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Jacob Ramon
Louis J. Denis
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Prostate Cancer

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J. Ramon · L. J. Denis (Eds.)

Prostate Cancer

With 47 Figures and 43 Tables

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Preface

Prostate cancer treatment dates back almost 100 years. However, in an era of rapid developments and innovations in cancer research and uro-oncology, there is an increasing need to update our knowledge and especially to guide our practice by innovations and evidence-based medicine. Prostate cancer is still evolving following improvements in disease detection and better understanding of disease characteristics. This book addresses the current state of the art in this still-developing field and presents the reader with the information needed to make rational patient decisions regarding treatment selection and outcomes.

The growing body of knowledge regarding epidemiology, pathogenesis, prevention, screening, diagnosis and staging is included in the first half of the book.

To determine the most appropriate treatment regimen for a prostate cancer patient, it is important to asses the individual's risk factors. Patient characteristics are one important factor in determining optimal therapy. Efficacy and survival benefits need to be balanced against the patient's quality of life.

When diagnosed with prostate cancer, the patient and his physician have to choose from a wide range of therapies. Treatment can be deferred until progression or until symptoms appear (watchful waiting) or in indolent cancer until curative treatment is indicated (active surveillance). The wide choice of treatment includes radical prostatectomy (open or laparoscopic), radiotherapy (interstitial or external), cryoablation, high-intensity focused ultrasound and hormonal therapy. The choice of therapy may influence survival as well as the risk of therapy-induced side effects.

To guide urologists and their patients with prostate cancer in the selection of an appropriate treatment, the evidence surrounding current treatment approaches is examined in the subsequent chapters of this volume.

The text addresses the time-honoured hormonal treatment, which has been the mainstay of prostate cancer management for some decades. Due to the increased diagnosis of prostate cancer at earlier stages and the increased use of hormone therapy in earlier disease stages many patients will receive hormone therapy for a long period. These patients are at risk of acute and chronic side effects of hormonal therapy. Therefore, the timing of initiating hormone therapy, the type of hormone therapy and the monitoring of patients on long-term hormone therapy have become crucial in the appropriate management of patients with prostate cancer.

Disease management in men with prostate cancer has recently expanded to include maintenance of bone health. The role of urologists in the management of patients with bone metastasis is changing. Symptom control and quality of life are the priorities for patients with metastatic disease. For patients with metastatic hormone-refractory prostate cancer (HRPC), there have been relatively few advances recently in terms of survival and quality of life.

In this book, therefore, we have covered in detail the main aspects of current prostate cancer management, and we believe we have created a comprehensive yet readable account of this rapidly expanding and fast-changing area. We hope that it will be of value to all those who are involved in prostate cancer treatment.

Finally, we would like to thank the contributors, together with all the staff of Springer, without whose hard work and devotion this book would not have been completed.

Jacob Ramon, MD
Louis J. Denis, MD

International Prostate Health Council

The International Prostate Health Council (IPHC) was established more than a decade ago as an independent, non-governmental, non-profit organization. Its main goals include assessment of the current knowledge base and practice pattern of physicians concerned with prostate disease, assessment of the level of awareness of these diseases on the part of the public, and the creation of worldwide educational programmes and resource materials for urologists, medical and radiation oncologists, primary care physicians and allied health workers.

This monograph, produced at the invitation of the editors of the prestigious Springer series Recent Results in Cancer Research, presents the latest information for the care of prostate cancer in a general clinical setting. IPHC is an active and dedicated believer in multi-professional collaboration to offer the best treatment and care for patients. For this reason we invited experts from outside the council to provide the reader with updated information on optimizing patient care and treatment. We are grateful for their contribution, which is yet another small step in facilitating the educational process aimed towards knowledge and treatment of complex prostate diseases.

In the spirit of modern health-care communication, we include the voice of Europa Uomo, the European Prostate Cancer Coalition, to inform readers of the coalition's vision and mission. We hope the present manuscript addresses most of our readers' needs.

Louis J.Denis
Chairman IPHC

Contents

1 **Epidemiology of Prostate Cancer** 1
Vera Nelen

2 **Natural History of Prostatic Carcinoma: The Pathologist's Perspective** 9
Ferran Algaba, Isabel Trias, Yolanda Arce

3 **Prognostic Factors in Prostate Cancer** 25
Johan Braeckman, Dirk Michielsen

4 **The Prevention of Prostate Cancer** 33
Keith Griffiths, Domenico Prezioso, A. Turkes, Louis J. Denis

5 **Prostate Cancer Screening** 65
P. Tenke, J. Horti, P. Balint, B. Kovacs

6 **Diagnosis of Prostate Cancer** 83
Jehonathan H. Pinthus, Dalibor Pacik, Jacob Ramon

7 **Does Localized Prostate Cancer Exist?** 101
Bernard Lobel

8 **Staging of Prostate Cancer** 109
Zohar A. Dotan, Jacob Ramon

9 **Guidelines and Counselling for Treatment Options in the Management of Prostate Cancer** 131
Axel Heidenreich

10 **Choices for Surgery** 163
Stéphane Larré, Laurent Salomon, Claude Clément Abbou

11 **Radiation Therapy in Prostate Cancer** 179
Moshe E. Stein, Dirk Boehmer, Abraham Kuten

12 **Cryoablation and High-Intensity Focused Ultrasound** 201
Chris D'Hont

13 **The Role of Hormonal Treatment in Prostate Cancer** 211
Stephan H. Flüchter, Ralf Weiser, Christoph Gamper

14 **Androgen-Independent Prostate Cancer** 239
Dirk Schrijvers

15 **Prostate Cancer Treatment and Quality of Life** 251
Domenico Prezioso, Raffaele Galasso, Mario Di Martino, Gennaro Iapicca

16 **Europa Uomo: The European Prostate Cancer Coalition** 267
Tom Hudson, Louis J. Denis

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1 Epidemiology of Prostate Cancer

Vera Nelen

Recent Results in Cancer Research, Vol. 175

Abstract

Prostate cancer is one of the most important cancers in men. With a worldwide incidence of 25.3 per 100,000 it is the second most common cancer in men, with large differences between countries. Important clues on risk factors remain to be found. Age, genetic factors and environmental influences have been studied. Incidence has been increasing over the last few decades, largely due to early detection procedures. The mortality rate of 8.1 per 100,000 mainly affects men at older ages; increases in this rate over time and differences between countries are markedly smaller than for incidence. For the future, prostate cancer will remain an important and—through evolutions in incidence and demography—growing health problem.

Introduction

The burden of cancer can be expressed in three measures: incidence, mortality and prevalence. Incidence is the number of new cases occurring in a population per year and can be expressed as an absolute number or as a rate per 100,000 persons. Mortality is the number of deaths occurring and can also be expressed as a rate per 100,000 persons per year. Prevalence describes the number of individuals alive with the disease at a certain point in time. In the year 2002, estimates are that 10.9 million new cases of cancer were detected worldwide, 6.7 million people died of cancer and 24.6 million persons were alive with cancer (within 5 years of diagnosis) (Parkin et al. 2005). Figures for Europe for 2004 reveal nearly 2.9 million new cases of cancer and 1.7 million cancer deaths (Boyle and Ferlay 2005). In 2002 about 7.3 million people had cancer in Europe (within 5 years of diagnosis) (Ferlay et al. 2004).

Prostate cancer is already one of the most important cancers in men and is still increasing. Therefore prostate cancer is an important public health topic and the rest of this article will deal with its epidemiology.

Prostate Cancer Incidence

Most recent world figures for prostate cancer date from the year 2002. In that year 679,000 men developed prostate cancer worldwide. The yearly prostate cancer incidence in the world is 25.3 per 100,000, which is an age-standardised rate according to the world population. Since the cancer risk increases with age, and demographics differ widely around the world, rates corrected for age improve comparability. This correction can be done by using a standard age structure called age standardisation. Of new cancer cases, 11.7% are prostate cancers. This makes prostate cancer the fifth most common cancer and the second most common cancer in men (Parkin et al. 2005).

In Europe 238,000 men developed prostate cancer in 2004, this is 15.5% of newly diagnosed cancer cases in men. Prostate cancer is the second most frequent cancer in European men, after lung cancer. It is, however, the most common cancer in men living in the European Union, comprising 18.1% of all incident cases. The lifetime risk (0–74 years) of developing prostate cancer in the European Union was 5.9% in 2004 (Boyle and Ferlay 2005).

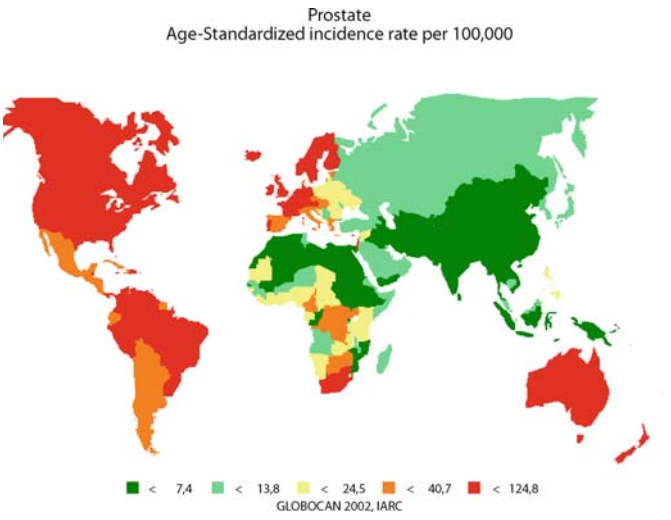

Fig. 1.1 Prostate cancer incidence worldwide, Globocan 2002 (Ferley et al. 2004)

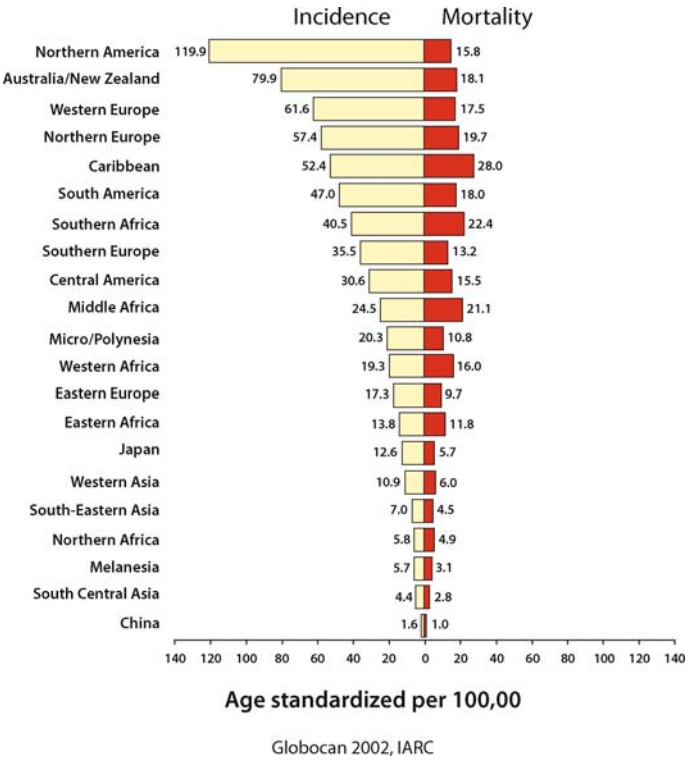

Fig. 1.2 Prostate cancer, age standardized incidence and mortality rates per 100,000 (Parkin et al. 2005)

Prostate cancer incidence differs between continents and from country to country (Figs. 1.1 and 1.2). Incidence is high in the United States, Canada, Australia/New Zealand and Northern and Western Europe. The lowest rates are found in China and other parts of Asia (Parkin et al. 2005).

Very few cases of prostate cancer are found in men under 50 years. Three-quarters of all cases are found in men aged 65 or more, and rates increase steeply with age. It is therefore more common in populations with higher proportions of elderly men. Prostate cancer amounts to 19% of new cases in developed countries and only 5.3% in developing countries (Quinn and Babb 2002). Some part of the variability in the incidence of prostate cancer is due to a different age structure in the populations, but large variability remains after age standardisation.

Latent cancer of the prostate, the slow growing intraprostatic microscopic foci of well-differentiated cancer cells, is comparatively common in men of all ethnic groups. These cancers are mostly discovered in autopsy or on microscopic examination after prostatectomy for benign prostatic hyperplasia and can influence incidence data reported to cancer registries. Nowadays screening of asymptomatic individuals for prostate cancer has become very common in some countries. This causes a temporary increased incidence when cancers are detected sub-clinically. The increase persists if latent cancers that would otherwise not clinically surface—and thus remaining undiagnosed—are discovered by needle biopsies (Schröder et al. 2003a, b). In the United States prostate cancer has become the most common cancer diagnosed in men, with an incidence of 124.8 per 100,000 and presents 33% of all newly diagnosed malignancies in men (Parkin et al. 2005; Quinn and Babb 2002). The lifetime risk for a man to develop prostate cancer in the United States is 1 out of 6 (National Cancer Institute 2006).

Some of the differences between countries might be due to interethnic differences in risk. African Americans have a markedly higher incidence than whites (82.5 versus 49.6 per 100,000). African Americans have a 9.8% lifetime risk of developing prostate cancer compared to 8% in whites. White people have higher rates than Asian origin populations (Chinese 14.9, Japanese 16.5) (Prezioso et al. 2004). Similarly in Brazil the risk for black males was 1.8 times that of whites (Parkin et al. 2005).

Incidence can be influenced by several risk factors including genetic susceptibility, environmental exposure in its largest sense and differences in health care and cancer registration (or a combination of the these). More data on risk factors will be discussed later in this chapter.

Prostate Cancer Mortality and Survival

Mortality rates are based on incidence and fatality—the inverse of survival—of a cancer and reflect prognosis. Prognosis for prostate cancer is relatively good. With 221,000 deaths worldwide in 2002 it is a less prominent cause of mortality than might be expected consider the incidence. Mortality per year is 8.1 per 100,000 (age standardised according to the world population) (Parkin et al. 2005). Prostate cancer is responsible for 3.3% of all cancer deaths and 5.8% of cancer deaths in men.

In Europe in 2004, 85,000 men died of prostate cancer, 8.9% of cancer deaths in men. The lifetime risk (0–74 years) of dying from prostate cancer in the European Union was 1.1% in 2004 (Boyle and Ferlay 2005).

Mortality rates for cancer in general differ less between developing and developed countries than incidence rates. For men, total cumulative mortality for all cancers before age 65 is 18% higher in developed countries. Differences in incidence are much larger. There are several reasons for this. A large group of cancers that frequently occur in developed countries and are associated with a Western lifestyle have a good prognosis: colon, rectum, breast and prostate cancer. Cancers of liver, stomach and oesophagus are more common in developing countries and have a poor prognosis. Prognosis in general is poorer in developing countries and the ratio of deaths to cases is less favourable, especially for cancers where early detection and treatment have an impact on prognosis (Parkin et al. 2005).

Mortality as a result of prostate cancer differs considerably around the world, but the differences are also much smaller than for incidence

(Quinn and Babb 2002). Survival for prostate cancer is better in high-risk countries: 87% in the United States versus 45% in developing countries. These figures are modified by inflation of incidence through early detection programmes that may cause lead-time and length-time bias, and by treatment effects. Since prostate cancer is a disease of the elderly, survival is impacted by co-morbidity with increasing age (Coebergh et al. 1999; Houterman et al. 2005). A Dutch study showed 51% co-morbid conditions in prostate cancer patients (Coebergh et al. 1999). Cancer-specific mortality is therefore variable by age. A Swedish study showed an 80% risk of dying of prostate cancer if diagnosed before age 60 years, 63% risk if diagnosed between 60 and 69, 53% for ages 70 to 79 and 49% for ages 80 and older (Grönberg et al. 1997).

The average 5-year survival for prostate cancer in Europe in the early 1990s was 67%. It varied across Europe from less than 40 to more than 80% with lowest rates in Eastern Europe, the United Kingdom, Denmark, Malta and Portugal and highest in Austria, Iceland, Germany and France (Fig. 1.3) (Coleman et al. 2003; Sant et al. 2003). In the United States relative 5-year survival for prostate cancer increased to 99.8% in the period 1995–2001 (Surveillance, Epidemiology, and End Results Program 2006).

Crude mortality rates for prostate cancer are an indication for the presence of invasive cancers in a population. Mortality rates are high in the Caribbean, Southern and Central Africa, Northern and Western Europe, Australia/New Zealand and North and South America. They are low in Asia and North Africa (Fig. 1.2). In particular,

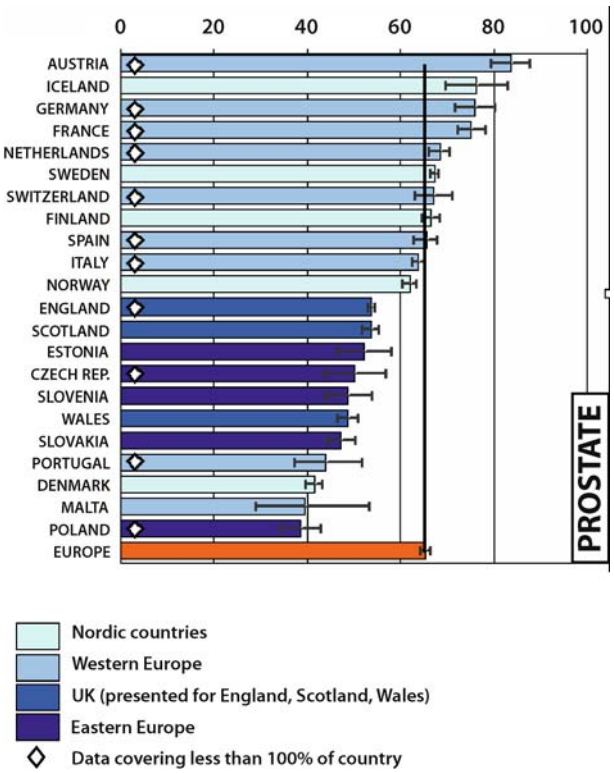

Fig. 1.3 Five-year survival (%) from prostate cancer, by country, Europe: age-standardised relative survival, adults (15–99 years) diagnosed in the period 1990–1994 and followed up to 1999 (Coleman et al. 2003)

prostate cancer mortality in the USA was not very different from levels in other developed countries despite the difference in incidence, suggesting that a large proportion of cancers in the USA have a good prognosis. However, mortality in Singapore, Japan, India and China was lower than in other countries and consistent with the pattern of incidence (Quinn and Babb 2002).

Prostate Cancer Prevalence

Since the number of men having prostate cancer at a certain point in time and within a certain period from diagnosis depends on both incidence and survival, it can differ largely between regions. The world prevalence, 5 years from diagnosis, in 2002 was 2,368,700 cases. Following breast (17.9%) and colorectal cancer (11.5%), prostate cancer is the third most prevalent cancer worldwide, with 9.6% of cases (Parkin et al. 2005).

Prevalence in Europe was 740,000 in 2002 and shows marked differences between countries (Fig. 1.4) with the highest prevalence of 600 per 100,000 in Sweden contrasted with the lowest, 40 per 100,000, in Poland (Quinn and Babb 2002; Ferlay et al. 2004).

Prostate Cancer Incidence and Mortality: International Trends

Until the 1980s the rates of prostate cancer were gradually increasing, partly due to a genuine rise in risk, partly due to detection of asymptomatic cancers by the increasing use of transurethral resection of the prostate (TURP) for treatment of benign prostate hyperplasia (BPH) (Quinn and Babb 2002). With the introduction of prostate-specific antigen (PSA) testing in the 1980s and improved awareness of the disease there was a huge rise in incidence, especially in localised disease. The largest increases in incidence were observed in high-risk countries, especially in younger men, but there were also marked increases in China, Japan and Hong Kong (Parkin et al. 2005; Newcomer et al. 1997; Mettlin 2000; Sim and Cheng 2005). Since 1992–1993, incidence in the United States has been decreasing, although it remains higher than in 1986.

The average increase in age-adjusted incidence worldwide from 1985 to 2002 was about 1.1% annually. A continued increase with this magnitude will lead to almost 900,000 new cases of prostate cancer annually by the year 2010 (Parkin et al. 2005). Even without changes in age-spe-

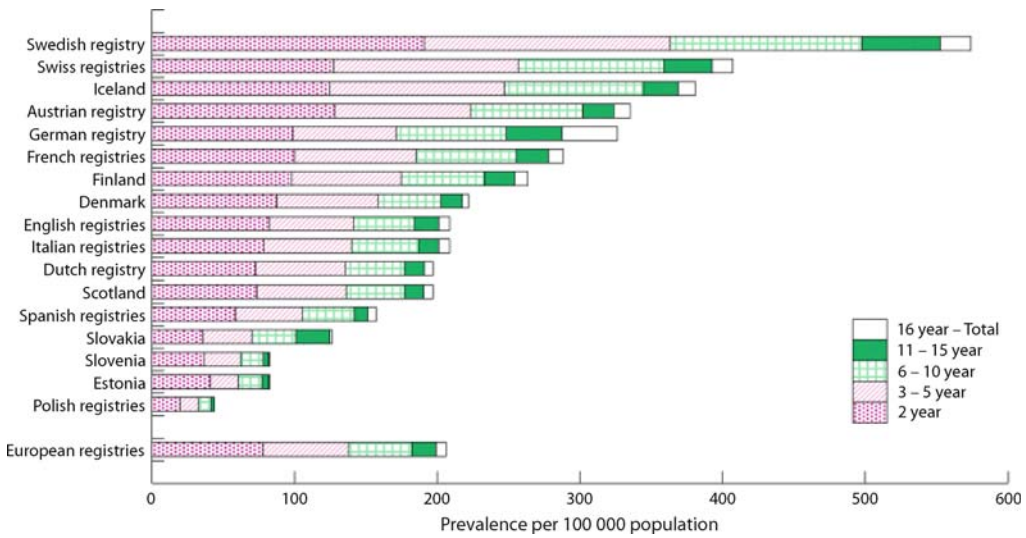

Fig. 1.4 Prevalence of prostate cancer in European countries by time since diagnosis, 1992 (Quinn and Babb 2002)

cific incidence and mortality, numbers in Europe and other developed countries will continue to rise due to ageing of the population (Quinn et al. 2003). Prostate cancer therefore remains a large and growing health problem.

Mortality rates for prostate cancer increased until the 1980s, but less marked than incidence, averaging 2%–8% every 5 years (Stanford et al. 1999). Especially in countries with the highest incidence increases, mortality rates did not follow the same pattern. Since the 1990s mortality declined in several developed countries as a consequence of decreased diagnosis of distant-stage disease and improved treatment (Parkin et al. 2005; Hsing et al. 1999; Newcomer et al. 1997; Mettlin 2000; Schröder et al. 2003b).

In the European Union mortality for prostate cancer increased from 1980 to 1993 (from 13.9/100,000 to 15.7/100,000). From 1993 to 1999 the rate declined approximately 10% to 14.1/100,000. These trends were mainly observed in the elderly and rates in the EU have remained stable for men below age 65 (Levi et al. 2004). Predictions for age-standardised rates mention a continuing 11% decrease by 2015, although timing and the extent of the decreases vary widely among countries. The number of cancer deaths in the European Union, however, will increase in the future when the older age groups—where incidence and mortality rates are the highest—will become proportionally larger. By the year 2015 there will be a 20% increase of people aged 65 years and older and 50% more people will be 80 years and over. This demographic shift alone results in a 25% increase in predicted cancer deaths. The effect of the demographic shifts towards the elderly outweighs that of decreasing trends in mortality rates in the predictions of mortality towards 2015 (Quinn et al. 2003). For prostate cancer, which mainly involves the elderly, these trends will be important.

Prostate Cancer Risk Factors

Large clues on risk factors for prostate cancer are still to be found. Notions on this subject are, however, important because they offer the possibility for primary prevention of the disease.

Prostate cancer is probably the result of a combination of factors. One of them is age. Prostate cancer rates increase with age faster than many other cancers. Autopsy studies show that histological cancer also increases with age, presenting 15%–30% in men older then 50 years and 60%–70% in men older then 80 (Pienta and Esper 1993). Although the incidence of clinical prostate cancer varies greatly around the world, this is not the case for histological cancer. The age-specific incidence of histological cancer is the same in the United States and Japan, while clinical incidence differs largely. These data suggest that the initiation of prostate cancer is the same around the world, and related to age. Differences between countries exist in progression to clinical cancer, which is related to other risk factors. Migration from low-risk to high-risk areas in the world evokes a marked increase in incidence in these populations and supports this theory. Prostate cancer incidence in Chinese and Japanese men respectively rose from 1.8 and 5.1 to 14.9 and 16.5 when migrating to North America (Prezioso et al. 2004).

Other risk factors include genetic factors. Several studies show an increased risk (Odd's ratio's from 2–6) for clinical prostate cancer in men with affected relatives (Steinberg et al. 1990; Cancel-Tassin and Cussenot 2005); concordance was reported higher for monozygotic versus dizygotic twins (4 versus 19%) (Grönberg et al. 1994) and large variations in prostate cancer incidence have been noticed in different ethnic groups. African Americans have higher incidence rates than white Americans of similar education and socio-economic background (Baquet et al. 1991).

Environmental risk factors in the widest sense were suggested: cigarette smoking, alcohol consumption, cadmium exposure, occupation, infectious agents, ionising radiation, ultraviolet light, physical activity, body mass index and dietary factors (Stanford et al. 1999). Most arguments are found for the relation with dietary fat. High intake of dietary fat seems to be related to a higher risk for prostate cancer (Sonn et al. 2005; Grönberg et al. 1996). Phyto-oestrogens, present in a soy-rich diet, have been associated with a decreased risk of prostate cancer. The low incidence in Asian countries may partly be explained by effects of a low animal fat and a soy-rich diet (Denis et al. 1999; Magee and Rowland 2004). Positive effects of other dietary factors such as vitamins, minerals and anti-oxidants were suggested but need

further confirmation (Sonn et al. 2005; Quinn and Babb 2002; Stanford et al. 1999; Pienta and Esper 1993). Molecular mechanisms implicated in inflammation of the prostate may provoke adverse cell proliferation and play a role in carcinogenesis (Naber et al. 2004). One study found that the risk of prostate cancer increased with the lifetime number of female sexual partners and with prior infection with gonorrhoea, supporting the influence of infectious agents (Rosenblatt et al. 2001). Studies have shown that prostate cancer is more frequent in regions with less exposure to sunlight. This may be in agreement with vitamin D being protective against cancer (Hanchette and Schwartz 1992; Polek and Weigel 2002).

Several studies report the interaction of endogenous hormones and prostate cancer. Higher levels of serum testosterone are associated with an increased risk of prostate cancer (Parsons et al. 2005). Altered androgynous hormone metabolism may be the cause of the evolution of histological to clinical prostate cancer. Oestrogens are also believed to play a role in the regulatory mechanisms of molecular growth in the prostate. Oestrogen levels, or changed oestrogen/androgen balance, can therefore play a role in the development of prostate disease in general and prostate cancer in particular (Prezioso et al. 2004). The steroid hormone system is a complex regulatory system that is influenced by genetic mechanisms as well as environmental influences (such as dietary fat, phyto-oestrogens, vitamins and smoking) and plays a role in inflammation. Other hormones, such as the insulin-like growth factor (IGF) family, have also been described in the regulation of physiological and pathological processes in the prostate and may play a role in prostate cancer development (Gennigens et al. 2005). The involvement of endogenous hormones would explain why unravelling the risk factors that interact with the development of prostate cancer has been so difficult (Naber et al. 2004; Pienta and Esper 1993).

Conclusion

Clues, derived from risk factors, for primary prevention of prostate cancer remain to be found. Final level arguments, effect on mortality, for the use of screening in the prevention of prostate cancer are expected from the large randomised screening trials to be completed in the near future. Meanwhile prostate cancer remains a large and, through evolutions in incidence and demography, growing health problem.

Epidemiology may be a more esoteric science compared to clinical practice, but studying figures and their patterns over time helps us to improve our understanding of the population's health and the effects of interventions (preventive and curative). In the end, this provides us with clues for individual patient's care.

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2 Natural History of Prostatic Carcinoma: The Pathologist's Perspective

Ferran Algaba, Isabel Trias, Yolanda Arce

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Abstract

The stem (basal) cells of prostate acini are considered the origin of prostate cancer. Between these cells and the final secretory cells, different intermediate or transit cells can be observed, and every one of them can evolve into malignant cells, explaining the biological variability of prostatic cancer. The exact changes between normal gland and prostatic intraepithelial neoplasia (PIN) are not yet known, but a post-inflammatory atrophy lesion is being studied in this respect. The PIN lesion is considered the pre-invasive change of prostatic cancer and its presence in needle biopsy is clinically used for follow-up of the patient. The progressive knowledge of the stromal invasion in prostate cancer (loss of some cell–cell adhesion molecules and expression of others) can be correlated with the Gleason grading system, and the molecular changes in the progression to androgen-independent carcinoma can be used as a prognostic marker in conjunction with the classical pathological markers.

Introduction

Prostate cancer is a glandular malignant neoplasia (adenocarcinoma), mostly of secretory or luminal cells. According to the current notion, the origin of such neoplasia is not to be searched for in the secretory cells (that are final differentiation cells that will disappear after serving their purpose) but in the precursor (or stem) cells with secretory differentiation. This hypothesis (hierarchical or stem cell model) [1] opposes the theory that all neoplastic cells may be tumour-initiating cells (stochastic model), but some isolated evidence exists that questions the hierarchical model [2]. Even so, in order to explain the pathologist's perspective regarding the natural history of prostate cancer, the stem cell (hierarchical) model will be followed.

Morphological and Molecular Structure of Normal Prostate Glands

The histological structure of acini and ducts is identical, probably because the prostate is a sparsely secreting gland, whereas the whole of it should be secretory. The cells that form the gland are arranged in two layers, basal and luminal (Fig. 2.1).

The cells of the basal layer (basal cells) have little cytoplasm and show no microscopic differences between each other. Most of them have growth factor receptors of the growth factors produced by the stromal prostate cells, they lack androgen receptors and they express Bcl-2. These cells are considered the stem cells. A small sub-population of these cells have androgen receptors, which has suggested the possibility that transit (intermediate) amplifying cells bearing stem cell characteristics exist, but the sensitivity to androgen enable them to differentiate to luminal cells (secretory cells), with androgen receptors in all of them [3].

This model is probably an over-simplistic definition of basal and luminal compartments, since the currently existing immunohistochemical tests are capable of stratifying the transit (intermediate) amplifying cells in early progenitors of intermediate stem cells (CK5 and CK18 positive, *c-met* positive, without androgen receptors), as well as in late progenitors of intermediate stem cells (K5 negative, CK18 with irregular expression, *c-met* positive and irregular expression of androgenic receptors) [4] (Fig. 2.2).

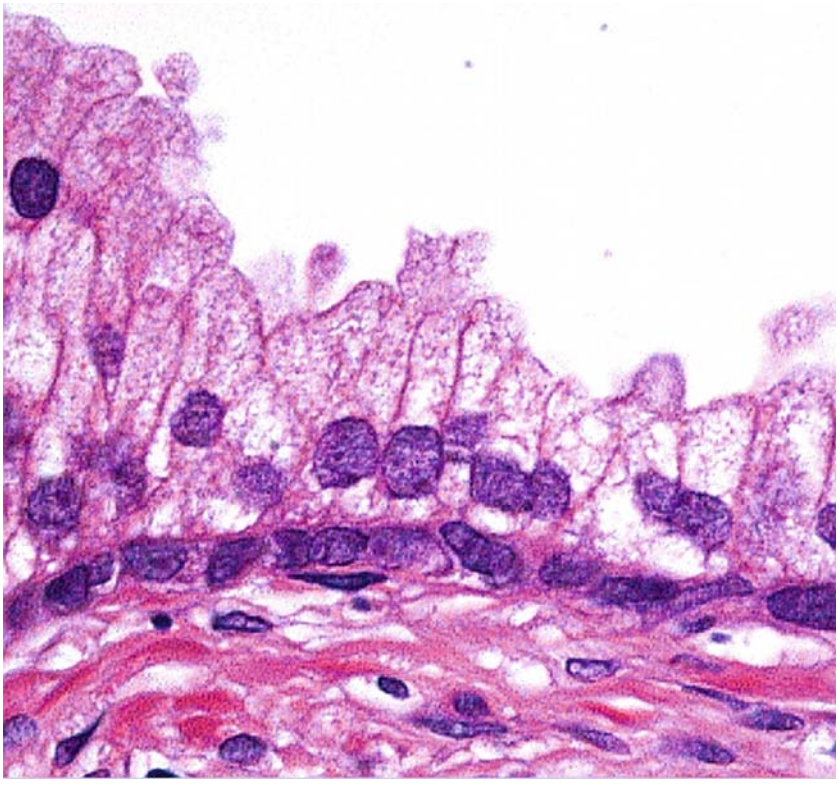

Fig. 2.1 Prostate acini. Basal and luminal cells

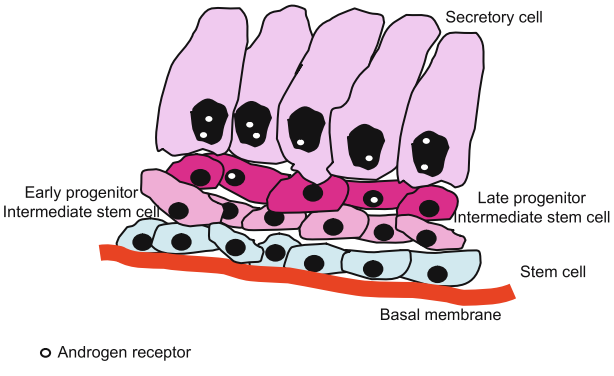

Fig. 2.2 Stem cell model of the normal prostate acini

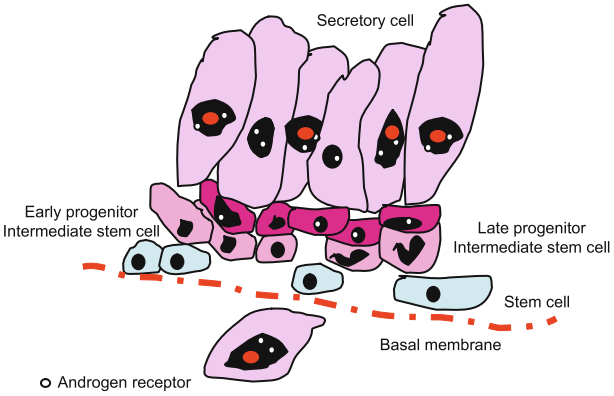

Fig. 2.3 Stem cell model of the malignant transformation of prostate acini, with stem cells loss, malignant transformation of intermediate stem cells and secretory cells. Every one of these cells can be the final differentiation of the prostate cancer, and for this reason the prostate cancer has different phenotypes

Molecular Definition of Tumoural Stem Cells of the Prostate

The problem that arises in the prostate cancer stem cell model is identifying which cells are the target of carcinogenics. It is possible that the early and late progenitors of the intermediate stem cells, rather than the stem cells themselves, justify the heterogeneity of prostate cancer, both regarding the expression of androgen receptors and the phenotypic characteristics [4]. These cells probably represent a minimal percentage of the tumour mass (<0.01%). It is quite difficult to recognise them using the classical methods, and they present with a differential phenotype with high clonogenicity and therapeutic resistances [5] (Fig. 2.3).

