certain limitations inherent in existing techniques.

In a broad sense, these approaches consist of: (1) intraoperative radiation at the time of lumpectomy with electrons or soft X-rays; (2) alternative radiation sources such as electronic brachytherapy and low-dose permanent seed implantation, as well as microbrachytherapy; (3) highly conformal delivery modalities using external radiation with electrons, photons, protons, or a high-dose rate ^{192}Ir source (AccuBoost), and; (4) development of intracavitary, single-entry hybrid applicators. We herein provide a brief review of the currently available APBI treatment modalities and those under development, focusing on novel catheter approaches and outlining the design rationale, potential advantages, and phase of clinical testing of each method. Additional delivery techniques and alternative radiation sources that have been developed are covered in complementary chapters in this text.

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23.2 Background: Multicatheter Interstitial Brachytherapy

Interstitial multicatheter breast brachytherapy has been in clinical use for several decades and has significantly more mature outcome data than any other APBI method (Polgar et al. 2007; Vicini et al. 2007; Swanson and Vicini 2008). The APBI application of this approach arose from its initial use to administer a boost dose to the tumor bed region in addition to whole breast irradiation. During this outpatient procedure, typically 15–25 needles are placed through the breast tissue. The needles are spaced about 1 cm apart in multiple planes in order to cover the surgical cavity plus a 1–2 cm margin, correlating with the region at highest risk of harboring residual microscopic disease. Advancements in image-guidance measures such as CT, ultrasound, and stereotactic digital mammography have significantly improved the accuracy and reproducibility of this APBI method (Cuttino et al. 2005; Patel and Das 2006).

Flexible catheters with buttons at the entry and exit sites replace the needles and remain in the breast for the duration of the one-week treatment course. The regimen is generally well tolerated with minimal discomfort; however, the first generation of these catheters had to protrude a few centimeters outside the breast tissue to allow connection to the transfer tubes of the remote afterloader machine. More recently, tail-less catheters (Comfort Catheters™ from Nucletron Corp.) have been developed with integrated numbers in the distal buttons. Since there are no catheters protruding from the breast with these improved catheters, the patient retains overall functionality and arm range-of-motion during the treatment course (Fig. 23.1). From a safety perspective, the HDR transfer tubes connect to

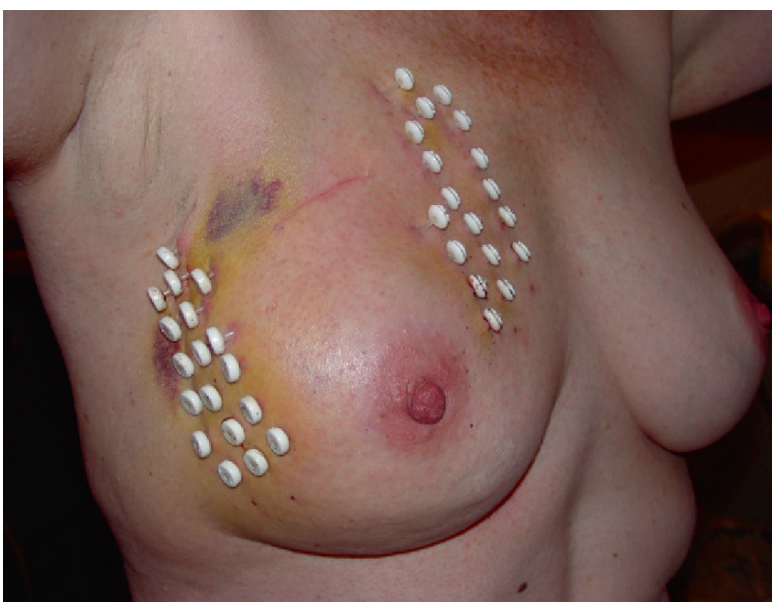

Fig. 23.1 The multicatheter tail-less comfort catheter system

newer blind-end inner catheters that are inserted into the interstitial breast catheters during each treatment visit, which results in a safer, completely closed system for the radioactive source to transit instead of relying on a connection at the surface of the breast.

Following the outpatient placement procedure, individualized treatment planning is performed, which specifies predetermined dwell times and the positions of the radioactive source within the multiple catheters. Importantly, in any catheter system the presence of multiple lumens offers a significant potential advantage by allowing maximal adjustment of the specific dwell positions and dwell times of the HDR source, resulting in highly tailored isodose distributions. This, coupled with more recent advanced 3D CT-based dosimetry with automatic catheter reconstruction tools and inverse optimization methods, has further improved target volume delineation, planning target volume coverage, avoidance of nearby critical structures, and dose homogeneity (Das et al. 2004). The multiple catheter interstitial technique offers the greatest control and tailoring of radiation dose delivery to variations in lumpectomy cavity size, shape, or location within the breast.

The primary disadvantage of this approach is the technical challenge and greater invasiveness of multicatheter insertion, which has diminished the use and restricted the adoption of this APBI technique to relatively few centers. Although the development of image-guided implant techniques has reduced the learning curve and improved reproducibility, this approach does require additional time, skill and specialized training.

23.3 Background: MammoSite Balloon Brachytherapy

In early 2002, the MammoSite (MS) Radiation Therapy System (HOLOGIC, Inc., Bedford, MA, USA) was developed to increase the availability of APBI by simplifying the breast brachytherapy procedure for physicians and patients alike (Edmundson et al. 2002). To date, this is the most widely utilized method of APBI, with over 47,000 patients estimated to have been treated. The applicator system consists of a semiflexible catheter that is 6 mm in diameter and 15 cm long with an inflatable balloon attached to the distal end. It can be placed easily either intraoperatively or postoperatively using a single entry into the breast, and is inflated symmetrically within the lumpectomy cavity. Three balloon sizes are currently available: a 4–5 cm diameter sphere, a 5–6 cm sphere, and a larger elliptical shape. After inflation with saline, the balloon is evaluated via CT (computerized tomography) or ultrasound to assure proper geometry, symmetry and conformance.

The catheter shaft has a single lumen that permits the transport of an HDR source into the center of the balloon, affording only a few dwell positions and thus a much quicker and simpler treatment planning process and a higher reproducibility of target coverage. The single entry into the breast approach used in this method offers the significant advantage of easy handling with a shorter learning curve than interstitial brachytherapy. Its primary drawbacks include the relatively restricted flexibility of treatment planning after applicator placement. This limits its applicability to appropriately selected patients, contingent upon several factors: (1) good conformance between the balloon surface and breast tissue (minimal air gaps); (2) optimal location and geometry of the surgical cavity, and; (3) appropriate skin-to-balloon distance. In the initial trial, 30% of patients proved ineligible for brachytherapy due to these reasons (Keisch et al. 2003).

23.4 Hybrid Intracavitary Devices

23.4.1 Design Rationale

An important consideration when modifying the current single-lumen balloon APBI method is that the toxicity profile is still evolving. For example, the skin-to-balloon distance measurement has been used as a simple method of estimating the likely maximum dose to the skin surface with MammoSite balloon brachytherapy. This becomes especially relevant when two-dimensional or plain film treatment planning is routinely performed, given that the gradient of radiation dose to the skin via a dose–volume histogram cannot be readily and rigorously assessed during the planning process. The typical maximum skin doses are significantly higher with single-lumen balloon brachytherapy relative to interstitial multicatheter brachytherapy, where multiple dwell positions allow tailored dose modulation, and so the original patient eligibility recommendation of a minimal skin spacing of 5 mm has been increased to 7 mm.

Several reports have demonstrated a correlation between balloon-to-skin spacing and acute and late skin toxicity. Nine institutions participated in a pooled analysis of data evaluating clinical experience of the MammoSite RTS for delivering accelerated partial breast irradiation. Between 2000 and 2004, 483 patients were treated and treatment parameters were analyzed to identify factors affecting outcome. A skin spacing of < 6 mm increased the risk of severe acute skin reaction ($p = 0.017$) and telangiectasia ($p = 0.028$). Importantly, the use of multiple dwell positions reduced the risk of severe hyperpigmentation ($p = 0.0278$), also suggesting that a reduction in the skin dose correlates with a reduction with skin toxicity (Cuttino et al. 2008). Similarly, in cases where the applicator is close to the chest wall, the dose to the ribs, lung and heart can be significant with the higher dose per fraction of APBI.

In an effort to merge the simplicity and reproducibility of the single-entry MammoSite balloon device with the customization and dose flexibility of the multicatheter interstitial technique, three novel hybrid breast brachytherapy catheter systems have been developed: Contura, SAVI, and ClearPath. These devices have key differences in applicator design, placement technique, treatment planning, and quality assurance measures. However, they share basic goals: (1) to provide optimal target volume coverage; (2) to minimize normal tissue dose/toxicity; and (3) to expand the number of patients that are eligible for APBI by overcoming previous technical limitations of tissue nonconformance, central lumen asymmetry, and reduced skin-to-balloon or chest wall distance.

23.4.2 Treatment Planning

The conventional regimen for most HDR APBI techniques is a dose of 34 Gy delivered twice daily at least 6 h apart over a period of ten fractions in one week. Several studies

have shown that CT-based three-dimensional planning is paramount in order to achieve reliable target coverage with maximal normal tissue sparing for multicatheter approaches (Das et al. 2004; Cuttino et al. 2005; Weed et al. 2005; Major et al. 2007; Ott et al. 2007; Patel et al. 2007). Compared to plain film dosimetry, which can be employed with a single-dwell MammoSite plan, this may pose a barrier to adoption in sites where there are limitations on treatment planning equipment, software or physics resources. However, there have been several key improvements in treatment planning hardware and software that facilitate the planning process, including contouring, automated catheter reconstruction, optimization tools and dose–volume histogram analyses (Fig. 23.2).

Treatment planning consists of outlining the lumpectomy cavity, which may contain seroma fluid and/or air plus an expansion of 1 cm of breast tissue. For all intracavitary HDR APBI methods, the planning target volume (PTV) is defined as the expanded volume minus the lumpectomy cavity (Fig. 23.3). Quality assurance films must be obtained prior to each fraction in order to verify the position and geometry of the applicator within

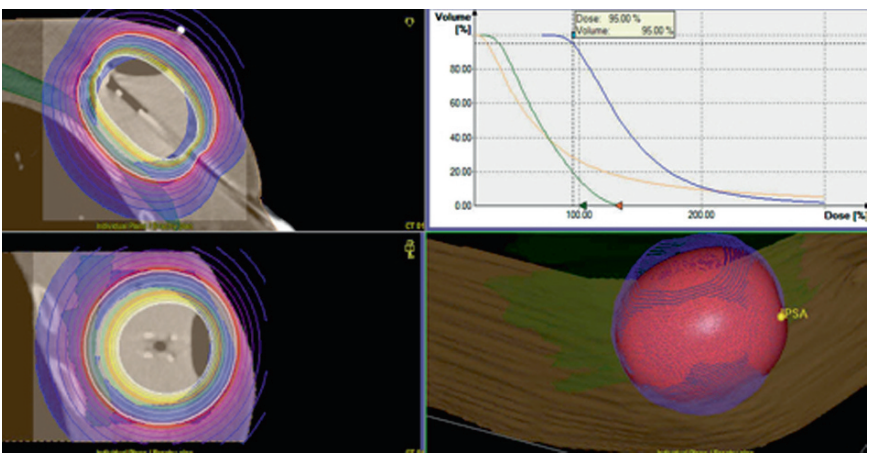

Fig. 23.2 Example of 3D treatment planning software, demonstrating dose optimization and dose–volume histogram analyses of a Contura Balloon using the Nucletron Oncentra Brachy planning system

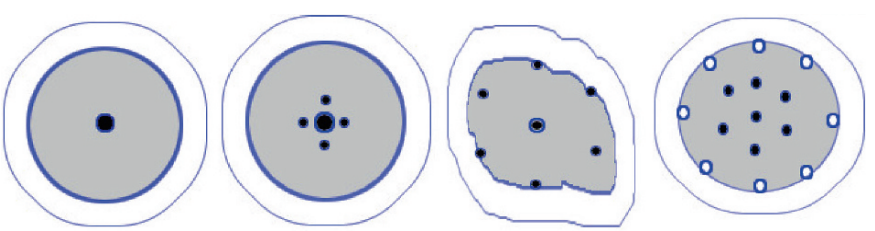

Fig. 23.3 A cross-section of the hybrid applicators; *closed, dark circles* are loaded treatment catheters and *white circles* are displacement struts. *From left to right*: MammoSite™; Contura™; SAVI™; and ClearPath™

the breast. This can be done via plain X-ray, CT scout, CT or ultrasound, and should be correlated with the relevant measurement at the time of initial treatment planning.