Pre-malignant Changes of Prostate Glands

The exact changes between a normal gland and a neoplastic one are not yet known. There is increasing evidence that predisposing genetic factors, oxidative damage and dietary or environmental factors may play a role in this step of the neoplastic transformation [6]. Very recent observations correlate phagocytic inflammatory cells and cancer with the release of oxygen- and nitrogen-based radicals. Together with dietary factors, this leads to oxidative stress and causes cell injury and regeneration with potential expansion of early or late progenitor intermediate cells [7].

The above-mentioned observations have suggested that gland dilatations with flattening of the secretory epithelium, previously considered secretory cell atrophy unrelated to the hormonal status (Fig. 2.4), could be re-interpreted differently when confirming that there may be surrounding lymphocytes, and that the apparent atrophic morphologic appearance is not consistent with its functional status due to the expression of bcl-2 (anti-apoptotic status), ki67 (active proliferative status), decreased expression of p27 (cyclin-dependent kinase inhibitor), and expression of glutathione-*S*-transferase p1 (GSTP1) and cyclooxygenase-2 (COX-2), all of them potential signs that these cells are subjected to oxidative stress [8]. For this reason these changes [globally called proliferative inflammatory atrophy (PIA)] are considered the kind of lesions that are potential precursors of prostatic intraepithelial neoplasia [9]; however, the potential premalignant role of PIA is controversial and the literature shows discrepancies that could be caused either by the weak inter-relation of both lesions or by the lack of homogeneous morphological criteria [10–12].

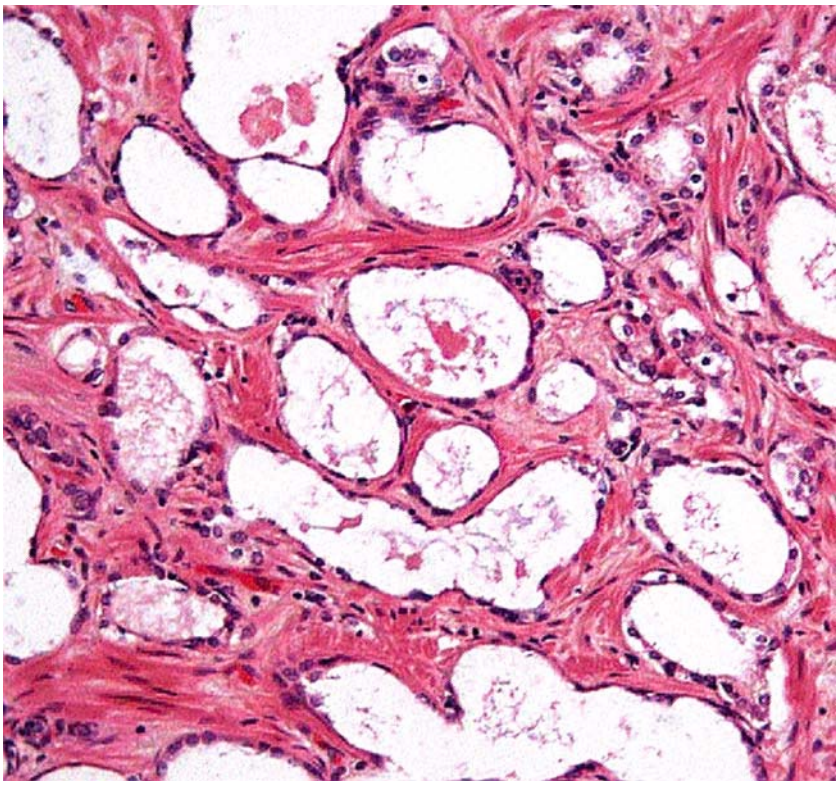

Fig. 2.4 Proliferative inflammatory atrophy (PIA)

Prostatic Intraepithelial Neoplasia

Prostatic intraepithelial neoplasia (PIN) includes lesions characterised by neoplastic nuclear atypia of the luminal cells with (total or partial) persistence of the basal layer and with no evidence of basal membrane rupture [13]. This definition spans from the mildest changes (low-grade PIN) to the most obvious ones (high-grade PIN) (HGPIN) (Fig. 2.5). Due to the poor reproducibility of the low-grade PIN, its diagnosis is usually avoided, and HGPIN is only reflected in the pathology reports [14].

As already mentioned, certain observations topographically relate PIA changes to HGPIN (proximity between both lesions in 42.5% of cases), and there is evidence of transition from normal secretory epithelium to atrophic epithelium and HGPIN changes (Fig. 2.6) [10], which, jointly with GSTP1 inactivation by hypermethylation, can explain the accumulation of genomic changes to the cancer transformation [7].

High-grade PIN's inter-relation with prostate cancer shows itself through some epidemiologic (both lesions undergo parallel increase with age), topographic (proximity of both lesions in the prostatectomy specimens in 70% of cases), morphologic (progressive loss of basal cells, atypia with increased size and nuclear irregularity) and genetic-molecular evidence (gain of chromosome 7q31 and 8q, loss of 8p, 10q, 16q and 18q and expression of α-methylacyl-CoA racemase-AMACR) [6, 15]. Together, these factors have led to high-grade PIN being considered the most likely precursor of prostatic carcinoma.

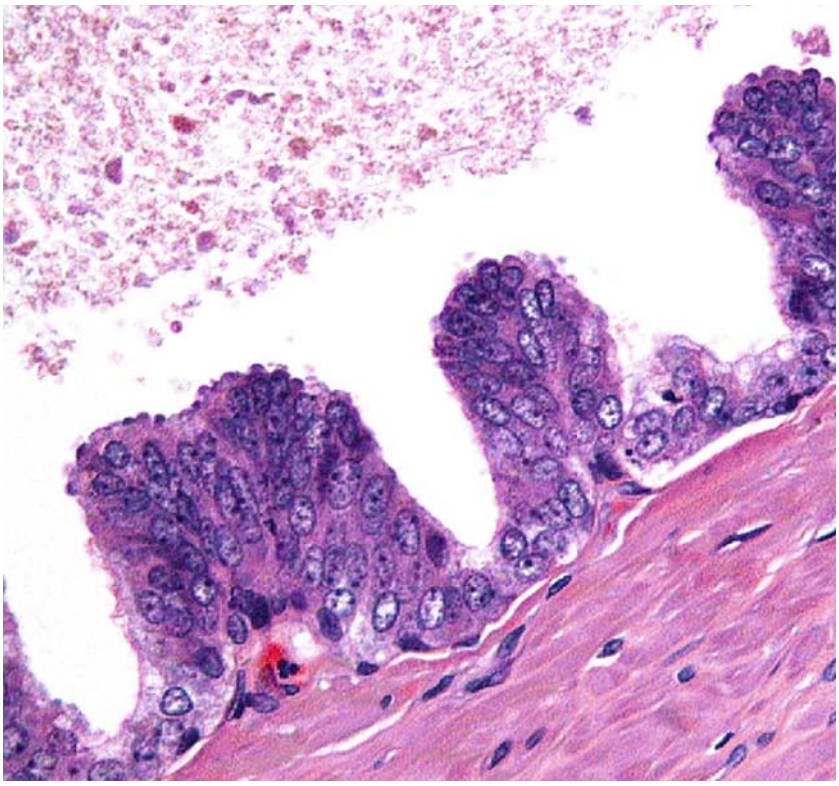

Fig. 2.5 High-grade prostatic intraepithelial neoplasia (HGPIN). Malignant transformation of the luminal cells with basal cells preserved

High-Grade PIN Evolution

Four architectural patterns of HGPIN (flat 28%, tufting 87%, micropapillary 85% and cribriform 32%) have been described (Fig. 2.7) [16]. Even though the patterns often merge with each other, the possibility of a progressive transformation of the flat pattern into a micropapillary one and a cribriform one is a tempting thought. Some authors' observation that the most central cells of the papillary and cribriform patterns are more undifferentiated and lose more heterozygosity than those that are closer to the basement membrane, and also that carcinomas associated with these patterns of HGPIN are clinically more aggressive, reinforce this supposition [17, 18, 19], which seems to be confirmed by the description of unusual cell types—such as signet ring cells PIN, and small cells or neuroendocrine cell PIN types—in cribriform types (Fig. 2.8) [20] similar to invasive carcinomas. All of these observations have been the reason why some authors consider the possibility that some of these changes indicate an intraductal carcinoma [21]. This notion, however, was rejected by consensus on many occasions owing to lack of reproducible criteria.

Another feature to be highlighted is the interrelation between HGPIN and the initial invasive carcinoma. Continuity between carcinoma and HGPIN was observed in 47.6% of cases with small foci of invading carcinoma (Fig. 2.9) [22], and some morphometric studies have linked the initial microinvasion with the clonal selection and the surfacing of clones that might be responsible for the invasive phenotype [23].

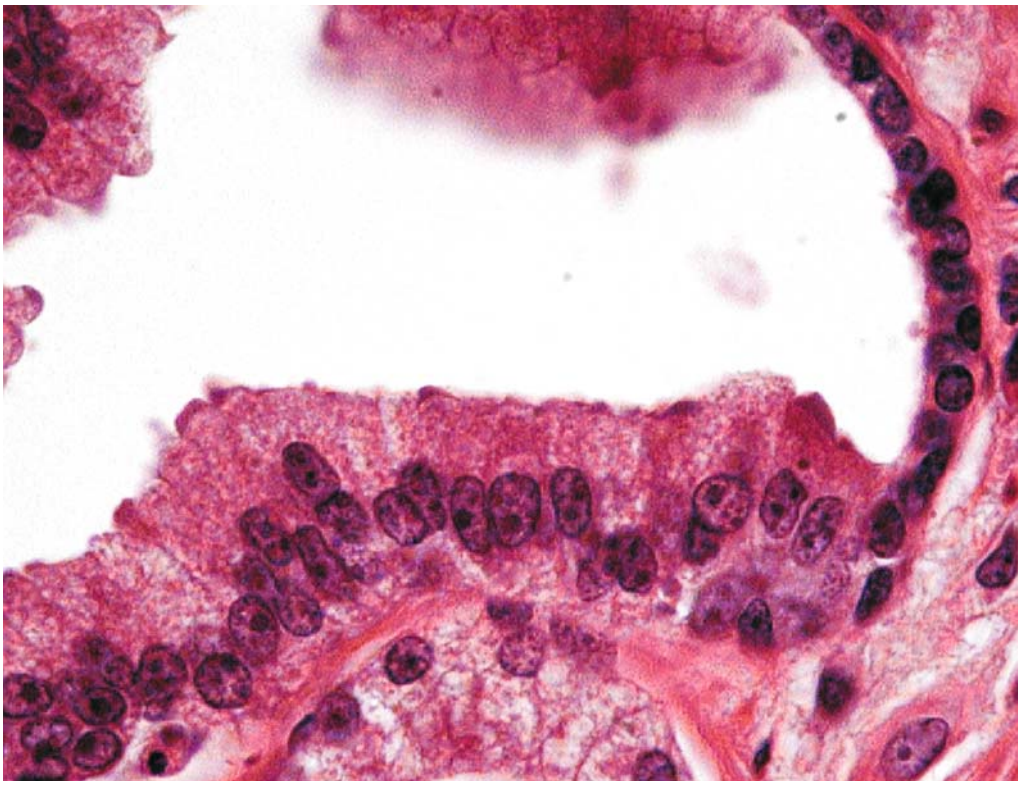

Fig. 2.6 HGPIN in continuity with PIA

However, and despite all that has been stated above, some authors consider it possible that the transition from normal epithelium to invasive prostate cancer occurs without an intermediate morphological stage [24].

Molecular Pathology of Stromal Invasion in Prostate Cancer

Stromal invasion requires cellular detachment, basal membrane degradation and the ability of the cells to grow in a stromal environment.

The loss of cell–cell adhesion correlates with the abnormal expression of adhesion molecules. Amongst these, E-cadherin and N-cadherin play the leading roles.

E-cadherin is coded at chromosome 16q21/22 and inter-relates with MUC-1 (EMA; episialin). It is expressed in the prostatic normal secreting cells. N-cadherin is coded at 18q 11.2 and it is not expressed in the normal prostate [25].

The loss of E-cadherin seems to play quite an important role in the invasive ability of prostate carcinoma (Fig. 2.10) [26]. This loss of expression of E-cadherin is accompanied by a progressive N-cadherin expression, which in turn evolves from a membrane pattern towards a dotted pattern, with intermediate stages of co-expression of both cadherins in a same cell [25]. These changes correlate with the progressive glandular pattern loss (Gleason model). The progressive appearance of N-cadherin in the prostate cancer cell membrane brings about a mesenchymal-like transformation of the malignant cells [27], as if such mimesis favoured the metastatic ability by means of adherence to the stromal cells.

We may thus consider E-cadherin a tumour-suppressing gene, and its cellular recovery could have great significance as a treatment of cancer, which looks possible [26, 28].

The loss of cell-stromal adhesion is associated with loss of hemidesmosome-forming proteins and related adhesive molecules as integrins [29].

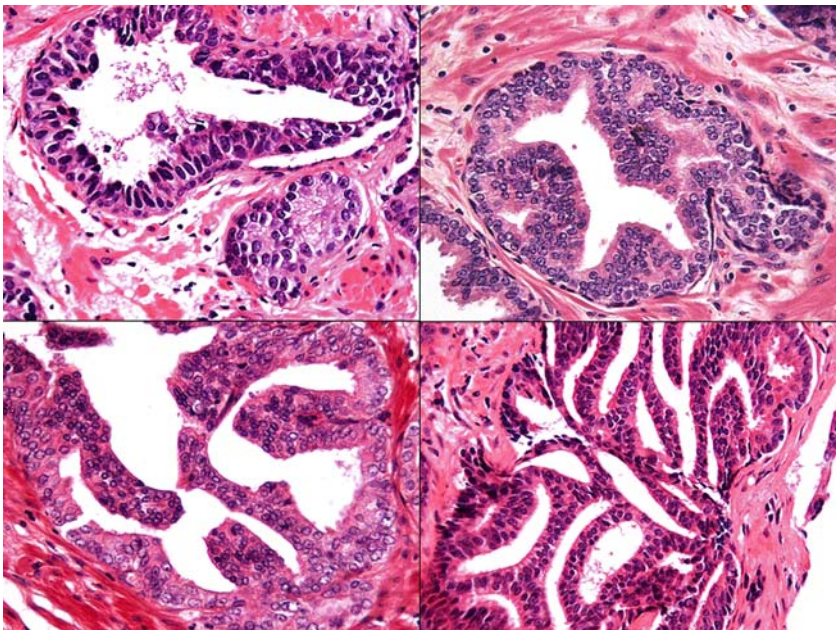

Fig. 2.7 Flat, tufting, papillary and cribriform patterns of the HGPIN

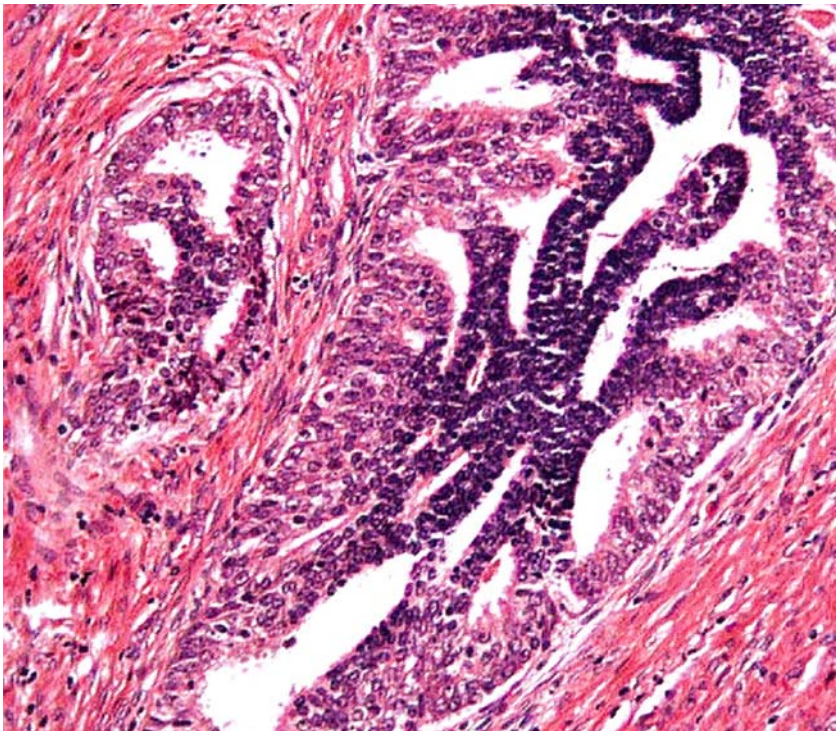

Fig. 2.8 Cribriform HGPIN with neuroendocrine (small cells) differentiation in the luminal area

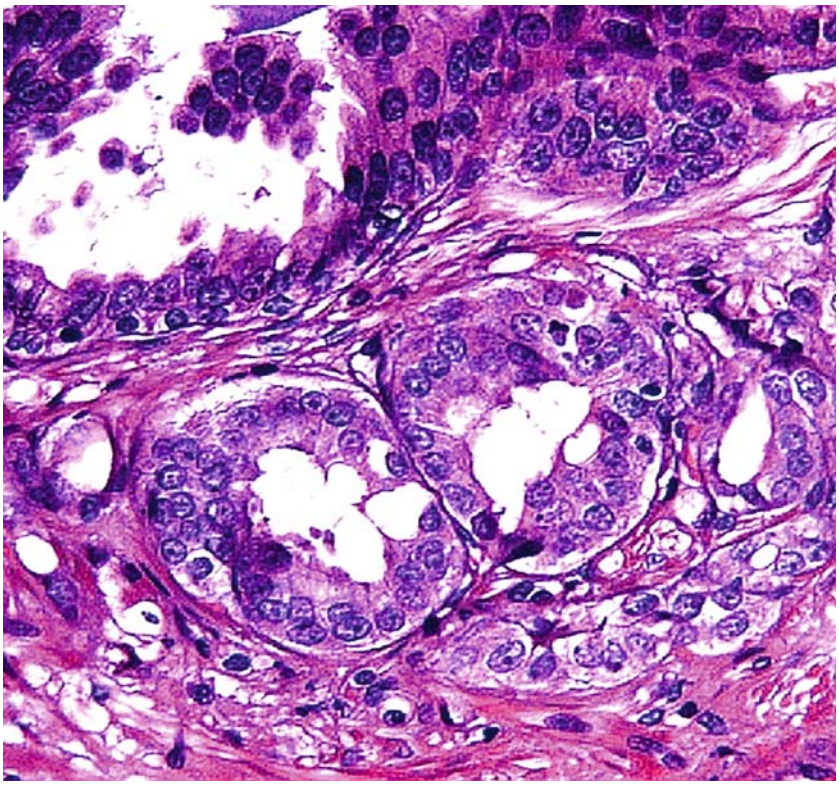

Fig. 2.9 HGPIN near to prostate carcinoma with microinvasion

To be able to proliferate, the cells need an attachment to the basal membrane, but cancer cells continue to proliferate when unattached, a phenomenon that is known as anchorage independence [30]. Such independence requires a false message to the nucleus that the cell is properly attached when actually it is not; this message is probably sent by the malignant cell with expression of laminin and collagen receptors through the synthesis of the basal membrane material [31].

Gleason Grading System of Prostate Cancer as a Model of Evolution

When the carcinoma becomes invasive, its aggressiveness increases with the increase of genetic (chromosomal) changes, evaluable through the changes of the nuclear matrix (increased size, contour abnormalities and nuclear chromatin irregularity). All of these changes are included within the notion of nuclear degree of differentiation; however, because the nuclear matrix, the cytoplasmatic filaments and the intercellular adhesion molecules are closely inter-related, the above-mentioned nuclear changes may also be expressed by means of changes in the architectural arrangement of the neoplastic cells [32].

In prostate cancer the most widely internationally accepted grading model is the Gleason score [33] based on the progressive loss of the gland pattern and the increased peritumoural stroma invasion (Fig. 2.11). This grading system can be considered a model of the invasive prostate cancer progress, since close relationship has been shown with the progressive loss of E-cadherin expression, and also the abnormal expression of other adhesion molecules [34].

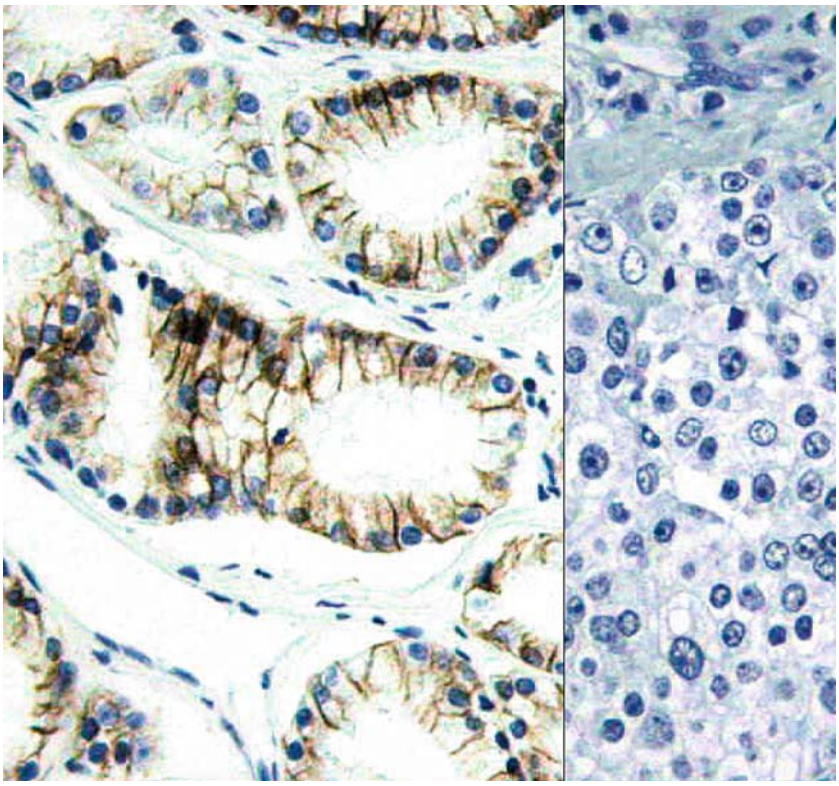

Fig. 2.10 E-cadherin expression in well-differentiated prostate carcinoma and loss of the expression in badly differentiated cancer

Differences Between Transition and Peripheral Zone Prostate Cancer

Following the Gleason's progression model, we may mention that 68.9% of carcinomas originated at the transition area show a Gleason score of 4 or lower, whereas in 65.8% of the carcinomas originated at the peripheral area the Gleason score is 7 or higher (authors observation). These findings are concurrent with those published by other authors, who found the average Gleason score of the tumours of the transition area to be 5, whereas those of the peripheral area are 7, and they correlate to indicators of lower cell activity and lower aggressiveness in the tumours of the transition area than in those of the peripheral area (Mib1-Ki67 expression in 1.5 versus 5%, aneuploidy in 13.3% versus 53.3%, p53 overexpression in 2% versus 11%, and bcl-2 expression in 6% versus 27%) [35].

The reason for these differences is unknown. One possible explanation could be the existence of different precursory lesions at each of the areas.

We should remember that the transition area is the one that develops benign prostate hyperplasia, and so the carcinomas in this area coincide with hyperplasia changes. There has been some speculation that certain forms of microglandular hyperplasia with atypia (atypical adenomatous hyperplasia, AAH) may play a role as cancer precursors [36]. This would explain why the carcinomas of the transition area develop a microglandular appearance very similar to Gleason's patterns 1, 2 and 3A; nonetheless, there is not enough scientific evidence of these lesions to be inter-related [37].

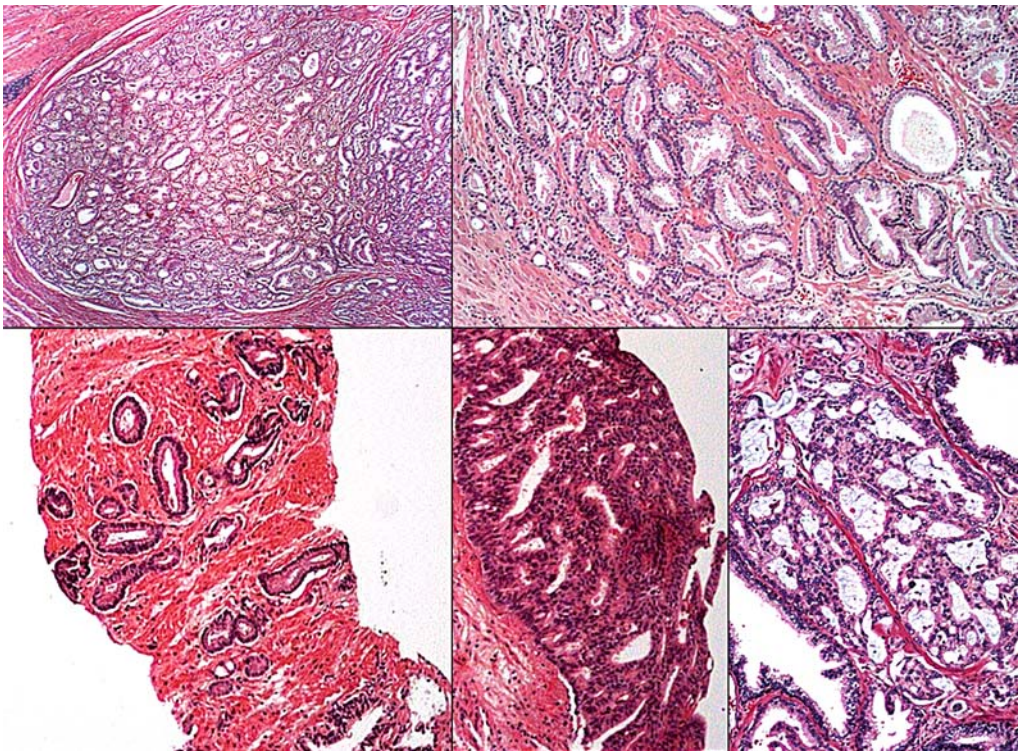

Fig. 2.11 Gleason model with patterns from 1 to 4

However, the HGPIN being the most likely precursor of prostatic carcinoma in the peripheral area, and observing the similitude between the cribriform pattern of HGPIN and Gleason patterns 3B and C with pattern 4 [38], it is not difficult to assume that when these HGPIN lesions turn into invasive carcinoma, they already show Gleason patterns 3, 4 and 5.

Molecular Pathology of Prostate Cancer Progression

In prostate cancer, progression does not only mean distant metastases but also the hormone independence of its cells (hormone refractory prostate cancer).

Metastasis

For a long time bone metastasis preference of prostate cancer was thought to be caused by a retrograde flow from the Batson plexus into the pelvic area during the Valsalva manoeuvre, but currently other metastatic factors are considered more important. Among them, the most widely studied factor is the expression of adhesion molecules with an "area code" for bone marrow (OB-cadherin and integrin α2β1), a selective adhesion via integrin of prostate cancer cells to bone marrow cells that probably contributes to bone metastasis [39]. Other metastasis-associated genes are: *KAI1* (11p11.2), whose loss is associated with greater metastasis [40]; protein p9Ka encodesd by calcium-binding protein gene,

located in cytoskeletal components in a pattern identical to actin filaments, which changes normal Ca++ metabolism [41], and the bone morphogenetic proteins that induce bone morphogenesis in vivo and are involved in the skeletal metastases of advanced prostate cancer. Nm23-H1 and CD44 are less solid factors [42].

Hormone-Refractory Prostate Cancer

The lack of response to hormone blockade may be due to many causes. The stem cell model, discussed above, explains the possibility that, according to the transformed cell being either the early or the late intermediate cell, the tumour may be less or more sensitive, respectively, to anti-androgen therapy [4]. Likewise, the extensive and multifocal neuroendocrine differentiation of prostate adenocarcinoma may represent a different path to androgen independence because these cells can maintain cell proliferation through a paracrine androgen-independent pathway [43].

Another explanation for hormone therapy resistance is the multifocality and heterogeneity of prostate carcinomas. Around 80% of prostate carcinomas are multifocal, and this multiplicity is not only topographic but may also correspond with genetic and molecular variability [44], and for this reason a patient may have hormone-dependent carcinoma foci concomitantly with hormone-refractory ones.

But not all the hormone-refractory neoplasias have a specific phenotype; in order to survive they may undergo a series of cellular adaptations, and thus, by means of androgen receptor amplification (30% of the hormone-refractory cases), they only need minimum amounts of androgens. Amplification of 8q24 (through *c-myc* amplification?) and changes in chromosome 7 have also been found in 80% of such cases [45, 46]. It is possible as well to find androgen receptor mutations leading to oestrogen sensitivity, and also overexpression of non-androgenic steroid androgen receptor coactivators [47, 48].

Bcl-2 could also play a role in the hormonal independence mechanism because it is more frequent in these tumours than in hormone-sensitive neoplasias [49].

Prostate Cancer Modifications After Treatment

At present there are various treatment alternatives to surgery, and also as adjuvants of radical treatments. All of them are able to induce a series or morphological variations that modify the characteristics of prostate cancer and make their interpretation difficult when biopsy specimens are taken.

Hormone therapy causes progressive atrophy of cells with hormone receptors (luminal or secretory cells), be them neoplastic or not, leading to an atrophic aspect of the whole glandular structure, with special emphasis on the basal cells. The luminal cells lose their prostate-specific antigen (PSA) expression of alpha-methylacyl-coenzyme A racemase (AMACR) ability, but they retain the expression of AMACR and of intermediate filaments such as CAM 5.2. (Fig. 2.12) [50]. Reduced incidence and extension of HGPIN post-hormone therapy has also been verified.

Treatments with radiation therapy, either external beam radiotherapy or brachytherapy, induce variations similar to those of hormone therapy, but with far more prominent nuclear atypia (Fig. 2.13) [51], which entails that sometimes the prostatic biopsies show changes difficult to interpret called glands of the indeterminated category (Fig. 2.14). These gradually disappear over time, and only 18% of the patients show residual active prostate cancer [52]. Other much newer treatments, such as cryotherapy and high-intensity focussed ultrasound (HIFU) specifically elicit changes related to necrosis, fibrosis and healing changes [53–55].

In view of all these variations, particularly those that modify the gland structure, recommendation has been issued not to evaluate the degree of differentiation (Gleason model) as we do not know the biological significance of such models after treatment [56].