23.4.3 Surgical Technique

Intracavitary devices can be placed at the time of surgery or during a separate procedure after lumpectomy. Placement of the applicator at the time of lumpectomy yields advantages that include the convenience of a single procedure, the ability to modify an inadequate cavity at the time of insertion, and a potentially shortened interval between surgery and the initiation of radiation. On the other hand, intraoperative placement requires device insertion prior to obtaining complete pathologic information that could provide high-risk factors for targeted breast irradiation. Examples include the findings of microscopically positive margins, multifocal or multicentric disease, involved regional lymph nodes, lobular histology, or an extensive intraductal component. The discovery of any one of these findings could lead to the removal of the device at some institutions, although absolute clinical patient selection criteria for APBI are not yet established.

Seroma has been reported as a common side effect in patients treated with the MammoSite after placement at the time of lumpectomy. In the ASBS registry trial, 23.9% of patients developed a seroma. This was seen more frequently in patients who had the device placed at the time of surgery compared to those who had the catheter placed after surgery, at a separate procedure (30% vs. 19% of patients) (Vicini et al. 2005). Evans et al. reported a persistent seroma (> 6 months) rate of 68.4% in 38 patients treated with MS after exclusive intraoperative placement. Multiple dosimetric, clinical, and treatment-related variables were analyzed, and only body weight had a positive correlation with the risk of seroma (Evans et al. 2006). It is possible that non-balloon devices, such as SAVI and ClearPath, would be less likely to cause seroma formation than a balloon device. It is reasonable to expect less trapped fluid with catheters in contact with the cavity wall rather than a tightly opposed balloon wall. Further clinical results and rigorous dosimetric correlation will be needed to evaluate this potential event.

If the device is placed postoperatively, the procedure requires image guidance, specifically using ultrasound. Stolier et al. (2005) have described the use of the scar entry technique in the outpatient setting with minimal patient discomfort and no required sedation. Zannis et al. have also described a postoperative ultrasound-guided technique. In a multi-institutional report, the results of 1,403 cases from 87 institutions were studied, and it was found that 44% of the applicators were placed using an open technique at the time of lumpectomy, 41% used an ultrasound-guided lateral incision, and 14% used the scar entry technique. As the trial progressed, the proportion of patients undergoing an open placement declined. In this large registry trial, there were no differences among the three placement techniques in regards to skin distance, cavity conformance or asymmetry, and no associations were found between placement technique and cosmetic outcome (Zannis et al. 2005). If the physician is not experienced with ultrasound-guided percutaneous methods, an alternative is to insert and leave a temporary balloon catheter indwelling at the time of lumpectomy surgery, which is then exchanged for the hybrid device.

23.4.4 SenoRx Contura

In May 2007, SenoRx, Inc. (Aliso Viejo, CA, USA) released the Contura multilumen balloon (MLB) radiation system. Since its clinical implementation, over 1,700 multilumen balloons have been placed (as of October 2008). The device has a polyethylene balloon at the end of a central shaft with four additional minimally displaced treatment catheters, all five of which can accommodate the HDR source. The Contura device also has a vacuum port on both ends of the balloon to remove fluid or air around the lumpectomy cavity, thereby improving tissue–balloon conformance. Unlike the non-balloon hybrid devices, the positions of the surrounding channels are not variable. They have a fixed 5 mm offset around the central channel. These channels provide additional source positions and thus allow increased dose flexibility compared to single-lumen devices. This can potentially lead to some increased sparing of normal tissues, including the heart, lung, chest wall, and skin. In addition, the additional dose flexibility may allow the treating physician to account for an asymmetric balloon implant with respect to the central channel, which was often a limitation of the single-lumen balloon method (Fig. 23.4).

23.4.5 Supporting Data

Todor et al. described the results of their dosimetric comparison between the SenoRx and MammoSite in ten patients previously treated with the MammoSite device. The authors of this study modified the MammoSite planning CT scans to account for the additional lumens available in the MLB catheter. For balloons located between 10 mm and 5 mm from the skin, SenoRx diminished the V_{150} to the breast by 20% and reduced the chest wall dose by about 40%. For balloons located ≤ 5 mm from the skin, the MLB device allowed the maximum dose to the skin to be less than 115%, typically 30% less than for MammoSite. Target volume coverage was also increased by 5–15% with SenoRx compared to MammoSite.

A multicenter registry trial has been initiated to compare the dosimetric advantages of a multilumen solution with those of a single central channel balloon brachytherapy method.

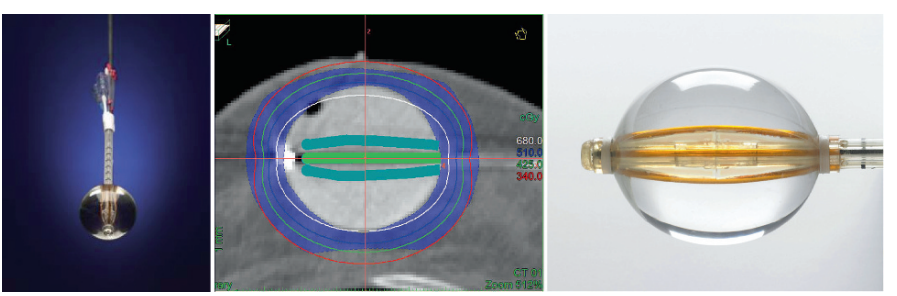

Fig. 23.4 The Contura™ multilumen balloon applicator

23.4.6 SAVI

The SAVI (strut adjusted volume implant) applicator (Cianna Medical, Aliso Viejo, CA, USA) was the first non-balloon hybrid device to reach the marketplace, and it also combines the dosimetric flexibility of multicatheter brachytherapy with the advantages of a single catheter entry into the breast. It is available in several sizes consisting of six, eight, or ten catheters that deploy into equal positions radially around a central strut. The device is inserted in collapsed form through a small skin incision. Once placed, it is then expanded to fit the lumpectomy cavity by rotating the hub of the device, which remains external to the patient's skin after deployment.

With up to 11 total catheter lumens to accommodate the HDR source, the multiple peripheral struts of the SAVI enable radiation dose modulation in amounts customized for cavity characteristics, including proximity to the skin and chest wall, in contrast to the spherically symmetric distribution associated with balloon catheters, where radiation comes from a single point or line source. Due to the nature of the design of the device, it is possible for breast tissue to "invaginate" between the struts; however, appropriate selection of device size (number of outer catheters) will help mitigate this effect. With the use of multiple dwell positions in each of the hollow struts, the flexibility in dose distribution can approach the conformality and distribution associated with multicatheter interstitial brachytherapy (Fig. 23.5).

23.4.7 Supporting Data

Gurdalli and colleagues have studied the dosimetric performance of the SAVI device. The authors of this study found that, in 15 patients treated with the SAVI device, the skin doses were 10–13% lower than published values for MammoSite, although the treatment plans were more complex than MammoSite plans, with an average number of dwell positions utilized of 106 (Gurdalli et al. 2008a, b).

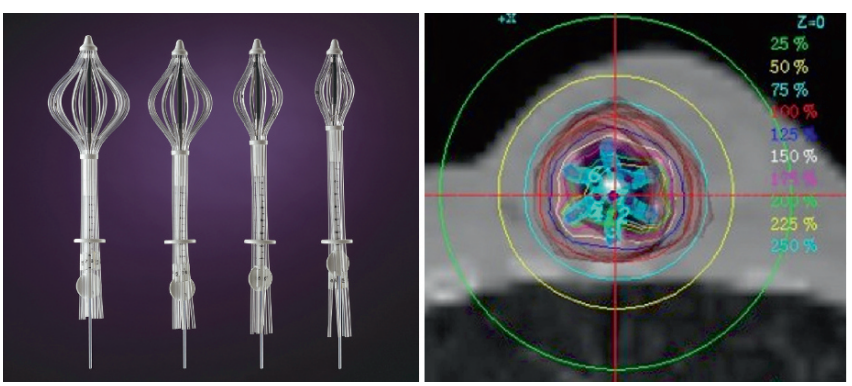

Fig. 23.5 The SAVI™ multilumen hybrid applicator

The same group performed a dosimetric comparison of SAVI, Contura MLB, and MammoSite breast brachytherapy by inserting each of the applicators into a 5 cm diameter lumpectomy cavity in a human cadaver. The target volume coverage was excellent and similar for all three devices; however, given a 3 mm skin distance, the maximum skin doses differed significantly at 85, 142, and 182% of the prescription dose for SAVI, MLB, and MS, respectively. This suggests that the dose modulation capability of the SAVI is the greatest of all the currently available HDR intracavitary devices (Gurdalli et al. 2008a, b).

Initial clinical experience has shown that the SAVI device is easy to place and remove, and that treatment was unaffected by seroma. Studies have also found that the multiple struts of SAVI allow for dose contouring, thereby reducing the toxicity secondary to the irradiation of normal tissues, including skin and chest wall. The group at the University of California at San Diego reported that the first twenty patients treated at their institution demonstrated excellent feasibility and favorable dosimetry relative to other intracavitary approaches (Scanderbeg et al. 2008). Mantz et al. have reported the initial clinical results of 18 patients treated with the SI catheter. For ten of 18 patients, the skin distance was less than 7 mm. Seroma was observed in three of 18 patients, and erythema was observed in four of 18 patients at one month. Cosmesis was rated as excellent in nine out of ten patients at three months. At early follow-up, no episodes of desquamation, fibrosis, or telangiectasia had developed (Mantz et al. 2008).