Clinical Application of the Pathological Natural History of Prostate Cancer

The body of observations commented upon above is useful as an introduction to understanding the natural history of prostate cancer; however, not

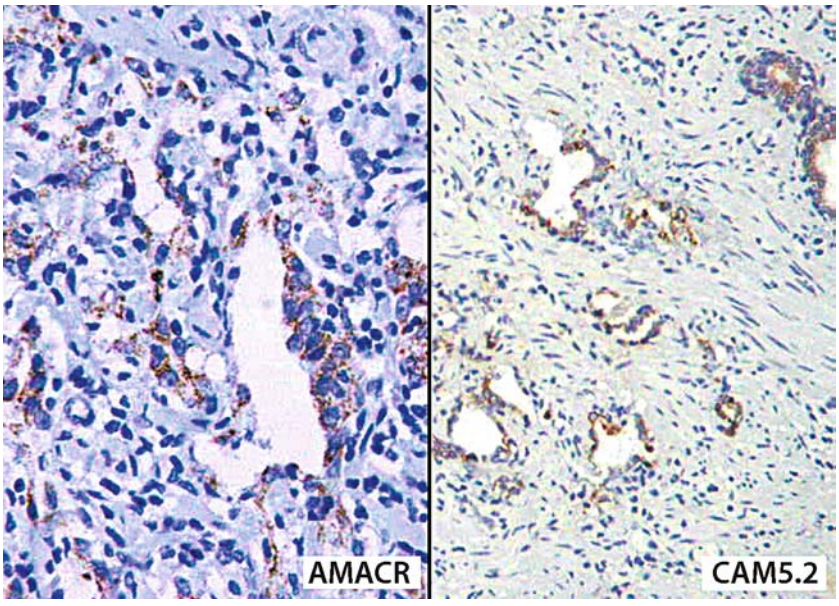

Fig. 2.12 Post-hormonotherapy expression of AMACR and CAM 5.2

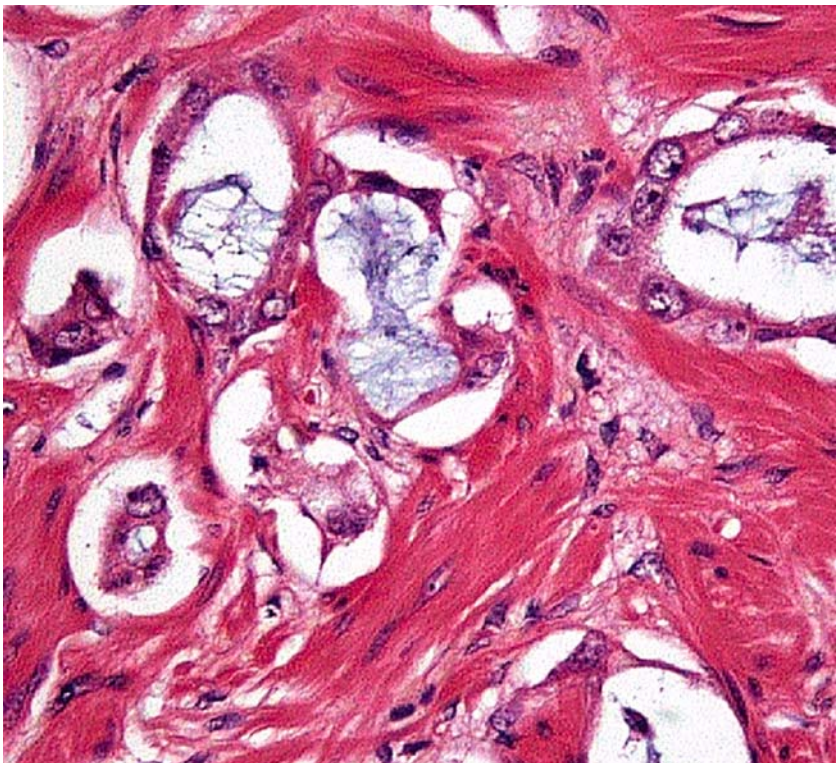

Fig. 2.13 Prostate cancer after radiotherapy

all of those observations are applicable in current practice.

The PIA lesion may represent an interesting preventive therapy target, provided it is shown to be a usual step between a normal gland and intra-epithelial neoplasia, and particularly if an efficacious anti-inflammatory treatment without side-effects is attained. Additionally, HGPIN is proving to be useful as a marker of probable concomitant prostate carcinoma. Furthermore, adhesion molecules enable us to know the dynamics of invasion and metastasis, but we still do not have the methods that allow us to affect progression.

By means of the Gleason model a correlation can be established with pathological extension (tumour volume) [57] and metastatic capacity (score 2 to 5: 14% metastasis; score 6: 32%; score 7: 50%; score 8: 75% and score 9–10: 100%) [58].

But the most common clinical factor still associated with prognosis is the stage or level of extension of the carcinoma. Following the UICC (T category) classification of 1992, we note that rates of lymph node metastasis for incidental localized carcinoma are respectively 2% (T1a), 26% (T1b), and 4% (T1c), while the rates for clinically localized carcinomas are 1% (T2a) and 25% (T2b) [59, 60]. This confirms that tumour volume remains quite reliable in terms of prognostic value (the incidence of lymph node metastases is the same in T1b tumours, i.e. involving more than 5% of the tissue, and T2b tumours, i.e. extensive clinical tumours) even in the needle biopsy [61]. For this reason, one of the primary roles of the pathologist is to determine extension (T stage).

As a refinement of local extension evaluation, microvascular invasion can be an important marker. It is present in 38% of the radical prostatectomy specimens and is commonly associated with extraprostatic extension (62%) and lymph node metastases (67%), and correlates with grade and progression [62]. Intraprostatic peri-

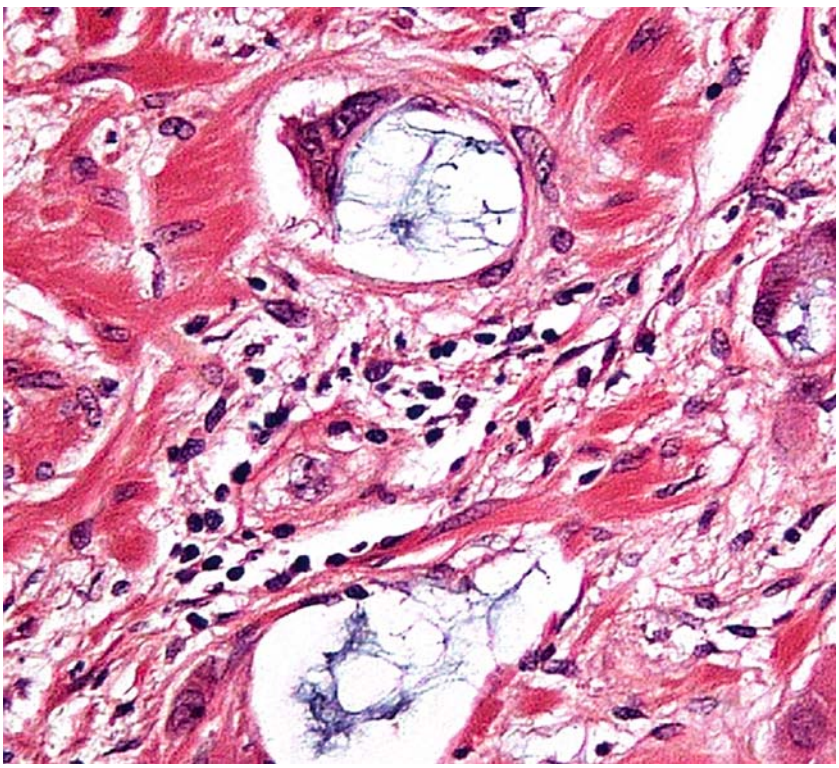

Fig. 2.14 Prostate glands of the indeterminated category, post-radiotherapy

neural invasion indicates tumour spread along the path of least resistance; only 50% of these patients have extraprostatic extension, so it is not very useful [63] and it is in relation to tumoural volume [61].

The neuroendocrine differentiation somewhat implies a poor prognosis, and in some cases it explains hormone independence [64], probably through the correlation with vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)-alpha (angiogenic factors) [65], and the absence of androgenic receptors.

From all of the above we may conclude that currently we are in front of the identification of a series of molecular markers, some of which may be of prognostic and therapeutic use. To date, the refinement in grade and stage evaluation, as well as hormone sensitivity determination, are the most widely used methods to identify and assess the severity of prostate cancer.

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3 Prognostic Factors in Prostate Cancer

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Abstract

In the nineteenth century the main goal of medicine was predictive: diagnose the disease and achieve a satisfying prognosis of the patient's chances. Today the effort has shifted to cure the disease. Since the twentieth century, the word prognosis has also been used in nonmedical contexts, for example in corporate finance or elections. The most accurate form of prognosis is achieved statistically. Based on different prognostic factors it should be possible to tell patients how they are expected to do after prostate cancer has been diagnosed and how different treatments may change this outcome.

A prognosis is a prediction. The word prognosis comes from the Greek word πρόγνωση and means foreknowing. In the nineteenth century this was the main goal of medicine: diagnose the disease and achieve a satisfying prognosis of the patient's chances. Today the effort has shifted towards seeking a cure.

Prognostic factors in (prostate) cancer are defined as "variables that can account for some of the heterogeneity associated with the expected course and outcome of a disease" [1]. Bailey defined prognosis as "a reasoned forecast concerning the course, pattern, progression, duration, and end of the disease" [2]. Prognostic factors are not only essential to understand the natural history and the course of the disease, but also to predict possible different outcomes of different treatments or perhaps no treatment at all. This is extremely important in a disease like prostate cancer where there is clear evidence that a substantial number of cases discovered by prostate-specific antigen (PSA) testing are unlikely ever to become clinically significant, not to mention mortal [3]. Furthermore, prognostic factors are of paramount importance for correct interpretation of clinical trials and for the construction of future trials. Finally, according to WHO national screening committee criteria for implementing a national screening programme, widely accepted prognostic factors must be defined before assessing screening [4].

Prognostic Factors May Be Tumour-Related, Patient-Related or Independent Variables

The anatomical extent or stage of the disease, measured with the International Union Against Cancer (UICC) Tumour Node, Metastasis (TNM) classification [5], is our first guide in prognosis, but does not include all relevant prognostic factors in prostate cancer, especially PSA and Gleason score [6]. Not surprisingly, the post radical prostatectomy (RP) margin status is also a very strong independent prognostic factor [6]. TNM stage, PSA, Gleason score and post prostatectomy margin status are strong, independent and tumour-related prognostic factors. Today it is obvious that patient or host-related factors such as age, ethnic origin, general condition, co-morbidity (especially immune status) and medication play an equivalent role in the determination of the individual patient's prognosis. Not to forget the personal preference of the patient confronted with different treatment possibilities, today's patients are better informed and more assertive, and participate more actively in the therapeutic decision making than ever before. The patient's personal choice, variably influenced by his subjective interpretation of treatment benefits and treatment risks, certainly has a greater impact on prognosis too.

Table 3.1 Components of the Veterans Administration Cooperative Urological Research Group (VACURG) system [41], the bin model [42] and the Partin tables for prognosis of prostate cancer

VACURG	T+Gleason
Bin	TNM+Gleason
Partin	TNM+Gleason+PSA

Unfortunately, even today prognosis is also affected by environment-related variables that are completely independent of the patient's life expectancy and his tumour. In some places these "external" factors, such as demography, national health-care policy and social obstruction to medical care, may change the outcome of this disease dramatically [7].

Patient assessment should include a complete personal and family history, co-morbidity and medication, presence of lower urinary tract symptoms, symptoms suggesting regional/distant spread, and a complete physical examination with digital rectal exam. Serum PSA level should be obtained, and depending on the risk category (Table 3.1) an isotope bone scan or computed tomographic examination (CT) of the abdomen and pelvis may be indicated. In patients with low risk of metastases the imaging studies are not mandatory, although one might have them done anyway, perhaps to obtain reference documents to compare with possible later positive studies in a given patient.

Standard treatment approaches for localized and locally advanced disease include active monitoring, RP, brachytherapy, external beam radiotherapy (EBRT), hormone therapy or a combination of EBRT and hormones depending on the tumour and patient characteristics. Estimated life expectancy is an important factor in determining whether local treatment should be utilized in management. Randomized clinical trials have shown the efficacy of adjunctive hormonal therapy in patients with high-risk disease treated with radiation therapy. In metastatic disease hormonal therapy is the mainstay of treatment and chemotherapy has recently been shown to prolong survival in patients with hormone refractory disease [1].

Anatomical Extent of Disease

The local extent of disease in the prostate has been demonstrated in multiple studies to be an independent marker of prognosis in prostate cancer [5]. It is assessed by digital examination and/or transrectal ultrasound and described by T category. Other methods include magnetic resonance imaging (MRI) with endorectal coil, ProstaScint(Cytogen, Princeton) [8] and positron emission tomography [9]. Each is being evaluated, but to date the results are inconclusive. The volume of the tumour itself does not seem to provide much useful prognostic information [10].

Certainly in the choice for brachytherapy and sometimes also for RP, the total prostate volume may be restrictive and then also becomes a prognostic factor. Pretreatment N and M categories can be assessed by cross-sectional and skeletal imaging. The sensitivity of both investigations depends on serum PSA and Gleason score. Low PSA values and Gleason scores are rarely associated with extraprostatic disease and in many countries the imaging studies are not performed when the odds are low. In Europe, increasing numbers of centres no longer perform bone scans in asymptomatic patients with PSA levels below 20. The presence and extent of pelvic lymph node disease correlates clearly with outcome [11]. In more advanced disease, increased tumour involvement on bone scan or visceral organs is of prognostic importance [12].

Histology

The histological tumour grade plays a key role in predicting progression and overall survival. Over the past two decades the Gleason system has become the preferred pathological grading system for prostate cancer [13]. Studies by Albertsen et al. [14, 15] emphasize the prognostic value of Gleason score, especially in men with localized disease. Young patients with high-grade T1–T2 disease are best treated surgically, whereas the therapeutic success rate of brachytherapy is poor in these patients. The second study states that aggressive treatment is not recommended for low-grade localized prostate cancer.

Unfortunately the Gleason score is first assessed by light microscopy examination of core biopsies and does not always correlate with the final pathological grade resulting from the examination of the RP specimen; neither does it prove to have perfect reproducibility [16]. Other histopathological factors such as DNA ploidy, microvascularization, perineural invasion and the percentage of positive cores on needle biopsy have been assessed and confronted with the outcome. Only the percentage of positive cores has been shown to be of independent prognostic significance in one study [17]. In another study both the number of positive biopsy sites and the highest percentage of adenocarcinoma at any biopsy site were significant predictors of small volume cancer in RP specimens [18].

Lymphovascular invasion, identified on the RP specimen, is an independent predictor of PSA relapse and cancer specific survival [19]. New histological assays are currently under investigation. Zinc α-2-glycoprotein (ZAG), detected by immunohistochemical staining of prostate cancer tissue, showed to be an independent prognostic factor, reversely correlated with the Gleason score [20].

Prostate Specific Antigen and Other Molecular Biomarkers

PSA is applied worldwide in the diagnosis and monitoring of prostate cancer. It is appreciated as an independent prognostic factor, both at diagnosis and relapse, either for localized or advanced disease [21, 22]. But as PSA is not cancer specific, one must be somewhat cautious, especially with lower PSA values in the early stages of the disease. Currently, for newly diagnosed prostate cancer patients the prognostic value of PSA becomes increasingly limited, as the majority of these patients have a PSA of less than 20 ng/ml.

A recent study found that PSA was only weakly associated with prostate cancer volumes in men treated with RP [23]. However, it is helpful to predict the risk of marginally positive disease at RP in conjunction with their T-stage and the Gleason score [24, 25]. In men with clinically localized disease selected for RP, PSA is also significantly associated with the risk of biochemical progression [26].

PSA variables have been proposed in order to increase its sensitivity to diagnose localized disease. These have met with limited success, with the possible exception of the measurement of percentage of free PSA. The rate of change of PSA over time, PSA velocity, and especially its doubling time showed to hold some prognostic value, mostly in recurrent and hormone refractory disease [27–30].

More work is being done on other derivates such as complex PSA and PSA-specific membrane antigen. Recent and ongoing research is also focussed on the prognostic role of cancer-related gene products such as p53, p16INK4A, p27KIP1, BCL-2, caspase proteins, cyclins, E-cadherin, Ki-67, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), angiogenesis inhibitors, and others [16, 31, 32, 33]. The prediction of the behaviour of prostate cancer with gene expression transcript profiles looks promising but has to be validated in upcoming clinical trials.

Age and Life Expectancy

Although age is a well-known prognostic factor for survival in prostate cancer in general, there is considerable controversy regarding its effect on outcome in patients with localized disease [34]. The controversy is highest in older patients. Life expectancy is a much better parameter in this situation. In more advanced disease older age at presentation and poor performance status are adverse prognostic features [12].

The presence of significant co-morbidity has a definite impact on outcome both in early and advanced stages [35].

Race

Race is also a well-known risk factor for developing prostate cancer, but surprisingly this disease also behaves differently in men of different races. Whether this is due to patient-related factors or to external factors is not clear yet. A study from Dayal et al. in 1985 suggested that the racial

difference between blacks and Caucasians in the survival prognosis for prostate cancer was to a large extent the result of differences in socio-economic status [36].

"External" Factors

Some studies have suggested that reduced access to health-care by lower socio-economic groups contributes to a higher death rate from prostate cancer [36, 37]. Whether this results directly from the socio-economic status itself or rather from of a higher awareness of the usefulness of early PSA testing in the "upper class" patients is not clear yet. One should first check the true incidence of prostate cancer in both groups, define the stage distributions and compare the treatments offered to the patients. Meanwhile, it has been shown that in more educated populations a majority of even the elderly patients with low-risk prostate cancer receive some form of treatment [38].

It is clear that access to quality care, possibly influenced by socio-economics but also by demography and national health-care politics, has an important impact on prognosis. This is especially applicable in early disease, where the ability to achieve free surgical margins or to propose appropriate radiation has shown to be of significance [39, 40]. In the first paper [39], Eastham et al. conclude that the "lower rates of positive surgical margins for high-volume surgeons" suggest that experience and careful attention to surgical detail can decrease positive surgical margins and improve cancer control with RP.

Combined Prognostic Factors

The obvious way to improve the usefulness of prognostic factors is to combine them. Early experience was obtained with the VACURG system, based upon T-category and Gleason score [41], and the bin model, combining the TNM information and the Gleason score [42]. Today nomograms like the Partin tables [25], for the prediction of the pathological stage, the margin status and possible lymph node involvement based on the biopsy Gleason score, the clinical stage and the PSA, are widely used in everyday urological practice. The components used in the VACURG, bin and Partin tables are listed in Table 3.1. In the late 1990s Kattan et al. presented useful pretreatment nomograms for patients treated with RP, conformal external radiotherapy or brachytherapy [44–46]. Although these tables are popular and widely used, at their best they have an area under the ROC curve (AUR) of 0.75 [47]. Ramsden and Chodac analysed risk factors for biochemical progression in prostatectomized patients with seminal vesicle invasion to validate Kattan's nomogram in this pathological subgroup [48]. They found that the components of the nomogram were not significant, but still useful in helping to direct adjuvant therapy. Recently Kattan et al. noted that adding molecular markers to the clinical parameters could improve the AUR to 0.83 [49]. In the future, much is expected from artificial neural networks that may be useful for simultaneous incorporation of the many different prognostic variables associated with prostate cancer [50].

Conclusion

The classical prognostic factors in prostate cancer are its TNM stage category, the serum PSA level and the Gleason score. In localized disease, low-, intermediate- and high-risk groupings have been proposed based upon these factors (Table 3.2). The groupings have been shown to predict for prostate cancer specific mortality [6]. The widespread introduction of PSA screening in many counties caused an important diagnostic shift towards early stage, low-risk prostate cancer. In the United States the proportion of patients presenting with high-risk disease dropped from 37% to 16% between 1989 and 2002 with a cor-

Table 3.2 Prognostic risk groupings for localized/locally advanced prostate cancer categories

Risk group	PSA (ng/ml)	Gleason score	UICC T category
Low (all of)	≤10	≤6	≤T2a
Intermediate (any of, if not low risk)	≤20	7	T1/T2
High (any of)	>20	≥8	≥T3

responding rise in the proportion of patients with low-risk disease from 30% to 47% [51]. It is clear that more and refined prognostic factors are necessary in order to select the proper patients for the proper treatments. Recent collaborative initiatives addressed this issue in an attempt to categorize different prognostic factors. From 1993 to 1999, under the auspices of the World Health Organization (WHO), the UICC or the College of American Pathologists (CAP), seven international conferences were at least partly organized with that intent [52]. The most recent meeting of the WHO in Paris classified the prognostic factors [53] as category I (factors that have been proved to be prognostic or predictive based on evidence from multiple published trails and that are recommended for routine screening), category II (factors that show promise as predictive factors based on evidence from multiple published studies but that require further evaluation before recommendation or are recommended despite incomplete data as diagnostic or prognostic markers) and category III (factors awaiting further study to clarify their value in the prognostic arena). The selected factors are listed in Table 3.3.

Table 3.3 Classification of prognostic factors for prostate cancer: recommendations of the 1999 WHO consensus conference. Modified from Bostwick and Foster [53]

Category 1
TNM stage
Histological grade (Gleason score and WHO nuclear grade)
Surgical margin status
Perioperative PSA
Pathological effects of treatment
Location of cancer within prostate
Category II
DNA ploidy
Histological type
Cancer volume in needle biopsy specimens
Cancer volume in radical prostatectomy specimens
Category III
Prostate-specific membrane antigen
Other serum tests (P5 M, hK2, insulin-like growth factor...)
Perineural invasion
Vascular/lymphatic invasion
Microvessel density
Stromal factors, including insulin-like growth factor β, integrins, ...
Proliferation markers and apoptosis
Nuclear morphometry and karyometric analysis
Androgen receptors
Neuroendocrine markers
Genetic markers
All other factors that do not appear in categories I and II

These factors are all tumour-related, but prognosis is also determined by the patient's personal data related to his age and even more to his individual life expectancy. The benefit of any treatment with curative intent in patients with localized low- and intermediate-risk disease remains controversial and is being addressed in ongoing trials. A refinement of prognostic factors for disease progression will be critical in resolving this therapeutic dilemma. In high-risk disease and advanced disease, the role and the timing of adjunctive treatment to improve progression-free and overall survival need to be evaluated. Ongoing and future trials should not only focus on the therapeutic outcomes but also on the identification of more useful prognostic factors to tell us which patient needs which treatment at what time. A better combination of clinical, pathological and molecular "disease predictors" should enable us to distinguish harmless from life-threatening prostate cancer. But even then, the old adage, "we don't treat tumours but patients", should always lead our decision-making, with respect to the patients individual life expectancy and expectations.

The health provider can also be a prognostic factor. This was already hinted at when we mentioned the relation between the skills of the surgeon performing a RP and the chance of margin-free disease. But it is clear that optimal guide counselling and commitment of treatment should only be done by people who know their business.

Finally, efforts to provide optimal health-care for everybody everywhere may seem a utopia,

but somehow it does not seem right when someone's socio-economic or demographic situation affects his prognosis significantly.

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4 The Prevention of Prostate Cancer

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Recent Results in Cancer Research, Vol. 175

Abstract

From our better understanding of the natural history of prostate cancer, it is not unreasonable to believe that the disease is preventable. Prostate cancer has become a major healthcare problem worldwide, as life expectancy increases. Moreover, the cancer is slow growing, with a period of about 20–25 years from initiation to the stage when the clinically detectable phenotype can be identified. This review provides a simple overview of the endocrinology of prostate cancer and discusses some of the pharmaceutical agents that have been or are being tested to restrain, possibly arrest, the progression of this slowly growing cancer. Also discussed are many of the dietary factors that may influence the molecular or endocrine events implicated in its development. Dietary factors are considered responsible for the geographical differences in prostate cancer incidence and mortality. Since about 50% of all men worldwide, from both East and West, show evidence of microscopic cancer by 50 years of age, growth restraint would appear to be the pragmatic option to the possibility of preventing initiation.

Some Introductory Perspectives

The concept that prostate cancer is preventable is by no means new. Questions posed by Huggins [1] at one of the earliest meetings to specifically discuss the biology of the gland are still relevant. He highlighted certain unresolved problems (Fig. 4.1) that today continue to exercise the minds of investigators, none more so than the reasons for the geographical differences in the incidence of prostate cancer. The disease is prevalent in Western developed countries, but rare in Asia [2]. Until recently the concept that dietary variability could influence the pathogenesis of cancer was considered with scepticism, but now interest centres on whether worldwide variability is caused by dietary factors such as the high intake of fat in the West, or prevented by particular constituents of the Asian diet.

Many constituents could impinge on the molecular events implicated in prostate carcinogenesis to provide health benefit [3, 4], and interest in chemoprevention has increased spectacularly. As our understanding of prostate growth regulation dramatically develops [5–8], potential roles for dietary factors become easier to appreciate [4, 9, 10] and there is little doubt that geographical differences in diet and lifestyle account for a large part of the worldwide variability in incidence.

The Natural History of Prostate Cancer

Prostate cancer is a disease of middle-aged men which presents clinically beyond 50 years of age and involves a slowly growing tumour that takes

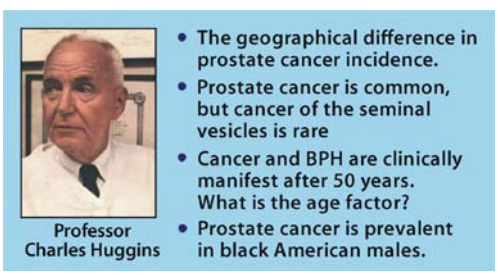


Fig. 4.1 The perceived important issues relating to human prostate disease in 1962 [1]

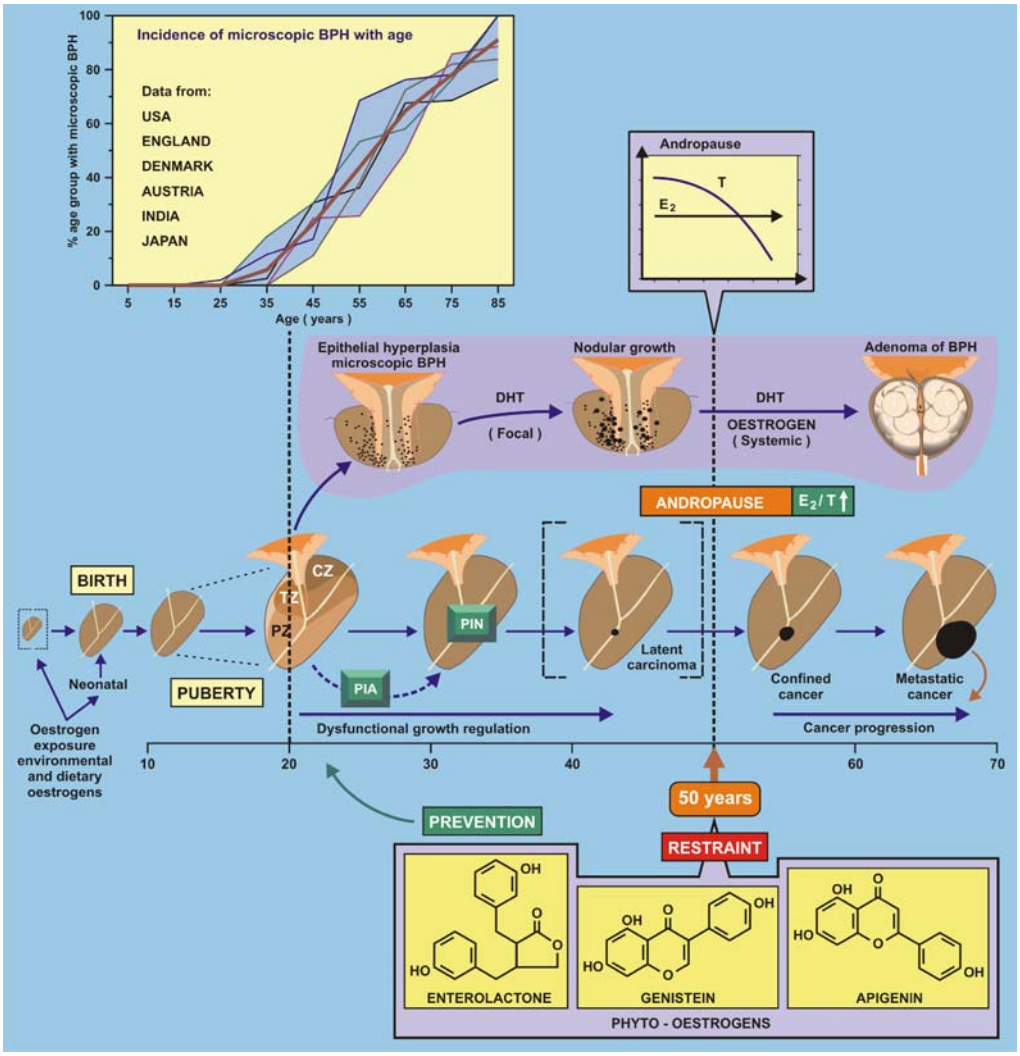


Fig. 4.2 Diagrammatic representation of the natural history of prostate disease that illustrates the slow-growing nature of prostate cancer

more than 25 years to develop from a focal lesion to the malignant phenotype (Fig. 4.2). Once outside the confines of the capsule, the disease is incurable. Its natural history is characterised by a 20-year development phase, followed by a 10-year preclinical, asymptomatic period. Secondary prevention through early diagnosis using serum prostate-specific antigen (PSA) analysis and prostate biopsy has dramatically increased incidence rates during the preclinical period, creating interest in population screening. The results of international randomised screening trials are awaited [11].

Particularly important, however, is that the preclinical period offers the potential for primary chemoprevention, which will probably not prevent initiation but certainly could suppress the rate of cancer growth and progression. The natural history highlights phases where preventive strategies can be focussed.

- Initiation would seem to occur soon after the dramatic hormonal changes associated with puberty and prostate growth. A male's developing sexuality through this time, possibly afterwards [12], may also constitute an endogenous risk factor [13, 14], contributing to the dysfunctional growth regulatory events recognised at this time: prostatic intraepithelial hyperplasia (PIN), latent focal cancer, microscopic benign prostate hyperplasia (BPH) and chronic inflammation associated with prostatitis and proliferative inflammatory atrophy (PIA).
- Inappropriate intrauterine oestrogen-mediated gene imprinting could significantly influence the prostate in later years by enhancing its propensity to induce precancerous lesions [15]. Genes associated with the insulin-like growth factor (IGF)-network and other oestrogen-related events have been implicated in imprinting, essentially comprising a mechanism by which certain genes are 'silenced'.
- After sustained prostate growth at puberty, homeostasis should normally be established, with a balance attained between the rates of cell proliferation and cell death. The balance, which should sustain a growth-quiescent gland, despite high levels of circulating testosterone [16–18], is not always established, and epithelial hyperplasia associated with microscopic BPH [19, 20] and PIN [21, 22], generally perceived as the precursor of microfoci of latent cancer [23], are lesions which occur in all men worldwide, irrespective of race.
- The progression of latent cancer to the invasive phenotype seems to be the feature of Western men and results in the geographical variation in prostate cancer incidence and mortality [9]. Relevant is that nearly 40% of all men worldwide will harbour latent prostate cancer.
- A possible relationship between PIN and cellular inflammatory lesions that characterise prostatitis deserve consideration with regard to adverse growth regulation [24, 25]. An important issue involves whether post-pubertal consequences of oestrogen-related imprinting relate to the induction of PIA [26–29].
- Cancer progression to malignancy occurs around the andropause [11], when plasma levels of testosterone fall relative to those of oestradiol-17β, and the oestrogen/androgen ratio can increase by up to 40%. Since this enhanced oestrogenic status is considered responsible for the stromal hyperplasia characteristic of BPH, it is not unreasonable to consider that oestrogens may also be implicated in the molecular events that support cancer progression [9, 12, 27, 30].
- Preventive measures that delay the development of clinical disease are clearly necessary, and compelling evidence supports such a role for certain isoflavonoids and flavonoids [4, 9, 27].

Pragmatically, of all the reported risk factors, nutrition presents the most reasonable means of rationalising the global variability of the disease. Of interest are studies [31] of Asian migrants to North America; within two generations they assume an incidence closer to that of indigenous males (Fig. 4.3). Moreover, as Asians acquire Western dietary habits, changes in cancer incidence must be monitored [32, 33]. Already in Japan a rising prostate cancer incidence [35] is seen to relate to a rising intake of dietary fat. Prostate cancer is a major health-care problem, now exacerbated by increasing life expectancy worldwide. Preventive strategies are being considered [34, 35, 36] through reviews of closed and on-going trials of various dietary and hormonal factors that were established to assess efficacy and associated adverse effects. Few of these have been completed and analysed.

Some Dietary Factors for Chemoprevention

Isoflavonoids and Lignans

Phyto-oestrogens, certain isoflavonoids and lignans offer an exciting approach to prevention [3, 4]. They are bioactive (Fig. 4.4) and, as weak oestrogens, may act either as antagonists or agonists [37–39] to modulate oestradiol-17β-mediated signalling. The presence of non-steroidal oestrogens in plants has long been known, with legumes such as soybean, lentils, beans and chickpeas being major sources of isoflavonoids [40]. These foodstuffs contain glycoside conjugates of

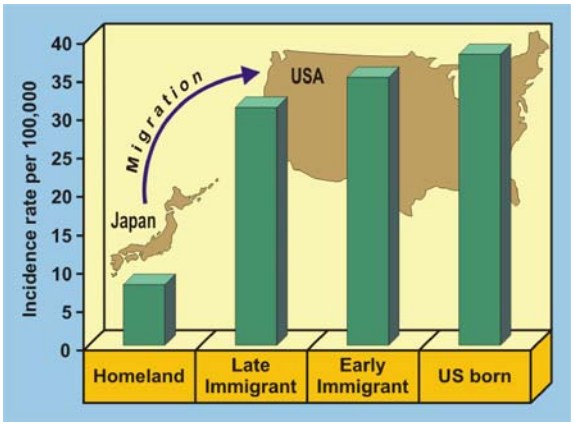


Fig. 4.3 Age-adjusted incidence rates for prostate cancer for native Japanese in the Miyagi Prefecture of Japan (1973–1981), for early and later immigrants and for Japanese-Americans in Los Angeles County (1972–1985), USA [31]

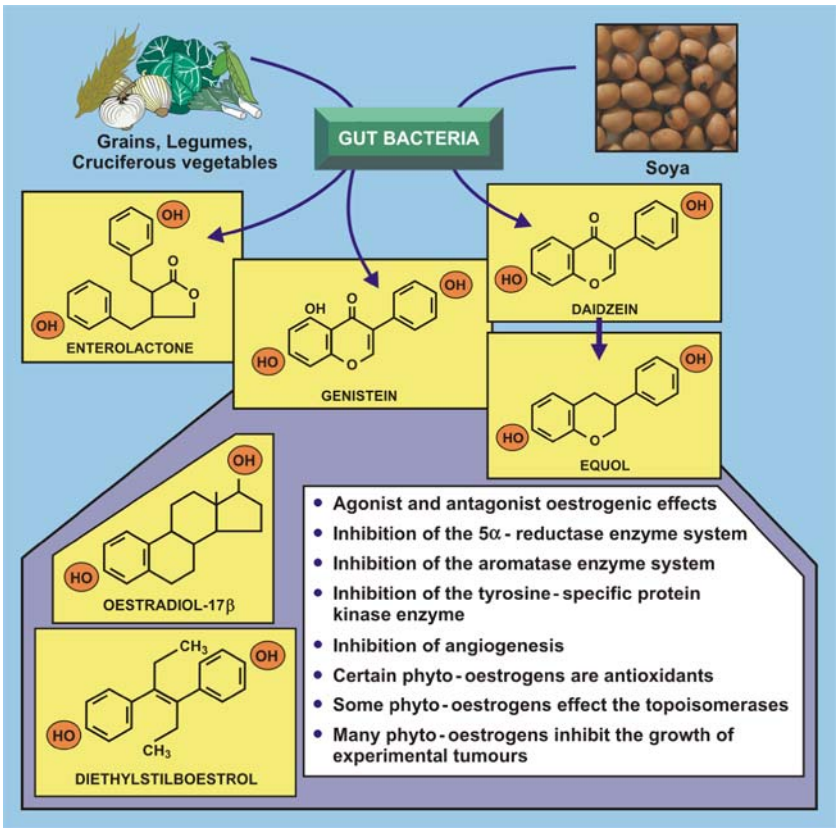


Fig. 4.4 A simple presentation of the formation of phyto-oestrogens from dietary constituents. The formation of equol from daidzein is illustrated, together with reported biological effects and structural relationships with oestrogens

genistein and daidzein, which are metabolised by normal gut microflora to produce the isoflavonoids. Soybean is a dietary staple in Asia, and many traditional diets of India, Africa, Mediterranean countries, and South America have a similar high legume content. The intake of legumes has fallen in Western countries over the last century [41]. Plant lignans, matairesinol and secoisolariciresinol, are similarly metabolised to produce enterolactone and enterodiol, which are also oestrogenic [4]. Flaxseed is a rich source of lignans, as are other seeds such as sesame and whole grain cereals like rye, fruits, berries and vegetables.