23.4.8 ClearPath

The ClearPath applicator (North American Scientific, Inc., Chatsworth, CA, USA) is a similar hybrid cage device comprised of an array of six outer flexible support struts and six inner treatment catheters surrounding a central channel (Fig. 23.6). In contrast to the SAVI catheter, the radiation source is not in direct contact with the breast tissue of the lumpectomy walls. This in turn leads to a different dosimetric heterogeneity profile (as measured by the dose homogeneity index, or DHI). The device is also expanded into the proper configuration after insertion within the lumpectomy cavity under ultrasound or CT guidance through a single entry either intraoperatively or postoperatively. A unique feature is that

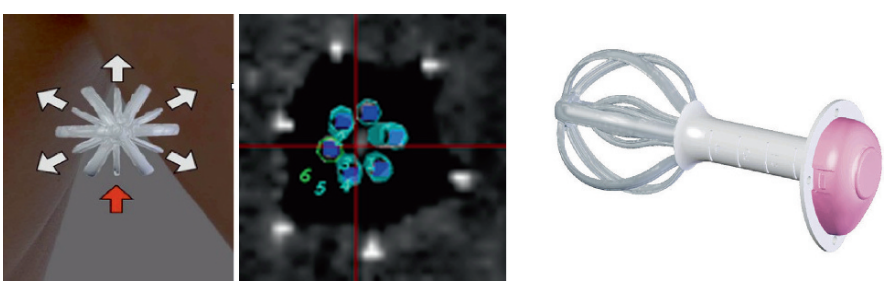

Fig. 23.6 The ClearPath™ multilumen hybrid applicator

once it is placed, the inner treatment catheters can be variably adjusted into a custom configuration, in contrast to the fixed treatment catheters in the other devices above. This affords further enhancement of target coverage and conformal avoidance of nearby healthy tissue such as the skin. The treatment can be delivered with a typical one-week outpatient HDR regimen or via an outpatient LDR approach during which the patient is provided with a shielded bra that remains in place for the duration of the treatment. Additionally, after the device is deployed, the base is detached from the device, and a cap is placed over the HDR channels such that there is no protruding portion of the applicator between fractions, which should lead to improved patient comfort during the one-week treatment course.

23.4.9 Supporting Data

Early dosimetric comparison with the MammoSite RTS demonstrated a reduced dose to both the skin and lung when applied to an identical lumpectomy cavity (Hodge et al. 2007). Dickler et al. reported a dosimetric comparison of the CP and MS catheters in 15 patients previously treated with MS. The authors of this study found that the two devices offered comparable target volume coverage, but that CP allowed significantly more normal tissue sparing. The mean ipsilateral breast V50 was 19.8% vs. 18.0%, the mean ipsilateral lung V30 was 3.7% vs. 2.8%, the mean heart V5 was 57.0% vs. 54.3%, and the maximum skin point doses per fraction were 312.2 and 273.6 cGy for the MS and CP methods respectively (Dickler 2007).

Haley and colleagues from University of Pittsburgh and University of Wisconsin performed a dosimetric analysis on patients who were deemed not to be candidates for treatment with the MS device due to inadequate skin distance (Haley 2008). The median skin distance in these patients was 5 mm. A phantom study was performed and the parameters of the CP catheter were superimposed on the MS planning CT scans. The authors found that the median maximum skin dose was 161% vs. 113% of the prescription dose for the MS and CP devices respectively. The reduction in skin dose was accomplished without compromising the PTV coverage or increasing the radiation dose to the critical normal organs. Clinical outcomes with the CP catheter have not yet been reported.

23.5 Conclusion

Based on favorable early clinical outcome data, accelerated partial breast irradiation is increasingly being offered as an alternative to conventional external beam whole breast irradiation following lumpectomy in select early-stage breast cancer patients. With the development and integration of more advanced imaging, sophisticated radiation treatment planning systems, and improved applicator systems, several innovative strategies of delivering higher-quality APBI have been introduced. The devices and approaches reviewed in this article represent a new iteration of treatment technologies that seek to increase applicability to a broader group of patients, significantly improve ease of use for the physician,

reduce normal tissue toxicity, and ultimately provide greater patient convenience without deteriorating existing breast cancer treatment outcomes. Further clinical experience is needed to define which patients benefit most from these different methods of APBI.

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Emerging Technologies Part II: Novel Sources and Delivery Systems

24

Jaroslaw T. Hepel, Shirin Sioshansi, Mark J. Rivard, and David E. Wazer

24.1 Introduction

Many of the other chapters in this text discuss in detail established techniques of accelerated partial breast irradiation (APBI), with significant attention given to techniques that are specific to certain institutions. Furthermore, some chapters stress the cohesion of established techniques through multi-institutional clinical trials and the implementation of uniform quality assurance practices. However, this chapter will focus on new directions for the future of APBI by looking at new and novel approaches to APBI delivery.

While one could consider using almost any new treatment modality for APBI, it is necessary to delineate the desirable features that these modalities should have, and how they should improve upon established techniques:

(a) The current team of care providers (surgeons, oncologists, radiation oncologists) should be able to use the modality in a cost-effective, time-sensitive, and easy-to-use manner
(b) It should be possible to deliver the therapy in a controlled manner which can be quantitatively confirmed through measurements and calculations
(c) It should provide therapy with improved dose homogeneity, dose conformity (nontarget tissue sparing), and patient-specific compatibility

The majority of the new and/or novel approaches listed in the following sections have some or all of these desirable features. This includes using novel sources and novel delivery systems, each of which presents unique potential advantages over established techniques.

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24.2 Electronic Brachytherapy

Radionuclide-based brachytherapy sources have been in clinical use for over one hundred years, since the discovery of ^{226}Ra by Madam Curie (Bell 1903). Currently, the most commonly used radionuclides are ^{103}Pd, ^{125}I, ^{137}Cs, and ^{192}Ir. Although these radionuclides are well established, they do have limitations:

(a) Dosimetric properties, such as their photon energy spectrum and subsequent tissue penetration, are fixed
(b) Dose rate is limited due to practical restrictions of source size
(c) Dose rate is nonuniform over the lifetime of the source
(d) The source strength decays logarithmically, requiring periodic source replacement and radiological waste disposal
(e) They require storage and security, each of which is becoming an increasing concern and expense

Advances over the last few decades have led to the development of microminiature electronic sources capable of X-ray production at high enough dose rates to be of therapeutic utility. These types of electronic brachytherapy (EBT) sources have become of great interest because they overcome some of the limitations associated with radionuclide-based brachytherapy. Currently available devices approved by the United States Food and Drug Administration (FDA) include the Intrabeam IORT system from Carl Zeiss, Inc. (Oberkochen, Germany) and the Axxent system from Xoft, Inc. (Fremont, CA, USA). Other sources are also currently under development. This section will focus on the Xoft Axxent system. Intraoperative radiation therapy with the Intrabeam device is discussed in detail in Chap. 19.

24.2.1 Xoft Axxent System

The Xoft Axxent system was approved by the FDA in 2005. It is a balloon applicator-based brachytherapy catheter similar to the MammoSite system. The Axxent system consists of three parts: the balloon applicator, the electronic source, and the controller module (Fig. 24.1).

The applicator consists of a balloon with a single central catheter for source insertion. The balloon applicator is placed into the breast lumpectomy cavity either intraoperatively or postoperatively in a similar fashion to other intracavity applicators. Unlike the MammoSite applicator, the wall of the balloon contains radiopaque material for CT visualization, and thus only saline without contrast is used for expansion, as iodinated contrast would markedly attenuate the 50 kV source. The balloon applicator is available in several sizes in order to achieve maximum conformity to the lumpectomy cavity.

The electronic source is a miniaturized X-ray tube that is 0.225 cm in diameter (Fig. 24.2). The source must be enclosed inside a flexible cooling catheter to prevent overheating. The source

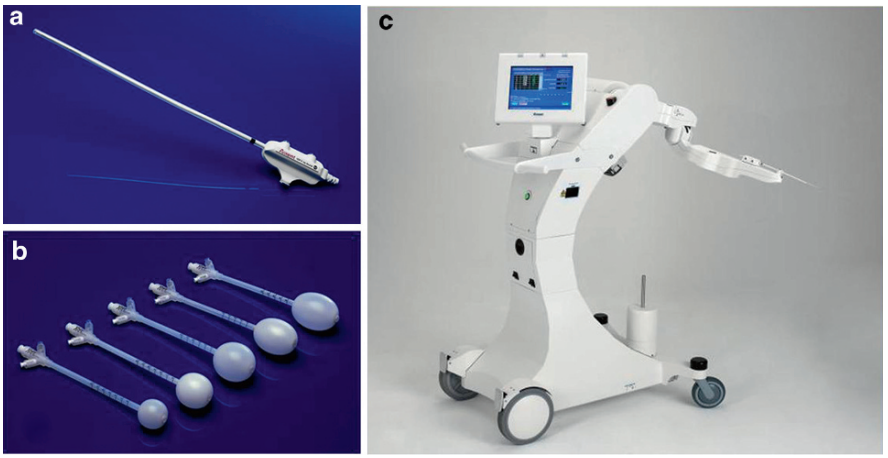

Fig. 24.1a–c Xoft Axxent electronic brachytherapy (EBT) system: **a** electronic X-ray source with cooling catheter; **b** intracavitary balloon catheters of various sizes; **c** controller module. Reproduced here with the permission of Xoft Inc.

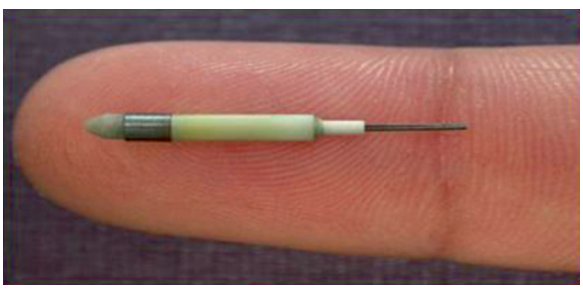

Fig. 24.2 Xoft microminiature 50 kV X-ray tube, model S7500. Reproduced here with the permission of Xoft Inc.

and catheter are disposable and are typically used for a single course of treatment. The source and cooling catheter attach to the controller module and insert into the balloon applicator.

The controller module is programmed to remotely control the source position and dwell time of the EBT source within the balloon applicator. Source positions and dwell times are determined with three-dimensional treatment planning on commercially available brachytherapy treatment planning systems, which are then transferred to the controller module. Source dwell separations as low as 0.5 mm are possible. Unlike for high dose rate (HDR) ^{192}Ir, the entire system does not require a highly shielded environment because of the rapid dose falloff associated with the low-energy EBT source.