The orientation of the hydroxyl groups of oestradiol-17β confers the molecule's oestrogenicity [9], and similarly that of phyto-estrogens (Fig. 4.4). Although their oestrogenic properties could influence prostate cancer progression, they also demonstrate an imposing array of other biological effects [4, 9]. Their ability to restrain the growth of experimental prostate cancer models [34–36] may result from their capacity to act as effective anti-oxidants, or as tyrosine kinase, 5α-reductase (5AR) and aromatase inhibitors, or to impede angiogenesis.

Enterolactone concentrations are high in urine of vegetarians [42], and interestingly, substantial amounts are found in expressed prostatic fluid of Portuguese men [43]. The plasma isoflavonoid content in Japan is high [44] relative to levels in the United Kingdom (Fig. 4.5), with higher levels in the elderly (Fig. 4.6) suggesting that younger people are not eating as much soy protein as their elders. Daily supplementation with a cereal bar containing the soy protein appropriate to the daily Japanese intake shows the rapid elevation of plasma concentrations of genistein and daidzein compared to those consistently sustained by Asian people (Fig. 4.7).

Trials are underway [34–36] to determine whether soy protein supplementation restrains the progression of HGPIN to invasive cancer; another study aims to assess efficacy in preventing further development of cancer in patients with stage I or II disease.

Flavonoids

Certain health benefits of polyphenolic flavonoids have also been known for a long time. Unlike the isoflavonoids, however, flavonoids are ubiquitous in nature and their influence on health could be profound. Their complex chemistry is well studied [45, 46] and Fig. 4.8 certain flavonoid structures relative to genistein. Onions are a source of apigenin, apples of quercetin,

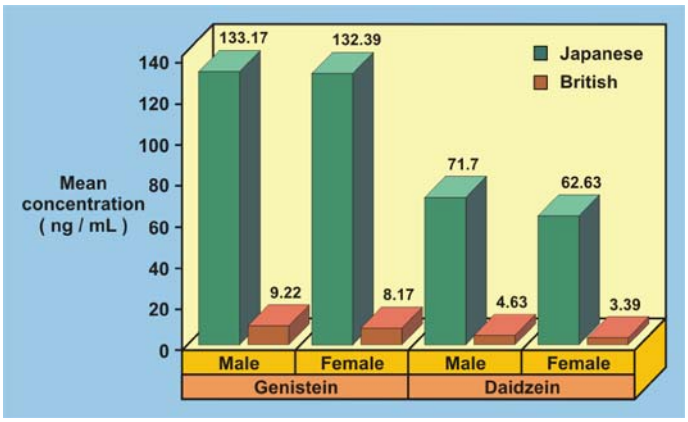


Fig. 4.5 Comparative mean concentrations of genistein and daidzein in Japanese and British male and female plasma samples. Data from the Tenovus Institute for Cancer Research, Cardiff

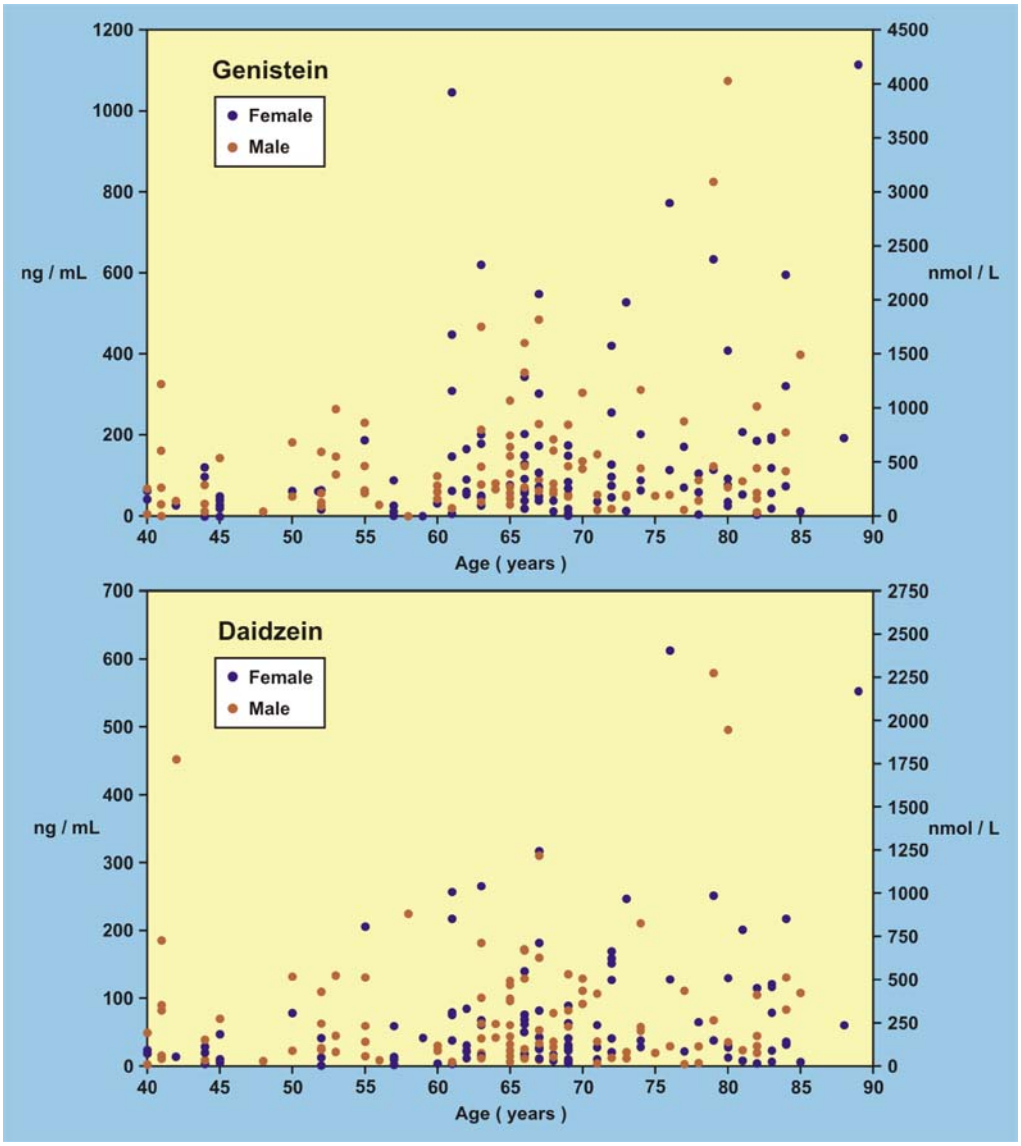


Fig. 4.6 Concentrations of genistein and daidzein in plasma samples from Japanese male and female subjects of varying age. Data from the Tenovus Institute for Cancer Research, Cardiff

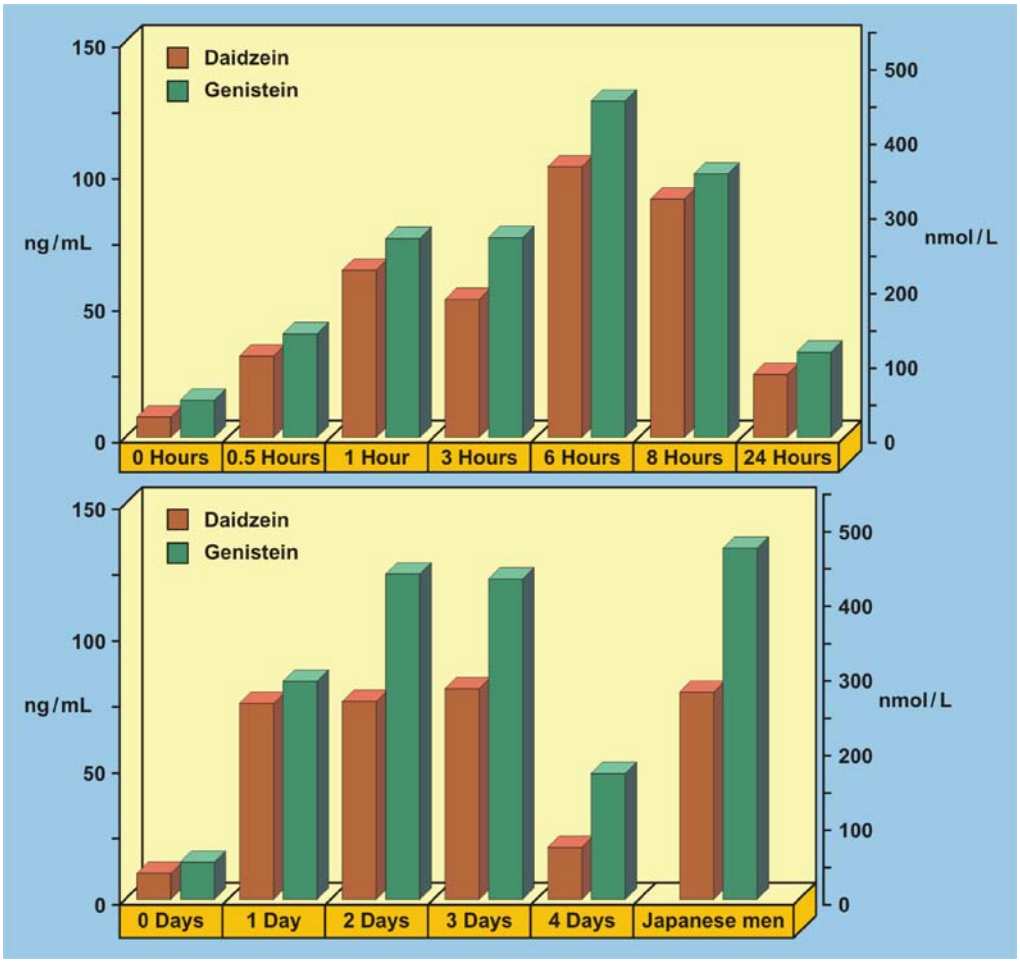


Fig. 4.7 Daily supplementation for 3 days with a soy protein-containing biscuit (Prevacan, XiMed Group, Oxfordshire, UK), showing concentrations of genistein and daidzein in plasma throughout the first day and during the next 3 days. The levels of these isoflavonoids in Japanese subjects are illustrated for comparison

green tea of catechins and various anthocyanidins and resveratrol are constituents of red wine. In ancient times, herbs and spices were synonymous with medicines, including the well-recognized thyme and parsley, garlic and chives and the cruciferous vegetables [47]. Cinnamon may suppress inflammatory disease. Curcumin, the yellow pigment of turmeric, as well as capsaicin in chilli pepper, are reported [48] to have cancer-restraining activity. Several flavonoids—apigenin and kaempferol, for example [49]—are also weak oestrogens; the former, like many flavonoids, is also an effective anti-oxidant. Others exercise a range of biological actions, such as the inhibition of angiogenesis or promotion of apoptosis [50, 51].

Selenium

For many years [52] selenium—an essential trace element found principally in fish, meat and grains—has been thought to be protective against cancer, although this has never been confirmed unequivocally [53]. An inhibitory effect on various experimental tumours was reported

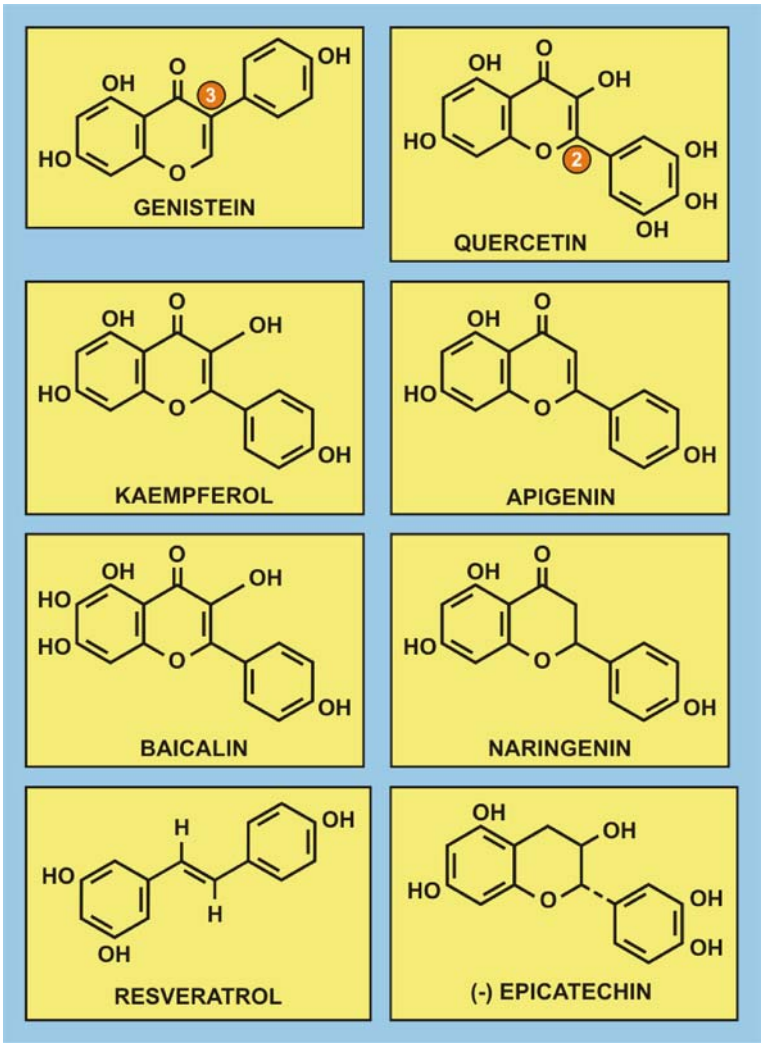


Fig. 4.8 Chemical structures of certain flavonoids relative to that of genistein. Flavonoids have a 2-phenylchroman nucleus, and isoflavonoids such as genistein have a 3-phenylchroman nucleus. Also illustrated are the structures of resveratrol, a constituent of red wine, and one of the catechins present in tea

[54, 55], together with an ability to promote apoptosis in prostate cancer cell lines [56]. Selenium, as selenocystein, is involved in catalysing glutathione-*S*-transferase (GST) π-regulated reactions, which remove from cells the hydrogen peroxide formed in tissues in response to inflammatory oxidative stress (Fig. 4.9). A recent study [57] indicated that men with a high long-term intake of selenium, as reflected in toenail paring levels, were at lower risk of developing prostate cancer. A daily intake of 86 μg was considered in the lower range and 159 μg in the higher level. More recently [58] a decreased incidence of prostate cancer was reported after selenium supplementation. The daily selenium intake could be 30–40 μg in the United Kingdom [59], low in relation to the 1 μg/kg per day recommended intake [34].

Current interest centres on the SELECT trial that is evaluating the efficacy of daily 200 μg

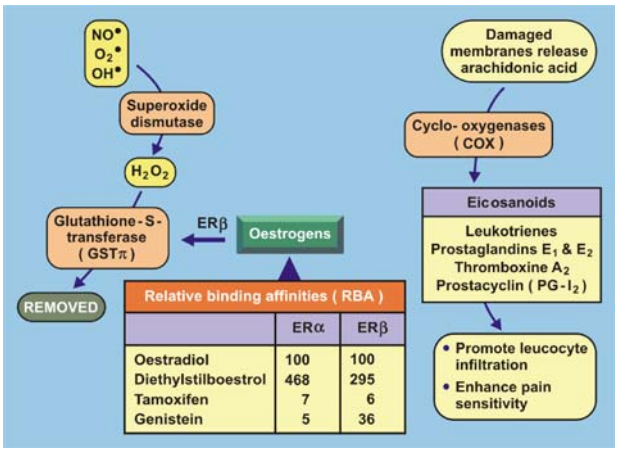


Fig. 4.9 Representation of some molecular events relating to PIA, inflammation and oxidative stress

selenomethionine intake on prostate cancer risk, testing selenium against selenium and α-tocopherol, 400 mg daily, for 7 years [34, 35]. More than 30,000 North American males are to be recruited, minimal age generally 55, but 50 for African-Americans, valuable therefore, in determining whether they effectively restrain progression to clinical cancer. Also of interest would be a study of early selenium and vitamin E supplementation on chronic inflammatory stress, the prevention of PIN and progression to HGPIN (Fig. 4.2).

Vitamins

Much of the epidemiological data relating to the cancer protective value of vitamin supplementation would seem somewhat equivocal. For example, in a meta-analysis of results from 12 case-control dietary intake studies and breast cancer risk [60], a consistent protective effect correlated with 'fruit and vegetable intake', with vitamin C considered the consistent factor. Conversely, another review [61] of data on vitamins A, C and E, concluded that the association between vitamin C and breast cancer risk was limited, although a modest, protective effect of vitamin A was recognised. To compound the inconsistency, results from the United States Nurses Health Study [62] found no association between the intake of vitamin C, vitamin E, nor β-carotene and risk, although again, a protective effect of vitamin A was identified.

Boyle [63, 64] emphasised caution in accepting conclusions derived from such studies, outlining the need for controlled trials before, for example, vitamin supplementation should be recommended as protective against breast cancer. Care was also thought appropriate in relation to data suggesting that prostate cancer risk increases with increasing intake of β-carotene, the conclusion from a study of 29,133 Finnish male smokers [65] whose diet was supplemented with vitamin E and β-carotene. The data (Fig. 4.10) suggest that vitamin E (50 mg/day) is protective in male smokers of this age group, whereas β-carotene supplementation is not, although both are effective anti-oxidants. Vitamin E had no effect on lung cancer risk.

Recent interest has centred on lycopene (Fig. 4.11), responsible for the red colouration of tomatoes and released by cooking and processing. Uncooked tomatoes are a less effective source. Lycopene is another effective anti-oxidant [66, 67], with a recent analysis of anti-oxidants in biopsies of adipose tissue showing [68] it to be the principal constituent. It restrains the growth of cultured cancer cells [69], possibly by inhibition of IGF-signalling networks [70]. Tomato powder, as distinct from purified lycopene, increased prostate cancer-specific survival, in *N*-methyl-*N*-nitrosourea-treated rats [71]. Giovannucci [72] considers that tomato intake

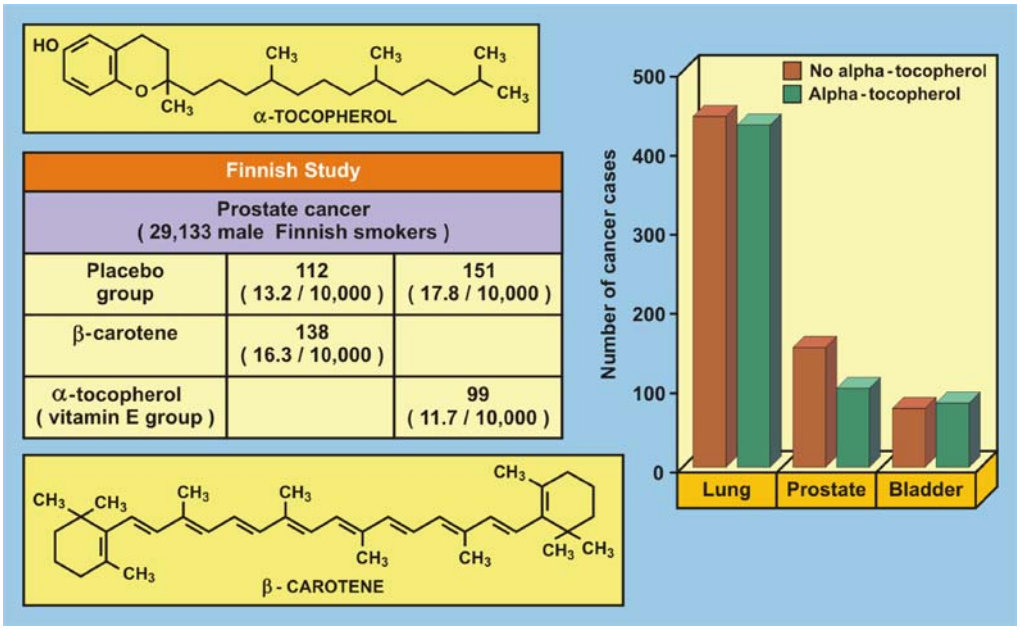


Fig. 4.10 Data from a Finnish study [65] on the potential beneficial effects of α-tocopherol and β-carotene on the incidence of cancer in 29,133 male subjects at 6.1 years follow-up. Illustrated are the numbers of cases of prostate cancer, also seen in relation to the incidence values for cancers of lung and bladder

consistently relates to a reduced risk of prostate cancer, which is inversely associated with plasma lycopene concentrations. As lycopene assumes a potentially important role in prostate cancer prevention, preliminary randomised trials are underway [34–36] to determine the efficacy of a tomato extract (30 mg lycopene/day) in suppressing progression of HGPIN lesions.

The influence of the carotenoids, vitamin A, retinoids and retinoic acid on prostate carcinogenesis would seem complex. Although vitamin A supports normal cellular differentiation and controls proliferation, it has a limited influence on established cancer. Various synthetic retinoid analogues have similar characteristics, and despite high toxicity are thought by some to offer anti-cancer properties [73]. Although more than 50 carotenoids manifest some 'nutritional activity' [74, 75], only β-carotene, derived from vegetables and fruit, is generally recognised as the principal source of vitamin A (Fig. 4.11) and β-carotene may have a role independent of vitamin A. Although it seems that vitamin A supplementation may increase the risk of prostate cancer [63, 64], Schroeder [76] reported a significant increased risk associated with a lower serum vitamin A levels.

Possibly relevant are the classical experiments of Lasnitski [77, 78], which demonstrated that methylcholanthrene-induced prostate epithelial hyperplasia was inhibited by retinoic acid as well as vitamin A. The receptors for retinoids are part of steroid superfamily, members of which not only specifically bind 5α-dihydrotestosterone (DHT) and oestradiol-17β but also retinoic acid and 1,25-dihydroxyvitamin D3 [79, 80]. DHT and oestradiol-17β receptor complexes specifically associate as homodimers to genomic recognition sites (Fig. 4.12). Retinoic acid receptors (RARs) can bind as heterodimers with other retinoic acid receptors, the RXRs [81, 82], to recognition sites composed of oestrogen response element (ERE) half sites, the nucleotide sequence AGGTCA 'repeating' along the DNA chain. In-

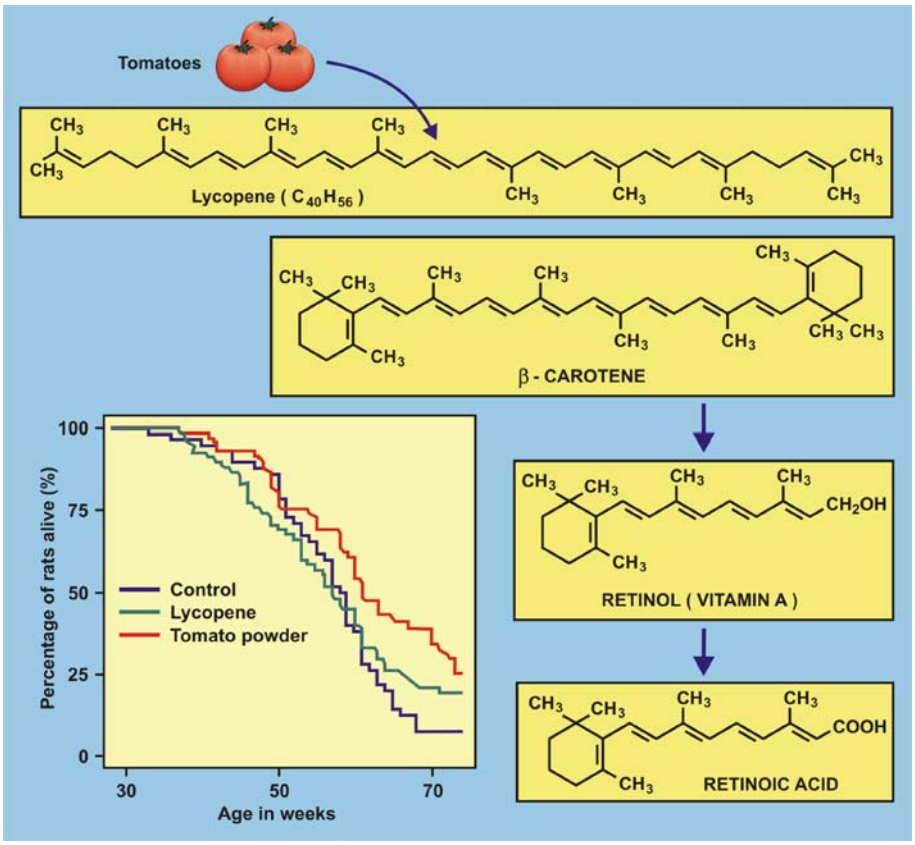


Fig. 4.11 Illustrated is the structure of lycopene, a dietary constituent of tomatoes and the synthetic relationship between β-carotene, vitamin A and retinoic acid. Results of a chemopreventive study [71] of lycopene are also shown. Prostate cancer-specific survival curves for rats, treated with *N*-methyl-*N*-nitrosourea and fed purified lycopene and a tomato powder are portrayed, indicating that at 50 weeks, 37% of controls were alive, compared to 39% fed lycopene and 54% given the tomato powder

duction of differential regulatory responses is thereby a consequence of different combinations of receptors, ligands and recognition sites [83]. Moreover, ligand-independent dimeric receptors [84] can repress gene transcription [85], with RARs—as well as the glucocorticoid receptor (GR) and 1,25-dihydroxyvitamin D3 receptor (VDR)—regulating AP-1 response elements by a protein–protein interaction (Fig. 4.13) with the Jun proteins [86], each protein mutually inhibiting the activity of the other [87]. RARβ expression in the prostate [88] is associated with apoptosis [89]. Since AR or ER status relates to RAR expression, any influence of β-carotene on cancer progression or any clinical effects of retinoids may therefore be dependent on the ER or AR content of the cancer [90, 91]. These subtle genomic protein–protein interactions provide another insight into the complexity of growth control in relation to prevention [92, 93]. Whereas retinoic acid can inhibit the expression of ER-responsive genes, there is also evidence that Fos and Jun proteins inhibit oestrogen responsive genes, with RAR and RXR, down-regulating transforming growth factor (TGF)-β1 expression by antagonising AP-1 activity.

The body's capacity to produce vitamin D is also closely correlated to the risk of prostate can-

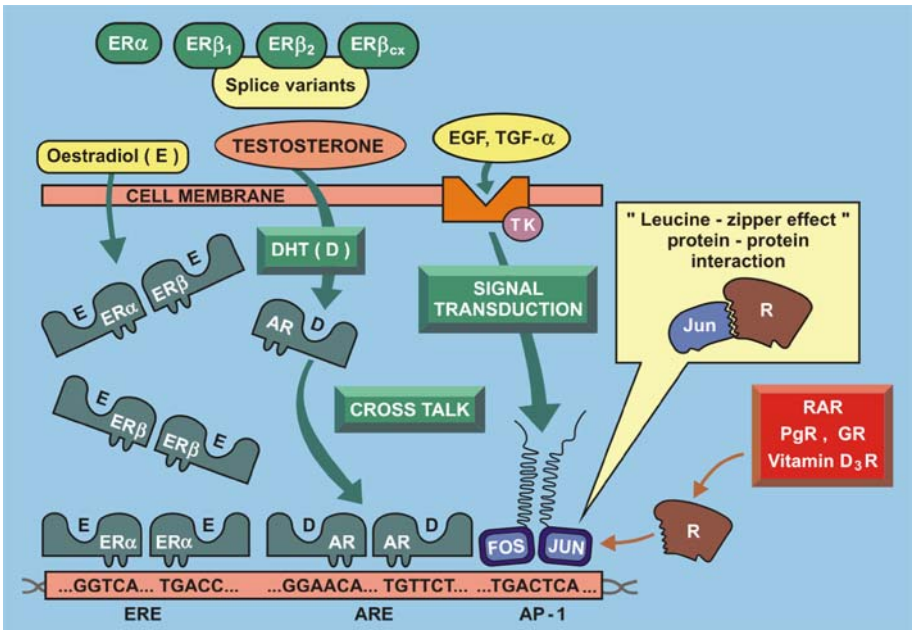


Fig. 4.12 A simple portrayal of the potential crosstalk between steroid hormone and growth factor signalling pathways with their capacity to influence the AP-1 recognition site through Fos-Jun action

cer [94], and Boyle [63, 64] refers to a 250,000 male cohort [95] in which 90 cases of prostate cancer were identified in African-American men and a similar number in Caucasians. The levels of 1,25-diOH-VitD3 in stored serum from these men were compared to controls, matched for age, race and for sample storage time. 1,25-diOH-VitD3 in cancer samples was reported to be a significant 1.81 pg/ml lower than controls; risk therefore decreases with higher levels of the vitamin. Noteworthy, however, was that risk was associated only with palpable tumours, not incidental cancer, suggesting that any influence is confined to the later stages of tumour progression.

The skin, the only source of vitamin D3, is where 7-dehydrocholesterol is converted by solar UV irradiation to the provitamin D3. Thermal isomerisation of provitamin D3 to vitamin D3, occurs in the epidermis from where it enters the blood. It is hydroxylated at the C-25 position in the liver and then, primarily in the kidney but also by keratinocytes, hydroxylated to 1,25-diOH-VitD3, the biologically active hormone, the biological effects of which are mediated [96] through VDR. Like vitamin A, it induces cellular differentiation and restrains proliferation; both effects are associated with the repression of the c-myc proto-oncogene [97] and induction of TGF-β expression [98]. VDR is associated with enhanced apoptosis, increased expression of Bcl-2 and G1S cell cycle blockade in prostate cancer cell lines.

In the USA, prostate cancer mortality is inversely proportional to UV-radiation [99], and in Finland, vitamin D deficiency similarly relates to UV-radiation and cancer. Levels of plasma 25-OH-VitD3, which have been falling during the past 25 years as prostate cancer incidence has increased, are markedly different between men in the rural north during winter than in the southern region. The risk that relates to vitamin D deficiency is higher in pre-andropausal men than those over 50, suggesting a risk factor which implicates androgens. This invokes the concept that normalising vitamin D levels by administration of ergocalciferol or enhanced intake of fish liver oil during the ages of 30–50 will provide protection against prostate cancer.

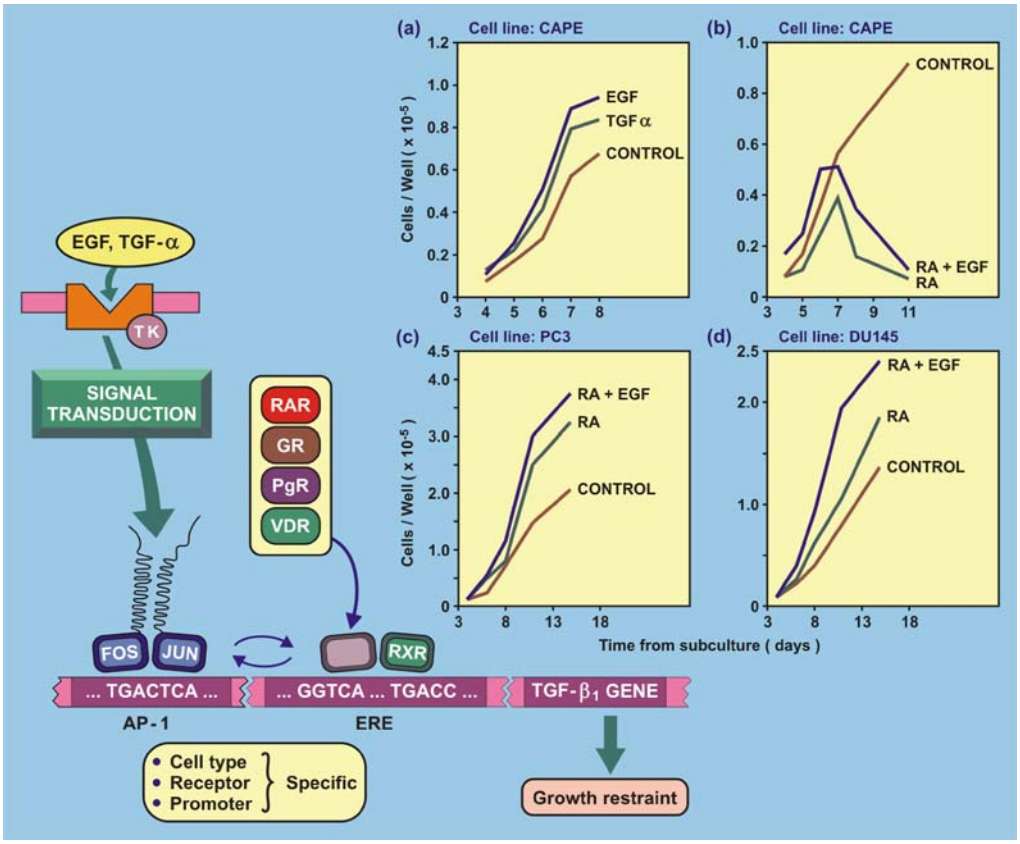


Fig. 4.13a,b Shown is a diagrammatic representation of the potential influence of retinoic acid receptors on the steroid- and growth factor-mediated action on the genome. Depicted is the interaction between RAR RXR heterodimers on the AP-1 response site. Also illustrated are some effects of retinoic acid on the proliferation of various prostate cell lines in culture. The growth of the normal canine epithelial cell line (CAPE) is promoted by EGF and TGF-α (a), an effect inhibited by retinoic acid (b). Retinoic acid did not restrain the growth of the human prostate cancer cell lines PC3 and DU145. Data taken from the Tenovus Institute for Cancer Research [90]

Hormonal Aspects of Prevention

Prevention with dietary factors offers an exciting prospect, but an anti-hormonal approach is more pragmatic. Until recently the principal risk factors for prostate cancer were functional testes and an 'age factor', the latter derived from the clinical manifestation of the disease beyond the age of 50, the former on the concept that cancer fails to develop in males castrated early in life [100]. Androgen-dependence of prostate cancer [101] and studies of men with an inherited 5α-reductase 2 deficiency [102, 103] demonstrated that the gland did not grow in the absence of DHT. Such males did, however, develop acceptable secondary sex characteristics, reasonable libido and a phallus, characteristics promoted by testosterone. These and supporting studies centred on prostate growth regulation [6], providing the incentive for an 'anti-androgen approach' to prevention.

The use of anti-androgens such as flutamide, bicalutamide or cyproterone acetate could offer benefit to men at high risk, but loss of potency, gynaecomastia, nausea and diarrhoea, are unwanted adverse features. Quite rightly, trials have

been instigated [34, 35], although anti-androgen therapy cannot be perceived as an acceptable preventive approach to recommend, for example, to all African-American males over the age of 40, men who must by now believe themselves at risk.

The development of finasteride [104, 105], a 5AR inhibitor, provided an innovative approach to suppressing intraprostatic DHT levels without compromising sexuality. Finasteride specifically inhibits 5AR2, whereas alternatives, dutasteride and epristeride, inhibit both 5AR1 and -2. The Prostate Cancer Prevention Trial (PCPT) involved treating patients for 7 years with either finasteride (5 mg daily) or placebo, followed by an end-point prostate biopsy. Plasma testosterone levels are sustained. Rather than biopsy and its confounding problems, some believe the only acceptable end-points should be survival, metastasis-free survival or disease-specific survival, which is an expensive approach requiring more subjects and longer periods of study, but one that could possibly offer unequivocal results. Second, there is the question as to whether such a trial should commence at an earlier age than 50. Such issues have been considered recently [106].

Finasteride restrains cancer growth, with a 25% reduced risk; the cumulative incidence of cancer was 18.4% for finasteride-treated men and 24.4% for those on placebo [107]. However, the greater prevalence of high-grade cancer in the finasteride group, with a Gleason score of 7 or more, tends to compromise any unequivocal recommendation regarding the clinical value of finasteride in preventive practise for men over 50.

The NCI-P01-0181 trial, which is evaluating flutamide against the combination of flutamide and the anti-oestrogen toremifene, offers a new approach to preventive therapy. Since oestrogens play a more significant role in prostate growth regulatory events than hitherto thought [7, 9, 27], the influence of an anti-oestrogen is awaited with interest. Toremifene represses HGPIN development and decreased prostate cancer incidence in TRAMP mice [108]. ERα knock-out mice do not develop HGPIN or invasive prostate cancer after androgen and oestradiol administration, whereas wild-type mice do [17, 109]. In a trial to determine the effect of toremifene on men with HGPIN, assessed by 6- and 12-month biopsy [110], prostate cancer was detected in 31.2% of the placebo group, compared to 24.4% in those taking anti-oestrogen.

Is There a Genetic Approach to Prevention

Recognising the long preclinical phase in the natural history of prostate cancer, the identification of men with a genetic predisposition to develop the disease would clearly be beneficial. Familial clustering [111] and evidence that family history constitutes a greater risk suggests underlying predisposing factors. Chromosomal analysis mapped the loci of cancer susceptibility genes, although segregation analysis [112, 113] indicates a low frequency, accounting for the 10% of the hereditary cases within the population. To date, hereditary disease has been mapped to the HPC-1 locus (1q24–25), PCAP (1q42.2–43) and CAPB (1p36), together with HPCX (Xq27–28) on the long arm of chromosome X.

The search centred on point mutations, deletion or insertion of nucleotides within a gene sequence that result in aberrant messenger (m)RNA expression and thereby mutant proteins. The AF-1 transactivation function of the N-terminal domain of AR is characterised by polymorphic CAG repeats. Decreased repeats from 24 to 18 relate to elevated AR transactivation activity and prostate cancer [114, 115], with the prevalence of shorter alleles highest in African-Americans and lowest in Asian men, reflecting the geographical variation in incidence. Mutant ARs that inappropriately bind an array of ligands [116] would seem rare in early prostate cancer, although prevalent in metastatic tissue. Gene amplification, whereby substantial lengths of nucleotide sequences are copied, sometimes more than a 100-fold, is a common feature of cancer. If the sequence contains genes encoding for growth regulatory proteins, the effect could support cancer progression. Gene deletion incurs cellular instability and restricted growth restraint; the loss of growth suppressor retinoblastoma (Rb) protein, for example, inevitably confers a growth advantage to the cancer cell. Loss of a p53 gene, which encodes the protein that prevents a damaged cell entering the cell cycle until DNA repair is complete, is

generally an event related to the later refractory phases of the disease.

Many low-penetrance susceptibility genes, mapped to frequently deleted regions in prostate cancers, are concerned with androgen metabolism. Genetic aberration of the SRD5A2 gene would influence the prostate, and mutations have been reported, with VL89 reducing enzyme activity, which is common in Asian men, whereas A49T relates to increased activity and poor prognosis [117]. The latter mis-sense mutation is associated with a sevenfold greater risk of prostate cancer in African-American men.

Aberrations of the HSD17B2 gene, 16q24.1–24.2, encoding for 17β-hydroxysteroid dehydrogenase type II, converting 17β-hydroxy to 17-oxosteroids—essentially the inter-conversions of testosterone and androstenedione, and oestradiol-17β and oestrone—could equally influence the prostate. Gene polymorphisms may identify men at risk, but also support the design of preventive strategies with shorter time-periods and lower costs.

Dietary Factors: Causative or Protective?

Some Reflections on Obesity and Fat Intake

Possibly of significance is that prostate cancer geographical variability is reflected in a similar pattern for cancers of breast, ovary and endometrium, for which oestrogens are risk factors. Sound arguments support some degree of homology between breast and prostate cancers [27, 118], and evidence has accumulated to suggest a major role for oestrogens in prostate growth control [9, 27, 119].

Once again, geographical variability in incidence directs attention to Asian and Western lifestyles, issues outlined by Doll [120] three decades ago, since when, after many retrospective and prospective investigations, the consensus viewpoint of three cancer agencies [121] was, very simply, that the consumption of vegetables and fruit correlates with reduced risk. The greater risk associated with red meat, primarily beef, thereby allowed governmental institutions to recommend frequent consumption of vegetables and fruit, with moderation in meat intake. This and lots of exercise provide health benefits. Broad recommendations, therefore, with the International Agency for Research on Cancer (IARC) suggest [121] that there is little support, at present, for various supplementary cocktails of vitamins and minerals, although the results of the SELECT trial are eagerly anticipated.

The influence of dietary fat on cancer risk remains controversial. Obesity is stated to affect more than 30% of adults in the USA [122], and it has long been standard practise to implicate dietary fat with cancer aetiology, particularly breast [123], although Skrabanek [124], in a derisory manner, once referred to 'the faddish infatuation with fat as the root of all dietary evil'. Some researchers have not been convinced [125] that eating a low-fat diet supports a longer life. Nonetheless, with greater fat intake in Japan, prostate cancer incidence increases [33]; whether this relates to a decreased consumption of soy protein, however, remains to be determined. A range of prospective cohort studies on total dietary fat intake and prostate cancer risk [126] failed to identify an unequivocal relationship, although a correlation with animal fat intake was recognised, a relationship believed by many to constitute the principal risk factor responsible for geographical variability. Important, nonetheless, was that obesity did relate to a greater risk of dying from prostate cancer. Any link between risk and obesity, or increased body mass index (BMI), does, however, remain controversial [126]. Whereas a Norwegian study [127] suggested a higher BMI increased risk, Giovannucci [128] indicated the contrary. A 58% increased risk for obese males, specifically between 50–59 years of age and therefore 'andropausal', does identify an age factor and suggests a possible adverse influence of oestrogens produced by the aromatisation of androgens in adipose tissue [9, 27]. Treatment with an aromatase inhibitor is of clinical value in the management of breast cancer; interestingly, enterolactone, genistein and equol all inhibit the aromatase enzyme in vitro [9, 129].

Possibly more important is the relationship of risk to obesity during puberty and the immediate post-pubertal years, with a report [130] that adolescent obesity increased the risk of dying from prostate cancer. Poor nutrition and lack of exercise through childhood, possibly leading to

some degree of insulin resistance in life's early years, could relate to prostate cancer aetiology [131–133]. Such a lifestyle would lead to elevated levels of androgens and IGF-I. Since the IGF-network supports proliferation and the progression of cells into the cell cycle (Fig. 4.14), IGF-I could be implicated in prostate cancer initiation and growth during the immediate post-pubertal years [134, 135]. Various studies support a correlation between risk and levels of plasma IGF-I [136–138], and Vihko [139] indicated that any hyperandrogenicity developed through puberty is retained into the third decade of life, possibly supporting dysfunctional cellular proliferation (Fig. 4.15).

Prostate Cancer: A Multifactorial Process

Prostate carcinogenesis is a multi-step process involving multiple interactive factors and endocrine, genetic and nutritional features that impact on growth regulatory events [6] that either support or restrain cancer progression through the continuum from initiation to the invasive phenotype. Interruption of these events is the basis of prevention. Such a strategy using anti-hormonal drugs is clearly an important issue. DHT is a predominant growth-promoting factor in prostate cancer development, and the PCPT trial provided evidence of a beneficial influence of finasteride therapy for part of a group of men treated beyond the age of 50. A controversial issue centres on whether the decline in intraprostatic DHT triggers a compensatory expression of alternative, more aggressive growth-promoting signalling in the more progressive cancerous lesions that will be harboured by a proportion of such males, with the consequent development of high-grade cancer. Selenium and vitamin E supplementation may provide benefit to men over 50, and this will be determined by the SELECT trial, but their beneficial influence on PIA and PIN for males in their 20s and 30s demands attention.

There is evidence that chronic, or recurrent intraprostatic inflammation, a feature of asymptomatic prostatitis and PIA, could be implicated in the early phases of prostate carcinogenesis [24, 25, 27]. The induction of COX-2 as part of the inflammatory response, with the consequent production of prostaglandins (Fig. 4.9), a feature of early cancer [140], together with the up-regulation of the enzyme in prostate cancer [141], has directed attention to the potential of COX-2 inhibitors or other appropriate anti-inflammatory agents [142] as an approach to chemoprevention. Moreover, a study by Coffey [27], emphasising a role for isoflavonoids in the suppression of prostatic inflammation induced in rodents by inappropriate intrauterine oestrogen imprinting, highlights the need for trials of soy protein supplementation during the adolescent and post-pubertal years. Moreover, genistein may influence the ERβ-mediated effect [143] of oestrogens on G5Tπ activity. Certainly at the andropause, the phyto-oestrogens may well suppress progression of latent cancer to malignant disease, and trials with soy protein would seem appropriate. Furthermore, soy protein supplements, as opposed to genistein alone, may be relevant, since it appears that only certain males can convert daidzein to equol (Fig. 4.4), which could exercise a specific, more effective preventive role [144] in these individuals. There is evidence that the presentation of a higher-grade prostate cancer is associated with an ability to produce equol.

Many dietary constituents could impact on prostate carcinogenesis, lycopene for one, but others from the diverse range of flavonoids may contribute to the body's natural defences against cancer. Although a recent study [145] found no evidence that 'flavonoid-rich foods' appeared to influence breast cancer risk, a decreased prevalence did relate to a high intake of lentils and beans, essentially legumes that provide a source of isoflavonoids. Anthocyanidins and resveratrol [146] of red wine offer health benefit [147, 148], as might other polyphenols such as (−)epigallocatechin and (−)epigallocatechin-3-gallate, effective anti-oxidants and constituents of green tea [149, 150]. Moreover, infusion of green tea leaves with hot water liberates secoisolariciresinol and matairesinol, precursors of enterolactone. The proanthocyanidins are more effective anti-oxidants than vitamins C and E, whereas resveratrol has anti-inflammatory properties and influences ER-signalling. The polyphenols of green tea are reported to influence the prostate of TRAMP mice [151] and an ongoing Italian

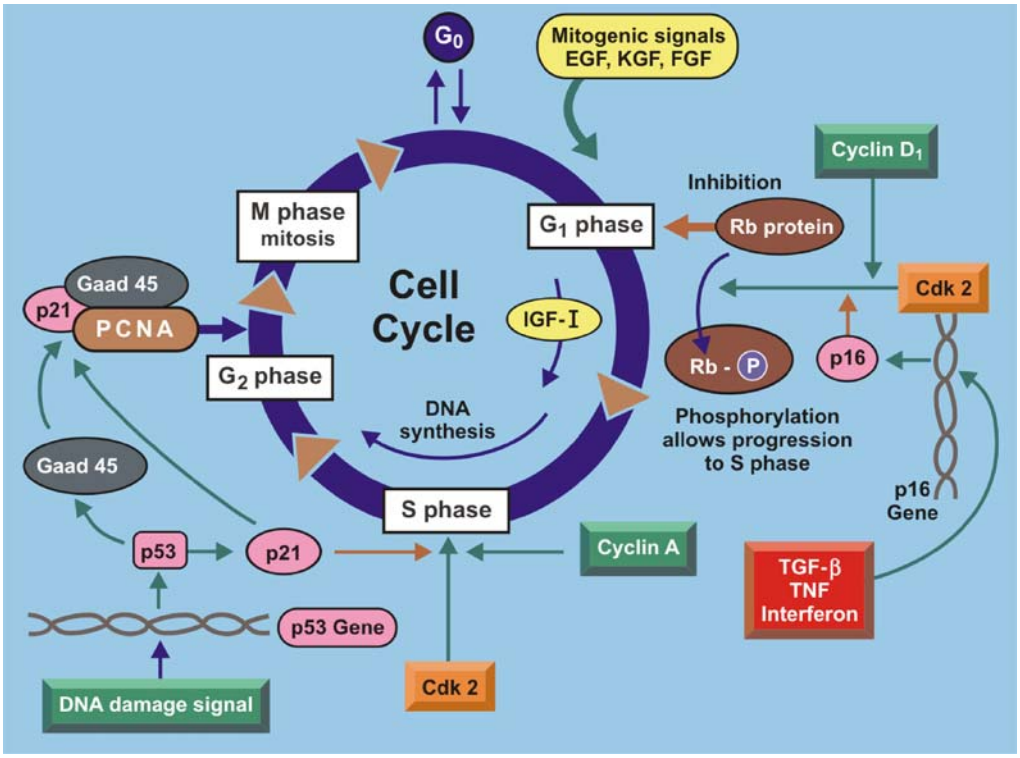


Fig. 4.14 The cell cycle and some of the regulatory factors that determine the progression from G_0 to G_1 and through the cycle

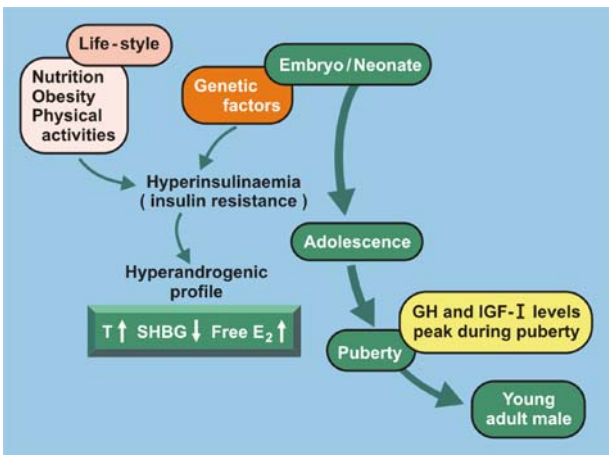


Fig. 4.15 Potential influence of insulin resistance on the development of a hyperandrogenic status in the younger adult male

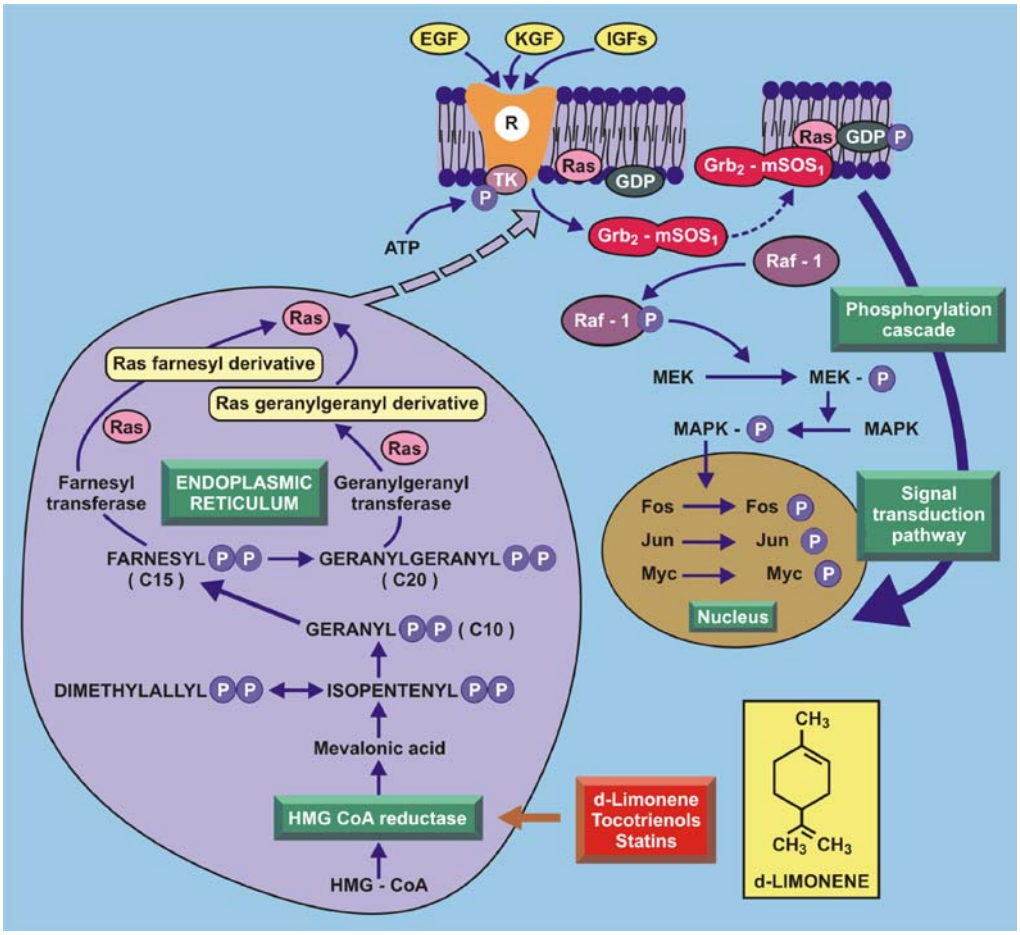
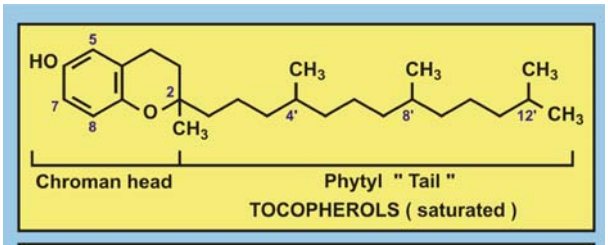
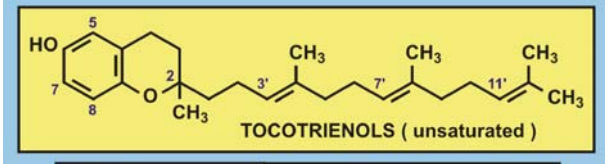


Fig. 4.16 The isoprenylation of Ras protein with products originating from hydroxymethylglutaryl (HMG)-CoA and mevalonic acid—events that impact on the growth factor-mediated complex signalling pathways. Statins, tocotrienols and limonene inhibit HMG-reductase. The mevalonic acid 6C-unit is the basic starter molecule of the cholesterol biosynthetic pathway, being converted first to the 5C-isopentyl pyrophosphate through two farnesyl units to lanosterol and then cholesterol

study [152] provides evidence that they inhibit the progression of HGPIN to clinical cancer. A recent case control study in south-eastern China [153] reports a significant correlation between green tea consumption and the risk of prostate cancer. There is evidence [154] that the tea polyphenols inhibit prostate cancer dissemination by repressing the PSA-triggered activation of matrix metalloproteinases that are concerned with fibronectin and laminin degradation and thereby support cancer cell invasion. Moreover, they can down-regulate AR expression in LNCaP cells [155]. In passing, there is a notion [156] that alcohol itself may promote the aromatisation of androgens.

The isothiocyanates of cruciferous vegetables, constituents such as sulphoraphane, could also exercise some degree of protection against prostate cancer initiation, possessing the capacity to detoxify particular animal carcinogens such as the heterocyclic aromatic amines produced by the charring of red meat [27, 157]. This is somewhat controversial, since risk appears to relate to the intake of red meat [10], despite such amines





Position of methyls	Trivial name	
5, 7, 8	α-tocopherol	α-tocotrienol
5, 8	β-tocopherol	β-tocotrienol
7, 8	γ-tocopherol	γ-tocotrienol
8	δ-tocopherol	δ-tocotrienol

Fig. 4.17 Tocotrienols, the unsaturated analogues of tocopherols

being produced by charring of chicken and fish. Nevertheless, sulphoraphane promotes apoptosis, decreases cyclin B1 expression and induces G2M cell cycle arrest in human prostate cancer cell lines.

Although cancer was simply considered an imbalance between cell proliferation and cell death, more recently, failure of cancer cells to undergo apoptosis has become the major issue [158, 159]. Since cancer cells are dying more slowly, therapy must be focussed on apoptosis-triggering mechanisms and many of the 'beneficial' dietary factors that promote apoptosis in experimental systems. Citrus fruits are seen as beneficial and interesting; although d-limonene, a monocyclic monoterpene in the peel of the fruit also promotes apoptosis in model systems [160], it is recognised that—like the 'statins'—d-limonene inhibits 3-hydroxymethylglutaryl CoA (HMG CoA) reductase [161] and thereby the synthesis of cholesterol (Fig. 4.16).

There is no doubt that the statins decrease serum cholesterol and benefit those with cardiovascular problems, but can they decrease cancer risk? HMGCoA reductase inhibition will suppress the synthesis of isoprenoid residues, thereby inhibiting isoprenylation of the p21 Ras protein, important for Ras GTP-ase signalling. Isoprenylation involves the transfer of either C15-farnesyl, or C20-geranylgeranyl isoprene residues to the p21-protein, thereby increasing its lipophobic nature that enables GTPase to be anchored, then re-located within the cell membrane. Ras mutations are a feature of prostate cancer, and repression of isoprenylation of the mutated p21 Ras protein provides growth control. Transfection of this mutated protein into mouse fibroblasts in the presence of insulin and IGF-I results in transformation and enhanced cell proliferation. Also interesting is that prenylflavonoids [162] such as isopentenyl-naringenin act as oestrogen agonists.

The less well known tocotrienols, natural analogues of tocopherol (Fig. 4.17), also suppress tumour growth, and the physiology that surrounds their preventive potential has been reviewed [163]. They also inhibit HMG-CoA reductase, promote apoptosis and inhibit DNA synthesis.

Although the precise role of oestrogens within the prostate remains somewhat of a conundrum, they consistently feature in preventive strategies; indole-3-carbinol, for example, a constituent of cruciferous vegetables such as cabbage, cauliflower, Brussels sprouts and broccoli, influences the metabolism of 2- and 16-hydroxylated oestrogens.

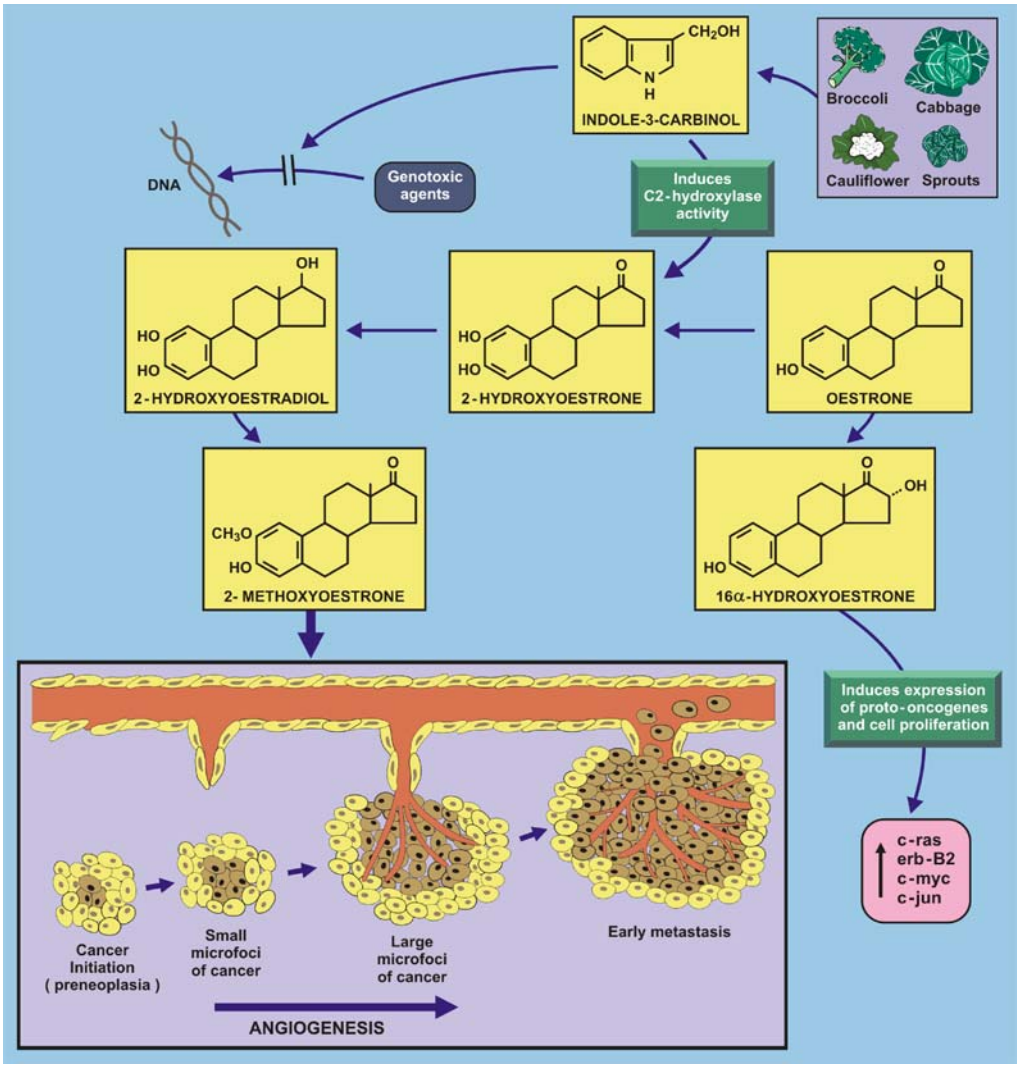


Fig. 4.18 The relationship of catechol oestrogens to angiogenesis and cell proliferation. Indole-3-carbinol is a product of cruciferous vegetables. The indole-3-carbinol can prevent genotoxic agents from reaching their target site and, second, induce 2-hydroxylase enzyme systems

Bradlow [164] reports that 16-hydroxylation relates to cancer initiation, whereas 2-hydroxylation is associated with suppression. Indole-3-carbinol induces the 2-hydroxylases (Fig. 4.18) and, like genistein, 2-methoxyoestradiol inhibits angiogenesis [165].

Important in the underlying events that control prostate growth is the recognition [38] that genistein, through ERβ-mediated signalling, regulates the capacity of ERα to promote AR expression and transactivation. This invokes interest in ERβ-mediated signalling pathways relative to those controlled by ERα. They can be quite distinct, sometimes complementary, but often mutually antagonistic, with differing affinities with various oestrogens [37, 39], and prostate carcinogenesis will be influenced by the cellular specificity and content of ER-isoforms. Can ge-

nistein suppress AR levels and thereby epithelial cell proliferation during the early male adult years? Loss of ERβ-mediated signalling in PIN lesions supports this putative role. Noteworthy is that genistein, presumably through ERβ, induces G2M cell cycle arrest and apoptosis in association with p53-independent up-regulation of p21 and down-regulation of cyclin B1 [29]. Should 20-year-olds undertake soy protein supplementation? Important, however, is the report [166] that the majority of primary prostate cancers, as well as metastatic tissue, do express ERβ.

Prevention: The Broader Acres

Despite a prevailing belief, inherited from folklore, traditional wisdom and possibly the words of Confucius, that 'an ounce of prevention is better than a pound of cure', the integration of preventive practise into the modern health-orientated, medicine-based society is far from complete. Scientifically credible preventive measures must be inextricably linked to curative medicine, based on a precise understanding of the natural history of a disease. Second, preventive strategies must be integrated into community screening programmes. The biological essentials of such measures centre, very simply, on the enhancement of the body's own natural defence mechanisms against disease. In the case of prostate cancer these mechanisms would seem reasonably effective during the extended preclinical period, when the gland's own capacity to restrain carcinogenesis can be emphasized [167].

As to whether nutritional factors can prevent initiation or extend the time to clinical disease remains to be proved. Governmental agencies recommend the benefits of a diet rich in fruit and vegetables, a moderate red meat intake and regular exercise. It is probably disappointing to mention this, but caution is indicated with regard to the efficacy of supplementation with specific dietary constituents on the basis that dose-responses and adverse effects are yet unknown, since few randomised controlled trials have been completed. The medical community may also believe the preventive concept to be a little premature. Such trials are costly and finances are limited. Despite prostate cancer's rise as a high-profile disease—often presenting in the incurable, advanced state—yet controversy flourishes as to the value of population screening to reduce mortality [11]. The concept that health gain can be derived from diet-related intervention initiatives, even if scientifically sound, could be difficult to finance.

Prevention must, however, be the keystone of medicine in the early decades of the twenty-first century, and discussion must centre on real costs, risks versus benefits of preventive strategies and whether it is a worldwide issue for the entire population, or merely appropriate for African-American males, possibly Finns, who are recognised as high risk, or simply complementary to current practise in the management of clinical disease. Such an approach is not in any way an alternative option to recognised clinical practice. If a preventive strategy could be offered to all men, however, only few would derive benefit, and any specific agent would have to be taken for a considerable period of time. The use of tamoxifen as intervention therapy for breast cancer requires 400 appropriate North American females to take the drug for a year to prevent one additional case [168]. Assuming a dietary agent reduces prostate cancer risk by 50%, a similar number of American males would be treated to prevent one additional case of prostate cancer [35]. Established drugs such as anti-oestrogens, 5AR inhibitors and COX-2 inhibitors are being tested with high-risk groups [34–36], and information is accumulating on efficacy and appropriate endpoints. Nonetheless, such drugs are generally perceived as 'chemicals', whereas a more positive but poorly perceived 'consumer attitude' extends to the 'more natural' dietary factors, being seen as purer and safer.

Rather than the broader advocacy of the benefits of fruit and vegetables, if appropriate specific dietary factors seem to provide some degree of protection against life threatening disease and to better sustain men's health, can such 'scientific messages' be credibly conveyed to the general public. Compelling evidence suggests that isoflavonoids may well provide health benefit to Asian and other ethnic populations worldwide, either through the intake of soy protein by healthy, reproducing Asians, or of other legumes, by the people of India and South America.