24.2.2 Xoft Axxent Dosimetry

The Xoft Axxent EBT source is capable of producing an X-ray spectrum with a maximum energy of 50 kV with an output of approximately 1 Gy min^{-1} at the treatment depth

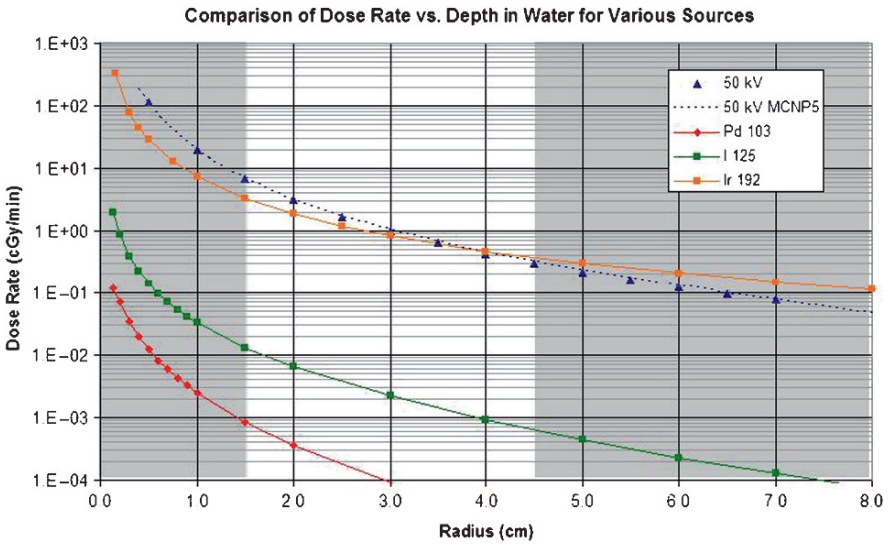

Fig. 24.3 Comparison of dose rate as a function of depth in water for Xoft 50 kV EBT, ^{192}Ir, ^{125}I, and ^{103}Pd sources. Reproduced from Rivard et al. (2006) with permission

(3 cm from the source) as measured in water (Rivard et al. 2006). This dose rate is comparable to that achieved with HDR ^{192}Ir. The Xoft source was purposely designed to mimic the dose rate and depth dose characteristics of HDR ^{192}Ir. A comparison of the dosimetric characteristics of the Xoft Axxent EBT source, HDR ^{192}Ir, ^{103}Pd, and ^{125}I is shown in Fig. 24.3. The dose-rate profile of the Xoft EBT source is markedly different from the dose-rate profiles of conventional low-dose-rate (LDR) ^{103}Pd and ^{125}I sources but similar to a HDR ^{192}Ir source over the treatment depth considered relevant to balloon catheter-based APBI. The most prominent dosimetric difference between HDR ^{192}Ir and the Xoft 50 kV EBT source is that the Xoft source is hotter at the balloon surface and cooler at depth, Fig. 24.4. The clinical significance of these dosimetric differences is unknown.

Dickler et al. (2007) performed a dosimetric comparison between the MammoSite catheter with a HDR ^{192}Ir source and the Xoft Axxent system with the 50 kV EBT source. This study showed that target coverage is essentially identical, though the dose delivered to tissues outside the target volume is significantly lower with the Xoft EBT source (Fig. 24.5). Note that the dose delivered to the heart, lung, and normal breast are all markedly decreased.

As compared to ^{192}Ir, the tradeoff for the favorable dose falloff at depth achieved with the Xoft EBT source is an increased dose at the balloon surface. Smitt and Kirby (2007) measured the volume of tissue exposed to a high dose for different Xoft balloon applicator sizes. The V_{300} was found to range from 1 to 4 cm^3 and the V_{200} was measured at 16–22 cm^3. Table 24.1 shows a comparison of the volume of the "hotspot" regions achieved with 50 kV EBT Xoft Axxent, HDR ^{192}Ir MammoSite, and HDR ^{192}Ir interstitial brachytherapy (IB). The V_{200} is largest for Xoft EBT as compared to that seen with HDR ^{192}Ir MammoSite or IB.

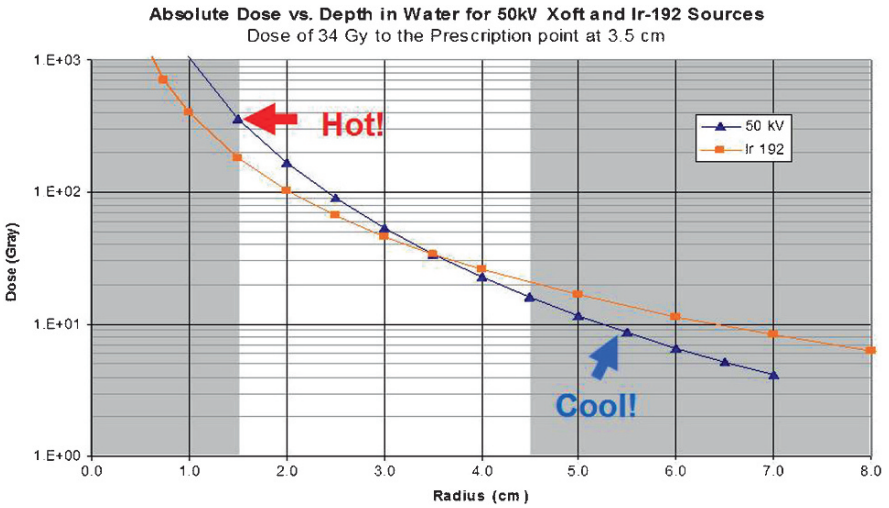

Fig. 24.4 Comparison of dose as a function of depth in water for the Xoft 50 kV EBT and HDR ^{192}Ir. The *white region* denotes typical treatment depth (from the source) for balloon brachytherapy. The 50 kV EBT source results in a higher surface dose but a more rapid dose falloff with depth. Reproduced from Rivard et al. (2006) with permission

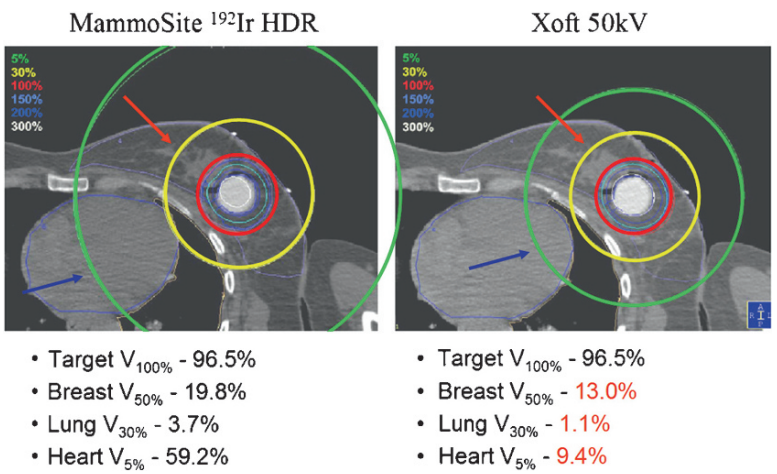

Fig. 24.5 Dosimetric modeling of balloon brachytherapy APBI with Mammosite HDR ^{192}I and Xoft 50 kV EBT. For the same target coverage by the prescription isodose line, the dose to normal breast, lung, and heart tissue is significantly reduced using the Xoft 50 kV EBT source. The *red arrows* denote the volume of nontarget breast and lung tissue encompassed by the 30% isodose line. The *blue arrows* denote the volume of heart tissue encompassed by the 5% isodose line. The volume of breast receiving 50% of the prescription dose ($V_{50\%}$), lung receiving 30% of the prescription dose ($V_{30\%}$), and heart receiving 5% of the prescription dose ($V_{5\%}$) is tabulated for each technique. Figure and data are reproduced from Dickler et al. (2007) with the permission of Elsevier

Table 24.1 V_{150} and V_{200} for various sources

Sources	V_{150} (cm^3)	V_{200} (cm^3)
50 kV intracavitary	30–61	16–22
^{192}Ir HDR MammoSite (single dwell)	20–37	0.5–8
^{192}Ir HDR MammoSite (multiple dwell)	37–36	6–15
^{192}Ir interstitial (fat necrosis)	69 ± 11.9	22 ± 3.3
^{192}Ir IB interstitial (no fat necrosis)	44 ± 3.6	13 ± 1.2

Data from Smitt et al. (2007)

24.2.3 Radiobiological Considerations for the Xoft Axxent System

Linear energy transfer (LET) specifies the amount energy transferred per unit length of the radiation track. As such, this is a measure of the density of ionization events for a specific radiation source. High-energy X-rays are sparsely ionizing and have a low LET. Typical LET values for high-energy X-rays are 0.2 keV μm^{-1} for 1 MeV photons and 2 keV μm^{-1} for 250 keV photons. As photon energy decreases, the ionizations per track length increase, resulting in a larger LET value. The Xoft Axxent 50 kV EBT source has an estimated mean LET value of 5 keV μm^{-1}. This is severalfold higher then the LET value of ^{192}Ir (Fig. 24.6).

Relative biologic effectiveness (RBE) is dependent upon several factors, including dose, dose per fraction, dose rate, biological endpoint, and LET. As the first four factors are the same or similar for different intracavitary APBI techniques, an important consideration is whether the increase in LET for the Xoft Axxent EBT source translates into a meaningful increase in RBE. Brenner et al. (1999) has estimated the RBE values for 20–40 kV EBT sources using dicentric chromosome aberrations of human lymphocytes as the biological endpoint (Fig. 24.7). For a 40 kV source, the RBE values were estimated to be in the range of 1.2–2.1 as compared with ^{192}Ir. Fowler et al. (2004) calculated the RBE value specifically for the 50 kV spectrum of the Xoft Axxent EBT source. He arrived at RBE values for Xoft EBT of 1.1–1.8 as compared to a value of 1.0 for ^{192}Ir over a dose range of 1–20 Gy. These results have led to a generally accepted RBE value of 1.2 for the clinical implementation of Xoft EBT for APBI. As the differences in the RBE values between the Xoft EBT source and ^{192}Ir may be clinically negligible, there is currently no dose adjustment that is recommended. However, as these values of RBE are calculated estimates and are not derived from clinical experience, additional investigation is required to establish their relevance.

Another special consideration in the use of Xoft EBT is the photoelectric effect. At source energies above 100 kV, as seen with ^{192}Ir, the predominant interaction of photons with tissue is through Compton scattering. The Compton effect is independent of the atomic number (Z) and is dependent exclusively on the electron density of the absorbing material. However, at lower energies, the photoelectric effect (which is highly dependent upon Z) constitutes a significant portion of the photon interactions. This is a critical factor in shielding, as high-Z materials (such as lead) can readily attenuate the radiation

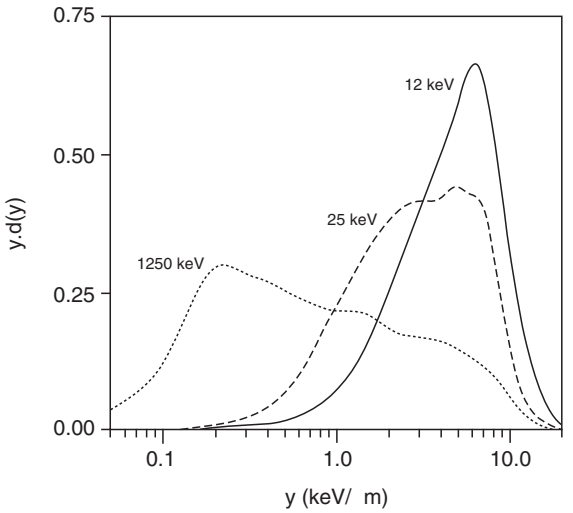

Fig. 24.6 LET as a function of photon energy. Measured microdosimetric energy deposition spectra in 1 μm site sizes for various monoenergetic photons. The representation is such that the area under the curves delimited by any lineal energy values (y, the microdosimetric correlate of LET) is proportional to the fraction of the dose deposited by photons in that energy range. As the photon energy decreases, there is a significant shift in the energy deposition pattern towards higher LET. Reproduced from Brenner et al. (1999) with the permission of the Institute of Physics

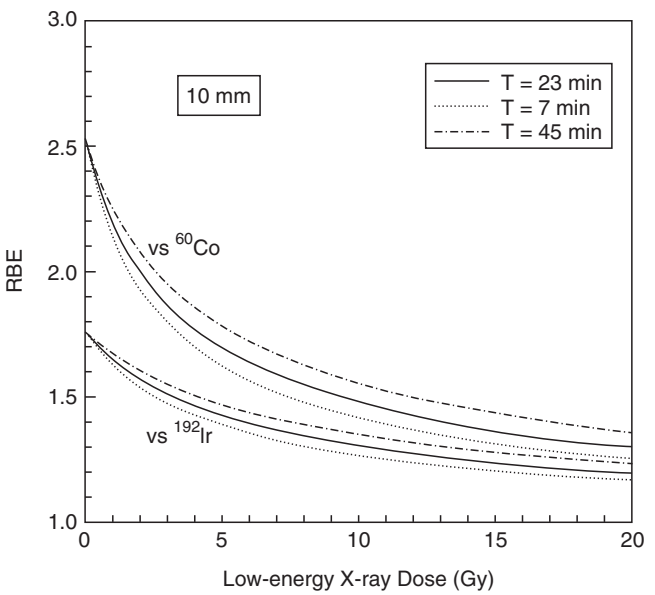

Fig. 24.7 Estimated values of relative biologic effectiveness (RBE) for a 40 kV EBT source as a function of low-energy X-ray dose for various treatment times at 10 mm depth compared with ^{60}Co, ^{192}Ir and ^{125}I. Reproduced from Brenner et al. (1999) with the permission of the Institute of Physics

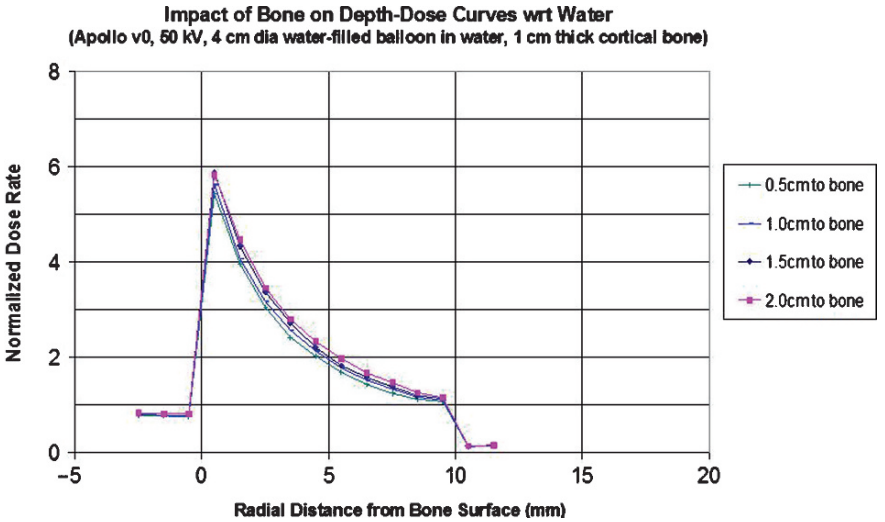

Fig. 24.8 Calculated relative dose to cortical bone for the Xoft 50 kV EBT at various source-to-bone distances. Reproduced here with the permission of Xoft Inc.

emitted from the source. The photoelectric effect is also important when considering the radiation dose that is absorbed by tissues that have a high value of *Z* (such as the calcium in bone). For APBI, the ribs are frequently in close proximity to the lumpectomy cavity and included in the target volume. High radiation doses to the ribs can lead to painful injury to the periosteum and rib fracture. Ebert et al. (Ebert and Carruthers 2003) calculated the dose to the first 1 mm of bone for the Intrabeam IORT 50 kV EB source. The dose was calculated to be 2.5–4.5 times higher in bone as compared to soft tissue. Calculations for the Xoft Axxent EBT source have also been performed, resulting in estimates of a 5.5–6 fold excess dose (as compared to that delivered with ^{192}Ir) in the most superficial 2–3 mm of bone (Fig. 24.8). The clinical significance of these findings is not yet known.

24.2.4 Xoft Axxent EBT Source Anisotropy

The Xoft EBT source has pronounced anisotropy such that the isodose profile constricts at the proximal end of the source, resulting in an asymmetric "tomato-shaped" dose distribution. The HDR ^{192}Ir source also has anisotropy, but is relatively symmetric at both the proximal and distal ends of the source and is less pronounced than that seen with the Xoft EBT source (Fig. 24.9). For the Xoft Axxent system, a single central dwell position results in a dose distribution that does not give optimal coverage to a typically defined target volume at 1 cm depth. The use of multiple dwell positions, however, can optimize the isodose

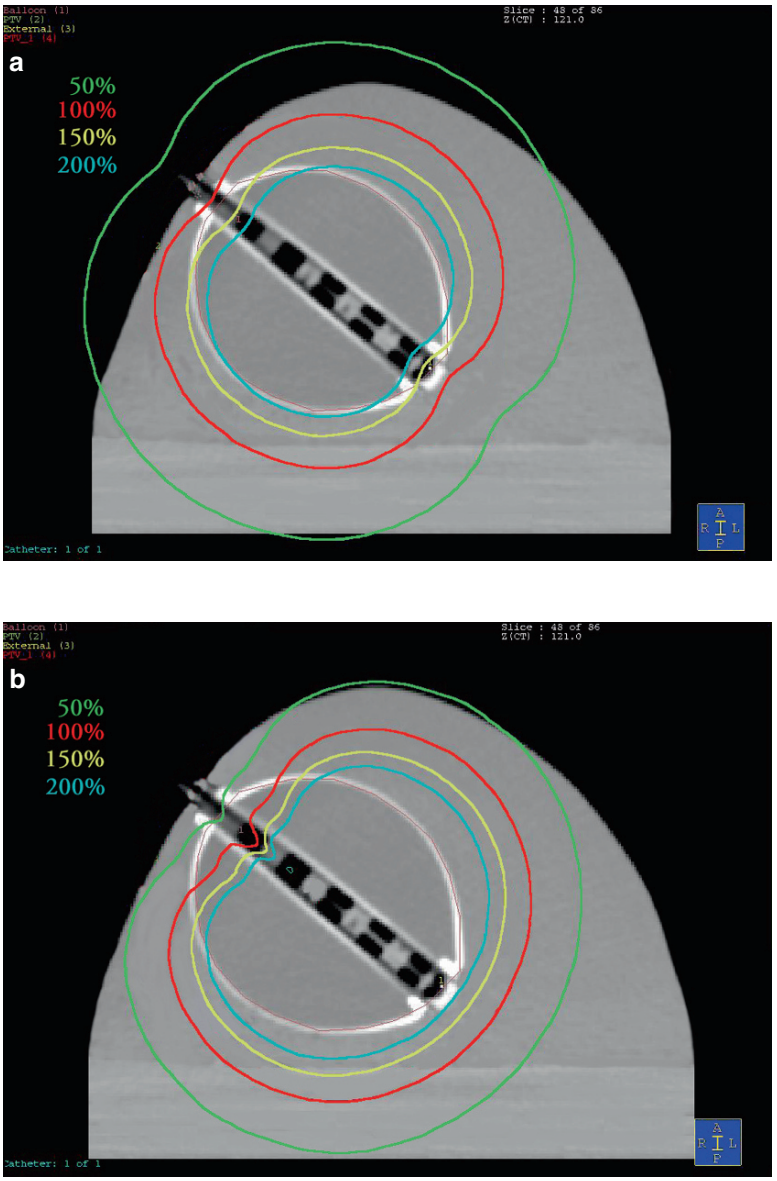

Fig. 24.9a–b Isodose distributions in a phantom demonstrating the anisotropy of a single central source position for **a** Mammosite HDR ^{192}Ir and **b** Xoft Axxent 50 kV EBT

distribution to a nearly spherical configuration. The insertion technique for placement of the Xoft balloon applicator can be modified to take advantage of the inherent source anisotropy in order to limit the dose to the skin or chest wall (Fig. 24.10) (Hepel et al. 2009).

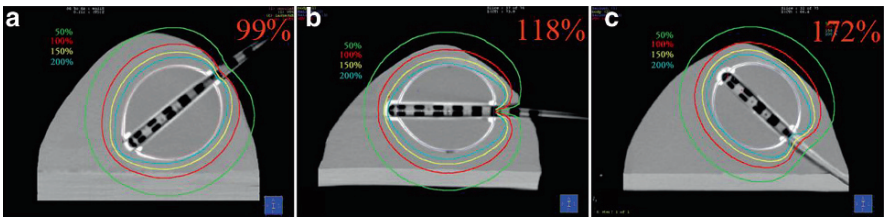

Fig. 24.10a–c Xoft Axxent 50 kV EBT isodose distribution, demonstrating the effect of balloon catheter insertion angle on surface dose. Catheters were inserted at perpendicular **a**, 45° oblique **b**, and parallel **c** orientations relative to the plane of the breast phantom surface, with a cavity-to-surface distance of 6 mm. Multidwell position plans were optimized to minimize surface dose. Maximum calculated surface dose is shown in the *upper right* for each catheter orientation. The effect of the phantom surface–air interface is not taken into account

24.2.5 The Future Potential of Xoft Axxent: Variable Energy, Beam Directionality, and Depth-Dose Modulation

The Xoft EBT source has unique potential for creative dose sculpting via variable energy emission, beam directionality, and depth-dose modulation (DDM). Though currently not commercially available, EBT sources have the potential to allow for variability or "tuning" of the X-ray energy output that they generate. The ability to vary the emitted energy allows the dose falloff perpendicular to the axis of the source to be changed. In theory, by integrating the width of source indexing with selected source energies, one can custom shape the dose profile to enhance the therapeutic index. The low photon energy of the Xoft Axxent EBT source can be simply collimated by a thin layer of high–Z material. This allows for internal shielding of a portion of the source, resulting in further dose sculpting through a directional beam (Fig. 24.11). The technique of depth–dose modulation (DDM) utilizes a complex combination of source collimation and indexing of dwell positions to modify the depth–dose profile of the EBT source (Fig. 24.12) (Hiatt et al. 2008). The combination of variable source energy, beam directionality and depth-dose modulation gives EBT a potential flexibility that is not available with radionuclide-based brachytherapy. As such, this will be an exciting area for further research and development.

24.2.6 Clinical Experience with Xoft Axxent

The Xoft Axxent system was introduced for APBI through a multi-institutional, single-arm, postmarket, Phase IV clinical trial that included patients > 50 years old with IDC or DCIS measuring less then 2 cm, and with negative axillary nodes and negative margins of at least 1 mm. The study endpoints are the feasibility of treatment as well as tumor control and toxicity.