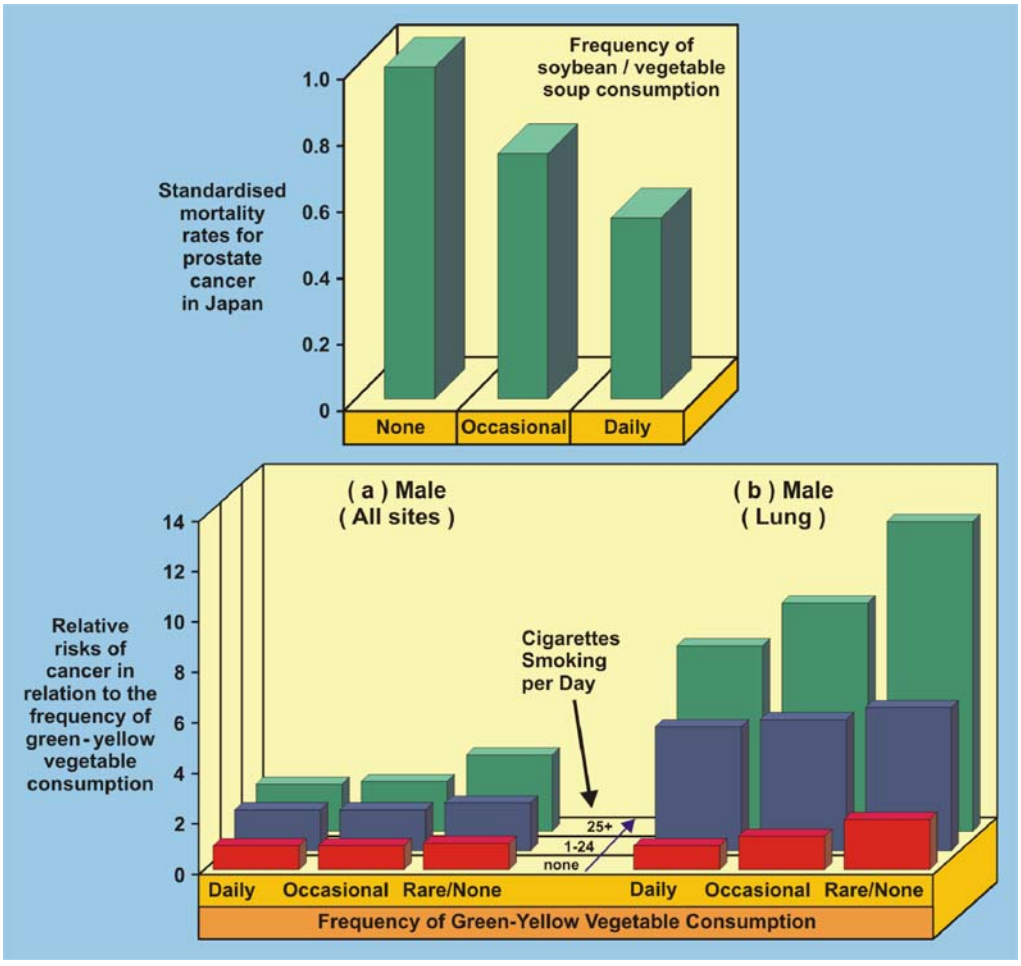


Fig. 4.19 Standardised mortality rates for prostate cancer in Japan, illustrating within this population the influence of regular intake of soybean soup. A similar influence was recognised by Hirayama [169] with regard to all cancers and lung cancer, with an impact even on those who smoked. There were 265,118 subjects studied

Definitive evidence from controlled trials may not be available for many years, so is it reasonable to suggest that since humans appear not to be adversely affected by exposure to these phytoestrogens, that a greater intake of soybean, or legumes, could be specifically recommended? A similar argument could prevail for the polyphenols of green tea. The geographical variability between ethnic groups offers valuable data, but the classical studies of Hirayama [169] that showed differences in cancer incidence within an ethnic group—the differences being dependent on the intake of soybean vegetable soup, daily, occasionally or rarely (Fig. 4.19)—provided particularly relevant information.

Undoubtedly, the importance of a properly balanced diet is now better appreciated by the general public, but any suggestion for the need for specific dietary change must be accompanied by readily assimilated science. People do not find it easy to understand 'scientific messages' although National Cancer Societies do provide excellent guidelines on diet, nutrition and cancer prevention. The 'prevention of cancer' can invoke

serious emotional challenges, but dietary change is not easy and a person's ability to understand the underlying science can be overestimated. While emphasising, however, that 30% of the 500,000 cancer deaths in the United States annually are related to smoking, the substantial proportion that can be attributed to dietary factors, very much a modifiable determinant of cancer risk, cannot be overstated. The costs assumed by a nation's health services in managing the consequences of poor nutrition and the associated lifestyle, especially cardiovascular disease and cancer, are probably many fold higher than those related to 'smoking'. The signal-transduction pathways that convey such salutary messages to the man-in-the-street must be very professional and the information scientifically sound, with consideration given to the renowned inability of the public to reach a consensus on almost any subject. Open dissent through the media tends to generate scepticism, upholding the view that scientists rarely agree on any such issues.

Sporn [170] has most eloquently argued the need for intervention initiatives directed to the early phases of carcinogenesis. He intimates his belief that a proportion of the medical community considers that cancer only 'begins' when the disease can be clinically detected, a time unfortunately when it may be invasive. Lots of vegetables and fruit can be recommended for men through their early years and possibly the three post-pubertal decades, but is this sufficient?

It would probably be naïve to advocate daily helpings of Japanese miso soup made from fermented soybeans, five cups of green tea each day, a bowl of blueberries and rye-bread toast sprinkled with cinnamon for breakfast, a vegetarian-style lunch of broccoli and spinach—with walnuts for α-linolenic acid, accompanied by two glasses of red wine—and a venison-burger with ketchup for supper. Alternatively, for the present, the government-sponsored production of capsules that contain 'dietary goodies' could offer a better way forward, the capsule containing the appropriate amount of soy protein, flaxseed for enterolactone, linolenic acid and selenium, vitamin E, and lycopene, to combat oxidative stress. It offers an interesting, precisely presented 'cocktail' and invokes a challenging strategy. The health benefits of statins as effective primary preventive agents against stroke [171] and for those with hypercholesterolaemia, or at even moderate risk of coronary or cerebrovascular problems, might support their inclusion in such a capsule.

All this may be facetious comment and, clearly, care is important [172]. The science is never simple. Although it might be presumed that all antioxidants, vitamin E, β-carotene, vitamin C and lycopene should demonstrate equal efficacy in restraining tissue damage induced by free radicals, clearly they are not. Tellingly, the CHAOS investigation [173] and the GISSI-Prevenzione Trial [174]—directed to vitamin E supplementation for protection against cardiovascular disease—provided contradictory results. Moreover, a meta-analysis of 19 trials and 135,967 subjects suggested [175] that a high vitamin E dose could enhance all-cause mortality. A recent study [176] failed to show any effect on prostate cancer risk, or any cancer, after supplementation with β-carotene. Subsequent data evaluation then suggested, however, that men with lower levels of plasma β-carotene, may benefit from supplementation, whereas those with higher levels may develop cancer. Too much β-carotene may also be bad for men. A goody bag capsule offers a logical way forward. But does society require unequivocal science from expensive and time-consuming, randomised trials, before forms of intervention can be established that do not compromise the credibility of medical science? Another recent review (177) describes the compelling evidence that dietary nutrients may prevent the development and progression of prostate cancer, with a meta-analysis (178) indicating that consumption of soy food was associated with a lower risk of prostate cancer.

These confounding issues are part of society's learning experience. The impact of intervention therapy on the ageing process and mortality, or premature death, could be profound; analysis is therefore necessary on the costs vs benefits of such strategies, which would change social structure. Research into the impact of dietary constituents on disease processes must be encouraged and appropriate controlled intervention trials quickly established as finance becomes available. These trials will provide the real science-based evidence of any benefit; but it is a fascinating challenge for medical science as well as societies to consider whether 'eat more fruit and vegeta-

bles' is going to be sufficient for those Web-savvy consumers of today, who appear to demand more information and a greater input into their governments' decision-making.

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5 Prostate Cancer Screening

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Recent Results in Cancer Research, Vol. 175

Introduction

Prostate cancer is a major healthcare problem worldwide, especially in the industrialized countries of the Western world. Prostate cancer has become the most common type of cancer among men and is the second leading cause of years of life lost from cancer in males [58]. Incidence estimates for the year 2000 indicate prostate cancer newly affected 542,990 men worldwide that year, 204,313 of whom have since died. Early detection and treatment of prostate cancer could theoretically reduce the burden of this potentially disabling and deadly disease. However, because no conclusive, direct evidence demonstrates that early detection and treatment improve length or quality of life, the value of prostate cancer screening remains controversial.

Prostate cancer is primarily a disease of elderly men. About 85% of all cases of prostate cancer are diagnosed in men older than 65 years, and 90% of deaths due to this disease are in men over age 65. Prostate cancer is diagnosed in very few men younger than 50 years (<0.1% of all patients with prostate cancer) [2].

There are large differences in the incidence of prostate cancer worldwide. Incidence is very high in North America and northern Europe (peaking at 63 per 100,000 white men and 102 per 100,000 African-Americans in the U.S.), but much lower in Asia (10 per 100,000 men in Japan) [18]. The lifetime risk for clinical prostate cancer among men in the United States is approximately 10%; approximately 3% die of this disease [43]. Despite these differences, the microfocal incidence of prostate cancer on autopsy is similar worldwide. Autopsy and cystoprostatectomy studies have shown a prostate cancer prevalence of 30% to 80%, depending on age, based on histological examination. For men over age 50 years, the weighted average of prostate cancer prevalence based on autopsy studies is 30% [13]. Approximately 30% of these cancers are believed to be clinically significant [48]. Thus, the risk for a 50-year-old man with a 25-year life expectancy of having microscopic cancer is approximately 30%; of having clinically evident disease, 10%; and of dying of prostate cancer, 3% [60]. The disparity between the 30% with microscopic cancer and the 3% lifetime risk of death shows the difficulty in distinguishing cancer as an indolent disease. Patients with very aggressive tumors, (i.e., high Gleason grade) have a significant risk of dying of prostate cancer. Patients with relatively nonaggressive prostate cancer have a smaller risk of dying of the disease [39, 49].

Epidemiology and Regional Variation

Prostate cancer is one of the few malignancies for which the incidence varies widely across different parts of the world. Hsing and colleagues classified 15 countries according to their level of prostate cancer risk. High-risk countries included the United States, Canada, Sweden, Australia, and France. Medium-risk countries included most of Asia [27]. The same group of investigators also examined trends in the incidence from 1973 to 1992. From 1998 to 1992, when prostate-specific antigen (PSA) testing became widespread, the incidence in the high-risk countries ranged from 48 to 137 per 100,000 person-years, while the incidence in low-risk countries ranged from 2.3 to 9.8 per 100,000 person-years. In general, prostate cancer incidence rose in all countries during these years, with the increment increasing by between 16.2% and 113.3% over the period [27].

The large geographical difference in the clinical incidence of prostate cancer, coupled with the marked discrepancies between the incidence of latent microfocal disease and clinical disease, raises the concept that environmental factors may play an important role in the prevention and/or progression of the disease. In the majority of men with pre-existing microfocal disease, the growth is stimulated. It seems likely that these differences are only rarely due to genetic factors [36].

Among the environmental factors that are supposed to be critical in the development of prostate cancer, nutrition is suspected to play a major role. Dietary habits vary greatly across the world. There is increasing evidence to suggest that several elements of the diet may play an important role in the prevention and/or progression of prostate cancer (Table 5.1) [53]. To date there have been 14 well-performed, case-control studies involving 4,797 prostate cancer patients and 5,779 control subjects [18]. Eleven of these studies have demonstrated a positive association between increased dietary fat or specific fatty foods and a higher risk of prostate cancer with an odds ratio (OR) of 1.3–3.4. Epidemiological studies have suggested that vitamin E may also influence the development of prostate cancer [25]. However, the preventative effect of dietary components has not been definitely demonstrated in any specifically designed prostate cancer-focused studies that would withstand rigid scientific scrutiny.

Table 5.1 Dietary factors and prostate cancer

Bad effect	Good effect
Fat	Antioxidants
High saturated fat	Vitamin E
High animal fat	Lycopene
Omega 6 fat	Carotenoids
Micronutrients	Micronutrients and vitamins
Calcium/dairy	Selenium
	Vitamin D
	Soy/phytoestrogens

Screening and Early Detection

There is a worldwide attempt to improve the terrible outcome of prostate cancer. We think that prostate cancer, when detected in a localized stage, can be cured or the survival rate and the patients' quality of life can be improved. If we diagnose prostate cancer in a late stage, it means an incurable status. Two approaches are accepted to achieve this goal at present: early detection and systematic screening. The first means evaluation on patients' request or as part of any other medical examination. The second is a planned examination of the affected population. The same clinical examinations are used in both methods. These are the digital rectal examination (DRE), the serum PSA level measurement, and transrectal ultrasound.

The latest has not been used for years because of the very low specificity, invasiveness, and high cost. DRE has low sensitivity alone, so it is not recommended for screening, but together with (PSA) testing, it improves the detection rate. PSA is a glycoprotein with serine protease activity produced primarily by epithelial cells lining the acini and ducts of the prostate gland. PSA is secreted into the lumina of the prostatic ducts and is present in high concentrations in seminal fluid. Plasma concentrations are normally low but are increased by conditions that disrupt normal prostate structure and function (i.e., inflammation, infection, hyperplasia, prostate cancer). Androgens regulate expression of the PSA gene. Men who have regular PSA tests have a much higher chance of finding out that they have prostate cancer compared to men who do not have PSA tests. With the use of an effective testing procedure, systematic screening shows a temporary but significant increase in the incidence, because we diagnose those patients whom we would otherwise diagnose clinically at a later time. Thus, lead-time is produced, which can last from 4 to 10 years. After the second or third screening round, lowering of the incidence is to be expected. This was seen in the United States' statistics very well [56]. The decreasing of mortality is expected only years after that. The cause of the lead time and the aggressive early treatment produce additional survival time, for which the

disease-specific mortality is the only endpoint in evaluating the effectiveness of screening.

However, screening for prostate cancer remains controversial. In some countries, screening is standard healthcare policy; for example, in the United States it is recommended that men older than age 50 years (40 years for African-Americans or first degree relatives of affected men) have a PSA test and DRE at least once every 1–3 years as long as their life expectancy exceeds 10 years [21]. In other countries, such as the United Kingdom, Austria, and the Netherlands, as well as in Scandinavian countries, there are no screening policies because solid evidence is lacking to support the effectiveness of screening and early treatment in terms of improving mortality. Differences in healthcare systems and other economic factors also have to be taken into consideration when comparing countries with high levels of testing with those that have a lower level.

The American Urological Association and the American Cancer Society recommend prostate cancer screening annually, both PSA and DRE from the age of 50 years for men who have at least a 10-year life expectancy, and to younger men who are at high risk. On the other hand, according to the statement of the European Association of Urology (guideline 2005), at the present time there is a lack of evidence to support or disregard widely adopted, population-based screening programs for early detection of prostate cancer aimed at all men in a given population. The use of PSA in combination with DRE as an aid to early diagnosis in well-informed patients is less controversial and widely used in clinical practice.

Effect of Screening

The decision about whether to pursue early detection of prostate cancer is complex. In brief, the dilemma exists because many men with prostate cancer will die of other causes. Treatment is not necessary for some patients. On the other hand, prostate cancer remains the second most common cause of male cancer deaths. Therefore, differentiating between patients whose cancer is clinically insignificant and those whose disease will progress is a challenge. To meet this challenge, a laboratory test must have maximum sensitivity for detecting a clinically significant disease and maximum specificity and positive value to eliminate as many unnecessary biopsies as possible.

Albertsen [1] in the United States and Johansson [30] in Sweden examined the spontaneous history of early-localized prostate cancer with conservative treatment. Albertsen found that 29% of the patients regardless of the Gleason score died of prostate cancer over the follow-up 20 years or more. He also scrutinized the mortality rates stratified by age and Gleason score at the time of the diagnosis (Fig. 5.1). He does not advise aggressive treatment of low-grade tumors. Johansson, however, saw a markedly worsening outlook in case of disease-specific mortality and the generalization of the disease after 15 years, which was continuous up to 20 years, both in low- and medium-grade (Fig. 5.2), so he advised early aggressive treatment in patients with long life expectancy. We should state that in both studies the patients came from the pre-PSA area, and the prostate cancers were mainly pT2. We cannot know the exact outcome of the T1c cancers, which are the most prominent part of the screened population. We can hope that this population could produce even more favorable survival data.

In the United States the most complete information on the epidemiology of prostate cancer has been assembled by the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute (NCI) [58]. The SEER incidence data for years 1973–1999 can be divided into pre-PSA and PSA eras with the PSA era beginning in the late 1980s. During the pre-PSA era there was a gradual rise in the incidence of prostate cancer, likely due to the increasing number of transurethral resections of the prostate (TURP) being performed. Once TURP became a routine part of prostate management, prostate cancer rates stabilized in the late 1980s until the advent of the PSA era. At that time, an abrupt rise in prostate cancer incidence was observed. The incidence of newly diagnosed prostate cancer peaked in 1992 with 237 cases per 100,000 person-years. Thereafter, the annual incidence rate declined until 1995, likely due to

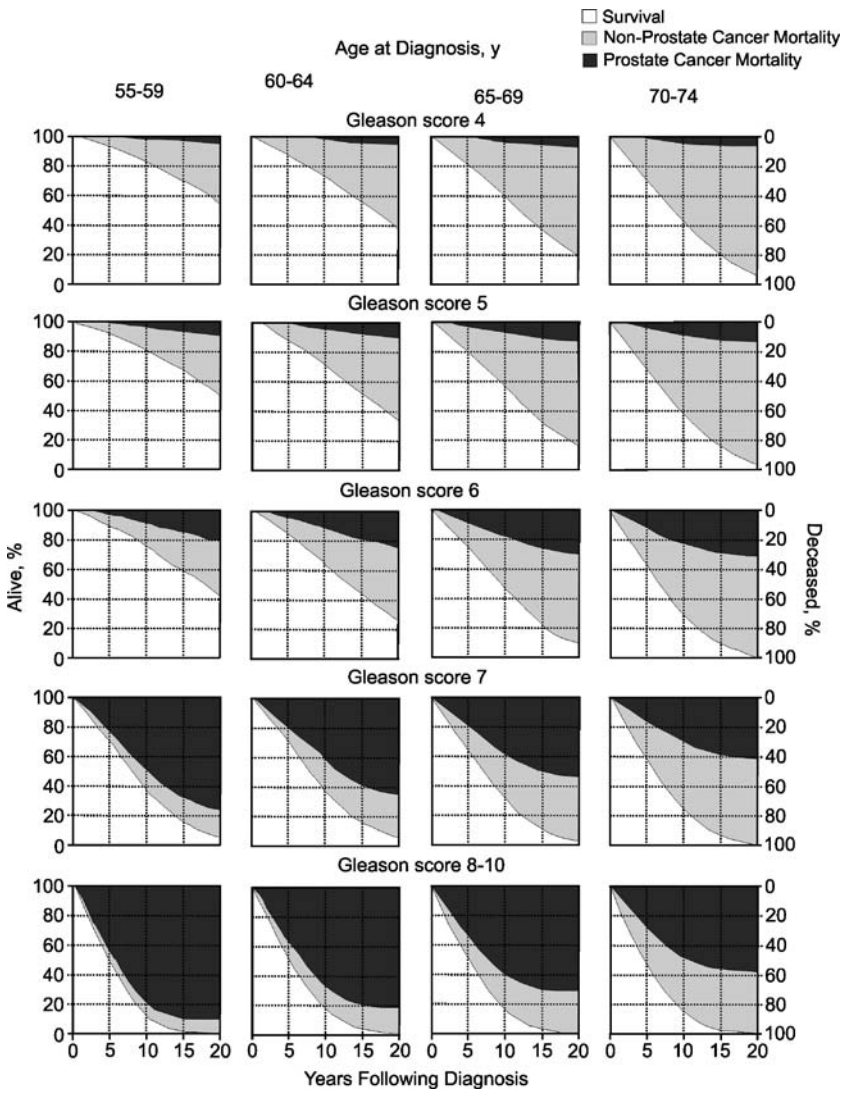

Fig. 5.1 Survival and cumulative mortality from prostate cancer and other causes up to 20 years after diagnosis, stratified by age at diagnoses and Gleason score [1]

the cull effect (removal of detectable cases in prior years resulting in fewer available cases for repeated screening). A relatively stable incidence rate was observed in the pre-screening era.

The U.S. Preventive Services Task Force (USPSTF) analyzed one randomized controlled trial (RCT) and three case-control studies examining the effect of screening on prostate cancer mortality. The single RCT of PSA and DRE screening, which reported a benefit from screening, was hampered by a low rate of acceptance of screening in the intervention group (23%) and by flaws in the published analysis [33]. No difference in the number of prostate cancer deaths was observed between the groups randomized to screening vs usual care using "intention to treat"

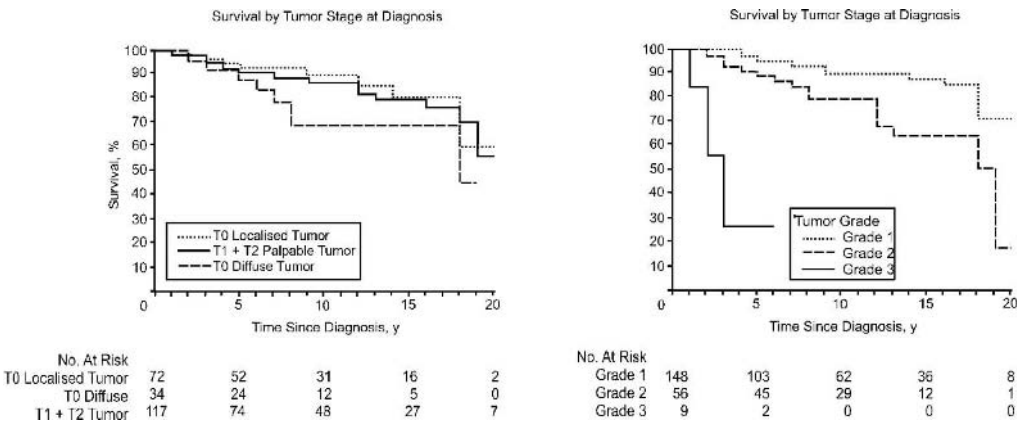

Fig. 5.2 cause-specific survival by stage of disease and tumor grade at diagnosis [30]

analysis. Three case-control studies of screening DRE produced mixed results [20, 29, 46]. In the absence of better data about which treatments are effective for which tumors, the USPSTF could not determine whether the increased detection of prostate cancer from screening would reduce mortality and morbidity.

A large, good-quality RCT, Bill-Axelson [5] examined the course of localized prostate cancer managed with radical prostatectomy or watchful waiting over 10 years. Of the patients, 76% had stage T2 tumor and only 12% had T1c. During the follow-up, significantly fewer men in the radical prostatectomy group than in the watchful waiting group died of prostate cancer (30 vs 50, p=0.01). They also found that the difference is greatest and almost limited to patients younger than 65 years. The difference in overall mortality was also significant (83 vs 106, p=0.04). They also stated the significant lowering of distant metastasis, local progression, and additional treatment in the prostatectomy group. We can therefore say that radical prostatectomy is able to reduce cancer specific mortality in stage T2 tumors in younger patients. This study does not establish a benefit of screening because only 5.2% of cases were found by screening.

The Canada Quebec trial was a population-based trial that started in 1988. A total of 46,193 men aged 45 to 80 years were identified through electoral lists, all residing in the province of Quebec; 30,956 were invited to be screened, of which 7,155 accepted. In the control group were 982 men who were also screened. This meant only 23%. The cutoff is a PSA level of 3 ng/ml; re-screening was annual. The relative risk of dying of prostate cancer was 3.7 times higher in the control group than in the screening group. This showed a 69% mortality rate reduction [20] among those who were screened yearly. When others re-analyzed this study according to screening principles (see the following section), no significant difference was found between the screening and control group with respect to prostate cancer mortality [6].

A reduction in prostate cancer mortality following the introduction of PSA screening has been reported by Bartsch [3]. In this study PSA testing was made freely available to men aged 45–75 years in Tyrol (Austria), and treatment of curative intent was offered to every patient diagnosed with prostate cancer between 1993 and 1998. There was a 44% decrease in prostate cancer mortality in 2000. The decreasing started in 1995. This was not freely observed in the rest of Austria, where PSA testing was not freely available (Fig. 5.3). However, it is difficult to prove the benefit of PSA screening in such a confined population. When age-adjusted prostate cancer mortality rates from the Austrian Central Statistics Office for Tyrol are compared with those for the rest of the country, most deaths and the greatest improvements in mortality occurred in the group aged 70–79 years (Fig. 5.4).

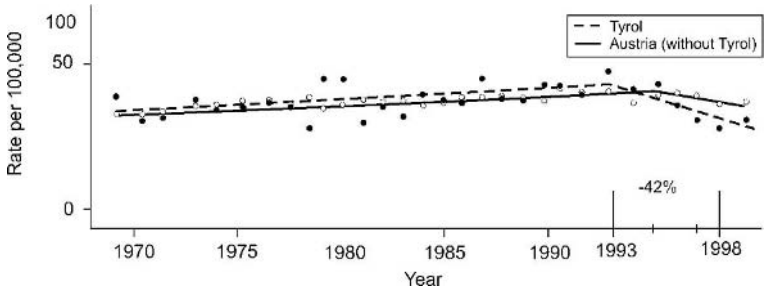

Fig. 5.3 Mortality from prostate cancer in Tyrol and the rest of Austria. Between 1993 and 1999 prostate cancer mortality decreased by 42% in Tyrol, where PSA testing was freely available, compared with modest downward trend observed in the rest of Austria, where it was not [3]

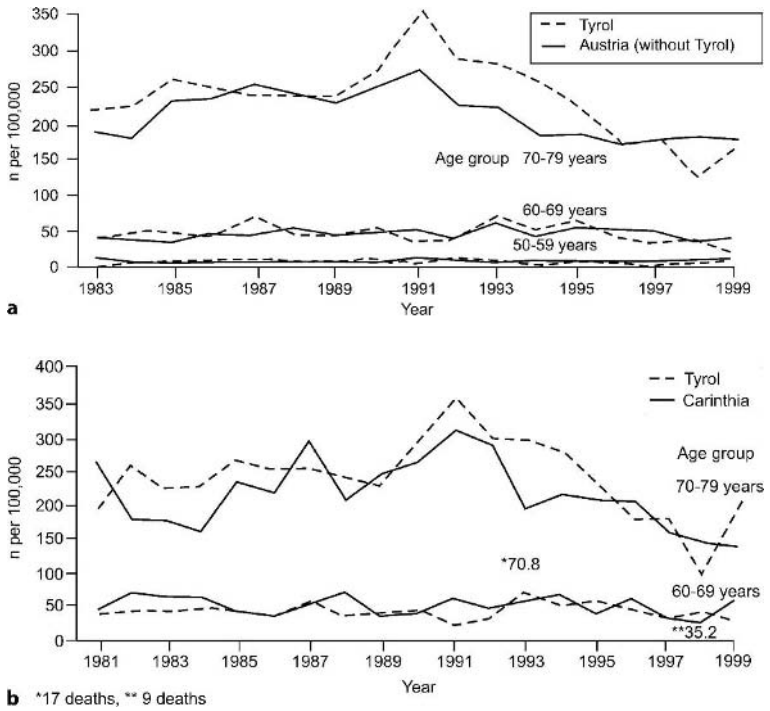

Fig. 5.4a,b Age-adjusted mortality from prostate cancer in: **a** Tyrol and the rest of Austria; and **b** Tyrol and Carinthia. **a** Most deaths and the greatest improvements in prostate cancer mortality in both Tyrol and rest of Austria occurred in the group aged 70–79 years, with very little difference in other groups. **b** There was no difference in prostate cancer mortality between Tyrol and Carinthia, an Austrian province of similar size to Tyrol with no formal screening program, in men aged 60–69 or 70–79 years [3]

This is a trend that is also observed worldwide and reflects the general improvement in medical care of this age group. In the other groups (50–59 and 60–69 years) there was very little difference in prostate cancer mortality between Tyrol and the rest of Austria. The other problem with this study is that the mortality decrease started too early, which makes uncertain the cause-effect relationship [9]. If we look at the morbidity dates of these areas from 1988 we can also assume a heavily pre-screened status of the inhabitants.

The Olmsted County Study analyzed the prostate cancer incidence and mortality between 1983 and 1995 in three different periods [47]. From 1991 a downward trend was noted in the mortality rate. The study had an 80% power to detect a 44% decline in mortality. Contrary to the changes in incidence, a 22% decline in mortality was seen, which was statistically insignificant.

Two big randomized prospective studies are ongoing in the field of prostate cancer screening, the European Randomized Study for Screening for Prostate Cancer (ERSPC) and Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial (PLCO), but for the results we will have to wait till the end of this decade.

The European Randomized Study for Screening for Prostate Cancer is a multicenter trial initiated in 1994 that plans to enroll up to 251,000 men in eight different countries [15, 50]. Enrolling criteria vary somewhat between centers, with the age of men ranging from 50 to 74 years, but mainly it comprises men 55–69 years of age. The first screening policy included a DRE, a PSA level with cutoff 4 ng/ml, and transrectal ultrasonography (TRUS). In 1997 there was a protocol change; the PSA cutoff level was lowered to 3 ng/ml and DRE and TRUS were omitted. The screening interval is also different between countries, ranging from 2 to 7 years, mainly 4 years. To date, 251,133 men have been randomized, 74,568 of whom are being screened. In the screened group, 3,928 cases of prostate cancer have been found, and there have been 2,291 cases in the control arm. Expected completion of the trial is 2008. In the Finnish arm of the trial, more than 5,000 participants have been screened; PSA levels exceeded 4 ng/ml in 8.5% of men aged 55 to 69 years. The cancer detection rate was 2.1% with a positive predictive value of 27%. More than 80% of the cancers were localized and well or moderately differentiated [37].

The PLCO trial started at the end of 1993 in the United States. Randomized into the screened were 37,000 men, with 37,000 in the control arm. Recruitment was completed in June 2001. The starting age group was aged 60–74, which was changed later 55 to 67 years, with a screening interval of 5 years.

A review of the age-specific incidence of prostate cancer shows that most countries report few cases for men younger than 50 years of age, with the incidence rising exponentially with advancing age and reaching a maximum after age 80. The incidence rate in men over the age of 75 is 20 to 83 times higher than in men aged 50–54 [27]. The rise in prostate cancer incidence in the PSA era has been most prominent in men between 50 and 59 years old, whereas the incidence in men above 60 years has gradually declined since 1992 [24]. These trends are characteristic of the screening effect. However, the available ecologic studies have not provided sufficient evidence that the decline in prostate cancer in the United States or other countries is attributable to screening; differences in prostate cancer treatment, underlying risk factors, and how deaths are classified can each introduce bias into ecological comparisons.

Principles of Screening

Screening is defined as the application of suitable screening tests to a general population at risk. Screening procedures for prostate cancer are used widely in North America and many European countries, in spite of the fact that their value has not been proved definitively by adequate randomized controlled trials.

Screening represents the use of laboratory tests, physical examination, or imaging modalities carried out on asymptomatic patients with the aim of identifying subclinical disease. Early detection involves discovery of a disease or condition before the appearance of obvious signs or symptoms; in patients with cancer this would lead to the detection of localized disease. Screening is usually further subdivided into mass screening or individualized screening [51]. The

former is performed with little regard for the risk profile of the individual patient. Most physicians are involved in the latter, which consists of recommending screening tests maintaining a constant patient–physician relationship.

The sensitivity and specificity of a specific test help to establish its effectiveness. Sensitivity is the equivalent of the proportion of the disease population who has a positive test (true-positive rate). The particularity of a test equals the proportion of healthy patients who have a negative test (true-negative rate). The terms sensitivity and specificity are only applied to situations in which the total number of cancers present in a given population is known. This is not the case in screening populations. The number needed in the denominator of the formulas that calculate sensitivity and specificity is often replaced by the number of men with positive or negative biopsy, which is usually obtained by the use of a standard biopsy indication such as abnormal DRE or a PSA greater than or equal to 4.0 ng/ml. More accurately, if this expression is chosen for comparison purposes, it should be termed "relative sensitivity" and "relative specificity." Patients and clinicians are often more interested in the positive predictive value of a test, which equals the proportion of patients with a positive test result who actually have the disease. The use of the term specificity in a situation in which the underlying prevalence of cancer is not known may be acceptable because of the usually large number of men who, in fact, do not have cancer. This minimizes the mistake made by applying this formula [40].

Criteria of Effective Screening Tests

For a screening test to be effective, certain criteria should be fulfilled [40]:

- The disease must constitute a significant public health problem with significant morbidity and mortality. It should have an available and acceptable treatment, and the potential for cure must be greater among screen-detected patients.
- It is essential that the screening test have appropriate sensitivity, specificity, and positive predictive value, making it capable of detecting a sufficiently high proportion of the cancers in their detectable preclinical phase.
- The screening test should be acceptable to the patient and society.
- There must be demonstrable improved health outcomes related to screening.
- The screening procedure should have a reasonable cost; adequate resources and health services should be available to accomplish the screening and to provide the necessary interventions triggered by a positive test result.

The degree to which prostate cancer screening tests fulfill the above-mentioned criteria is controversial. It is leading to different specific policy recommendations from various organizations, although all groups agree that the testing process should be conducted within the context of an informed patient–physician relationship. Patients should be informed of the known risks and the potential benefits.

Factors That Have an Impact on the Assessment of Screening Tests

Lots of biases can be hidden in the conduct of screening tests that can have an impact on apparent survival measures. These can affect the valid assessment of screening test effectiveness [59]. In particular, lead time bias makes the assessment of mortality improvements difficult. Early detection of cancer causes a backward shift in the starting point for measuring survival (earlier diagnosis), which may artificially raise the incidence and lengthen survival.

Autopsy studies have shown that at least 30% to 80% (depends on age) of men who die have latent prostate carcinoma. This rate is much higher than the mortality rate (3%) due to prostate cancer. Screen-detected incidental cancers represent length bias. Individuals with slower progressive disease will tend to be detected. Length bias increases the incidence of early-stage disease and lengthens apparent survival, but has no effect on mortality rates or advanced-stage disease. Over-diagnosis might also be problematic since non-life-threatening prostate cancer is found in every PSA range, though it is more common in men with a PSA level of less than 3.0 ng/ml. In the ERSPC Rotterdam section, approximately 15% of men with a PSA level of 3.0–3.9 ng/ml had possibly unharmful disease,

defined as a tumor volume of less than 0.5 ml and no Gleason scores at 4 or 5 [59]. The diagnosis of nonorgan-confined disease can be another restriction of prostate cancer screening. For example, the result from a randomized study in Canada of screening vs no screening found that approximately 25% of patients had clinical stage T3–4 metastatic disease [14]. Moreover, during an 8-year follow-up a further 9% of patients were diagnosed with nonorgan confined disease.