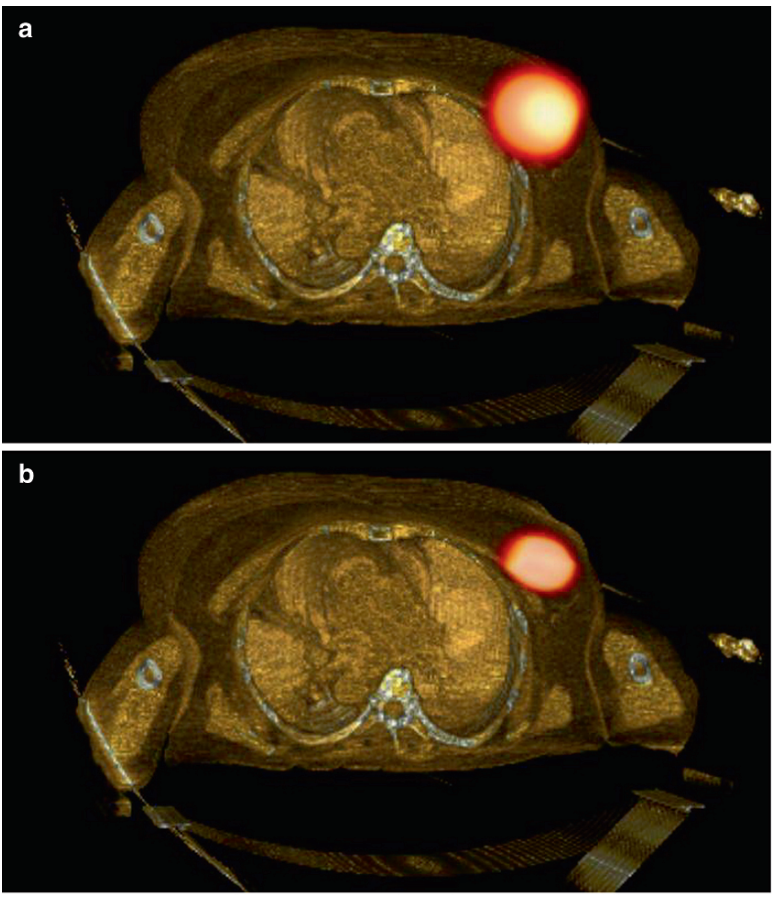

Fig. 24.11a–b Xoft Axxent 50 kV EBT, demonstrating the effect of beam directionality via internal shielding: **a** standard unshielded source dose distribution; **b** internally shielded source dose distribution, demonstrating a reduced dose to chest wall and skin. Reproduced here with the permission of Xoft Inc.

24.3 AccuBoost

Image guidance and methods to account for or reduce target motion have become an integral part of radiation therapy. The application of these principles to breast irradiation with a brachytherapy technique could result in markedly improved accuracy in the delivery of tumor bed boost irradiation as part of conventional whole breast irradiation and provide an alternative to 3D-CRT external-beam APBI. AccuBoost (Advanced Radiation Therapy, Inc., Billerica, MA, USA) is an image-guided, noninvasive brachytherapy system for the delivery of partial breast irradiation that is designed to address these issues. The AccuBoost

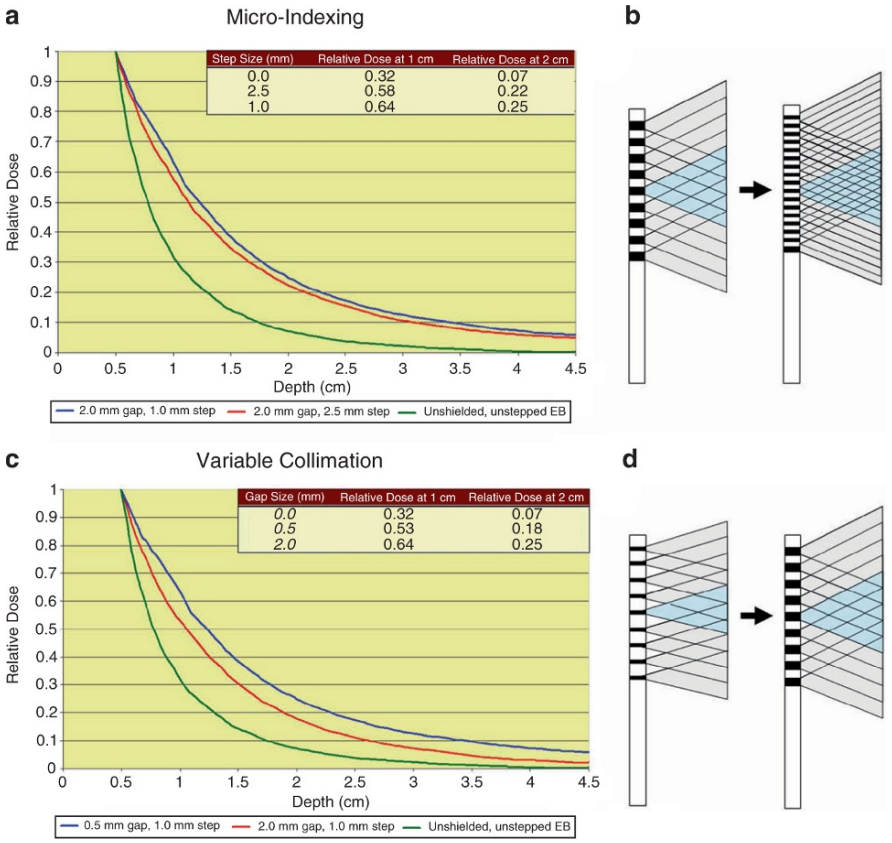

Fig. 24.12a–d Depth dose modulation (DDM) for the 50 kV EBT source. **a** Measured relative depth dose of a collimated source without indexing and with indexing at 2.5 mm and 0.5 mm step sizes. **b** Schematic demonstrating the effect of microindexing. With decreasing step size, there is an increase in the number of overlapping collimated beams, resulting in an increase in relative dose at depth. **c** Measured relative depth dose of an uncollimated source and a source with 0.5 mm and 2 mm collimation. **d** Schematic demonstrating the effect of collimation. With increasing angle of the collimated beam, there is an increase in the number of overlapping beams, resulting in an increase in relative dose at depth. Reproduced from Hiatt et al. (2008) with permission

system consists of three components (Fig. 24.13): (a) a mammography unit (for breast immobilization and image-guided targeting); (b) a digital cassette radiograph image recording system; (c) a series of tungsten-alloy applicators designed to accommodate any commercially available HDR ^{192}Ir remote afterloading device.

24.3.1 Why is Image-Guided Noninvasive Breast Brachytherapy Therapy Desirable?

The benefit of boost irradiation in women undergoing breast-conserving therapy has been sup-ported by two prospectively randomized trials (Bartelink et al. 2001; Romestaing et al. 1997).

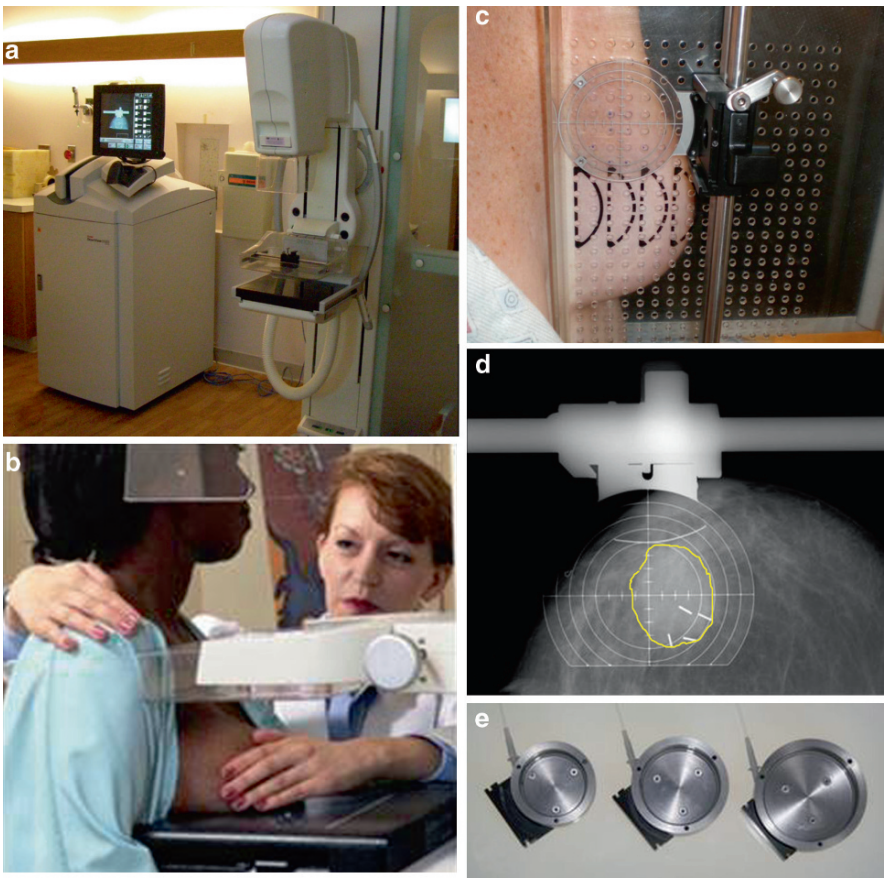

Fig. 24.13a–e AccuBoost System for partial breast irradiation: **a** mammography-based immobilization and imaging unit; **b** breast compression and immobilization plates; **c** targeting grid; **d** digital localization radiograph demonstrating tumor bed and brachytherapy applicator targeting grid, and; **e** tungsten HDR ^{192}Ir brachytherapy applicators (various sizes). Reproduced with the permission of Advanced Radiation Therapy Inc.

As such, the use of a tumor bed boost as part of conventional whole breast irradiation is a generally recommended practice, but no standard boost technique has been established. Clearly, for a boost field to contribute to maximum tumor control, the treatment field must accurately encompass the postoperative tissue at risk. The traditional method of boost planning is a remarkably unsophisticated process guided primarily by the location of the surgical scar, physical examination, clinical and operative notes, and patient recollection. Most typically, this consists of centering the electron field on the surgical scar with a 2–3 cm margin (scar-based planning). Several studies have clearly shown that scar-based planning will miss all or part of the intended target volume in over 50% of cases (Oh et al. 2006; Benda et al. 2003; Bedwinek 1993; Harrington et al. 1996). In the EORTC boost versus no boost randomized trial, scar-based boost planning resulted in late local failure rates as high as 20% in one patient subgroup, suggesting that clinical results can be markedly improved with more accurate boost targeting.

With respect to APBI, AccuBoost can reduce the volume of irradiated breast as compared to commonly practiced external-beam 3D-CRT techniques. While appealingly simple to implement, 3D-CRT APBI requires a PTV expansion of 2.5 cm to account for intra- and interfraction targeting inaccuracy due to respiratory motion and daily set-up error. The need for such expansive margins was illustrated by White et al. (2007), who evaluated interfraction positional accuracy for external-beam breast irradiation using daily cone beam imaging. They found that an average margin of 8.8 mm was needed just to account for daily set-up error when using skin markings alone. In general, brachytherapy techniques (interstitial or balloon catheter) for APBI result in far less normal tissue exposure due to a markedly reduced PTV as compared to commonly employed 3D-CRT techniques. By virtue of breast immobilization (through mild compression) and precise targeting confirmed by image guidance, AccuBoost appears to have attractive dosimetric properties that could serve as a noninvasive brachytherapy alternative to APBI delivered by external-beam 3D-CRT (Fig. 24.14).