Another complication of screening for prostate cancer is the fact that sextant biopsy can miss up to 25% of detectable prostate cancer that might be of significant value or become so with time.

People who agree to take part in screening are a self-selected group who may be more worried of the disease in question and more health conscious. Selection bias can happen whenever the group actually screened differs from the potential population of individuals to be screened. This bias also can cause apparent increases in survival of individuals with screen-detected cancers. Inattentive misclassification of the cause of death or attribution bias can occur when a screen-detected abnormality is labeled as "cancer" on the patient's chart when in fact this abnormality would never have been clinically diagnosed in the absence of screen detection.

Because of these biases, case survival cannot be used to estimate the effect of screening on mortality. Instead, prospectively determined mortality from the disease over a follow-up period beginning with randomization should be used. Also, one generally cannot make valid estimations by comparing people screened with those who were unscreened in the past. The only way to find out the advantages without bias is by comparing people who are offered screening with a group of truly comparable people who are not offered screening.

Some common methodologies used in observational epidemiology, particularly case-control and cohort studies, are sometimes used to assess screening. With the purpose of valid application of these approaches screening should take place in a community for a sufficient length of time so that the benefit is detectable if there is any. This period for PSA is probably just approaching. Case-control studies have limitations because differentiating a screening test from a diagnostic test for prostate cancer can be difficult, and this inaccuracy in classification can distort the results of such studies.

National Trends in the Epidemiology of Prostate Cancer

Proponents of the benefits of PSA screening have found evidence of its effectiveness based on the recent trends in prostate cancer incidence and mortality. Based on data obtained from the SEER program of the NCI, age-adjusted rates for prostate cancer incidence increased significantly in the late 1980s, reached the peak in 1992, and then declined through 1996 [28]. Age at diagnosis for whites became lower after the introduction of PSA screening. Stage at diagnosis also showed a downward shift to more organ-confined and less metastatic disease. An increase in the incidence of moderately differentiated tumors (Gleason score 5 to 7) seems to be leading the overall incidence trend [51]. After 1991, the incidence of well-differentiated tumors has been decreasing faster than tumors with higher grades. Blacks exhibited similar trends but with a 1-year lag time, although they experienced a relative increase in high-grade, poorly differentiated disease. These data confirm studies conducted in smaller regions [16, 28].

Prostate cancer mortality increased an average of 1% per year between 1973 and 1990. Since 1990 the prostate cancer death rate in the United States has fallen to an average of 1.1% annually, the decrease totaling 6.7% from 1991 to 1995 [51].

With the successful screening test now in use, prostate cancer incidence is constantly changing. This PSA test can detect slower growing tumors with an effect of lead-time bias due to early detection of prostate cancer beginning in the late 1980s and early 1990s [19]. Some of the increased incidence of localized stage disease may be due to length bias. The decrease in early-stage cancer in recent years also suggests that lead-time bias has taken place. The effect of lead-time bias is further supported by the fact that the increase in early-stage disease was followed by a decrease in advanced-stage disease.

However, other factors also may be involved in these trends. For example, the increase in moderately differentiated tumors actually began in 1986

before PSA testing became widespread. Changes in treatment practices also may be confounding the view of mortality. In the late 1980s and early 1990s the use of gonadotrophin-releasing hormone analogs and androgenic receptor blockers became prevalent, replacing the use of castration therapy or estrogen supplements. This change in treatment patterns could bring about the recent declines in mortality rates for prostate cancer.

Other factors also could have contributed to the shift in the tumor grade distribution before 1992, including an increase in the radical prostatectomy rate, a decline in TURP rates for benign prostate hyperplasia (BPH), and an increase in biopsy rates. The changes in prostate cancer mortality experienced since the introduction of PSA testing in the general population are also consistent with the hypothesis that a fixed percentage of the rising and falling pool of recently diagnosed patients who die of other causes may be mislabeled as dying from prostate cancer [19].

Effectiveness of Screening Tests

Digital Rectal Examination

The DRE is still the basis in the diagnosis of prostate cancer due to its prompt availability, low cost and risk, and contribution to detect cancer in males with normal or minimally high PSA levels. The DRE has been well known in the last few centuries and was termed as *palpatio per anum* in Latin. Several physicians precisely explained the use of DRE in the diagnosis, staging, and follow-up of prostate cancer almost a century ago. The prostate allows for easy access due to its anatomic position in the pelvis, below the bladder neck for palpation using finger placed per rectum. DRE should also be used to diagnose benign prostate hyperplasia, prostatitis. Generally, DRE is useful to detect prostate cancer because the majority of cancers arise from the peripheral zone of the prostate. Nevertheless, DRE is moderately sensitive at diagnosing small, early-stage prostate cancer and it is not sensitive in identifying disease minimally extended beyond the prostate capsule. Indeed, early studies indicate only 26% to 34% of men with suspicious finding with DRE have positive histology after biopsy for cancer, and the overall positive predictive value is 28.0% for DRE [38]. In a most recent trial the positive predictive value (PPV) of an abnormal DRE was 8.8%, among a cohort of patients with less than 4 ng/ml PSA [7].

The sensitivity of the DRE in the detection of prostate cancer is low, and the results diverge with selection of patients, their age, symptoms, and the clinical experience of the physician. Urological associations commonly recommend routine annual DRE. Doubtful DRE should be followed by transrectal echography and prostate biopsy.

Prostate-Specific Antigen Testing

PSA is a serine protease produced by epithelial cells of the prostate gland. Releasing from prostatic stroma, PSA appears in the blood. Like other serine proteases, serum PSA exists mostly in a complex and inactive form; however, a small proportion remains in a free but inactive form. PSA is finally metabolized by the liver with a 2.2- to 3.2-day serum half-life. There are several major causes of increased serum PSA, including BPH, prostate cancer, prostate inflammation or infection, and prostate or perineal trauma. BPH is still the most common cause of elevated serum PSA. Despite the fact that PSA is not cancer-specific, the PPV for prostate cancer even in asymptomatic men is approximately 30%. Using PSA test combined with DRE the results are significantly better. In a screening trial, Catalona combined serial measurements with DRE and found out that the organ-confined rates of tumor increased to 75% compared to 50% or less when screening was performed with DRE alone [54].

Prostate-Specific Antigen Velocity

PSA velocity (PSAV) is defined as a change in PSA value within a time frame. It was observed more than a decade ago that PSA will go on rising more rapidly in men with significant cancer than in males with benign prostate hypertrophy. The acceptable rate of slope cannot be precisely determined. Carter et al. [10] suggested a value of 0.75 ng/ml as an indicator of the presence of prostate cancer. They demonstrated that in men

with prostate cancer the early linear PSAV slope turned to an exponential phase of PSAV beginning 7.3 years before the diagnosis in men with localized disease and 9.2 years before the diagnosis in men with advanced stage disease. Using PSAV, 10%–30% of biopsies can be avoided among men with elevated serum PSA and prior negative biopsy. The specificity of diagnosis increases to over 90% with 72% sensitivity in predicting occult prostate cancer in men with PSA less than 10.0 ng/ml. To obtain maximal benefit from using PSAV measurements, at least three PSA measurements should be taken at intervals of 1.7–2.0 years. On the other hand, an exponential increase in serum PSA level is an independent risk factor for early relapses. D'Amico et al. [34] have demonstrated that men whose PSA level increases by more than 2.0 ng/ml during the year before the diagnosis of prostate cancer may have a relatively high risk of death from prostate cancer, despite the early diagnosis and radical prostatectomy.

As a conclusion, the significant intraindividual variability and frequent inconsistency in PSA measurement, particularly in the setting of relatively short time intervals between PSA tests and PSA in the low ranges, may impede the performance and use of PSAV [44]. The clinical application of PSA doubling time (PSADT) arises from the hypothesis that the growth of prostate cancer is exponential and the doubling time will indicate biologic tumor activity. It has been presumed that prostate cancer has a constant growth rate that is often relatively slow. Although assessments of changes in serum PSA have a well-established role in follow-up patients who have undergone treatment, its role as a marker for early diagnosis in untreated patients remains controversial.

Prostate-Specific Antigen Density

PSA density (PSAD) is the ratio of the serum PSA and prostate gland volume measured by TRUS. Using this ratio PSAD adjusts for PSA changes contributing to the benign prostatic enlargement. There have been several reports on improved differentiation between patients with BPH and prostate cancer. These reports have demonstrated that average PSAD in men with prostate cancer is significantly higher than in men with prostate hypertrophy. Benson et al. enrolled 595 patients into a large screening study with a PSA values between 4.1 and 10.0 ng/ml. Within this intermediate range of PSA, Benson et al. were not able to identify malignant prostatic disease by PSA values. However, there was a strongly significant difference in PSAD values between patients with positive or negative biopsy (0.297 vs 0.208), respectively [4]. Furthermore, of patients with a PSAD of 0.1 or greater, 97% had prostate cancer [11]. Regardless of these promising early results, the calculation of PSAD involves the use of measurements that may vary because of ultrasound operator variability or sampling bias. In a large multicenter study, PSA and PSAD were compared for early detection of prostate cancer. If a PSAD cutoff of 0.15 were to be used in a group of men with a PSA count from 4 to 10 ng/ml, 47% of the cancers would be missed. In summary, although applying PSAD may achieve increased specificity and avoidance of up to 37% of biopsies, the risk is unacceptable to ignore large number of clinically significant cancers.

Age-Specific Prostate-Specific Antigen Range

Age-specific PSA reference ranges (ASRR) were recognized by the rationale that the prostate gland normally enlarges with age. Even though the incidence of prostate cancer increases noticeably in men older than 60 years of age, the presumption is that using a higher total PSA cut point for older men is unlikely to result higher morbidity or mortality from this disease. The use of age-specific PSA levels also implies that it is more important to diagnose prostate cancer in younger men because their longer life expectancy and greater number of risk years puts them at greater risk of disease progression, metastasis, and death. Using a higher upper-cut limit for older men, it was believed that the number of biopsies in this group would decline while the detection of prostate cancer would not be jeopardized. Initially the upper limit of PSA, 4 ng/ml, was set up by the test manufacturer based on measurements of PSA levels in 860 healthy vol-

unteers. ASRR were recommended by Partin and Oesterling over the standard 4 ng/ml cut point based on their findings [41]. Using age-specific cut points of 2.5, 3.5, 4.5, and 6.5 ng/ml for the age groups 40 to 49, 50 to 59, 60 to 69, and 70 to 79 years, they were able to identify an additional 18% of prostate cancers in the groups under the age of 60 years. On the other hand, using these references ranges 22% of the cancer would have been missed in older men. Adjusting the PSA cutoff from 4.0 to 4.5 ng/ml for men in the 60–69 age group would eliminate 15% of biopsies, while missing 3% of cancers. Of the cancers missed, 95% were considered as clinically insignificant.

Several publications highlighted disturbing numbers of clinically serious cancers or advanced stage disease is missed in older men when using similar age-specific ranges. The percentage of avoided biopsies was also not as significant in numerous follow-up studies. For the time being a widely accepted, ideal cutoff point to define a serum PSA level as normal does not exist. Recent studies have shown that up to 25% of men with prostate cancer have a PSA value of less than 4 ng/ml, and 32% of the men with cancer have normal PSA levels [8]. In a large study of 6,000 men over the age of 50, it was found that increasing the PSA thresholds in older men may result in 44% fewer biopsies, but at the expense of missing up to 47% of organ-confined cancer [45]. In general, although this modification may increase the test sensitivity in younger men, it will also decrease the sensitivity in the older population.

Free Prostate-Specific Antigen

PSA exists in numerous different molecular forms in the serum or in seminal fluid. The total PSA contains all the measurable PSA in the serum. A large proportion of total PSA is complex and inactive; however, a smaller fraction remains in a free but also inactive form. This free PSA can be measured by monoclonal antibodies. It was postulated by Stenman that men with prostate cancer tend to have higher ratios of complex PSA to total PSA than men without prostate cancer [57]. Several studies demonstrated a significantly lower free PSA to total PSA ratio in cancer patients as compared to BPH. The representative free PSA ratio was 15%–18% in cancer patients, which significantly differed from the average of free PSA ratio of 28%–30% in patients with BPH. More recently, a prospective multicenter trial was designed to assess the optimal free PSA threshold using 773 men aged 50 to 75 years with PSA levels between 4 and 10 ng/ml [12]. There was no difference in total PSA concentrations between the men with benign prostate hypertrophy vs malignant disease (total PSA 5.6 vs 5.9, respectively). The free PSA was able to distinguish the group of men with benign disease (mean free PSA of 18%) from those with cancer (12% free PSA). A 25% cutoff identifies 95% of cancers while avoiding 20% of unnecessary biopsies. The few amounts of cancers associated with a free PSA greater than 25%, were more often observed in older patients with a lower grade and volume of the disease. Free PSA has an inverse correlation with tumor aggressiveness; a lower free PSA is associated with a more aggressive form of prostate cancer. The ability of this molecular form to differentiate between prostate cancer and benign conditions has proved to be the most useful PSA modification to increase the performance of PSA testing.

Imaging for Detection and Early Diagnosis

Although imaging studies do not have a basic role in the early detection of prostate cancer, imaging technique plays a role in the diagnosis of the disease. Transrectal ultrasound is used to guide biopsies of the prostate gland in patients with an abnormal DRE or elevated serum PSA level. The prostate can be imaged with transrectal approach. In healthy young men, the zones of the prostate are not sonographically evident. The transition zone usually becomes distinguishable in patients with benign hyperplasia. Prostate cancer placed in the peripheral zone can be consistently observed by sonography. Prostate cancer most commonly appears in the hypoechoic zone compared to the normal surrounding [17]. However, lesions up to 40% are isoechoic; therefore they are not detectable by sonography. The finding of a hypoechoic lesion on transrectal ultrasound sonography is not spe-

cific for carcinoma. The low positive predictive value of TRUS (20%–50%) for the diagnosis of prostate cancer makes it unsuitable as a screening tool at the present technical level. Computer tomography lacks the soft tissue contrast resolution needed for the detection of intraprostatic cancer and offers no advantages over TRUS in biopsy guidance through screening procedures. Although at present magnetic resonance imaging (MRI), as well as TRUS, are the best imaging modalities for demonstrating the normal zonal anatomy of the prostate, they have no established role in prostate cancer detection [26]. Prostate cancer usually appears as an area of abnormal low signal intensity surrounded by the normal homogeneous high signal intensity background of the peripheral zone. Low signal intensity lesions in the peripheral zone display a sensitive but not specific finding for cancer. In addition, prostate biopsy may cause bleeding and irregularity in signal intensity that lead to false-positive and false-negative results. To avoid this source of bias, MRI should be postponed for at least 3 weeks after biopsy. Proton three-dimensional magnetic resonance spectroscopic imaging (3D-MRSI) is a newly developed technique to obtain metabolic information about the prostate gland. MRSI assesses prostatic metabolites, such as choline and citrate. Within cancer tissue there are significantly higher choline and significantly lower citrate levels compared to the healthy field in the peripheral zone. When the metabolic data from 3D-MRSI is combined with morphologic data from the MRI, it is possible to make a more reliable diagnosis and much more precise localization of prostate cancer than with the data from MRI alone [32]. A combined positive result from the MRI and 3D-MRSI argue the presence of tumors. If both MRI and 3D-MRSI provide combined negative results the presence of cancer can be excluded. The lack of an adequately high positive predictive value for cancer detection, combined with its high cost and limited availability makes MRI inappropriate for cancer screening.

Potential Adverse Effects of Screening

The screening process is likely associated with some increase in anxiety, but the number of men affected and the magnitude of the increased anxiety are largely unknown. The possible harms associated with screening must consider the psychological consequences of positive screening results or an actual cancer diagnosis, and the reality of false reassurance with negative biopsy results [31,35]. Some screening procedures cause transient discomfort. Fewer than 10% of men have ongoing interference with daily activities after biopsy, and fewer than 1% suffer more serious complications, including infections [27].

At present, over-diagnosis probably represents the biggest problem related to prostate cancer screening. Over-diagnosis can be defined in many ways, such as the diagnosis of cancers that will not be diagnosed clinically, the diagnosis of a cancer that will not kill a given patient, and, in an epidemiologic sense, the difference in incidence in a screened population and a matched unscreened population. Over-diagnosis is closely related to the production of lead-time by screening, but also to comorbidity and the risk of intercurrent deaths in population of men who undergo screening tests. The risk of over-detection has been estimated between 16% and 56%. At present, there is clear evidence that screening increases, at least temporarily, the incidence/mortality ratio from 2 to approximately 5 in the United States, where screening is prevalent [22]. In the controlled setting of the ERSPC (Rotterdam section) during the prevalence screening, a crude incidence ratio of 6.51 per 1,000 person-years was seen between the screening and control groups. Estimates from the ERSPC suggest that for a screening program with a 4-year screening interval from age 55 to 67 the estimated mean lead time is 11.2 years (time from detection to the cancer that becomes clinically apparent) and the over-detection rate is 48% (range, 44% to 55%) [37, 50]. In the same setting, taking into consideration the prostate cancer mortality rate in the Netherlands in 1997, an incidence/mortality ratio of 14.6 was found [52].

Perhaps more important are morbidity and mortality associated with the cascade of procedures from diagnosis to treatment. The complications of radical prostatectomy include a low mortality risk (0.2% to 0.4%), but considerable morbidity affecting the quality of life may be associated with this surgery (incontinence and

erectile dysfunction) or from radiation (bowel dysfunction and rectal bleeding). Penson [42] examined the five-year outcomes of the urinary and sexual function after radical prostatectomy. He found that only 45% of the patients had no incontinence problems, 14% had frequent leakage or total incontinence, and 71% of the patients did not have firm enough erections for intercourse. Steineck [55] found 80% of erectile dysfunction and 49% of urinary leakage after radical prostatectomy in Sweden. One year after radiation therapy, 28.9% of the patients experienced decline in sexual function and 5.4% had bowel functional problems [23].

At present, the true extent of over-diagnosis in cases that do not require treatment and how these can be avoided is not known.

Cost and Cost-effectiveness

Given the uncertainties about the effectiveness of screening and the balance of benefits and harms, the cost-effectiveness of screening for prostate cancer is impossible to determine. If one makes favorable assumptions about efficacy of screening, PSA screening may be cost-effective for men aged 50 to 69 [58]. If efficacy of early treatment is lower, harms could exceed benefits and PSA screening would not be cost-effective. Current models show that men older than 70 to 75 are unlikely to benefit substantially from screening because of their shorter life expectancy and higher false-positive rates [58]. Cost-effectiveness of different screening intervals or variations of PSA measurement is unknown.

Summary and Conclusion

Prostate cancer incurs a substantial incidence and mortality burden, similarly to breast cancer, and it ranks among the top ten specific causes of death in the United States. It is inherent as we maximize the detection of early prostate cancer that we increase the detection of both nonaggressive (slow growing) and aggressive (faster growing) prostate cancers. The evidence clearly supports the use of PSA screening in conjunction with DRE as a means of early detection of prostate cancer. Widespread implementation of prostate cancer screening in the United States has led to the phenomenon of stage migration with more cancers being detected at a lower stage. Such a trend has decreased the incidence of metastatic disease at diagnosis and paralleled the decrease of the mortality rate from prostate cancer.

Our understanding of the natural history of prostate cancer is progressing over time, but the question of its length is unanswerable. The relatively long doubling time (on average) of early prostate cancer of 3 to 4 years or more indicates a relatively good prognosis for many men with this disease, even without early detection and treatment. Unfortunately, the poor specificity of the PSA test in men with benign prostatic hyperplasia (BPH) leads to high rates of prostate biopsy and attendant illnesses and costs.

Early detection is more apt to detect a slow-growing prostate cancer than a faster growing cancer that is associated with a more rapid course of progression to metastatic disease. Hence, the launching of mass screening programs for the early detection of prostate cancer is premature. However, in the absence of solid evidence of benefit, one reasonable approach to screening at the individual level is to involve the patient in decisions about whether or not to perform a PSA test. Thus, "offering" PSA testing must be accompanied by informed discussion within the context of an ongoing patient–physician relationship. This is to be distinguished from the use of PSA testing for the purpose of "mass screening." Concepts that must be explored with the patient include:

1. The long-term ramifications of screening
2. The relatively high probability of further evaluation and biopsy with positive results
3. Potentially difficult decisions that may arise about using treatments that are associated with considerable morbidity and uncertain benefits (at the time) if cancer is discovered

We should identify a future path that is evidence-based, focused on the issues that make a difference to patients, and results in better and longer lives of those with the disease and those who are at risk of getting it. If that path leads to treating fewer patients in the future, even if sometimes more aggressively, we should pursue it definitely and consequently.

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6 Diagnosis of Prostate Cancer

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Abstract

The contemporary challenge of prostate cancer diagnosis has been changed in the past decade from the endeavor to increase detection to that of detecting only those tumors that are clinically significant. Better interpretation of the role of prostate-specific antigen (PSA) and its kinetics as a diagnostic tool, the adoption of extended prostate biopsy schemes, and perhaps implementation of new transrectal ultrasound (TRUS) technologies promote the achievement of this clinical mission. This chapter reviews these issues as well as the change in practice of patient preparation for TRUS-biopsy and analgesia during it, the role of repeat and saturation prostate biopsies, and the interpretation of an incidental prostate cancer finding.

Currently, the lifetime risk of a diagnosis of prostate cancer for North American men is 16%, compared to the lifetime risk of death from prostate cancer, which is 3% (Carter 2004). The advent of prostate-specific antigen (PSA) screening and transrectal ultrasonography (TRUS) has significantly impacted the detection of prostate cancer over the last 20 years. The mean age at diagnosis has decreased (Hankey et al. 1999; Stamey et al. 2004) and the most common stage at diagnosis is now localized disease (Newcomer et al. 1997; Stamey et al. 2004). The goal of prostate cancer screening is to detect only those men at risk for death from the disease at an early curable phase. The ambiguous natural history of this most common malignancy in men, being latent with questionable life-threatening potential in a large number of cases on the one hand, with only a relatively small number (though not negligible) of highly malignant cases on the other, propels many doubts about whether this is possible. This was famously phrased more than 20 years ago by Whitmore who asked: "Is cure possible for those in whom it is necessary; and is it necessary for those in whom it is possible?" This is probably even more relevant nowadays. During the past decade two factors influenced significantly the increased detection rate of prostate cancer in general and that of clinically insignificant prostate cancers in particular: the widespread use of serum PSA as a screening tool to a large extent and to a lesser though significant extent the application of extended multiple core biopsy schemes (Master et al. 2005). In fact, 75% of men in the United States aged 50 years and older have been screened with the PSA test (Sirovich et al. 2003). Outside of the screening context, which is dealt with in depth in Chap. 5, clinical suspicion of prostate cancer is raised usually by abnormal digital rectal examination (DRE) and/or by abnormal levels of serum PSA. Final diagnosis is achieved only based on positive prostate biopsies.

Serum PSA Levels as a Diagnostic Tool

The indications for prostate biopsy in patients with elevated/abnormal PSA are in transition due to emerging data on its performance as a screening tool in serum levels of less than 10 ng/ml in general and less than 4 ng/ml in particular.

The Prostate Cancer Prevention Trial (PCPT) (Thompson et al. 2003) afforded the examination of PSA as a marker for prostate cancer. Almost 9,500 healthy men with negative DRE and serum PSA levels lower than 3 ng/ml were receiving placebo and were followed by annual DRE and serum PSA examination. At the end of the study period (7 years) routine prostate biopsies, parts of the study design, found that almost a quarter were diagnosed with prostate cancer. Subanalysis of prostate cancer incidence

among 2,950 men treated with placebo and who never had a PSA level of more than 4.0 ng/ml or an abnormal digital rectal examination revealed that biopsy-detected prostate cancer, including high-grade cancers, is not rare among men with PSA levels of 4.0 ng/ml or less—levels generally thought to be in the normal range (Thompson et al. 2004). The prevalence of prostate cancer was 6.6% among men with a PSA level of up to 0.5 ng/ml, 10.1% among those with values of 0.6 to 1 ng/ml, 17% among those with values of 1.1 to 2.0 ng/ml, 23.9% among those with values of 2.1 to 3 ng/ml, and 26.9% among those with values of 3.1 to 4.0 ng/ml. The prevalence of high-grade cancers increased from 12.5% of cancers associated with a PSA level of 0.5 ng/ml or less to 25.0% of cancers associated with a PSA level of 3.1 to 4.0 ng/ml.

Accordingly, there is no serum PSA level below which there is no risk of having prostate cancer, although the risk of prostate cancer increases with the levels of serum PSA. The question as to whether we should lower the serum PSA threshold for detection would remain a matter of personal opinion at this point due to lack of firm data to support or defer early detection. Lowering the PSA value will lead unequivocally to the detection of an enormous number of inconsequential tumors leading to a "prostate cancer epidemic" on the one hand, but will also result in the detection of clinically significant tumors, as supported by the finding that almost a quarter of prostate cancers detected in men with PSA between 2.1 and 3 ng/ml are of a Gleason score (GS) of 7 or more (Thompson et al. 2004).

To add to this complexity, the drastic change in the disease characteristic of prostate cancer over the past decade with more patients that are diagnosed with small-volume cancers at lower stages and with lower PSA levels impose caution in analyzing previous data from population-based studies of the early 1990s and adopting it to current practice in an attempt to redefine the indication for biopsy based on PSA levels. Accordingly, Stamey recently radically criticized the overusage of PSA for prostate cancer diagnosis, stating that the PSA era in the United States is over for prostate cancer (Stamey et al. 2004).

Ignoring the dilemma of what is the adequate PSA threshold that should promote biopsy, it is worthwhile to acknowledge several inherited caveats of serum PSA levels as a diagnostic tool: intra-individual day-to-day variation in PSA is 34% (Bunting 1995). This as well as unavoidable analytical variation obviously creates inherent problems, particularly in the interpretation of PSA kinetics in certain values (Nixon et al. 1997).

Biologic variability in PSA levels may often stem from inflammation and infection. Moreover, prostatic manipulations are notoriously known for alarming variations in PSA level: DRE, TRUS, cystoscopy, and ejaculation have minimal effects. However, since some authors showed that it may have an effect on serum PSA levels, at least when one interprets interindividual PSA dynamics, one should be aware of potential influences of such manipulations: PSA testing within 24 h after ejaculation may lead to an erroneous interpretation of the results of measurements of both total and percentage of free PSA in a small proportion of men (Herschman et al. 1997). DRE may result in a change of free but not of complex PSA levels (Lechevallier et al. 1999). On the other hand, prostatic massage, needle biopsy, TURP, and prostatitis can cause significant elevations of serum PSA (Klein and Lowe 1997). Additionally, in patients who receive intravesicle therapy for superficial bladder TCC, serum PSA levels should also be evaluated with caution: intravesical bacille Calmette-Guérin (BCG) therapy may be associated with significantly elevated PSA in up to 40% of cases. This effect is self-limited and PSA reverts to normal in 3 months (Leibovici et al. 2000).

PSA levels are influenced by body weight. Recently, Baillargeon et al. (2005) showed in a cohort of 2,770 men without prostate cancer that the mean PSA values decrease linearly as body mass index increases. This important association should be remembered, as obesity becomes a major public health problem in the Western world.

Digital Rectal Examination as a Diagnostic Tool

Although abnormal DRE is considered an absolute indication for prostate biopsy, its central role as a diagnostic tool was superceded by the wide-

spread application of serum PSA. Analyzing data from the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer, Schroder et al. evaluated the usefulness of DRE as a standalone screening test and in conjunction with measured serum PSA levels of 0–3.9 ng/ml and TRUS (Schroder et al. 1998). Although they showed that DRE has a poor performance in low PSA ranges with a calculated positive predictive value of DRE and TRUS at PSA 0 to 4.0 ng/ml of only 9.7%. (Schroder et al. 2000), 17.3% of the cancers identified in their cohort would have remained undetected by PSA-based screening alone (Schroder et al. 1998).

Regardless of serum PSA levels, a DRE finding of a firm nodule or diffusely firmed prostate should promote prostate biopsy, as 5%, 14%, and 30% of men with PSA 0–1.0, 1.1–2.5, and 2.6–4.0 ng/ml, respectively, have prostate cancer (Carvalhal et al. 1999). Carvalhal et al. found that the majority of cancer cases detected by DRE in patients with serum PSA of less than 4 ng/ml have features of clinically important and potentially curable disease (Carvalhal et al. 1999). Although for screening purpose DRE is fairly inferior to PSA, its role in combination with PSA for diagnosis is imperative, as it gives essential clinical information for staging.

Transrectal Ultrasound as a Diagnostic Tool

TRUS was introduced in 1968 (Watanabe 1989) and rapidly gained popularity among the practicing urologist as a tool for volume measurement of the prostate and to direct the biopsy needle to various locations within the prostate. Apparently its role as an additional diagnostic tool is limited due to low specificity and sensitivity for detection of prostate cancer. Using gray-scale ultrasound analysis, Dahnert et al. (1986) demonstrated that 54% of prostate cancers are echopenic, 22% are hypoechoic, and 24% are isoechoic. Later reports classified most (60%) prostate cancers as hypoechoic (Shinohara et al. 1989). In one recent analysis of 3,912 consecutive TRUS-guided prostate biopsies, Onur et al. confirmed that despite the higher prevalence of cancers discovered in prostates with hypoechoic areas, the hypoechoic lesion itself was not associated with increased cancer prevalence compared with biopsy cores from isoechoic areas (Onur et al. 2004). Moreover, the echogenic features of the tumor on TRUS do not impact on its prognosis (Scherr et al. 2002).

In attempts to increase the accuracy of TRUS as a diagnostic tool, several authors tried to integrate new technologies (Sedelaar et al. 2001). These techniques include color Doppler, power Doppler, three-dimensional (3D) ultrasound imaging of the prostate alone or in combination with ultrasound contrast agents with some encouraging results. The rational is that adding vascular information could improve the detection of cancerous lesions, as tumor growth is associated with neovascularization that could possibly result in altered blood flow. Indeed, several studies demonstrated that color Doppler ultrasound of the prostate might improve biopsy yield by directing systemic biopsies to distinct areas in patients with elevated PSA and no focal gray-scale abnormalities as well as in the detection of diffuse prostate lesions (Sedelaar et al. 2001). Moreover, nonpalpable cancers with hypervascularized lesions were shown to have a significantly higher GS than nonhypervascularized lesions (Cornud et al. 1997). In their review of the literature, Sedelaar et al. (2001) calculated that Doppler ultrasound of the prostate increased the sensitivity and specificity of detecting prostate cancer from 17%–57% and 40%–63% achieved by conventional gray-scale TRUS, to 75%–78% and 80%–87% respectively. The application of contrast-enhanced Doppler ultrasound also showed promising results (Ragde et al. 1997; Goossen et al. 2003) but the number of studies that examine its role is very limited.

Unal et al. suggested that the combination of transrectal 3D contrast-enhanced power Doppler ultrasonography can significantly increase the sensitivity and specificity of prostate cancer detection and in particular its combination with PSA level (Unal et al. 2000). Caveats of these promising technologies are that they are relatively complicated to interpret and are dependent on expert observers. In addition, they are subject to motion artifacts and false positive results due to inflammatory processes like prostatitis, which decrease their specificity as a diagnostic tool. Ac-

cordingly, none of these technologies can currently replace systemic biopsies for the early detection of prostate cancer (Sedelaar et al. 2001) and none of them is ready yet to be adopted into routine clinical practice.

Prostate Biopsy

TRUS-guided systematic prostate biopsy is the standard test for prostate cancer diagnosis. Prostate biopsy strategies have significantly evolved over the past decade. The current practice for initial biopsy using extended biopsy schemes (10–13 cores) including laterally directed biopsies has significantly reduced the false-negative rate of the previous dominant classic sextant biopsy. The increased diagnostic scheme of this state-of-the-art approach not only results in lower detection rates of re-biopsies but was demonstrated to provide valuable staging information (Singh et al. 2004; Naya et al. 2004).

Patient Preparation to the Biopsy

With the widespread application of TRUS-guided prostate biopsy it became evident that anesthesia and/or analgesia improve the patient's tolerance and comfort. The procedure can be painful (Irani et al. 1997). Thus, especially with the introduction of extended schemes of primary and repeat biopsies, the application of anesthesia and/or analgesia is the gold standard in clinical practice with several randomized studies proving its necessity (Leibovici et al. 2002; Chang et al. 2001). Indeed, up to 90% of patients undergoing TRUS-guided biopsy of the prostate claim to experience discomfort (Clements et al. 1993). Many methods to decrease pain during the procedure were described and are meticulously reviewed by Autorino et al. (2005). Of the various methods, periprostatic nerve block alone or with lidocaine gel has been shown to be safe, easy to perform, and highly effective. The application of gel instillation should not replace periprostatic nerve block, as prospective randomized studies comparing the two methods clearly demonstrated the superiority of the latter (Autorino et al. 2005).

The use of antibiotic prophylaxis for transrectal prostate biopsy significantly reduces the incidence of infective complications (Sieber et al. 1997). Taylor and Bingham (1997) reviewed the literature and found that oral antibiotics are inexpensive, well-tolerated, and effective for reducing the incidence of urinary tract infection and fever following transrectal prostate biopsy. Their recommendations, which are widely practiced, are to use oral quinolones such as ciprofloxacin or norfloxacin (Taylor and Bingham 1997). The duration of treatment varies between different institutions and was demonstrated to be effective even with the use of levofloxacin at 600 mg for 1 day as prophylaxis (Shigemura et al. 2005). Similar data from a prospective randomized trail in Canada support that there is neither clinically nor statistically a significant difference between a 1-day and 3-day antibiotic prophylaxis regimen for patients undergoing TRUS-guided biopsies (Sabbagh et al. 2004). Moreover, Griffith et al. showed that a single 500-mg dose of levofloxacin before transrectal needle biopsy of the prostate is effective and safe in patients at low risk (Griffith et al. 2002). Obviously those patients considered at risk for endocarditis need a strictly different parental regimen in accordance with published American Heart Association recommendations. The application of cleaning enemas before the procedure is recommended to facilitate the transrectal prostate imaging and to reduce infectious complications, although there is no substantial evidence to prove it (Scherr et al. 2002).