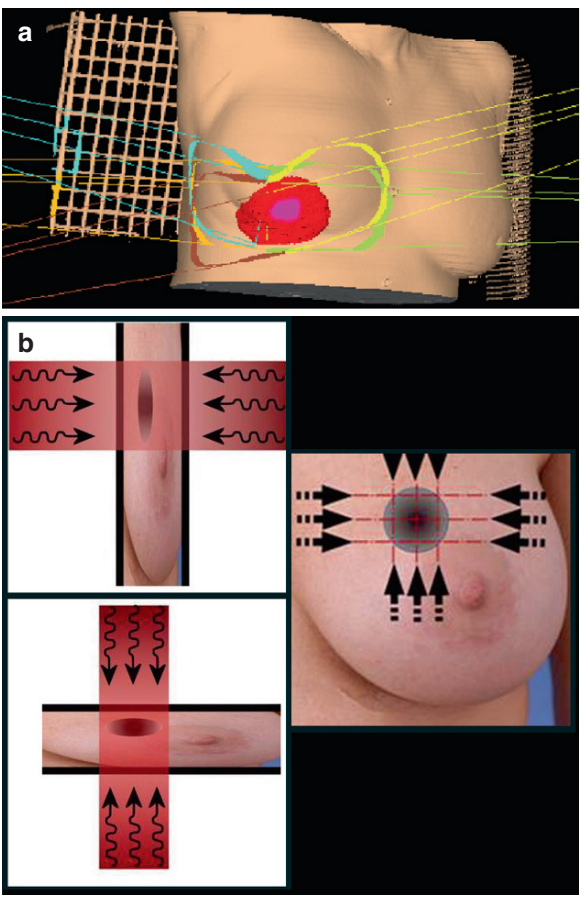

Fig. 24.14a–b Comparison of APBI techniques. **a** 3D-CRT technique using a five noncoplanar beam arrangement. *The purple contour* denotes the tumor bed, which is expanded by 1.5 cm to create the clinical target volume (CTV) and an additional 1 cm to create the planning target volume (PTV), denoted here by the *red contour.* The surface path of each beam is also shown. **b** AccuBoost using parallel opposed mediolateral (ML) and craniocaudal (CC) axes compression. This technique helps to minimize the volume of normal, nontarget breast tissue within the irradiation field

24.3.2 AccuBoost Applicators and Dosimetry

The AccuBoost applicator is constructed of a tungsten-alloy shell with a circumferential channel where a HDR remote afterloading ^{192}Ir source can be directed to predetermined dwell positions (Fig. 24.15). This applicator configuration collimates the ^{192}Ir photon emissions into a directional beam. Several applicator sizes and shapes are available. Figure 24.16 depicts the depth–dose profile of a single applicator. Treatments are delivered with a parallel opposed technique along the mediolateral (ML) and craniocaudal (CC) axes. This "two axes" technique distributes the entry and exit doses over both the ML and CC compression fields such the total accumulated dose at the target is 30–70% higher than that delivered to the skin; see Fig. 24.17. Relative to other brachytherapy techniques, the dose distribution within the target volume is remarkably uniform, resulting in a dose homogeneity index (DHI) that approaches 1.0. Further, the AccuBoost system achieves a high level of target dose conformity. In most cases, greater than 95% of target coverage is associated with less than 20% of the normal breast volume receiving more than 50% of the prescription dose. The extent of normal tissue sparing is likely underestimated by conventional three-dimensional dose–volume analyses, as the breast compression used for immobilization results in marked displacement of nontarget breast tissue outside of the radiation field that cannot be adequately accounted for in current calculation models. Further, in contrast to en-face electron beam and some balloon catheter brachytherapy techniques, AccuBoost

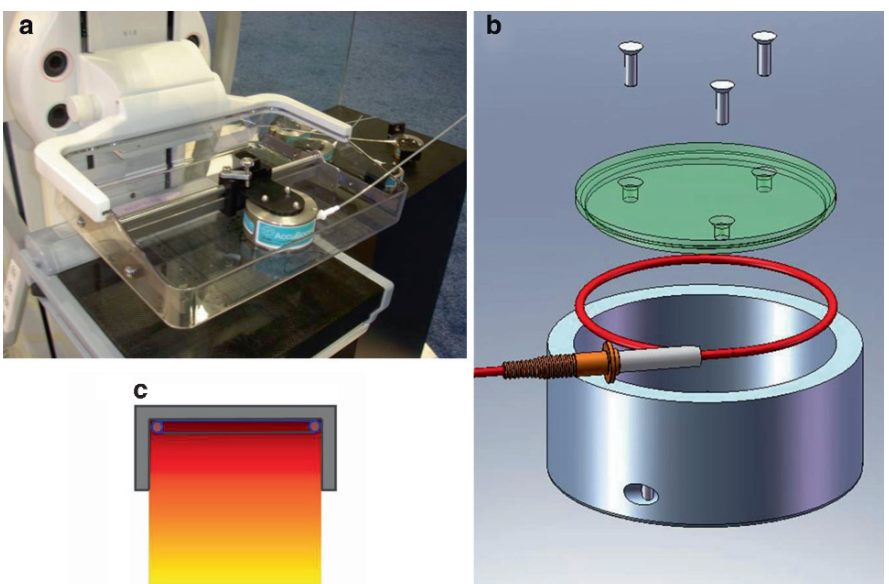

Fig. 24.15a–c AccuBoost HDR ^{192}Ir applicator. **a** Applicator position on the breast immobilization plate and targeting grid. **b** Schematic of applicator design demonstrating the circumferential channel for HDR source dwell positions. **c** Schematic cross-section of the applicator and the resulting collimated photon emissions. Reproduced here with the permission of Advanced Radiation Therapy Inc.

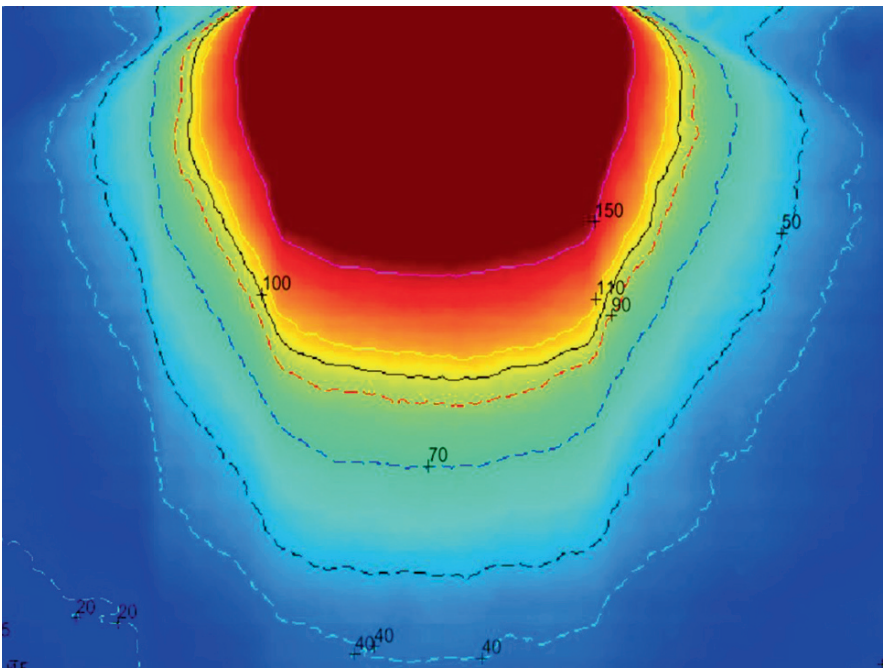

Fig. 24.16 Cross-section of the measured dose distribution as a function of depth for a single, unopposed 6 cm applicator. *Isodose lines* correspond to percent of prescription dose. Reproduced from Rivard et al. (2007) with permission

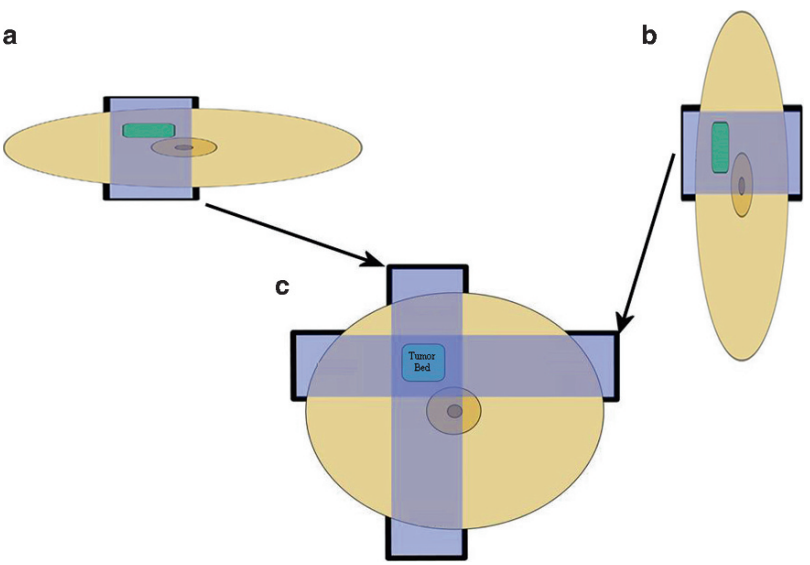

Fig. 24.17a–c Parallel opposed applicator technique using craniocaudal (CC; **a**) and mediolateral (ML; **b**) axes to minimize skin dose and volume of irradiated normal tissue (**c**)

confines irradiation to the CC and ML treatment axes such that the incidental doses to the chest wall, heart, and lung are negligible.

An additional aspect of the AccuBoost system is that since imaging and dose delivery share a common platform, the image recording plate can be used to record the delivered treatment. Thus, a complete dose map of each treatment fraction can be generated, resulting in practical dose-guided radiation therapy (DGRT).

24.3.3 Indications/Patient Selection

AccuBoost is indicated for tumor bed boost in conjunction with whole breast radiation therapy or for APBI as an alternative to external-beam 3D-CRT techniques. In addition to the usual selection criteria for breast-conserving treatment or APBI, patients must also generally meet the following criteria:

(a) The tumor bed must be readily identifiable on mammography (in most cases with the assistance of radiopaque markers)
(b) The PTV in the compressed breast must be fully encompassed by the available applicator sizes and shapes
(c) The breast should be compressible such that the imaging/target localization plates are separated by 7 cm or less

Contraindications for the use of AccuBoost include:

(a) The patient cannot tolerate mild breast compression
(b) The imaging/target localization plate separation is greater than 7 cm
(c) The PTV cannot be adequately encompassed by available applicator sizes and shapes

24.3.4 Special Circumstances

24.3.4.1 Asymmetric Tumor Margin Proximity to the Lumpectomy Specimen

The precise image guidance of the AccuBoost system allows for more sophisticated incorporation of "tumor mapping" information obtained from lumpectomy specimen orientation, marking, and measurement of margin width compared with current boost or APBI techniques. For example, if tumor proximity to the specimen margin edge is confined to a single geographic region, the AccuBoost applicator can be accurately positioned so as to cover the residual tissue at greatest risk (Fig. 24.18). Additionally, AccuBoost can readily weight the relative radiation dose toward the residual tissue at the greatest risk for harboring microscopic tumor foci by simple asymmetric weighting of the source dwell times within the applicators. The DGRT capabilities of AccuBoost then allow for such a customized treatment delivery to be verified through a precise dose map of each fraction.

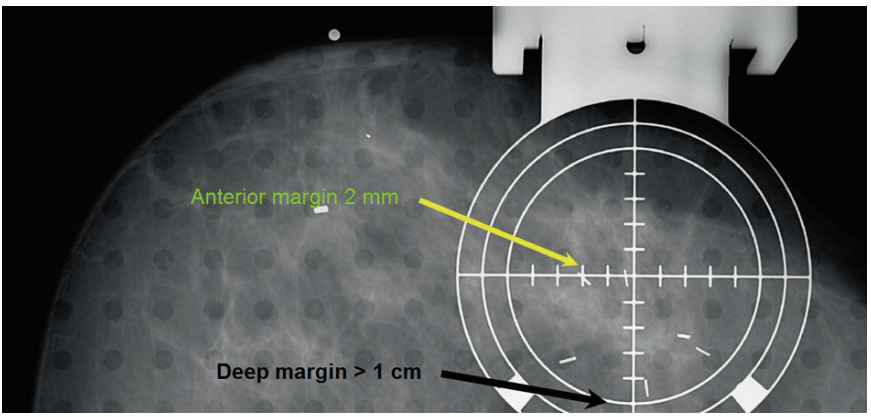

Fig. 24.18 Localization radiograph demonstrating eccentric applicator placement for a patient with widely negative posterior and close anterior pathologic specimen margins. Reproduced here with the permission of Advanced Radiation Therapy Inc.

24.3.4.2 Tumor Bed Close to the Chest Wall

When the tumor bed is deeply situated in the breast and is close to the pectoralis fascia, a "D" shaped applicator is available to facilitate positioning and treatment (Fig. 24.19).

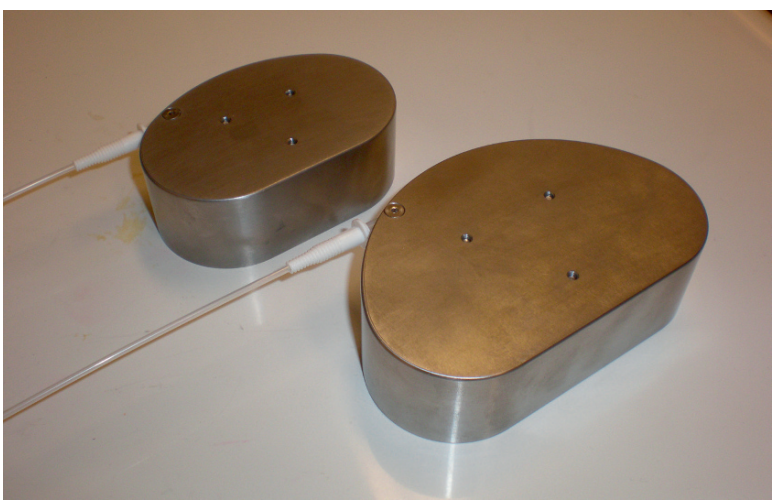

Fig. 24.19 "D"-shaped brachytherapy applicators for deep tumor beds abutting the chest wall. The D45 and D60 applicators are shown

24.3.4.3
Small Breast, Close Proximity to Skin, or Subareolar Location

Small breast size, a tumor bed in close proximity to the skin, and a target in a subareolar location are all generally amenable to treatment with AccuBoost. The applicators can be positioned eccentrically at the edge of the breast, resulting in a "flash" of the treatment beam beyond the tissue edge. The resultant dose distribution throughout the target volume (including at the skin surface) is remarkably consistent, within 4%, compared with the dose distribution in the absence of the "flash" (Fig. 24.20) (Rivard et al. 2008).

24.3.5
Conclusion

The AccuBoost system is a noninvasive brachytherapy alternative for tumor bed boost or APBI which allows for precise dose delivery via breast immobilization and daily image guidance. The system achieves target conformity comparable to that seen with invasive brachytherapy, yet it provides a dose homogeneity comparable to that delivered by external-beam 3D-CRT techniques.

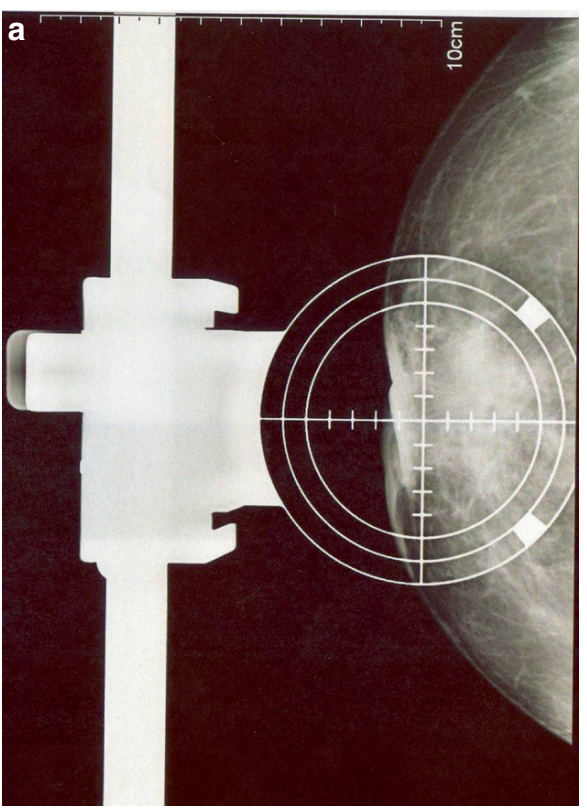

Fig. 24.20a–b Eccentric applicator placement for a superficial tumor bed. **a** Localization radiograph showing eccentric applicator placement with a skin "flash" for a patient with a superficial tumor bed

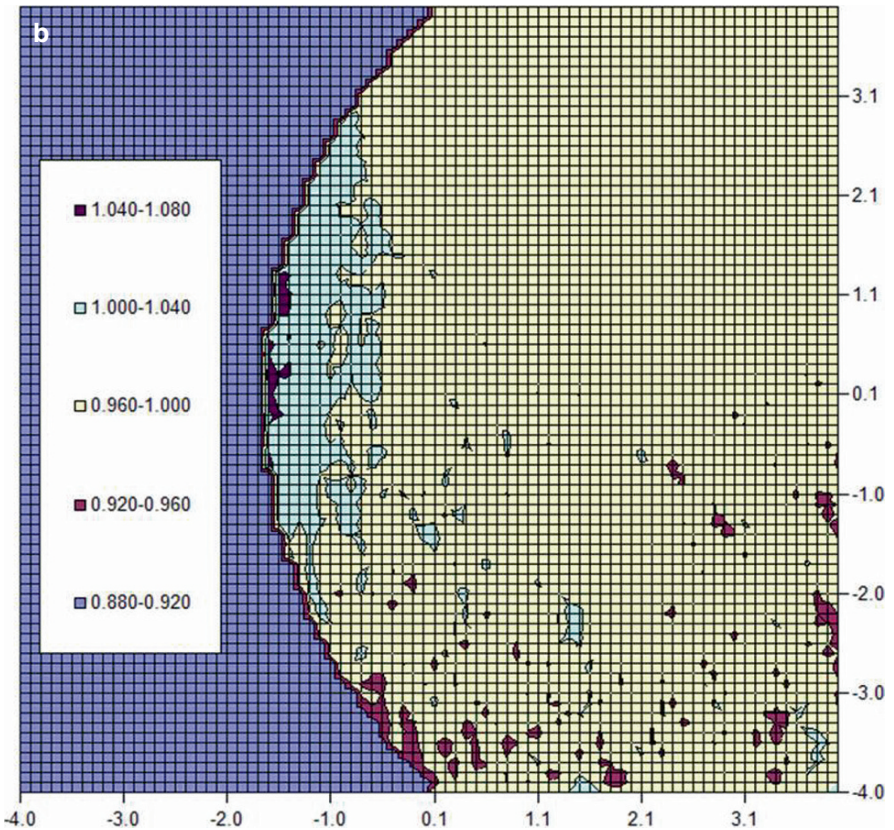

Fig. 24.20a–b (continued) **b** Monte Carlo dose modeling of an eccentric applicator placement with a skin flash. The dose modeling demonstrates a highly consistent dose distribution (±4%) throughout the target volume in the presence and absence of the skin flash. Reproduced from Rivard et al. (2008) with permission

24.4 Alternative Radionuclides

Novel radionuclides and delivery systems with putative advantages for APBI are being explored. Permanent breast seed implant (PBSI) with ^{103}Pd is discussed in depth in Chap. 15. We will briefly describe intraoperative avidination for radionuclide therapy (IART) with ^{90}Y.

24.4.1 Intraoperative Avidination for Radionuclide Therapy (IART)

This novel approach to targeted therapy consists of two steps. The first is "avidination" of the target area, with avidin injected by the surgeon into and around the tumor bed at the

time of lumpectomy. The second is the targeting of the avidin-marked tumor bed with an intravenous infusion of radiolabeled biotin. Avidin is a glycosylated glycoprotein that has a high affinity for biotin. Avidin is retained at the injection site for several days. Biotin can be easily labeled with ^{90}Y to create ^{90}Y-DOTA-biotin. ^{90}Y is a suitable radionuclide for targeted therapy. It is a pure β emitter with a short half-life ($t_{½}$ = 64.1 h) and a long penetration range in tissue (R_{max} = 11.3 mm). Paganelli et al. (2007) reported a feasibility study where this technique was used with ^{111}In-DOTA-biotin and scintigraphic imaging to determine dosimetry and pharmokinetics in ten early-stage breast cancer patients. The uptake of radiolabeled biotin in the tumor bed was rapid and long-lasting. BED-corrected doses to the tumor bed of 20 Gy could be delivered with a 3.7 GBq (100 mCi) ^{90}Y-DOTA-biotin infusion. Doses absorbed systemically were very low, except for the kidney and bladder, where labeled biotin is excreted.

This technique is an interesting targeted approach to partial breast irradiation. However, the major limitation is the dose delivered to the urothelial tract, which prevents this technique from being used as a sole modality for breast treatment. It is, therefore, being evaluated as a boost technique that is combined with a shortened course of external-beam irradiation in order to accelerate breast treatment.

24.5 Conclusion

Many new and exciting approaches to partial breast irradiation are being explored. Miniature electronic brachytherapy sources have a capacity for dose sculpting that was not previously possible with traditional radionuclide sources. The AccuBoost system delivers treatment with precise immobilization and daily image guidance, thus eliminating delivery and set-up uncertainty. Intraoperative avidination uses molecular targeting for tumor bed irradiation. These advances are expanding the options that may define the way partial breast irradiation is delivered in the future.

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