Transrectal Ultrasound-Guided Prostate Biopsy Techniques

The traditional sextant biopsy as described by Hodge et al. (1989) comprises six core biopsies taken from the apex, mid and base of the right and left prostate at the parasagittal plane. With this sextant biopsy approach that was widely practiced in the 1990s, false-negative rates were at the range of 30%–35% (Levine et al. 1998; Karakiewicz et al. 2005). Decreasing yield of sextant biopsy was strongly associated with increasing gland volume (Karakiewicz et al. 1997). Another cause for the reduced detection rate with the routine application of the sextant biopsy scheme was

that the parasagittal plane of sampling does not sample the more lateral peripheral zones. As a result, Stamey suggested shifting the sextant biopsies template laterally in order to better sample the peripheral zone where most of the cancers are located (Stamey 1995). However, application of Stamey's modification for sextant biopsies alone, with a single set of lateral sextant biopsies, may miss clinically detectable prostate cancer in more medial parts of the peripheral zone.

Similarly, Chang et al. found that in 20% of men diagnosed with prostate cancer, the tumor was found exclusively in the laterally directed biopsies (Chang et al. 1998). These data are supported by elegant computer-based analysis studies (Chen et al. 1997; Zeng et al. 1999), which clearly demonstrated that laterally directed biopsies that can sample the anterior horn increase the detection rate. Indeed, Epstein et al. (2001) demonstrated the importance of posterolateral prostate biopsies in an ex vivo model. In their study, using ex vivo needle biopsies of 150 specimens removed by radical prostatectomy, 25% of the cancers were missed by sextant biopsy scheme. Maximum cancer detection was yielded from combining both routine sextant and posterolateral needle biopsies (Epstein et al. 2001).

Acknowledging the significance of a larger number of cores as well as for more lateral location of needle placement, different investigators studied alternative extended prostate biopsy schemes to the traditional sextant biopsy. Presti (Chon et al. 2002) introduced a 10-core systemic biopsy scheme comprising four laterally directed biopsies of the peripheral zone plus the conventional sextant biopsy template. Patients with prostate volume larger than 50 cc underwent also transitional zone (TZ) biopsy, which increased the detection rate by 5.5% (Presti et al. 2000). The sextant biopsy component of their scheme missed 20% of the cancers ultimately detected. Discarding the parasagittal base biopsies from this 10-core template had only minimal effect on the cancer detection rate (96% to 95%), thus leaving an 8-core biopsy scheme (Presti et al. 2000). Later, Meng et al. suggested another scheme for an 8-core prostate biopsy. They claimed that apical anterior horn prostate biopsies can target cancers that are in a region that is usually undersampled using traditional schemes and recommended adding it to the classic sextant biopsy pattern (Meng et al. 2003).

Chen et al. (1999) used a computer model to evaluate different prostate biopsy schemes. Their simulation suggests that a multisite-directed 11-core biopsy is superior to all others. Eskew showed that a 13-core biopsy scheme has a significantly better detection rate compared to that of the sextant scheme (Eskew et al. 1997). In his biopsy template Eskew added to the traditional sextant scheme additional biopsy cores from the far lateral and mid regions of the gland to improve the sampling of the peripheral zone. His technique, named the 5-region prostate biopsy, includes sampling 5 separate regions of the peripheral zone (laterally directed—base, mid and apical cores—plus mid lobar sampling of the apex and base). This scheme was shown to result in significantly better diagnostic yield compared to the sextant biopsy template but equivalent to the 12-core scheme (Gore et al. 2001). In a recent study, Elabbady compared the diagnostic yield and accuracy of final GS prediction (i.e., at radical prostatectomy) between 113 patients who underwent TRUS-guided lateral sextant biopsy and 176 patients who underwent extended 12-core biopsy who had similar clinical characteristics (Elabbady and Khedr 2006). The cancer detection rate was 24.8% and 36.4% in those who underwent sextant and 12-core biopsy respectively. The agreement between the biopsy and prostatectomy specimen was significantly higher in patients who underwent 12-core biopsy (82.5%) than those who underwent sextant biopsy (50%).

Altogether, the well-proven role of extended scheme prostate biopsy in increasing the detection rate of prostate cancer stems from the fact that it reduces the odds for sampling error. Whether it also translates to providing better prognostic information is still questionable to some extent. In the era of increased awareness of the clinically insignificant nature of many newly diagnosed early prostate cancers and consequently to the viable option of expectant management (watchful waiting), adequate–informative prostate biopsies play a key role (Klotz 2002). Accordingly, a finding of a small focus of cancer in a sextant biopsy set reflects similar finding in radical prostatectomy only in the extreme minority of the

cases—10%. In another words, up to 90% of these patients would suffer from clinically significant cancer in terms of cancer volume. Furthermore, the volume of prostate cancer in the biopsy specimen cannot reliably predict the volume of cancer in the radical prostatectomy specimen (Cupp et al. 1995; Weldon et al. 1995; Gardner et al. 1998). However, when analyzing the relationship between the numbers of positive cores obtained at extended biopsy (10–11 cores) and tumor volume in radical prostatectomy specimens, Ochiai et al. (2005) could clearly demonstrate that the number of positive cores was significantly related to total tumor volume. Moreover, the probability of insignificant cancer (defined as volume less than 0.5 cc and GS6 or less) was directly related to the number of positive cores. Tumor length in a core, GS, and prostate volume significantly enhanced the prediction model for insignificant cancer in men with one positive core who underwent extended biopsy.

Unfortunately, the inclusive tumors' GS as obtained from radical prostatectomy specimen is often higher than that determined by the prostate biopsy with the most common error being underscoring of tumors, which are subsequently shown to be GS7 tumors (Sved et al. 2004). Several studies using different methodologies for prostate biopsy documented a wide range of 12%–92% rate of up-scoring from prostate biopsy GS6 to radical prostatectomy GS7, with most reporting discordance rates in the range of 30%–50% (Pinthus et al., 2006). Some reports suggest that increasing the total numbers of cores taken at the prostate biopsy could reduce undergrading (Emiliozzi et al. 2004; Elabbady and Khedr 2006).

Other studies, however, do not support this (King and Long 2000; Fukagai et al. 2001). King et al. could not demonstrate an advantage of extended biopsy patterns of as many as 18 cores in improving grading error rate (King and Long 2000). However, following sextant prostate biopsy of GS6 tumors, Fleshner et al. found that the rate of undergrading decreased from 58% (32 of 55 patients) to 28% (5 of 18 patients; Fleshner et al. 1998). Thus, re-biopsy may be warranted when the presence of GS7 would alter an individual's treatment plan.

An inevitable consequence of the routine use of extended pattern prostate biopsy templates is the detection of smaller volume prostate cancers, independent of PSA and Gleason grade. In a recent study, Master et al. compared the pathological characteristics of tumors, removed at radical prostatectomy by a single surgeon, following biopsies with at least 6 cores. Both groups were evenly matched in terms of age, PSA, and biopsy GS. The authors found that the use of increased number of prostate biopsies contributes to the detection of smaller tumors, and contributes to over-detection independent of serum PSA. In contrast, Siu et al. (2005) could not find a significant association between an increased numbers of needle cores at initial prostate biopsy and finding of smaller and clinically insignificant cancer in their retrospective analysis of 740 cases.

Using a computer simulation, Karakiewicz et al. could clearly demonstrate that regardless of the gland volume, detection of minimal volume disease increases with increasing amount of sampling, although as expected this was more frequent in smaller glands (Karakiewicz et al. 1998).

Taken together, extended biopsy templates have certainly contributed to the downward stage migration of prostate cancer detection and perhaps also to the risk of over-detection. However, increased detection of clinically insignificant disease is an unavoidable trade-off for the improved detection of clinically significant prostate cancer.

Role of Transitional Zone Biopsies

There is some debate as to the role of additional TZ biopsies at the time of the initial biopsy. In general, tumors arising in the TZ of the prostate gland are well-differentiated and considered clinically unimportant. However, a study from Stamey's group that examined 79 volume-matched cases of TZ prostate cancer to 79 pure peripheral zone cancers (with no secondary tumors) demonstrated that cancer volume and the percentage of Gleason grade 4/5 diseases were the same in both groups. However, at 5 years of post-radical prostatectomy follow-up, 49.2% of the men with peripheral zone cancer had undetectable PSA compared with 71.5% of those with TZ cancer

(Noguchi et al. 2000). Shannon et al. (2003) reviewed 187 cases of TZ cancers from radical prostatectomy specimens of which 76 represented the index (main) tumor. These were compared with a volume-matched group of 76 peripheral zone (PZ) carcinomas. Of 76 TZ index carcinomas, 59 had additional minor tumors mainly located in the PZ. Compared to PZ tumors of similar size, TZ tumors had significantly lower GS, less Gleason grade 4/5, and lower rates of capsular penetration and positive surgical margins. Nevertheless, a subset of TZ carcinoma (10%), characterized by high tumor grade was found to have a significant risk of extra-prostatic spread, margin positivity, and possible biochemical failure. Interestingly, the best method to pre-operatively diagnose these tumors was by transperineal biopsy. For patients initially evaluated because of high PSA, a positive DRE, or both, the incidence of having cancer exclusively in the TZ only in the first set of biopsies was found to be merely 2.1% but was increased to 18.7% in repeat biopsy that included sampling of the TZ when the patients had already at least one previous negative biopsy of the peripheral zone (Deliveliotis et al. 2002). Based on their study, Deliveliotis et al. (2002) concluded that the low yield of transitional zone biopsies (2.1%) during first-time sampling of the prostate does not warrant their systematic use for the early detection of prostate cancer. Instead, the effectiveness of biopsies in that area is higher when the biopsy is repeated after an initial previous negative biopsy of the peripheral zone. Abdel-Khalek et al. (2005) also evaluated the importance of TZ biopsy in benign prostatic hyperplasia (BPH) patients with serum PSA more than 10 ng/ml and prior negative PZ biopsy and to estimate the sensitivity of TZ biopsy. A total of 273 BPH patients with PSA more than 10 ng/ml and prior negative PZ biopsy underwent an extended biopsy protocol. In patients with a TZ volume of less than 25 cc, four TZ biopsies were taken (two cores per side from the apex and base). In patients with a TZ volume greater than or equal to 25 cc, six TZ biopsies were taken (three cores per side from the apex, middle, and base). TZ biopsy detected only 61.3% (19/31) of TZ cancers, and the incidence of pure TZ cancers was 7.3%, with the majority (74%) of TZ cancers detected at the apex site. Patient age, serum PSA, TRUS findings, and PSA density did not correlate significantly with the detection rate of TZ cancer, but prostate volume (p=0.023), TZ volume (p=0.027), and PSA/TZ density (p=0.007) were predictive of TZ cancers. Similarly, Durkan et al. (2002) showed that routine TZ biopsies should be considered in the framework of extended prostate biopsy for men with serum PSA levels exceeding 10 ng/ml whom they found to be at increased risk for TZ prostate cancer. It seems therefore that TZ biopsy should be performed in the setting of repeat biopsy, especially in a selected group of patients.

Nonetheless, others could not show any advantage to TZ sampling at the initial biopsy (Bazinet et al. 1996; Lui et al. 1995). In general, the addition of TZ biopsies to the initial biopsy strategy increases detection rates by only 1.8% to 4.3%, and there are few data to support the recommendation for routine TZ sampling (Matlaga et al. 2003).

Based on a literature review, Karakiewicz et al. (2005) recommended 12-core peripheral zone biopsies as standard care. This scheme incorporates the traditional sextant biopsy plus six laterally directed biopsies taken from the base, mid, and apex. In prostates larger than 60 cc they add a biopsy core for each additional 5 cc of peripheral zone tissue, based on their computer simulation studies, which showed that maximum detection rates are obtained when one biopsy core was taken for each 1.5 to 3.5 cc of prostatic tissue (Karakiewicz et al. 1998). Similarly, Basillote et al. (2003) demonstrated that the percentage of prostate cancer missed on the initial biopsy and detected on the repeat biopsy increases as the prostate volume increases. Their conclusions were based on their institutional experience with 4,376 men who underwent TRUS-guided sextant biopsy of the prostate, of whom 556 underwent a repeat sextant biopsy. Of the men who underwent a repeat biopsy, 22% were found to have prostate cancer. The percentage of men with cancer missed on the initial biopsy but detected on the repeat biopsy for each volume was investigated. Using the cutoff volume of 50 cc (mean gland volume of all the men in their study), a statistically significant difference was found in the percentage of prostate cancer not detected between men with prostate volumes less than 50 cc and those with volumes of 50 cc or greater.

This statistically significant difference was maintained when the cutoff volume of 37.5 cc (the median prostate volume of all the men found to have cancer in their study) was used. Specifically, prostate cancer was missed and subsequently diagnosed on the repeat biopsy in 13.7% and 6.5% of men with a prostate volume 50 cc or greater and less than 50 cc, respectively. Consequently, the false-negative rate more than doubled as the prostate volume exceeded 50 cc.

Using data from the European Prostate Cancer Detection Study (EPCDS) for PSA counts less than 10 ng/ml, Remzi et al. recently developed their Vienna nomogram (VN) prostate biopsy model (Remzi et al. 2005). This model optimizes the number of biopsy cores taken based on patient age and total prostate volume in the PSA range 2–10 ng/ml. The number of cores ranges from 6 to 18 based on the patient's age and prostate volume. Accordingly, the older the patient the lower the number of cores needed for optimal prostate cancer detection, whereas more cores are taken for larger prostates. Thus, for a given prostate volume equal to or less than 30 cc, for example, a 50-year-old or younger patient would undergo an 8-core biopsy, whereas a patient older than 70 years would need only a 6-core biopsy. For prostates larger than 70 cc, 18-core and 14-core biopsies would be needed for an optimal detection of prostate cancer in a 50-year-old or younger patient and a 70-year-old or older patient, respectively. The overall prostate cancer detection rate in this model is 36.7%, which is comparable to other extensive biopsy protocols (Scherr et al. 2002). The clear advantage of this model, though, is that it may reduce the detection of clinically insignificant tumors, as their detection inevitably increases with more extensive templates of prostate biopsy (Remzi et al. 2005). Accordingly, in the VN, less biopsy cores are taken from older men, avoiding oversampling and over-treatment of small-volume tumors that are not likely to cause cancer-specific mortality, unlike young men in whom these tumors are expected to grow and even affect survival.

It is imperative to emphasize that regardless of the number of cores taken, any suspicious area (whether by DRE or because of TRUS finding of hypo-echogeneity in the peripheral gland) should undergo separate directed biopsy and should be sent as a separate specimen for pathological examination.

Repeat Biopsy

One of the most complex clinical decisions in prostate cancer diagnosis is when one should repeat a prostate biopsy in the presence of solid clinical suspicions of prostate cancer. The data used by most authors to construct algorithms to address this issue were based on first-set negative sextant biopsy. It is tempting to consider that the risk of prostate cancer diagnosis on repeat biopsy following extended initial prostate biopsy is lower than that following initial sextant biopsy merely due to the reduction in sampling error. Along this rationale, when Djavan et al. (2001) examined the risk for prostate cancer in the first, second, and third repeat biopsies following initial negative sextant biopsy they found a sharp decrease in detection rates between the first repeated biopsy (22%) and the following repeated biopsies (5% and 4% respectively; Djavan et al. 2001). Indeed, Brossner et al. showed that the use of an extended (10-core) biopsy protocol at the initial evaluation reduces the number of prostate cancers in repeat biopsy as compared to the use of sextant core biopsy in the first biopsy (Brossner et al. 2005). Several clinical and pathological risk factors have been identified as predictors of prostate carcinoma in repeat biopsies. Well-established clinical risk factors are suspicious DRE, total serum PSA levels, percentage of free PSA, hypoechoic lesion on TRUS, PSA density (PSAD), and TZ-PSAD. Pathological risk factors that traditionally promoted repeat biopsy were the presence of high-grade prostatic intraepithelial neoplasia (HGPIN) and of atypical small acinar proliferation (ASAP) on initial sextant biopsy (Epstein and Potter 2001). Nowadays, however, when sextant biopsy is not considered adequate for primary diagnosis as detailed above (and even more so for repeat biopsies), and as greater numbers of patients with different clinical characteristics (normal DRE and lower levels of serum PSA) are subjected to prostate biopsies, some of these pathological factors are not as valid as factors that encourage a repeat biopsy. In the era of sextant biopsy, the presence of HGPIN in

the initial biopsy was associated with up to 79% of prostate cancers on subsequent repeat biopsy (Epstein and Potter 2001). With an initial 11-core biopsy scheme, this risk is reduced to 22% (Kamoi et al. 2000) and not higher than the general risk of having prostate cancer on repeat biopsy (Fowler et al. 2000). Based on their literature review, Karakiewicz et al. concluded that with an extended initial prostate biopsy (11–13 cores), the presence of HGPIN by itself is no longer an indication for repeat biopsy (Karakiewicz et al. 2005). Unlike HGPIN, in the era of extended initial prostate biopsy the presence of ASAP is still an indication for repeat biopsy, as it was shown to be associated with 43% of prostate cancer diagnosis on repeat saturation biopsy (Stewart et al. 2001).

Interestingly, Djavan et al. showed that with an 8-core (sextant biopsy and two additional TZ biopsies) biopsy scheme, biochemical and pathological features of cancers detected on initial and repeat biopsy in the PSA range 2.0 to 4 ng/ml are comparable in terms of PSA, grade, stage, and cancer volume (Djavan et al. 2005). This implies that a prostate cancer undiagnosed in a low-risk patient's first set of biopsy, but rather on his repeat biopsy, does not mean that it has more favorable tumor characteristics. Thus, at least for this limited sampling scheme, a repeat prostate biopsy in case of a negative finding on initial biopsy is strongly recommended.

In order to stratify the risk factors for detection of prostate cancer in repeat biopsy, using recursive partitioning analysis, Garzotto et al. recently constructed a model of four distinct risk groups that can practically serve to characterize high-risk, intermediate-risk, and low-risk groups for the subsequent detection of prostate carcinoma (Garzotto et al. 2005). This model segregates patients into distinct 2- and 5-year cancer detection rate according to their PSAD, PSADT, and the presence and absence of HGPIN. Patients in the highest risk group (those with a PSADT of ≤5 years and a PSAD of >0.25 ng/ml per cc) have an estimated carcinoma detection rate of 66±9% and 100%, respectively at 2 years and 5 years. Therefore, these patients should be strongly considered for a repeat prostate biopsy within a few months. Conversely, patients in the lowest-risk group (those with a PSAD of <0.25 ng/ml per cc, a PSADT of >5 years, and no HGPIN) can be considered for less rigorous follow-up because the estimated carcinoma detection rate in this group was found to be only 3±1% at 2 years. Patients with a PSADT of >5 years and a PSAD of <0.25 ng/ml per cc with HGPIN detected in the initial biopsy specimen had a 28%±5% risk of carcinoma detection at 2 years compared with only 3%±1% when HGPIN was absent. The presence of HGPIN lost significance when either the PSADT was short or the PSAD was increased (Garzotto et al. 2005).

It is imperative to emphasize that in any case of repeat biopsy, the extended biopsy scheme is indicated. The recommendation is to include also TZ biopsies in the repeat biopsy. Keetch and Catalona found a yield of 10% by sampling the TZ in repeat biopsies (Keetch and Catalona 1995). Higher yield is expected if PSA values are high and DRE is negative as indicated by Lui et al., who found 53% of prostate cancers to be detected only in the TZ in this clinical scenario (Lui et al. 1995).

Some authors have suggested performing saturation biopsy in cases where the repeat biopsies are negative in the presence of strong clinical suspicion of prostate cancer.

Saturation Biopsy

The indications for saturation biopsy are undefined yet. Patients who are considered at increased risk for prostate cancer, but had previously negative biopsies, cause a diagnostic challenge. The introduction of a saturation biopsy approach increased the detection of prostate cancer at the expense of a potentially higher detection rate of clinically insignificant prostate cancer. Stewart et al. from the Mayo clinic were the first to developed a saturation needle biopsy method for repeat prostate biopsy following negative sextant biopsy and a persistent indication for repeat biopsy (Stewart et al. 2001). Patients underwent this procedure in an outpatient surgical setting under general, regional, or intravenous sedative anesthesia. A mean of 23 cores (range 14 to 45) were obtained at each biopsy. Larger prostates underwent more biopsies than smaller prostates. A total of 3 TZ biopsies were

obtained. Technically, the saturation biopsy was performed using an inward radial step approach, starting at the far lateral peripheral zone (anterior horn) and continuing until the mid gland was reached. The process was then repeated on the contralateral side. Diagnostic yield was 34%. However, the incidence of insignificant cancer detected by saturation biopsy increased from 11.1% to 15.4% or to 22.2% in patients with 1, 2, or more than 2 previous negative biopsies, respectively. Of the 49 tumors removed at prostatectomy, 15 (30.6%) were less than 0.5 cc. Rabets et al. reported their experience with office saturation biopsy in 166 patients at increased risk for prostate cancer who had at least one negative prior biopsy (Rabets et al. 2004). In their series, most patient underwent more extensive prior sampling of the prostate as compared to Stewart et al. (2001). Using periprostatic nerve block, 24 biopsies were obtained in the first 80 patients. The 12 locations on either side were the lateral base (2), lateral mid zone (3), apex (3), parasagittal mid zone (2) and parasagittal base. In the last 36 patients they changed their biopsy scheme to include only 1 parasagittal mid zone and 1 parasagittal base biopsy from each side, thus decreasing the total number of cores sampled from 24 to 20, since in the first 80 patients medial parasagittal cores were never positive in the absence of apical, lateral mid zone, or lateral base positivity. In this scheme the TZ was visualized and sampled in medial parasagittal biopsies by advancing the needle through the surgical capsule and sampling the most anterior tissue. The apex was well sampled, including the anterior horn tissue, and the adjacent lateral mid zone and parasagittal mid zone biopsies. Overall diagnostic yield was 29%. But this was increased to a 64% cancer detection rate in patients who underwent a single prior sextant biopsy. They also noted an inverse correlation between the cancer detection rate and the number of prior biopsies (33% with 1 biopsy and 23% with 2 or more). Importantly, they showed that the risk of diagnosing clinically insignificant prostate cancer with their technique of saturation biopsy was similar to that in other series in which the diagnosis of prostate cancer was made with fewer biopsy cores. Fleshner and Klotz (Fleshner and Klotz 2002) evaluated the role of saturation biopsy in 37 patients who had undergone at least three prior sets of TRUS-guided biopsies (ranging up to 6), including TZ assessment. In all cases, the PSA parameters were significantly changing from baseline levels, including rising total PSA or a significant lowering (less than 0.10) of the free/total PSA ratio. All procedures were done under general or spinal anesthesia. The biopsy scheme included 24 laterally (4 from each sextant) placed TRUS-guided peripheral zone cores, 6 to 12 TZ cores, and 2 transurethral samples from the lateral prostatic lobes under resectoscopic guidance. However, despite this extensive sampling protocol among this high-risk cohort, only five (13.5%) of the 37 patients demonstrated carcinoma at saturation biopsy. Other notable pathologic features at saturation biopsy were acute prostatitis (n=7), chronic prostatitis (n=11), and HGPIN (n=1). In 3 of 5 cases, carcinoma was detected in the first 12 peripheral zone cores—transurethral and TZ cores were positive in only 2 patients who also had positive peripheral zone cores. Analyzing the pattern of this aggressive prostate assessment by looking at each separate biopsy location, the authors noted that all cases of cancer were identified in the first 18 peripheral zone cores. In addition, only 1 case would have been missed had only 12 cores been taken. They concluded that 12- to 18-core peripheral zone sampling should suffice among patients deemed candidates for repeated biopsy.

Thus, the indications for saturation biopsy are still questionable, specifically when contemporary protocols already apply extended (10–13) cores for the first biopsy.

Transperineal Prostate Biopsy

Transperineal prostate biopsy has a particular role in two distinct clinical scenarios: as a mode for repeat biopsy usually in the setting of saturation biopsy and in patients who have no rectum. One of the advantages of transperineal biopsies, particularly in the setting of repeat biopsy, is that transperineal approaches are appropriate for sampling from the anterior half of the prostate gland (Satoh et al. 2005; Demura et al. 2005), and it was also shown to enhance the identification of TZ cancers not detected by previous transrectal

prostate biopsy in patients at high risk of prostate cancer (Pinkstaff et al. 2005). Similar to transrectal prostate biopsy, prostate volume is the most relevant variable in the planning of the optimal number of cores in the extensive first biopsy set (Ficarra et al. 2005). Pinkstaff et al. demonstrated that systematic transperineal template biopsy of the prostate has an overall cancer detection rate of 37% in patients at high risk of prostate cancer despite negative findings on previous biopsies (Pinkstaff et al. 2005). The transperineal saturation biopsy is done under general anesthesia in a setup similar to that of standard brachytherapy techniques, namely using TRUS guidance and a template fixation device, grid, and probe cradle positioned adjacent to the perineum. Eighteen-gauge biopsy cores are obtained transperineally through the template grid moving anteriorly to posteriorly with the addition of more cores in larger volume prostates to improve the sampling in the apical region. A relatively frequent complication of transperineal prostate biopsy is urinary retention (11%). The number of needle incursions and prostate size are predictors of post-procedure urinary retention (Buskirk et al. 2004).

In patients who have lost the rectum to malignancy or inflammatory bowel disease and present with high or rising PSA, transperineal prostate biopsies are applied (Matlaga et al. 2003). This is done either the guidance of transperineal (Shinghal and Terris 1999) or transurethral (Seaman et al. 1996) ultrasound. Worldwide experience is relatively low, but it seems that the diagnostic yield is lower than with TRUS-guidance biopsies, emphasizing the need for prostate cancer screening before removal of the rectum (Matlaga et al. 2003).

Incidental Prostate Cancer

Incidental prostate cancer is defined as prostate cancer that is not diagnosed clinically but is rather diagnosed incidentally from histopathologic examination of a surgically obtained specimen. Two common clinical scenarios can lead to incidental diagnosis of prostate cancer. The first is through specimens obtained by transurethral resection of the prostate (TURP) or open enucleation of the prostate, and the second is following radical cystoprostatectomy (RCP) for transitional cell carcinoma of the bladder. The UICC Tumour Node, Metastasis (TNM) classification of prostate cancer relates to the first scenario, classifying tumors as T1a or T1b if the tumor is found in less or more than 5% of the resected prostatic tissue respectively. Another criteria to differentiate between T1a and T1b tumors is the tumor grade, which has to be of a GS equal to or less than 7 to be T1a, or more than 7 to define it as T1b. The incidental finding of T1a or T1b tumor was reported in about 15% of patients undergoing transurethral or open surgery for BPH (Bostwick 1995). However, nowadays the incidence of such a finding is probably lower, as many patients undergo PSA screening and there is an increase use of medical therapy (α blockers and 5 α reductase inhibitors) for BHP. In an elegant comparative analysis, Mai et al. (2000) reviewed consecutive TURP specimens from the two time periods (before and during the PSA screening era) to identify incidental PCA; they showed that some prostate cancers previously staged as T1b are now staged as T2 carcinomas, as a result of PSA screening and earlier clinical detection. The introduction of PSA screening has had no influence on the incidence of T1a prostate cancer. While it is clear from previous studies that T1a and T1b tumors have a different progression rate (Zincke et al. 1991), the recommended work-up and treatment plan for both stages is not clear.

Previous studies demonstrate progression rates without treatment as high as 16%–25% at 8–10 years (Matzkin et al. 1994). Cheng et al. (1999) attempted to identify clinical predictors of cancer progression in a large series of untreated T1a prostate adenocarcinoma patients with lengthy follow-up (median 9 years). Interestingly, the only potential predictor that was associated with progression was the amount of resected prostate tissue (TURP weight). Patients with a TURP weight greater than or equal to 30 g had 100% progression-free survival at 10 years compared with a progression-free survival rate of 73% in patients with a TURP weight of less than 12 g. GS, tumor volume, number of chips involved by tumor, number of tumor foci, and the presence of high-grade prostatic intraepithe-

lial neoplasia were not significant in predicting cancer progression.

Serum PSA levels should significantly decrease after TURP (Wolff et al. 2000; Aus et al. 1996) or prostatic enucleation, but their application as a prognostic marker for the follow-up of incidental prostate cancer is not reliable (Feneley et al. 1995; Aus et al. 1996). Thus, in the absence of adequate clinical predictors, it seems reasonable to follow patients who were just diagnosed with stage T1a or T1b prostate cancer by prostate biopsy to gain more satisfactory data on the tumor characteristics that by being detected in the prostate biopsy will become a stage T1c, for which treatment recommendations are more established. Without classifying these incidental tumors by proper prostate biopsy, their clinical behavior is unpredicted and often underestimated as reflected by previous studies like that of Epstein et al., who reported their experience with radical prostatectomy for T1a and T1b prostate cancers (Epstein et al. 1994). Of the 64 cases of stage T1a disease, 13 (20%) showed substantial tumor, including 7 with more than 1 cc of tumor, 5 with capsular penetration, and 1 with a Gleason grade 4+5=9 tumor. Based on preoperative pathological parameters, one could not predict which cases had minimal versus substantial tumor. For cases with stage T1b carcinoma, Epstein et al. (1994) found that 26% had capsular penetration and 10% had invasion of the seminal vesicles.

Coexistent prostate cancer in RCP specimens has been reported as high as 46% (Tal and Baniel 2005). The majority of these cancers were clinically insignificant. Indeed Ohori et al. (1994) compared the characteristics of PC found incidentally in the prostates of 88 patients who underwent RCP for bladder cancer to 307 prostate cancers that were detected clinically and treated by radical prostatectomy. Normal DRE served as the only pre-RCP screening test. The authors defined clinically important prostate cancer as a tumor with one or more of the following characteristics: volume of 0.5 cc or more, Gleason grades equal to or greater than 4, or a tumor that is not confined to the prostate. Important tumors were farther defined as curable or advanced based on the extent of extra-capsular extension and the presence of seminal vesicle invasion or lymph node metastases. Only 23% of the prostate cancers that were diagnosed in the RCP specimens were clinically important. All were curable and none was advanced, as opposed to most (91%) clinically detected tumors.

Conclusions

Prostate cancer, always considered the most common noncutaneous malignancy among men, is becoming even more commonly diagnosed at the present time due to PSA screening followed by extended prostate biopsy protocols. Consequently, overdiagnosis of clinically insignificant tumors occurs and should be regarded now as an inevitable trade-off for the potential detection of clinically significant tumors. Thus, in the absence of alternative noninvasive diagnostic tools, extended biopsy schemes should be performed not only at first biopsy but especially when repeated biopsy is needed. The widespread use of local anesthesia makes the procedure more comfortable. Future improvement of imaging techniques, the development of better clinical algorithms, and hopefully the discovery of better prostate cancer markers may decrease the rate of unnecessary biopsies.

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7 Does Localized Prostate Cancer Exist?

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Recent Results in Cancer Research, Vol. 175

Abstract

Does localized prostate cancer exist, and how do we diagnose it? Early diagnosis and screening programs for prostate cancer (PC) have led to a greater proportion of patients with a low-stage disease at diagnosis. More men are treated with curative intent by radical prostatectomy (RP), external beam radiotherapy, or brachytherapy. However, a substantial percentage of patients still experience a prostate-specific antigen (PSA) relapse within 5 years. Biochemical recurrence is observed in approximately 40% of patients who undergo RP, with 95% of those relapses in the first 5 years. To avoid the risk of recurrence, the recent tendency has been to detect PC at a lower PSA level than the level widely accepted (≥4.0 ng/ml). But the risk of overdiagnosis and overtreatment is a real problem in the PSA era. Discussion around the wide discrepancy between the high prevalence of histological changes recognizable as cancer and the much lower prevalence of clinical disease is prominent. The recent experience from studies on watchful waiting and the results of randomized trials between surgery and active surveillance have clearly demonstrated that many localized PC are overtreated. New screening and management strategies are required to target aggressive disease at an early stage while avoiding overdiagnosis and overtreatment.

Introduction

Early diagnosis and screening programs for prostate cancer (PC) have led to a greater proportion of patients with a low-stage disease at diagnosis. More men are treated with curative intent by radical prostatectomy, external beam radiotherapy, or brachytherapy. However, a substantial percentage of patients still experience a prostate-specific antigen (PSA) relapse within 5 years [3]. Biochemical recurrence is observed in approximately 40% of patients who undergo radical prastaectony (RP) with 95% of those relapses in the first 5 years [8]. To avoid the risk of recurrence, the recent tendency has been to detect PC at a lower PSA level than the level widely accepted (≥4.0 ng/ml). The rationale for screening at a low PSA value is supported by the more favorable expected characteristics of tumors detected in the range of PSA between 2.4 ng/ml and 4.0 ng/ml. However, the concept of localized PC is highly controversial as an entity situated between "potentially insignificant cancer" and what is already "non-organ confined tumor." The risk of overdiagnosis and overtreatment is a real problem in the PSA era. Discussion around the wide discrepancy between the high prevalence of histological changes recognizable as cancer and the much lower prevalence of clinical disease is prominent. Does localized PC exist and how do we diagnose it?

How to Define Localized Prostate Cancer?

We have learned from our experience with RP how difficult accurate preoperative staging and evaluation of tumor aggressiveness can be.

Clinical and Pathological Criteria (TNM Classification)

Localized PC is a cancer confined within the prostate gland (T1–2) without extension through the prostatic capsule (T3) in the extracapsular

tissue (T3a), the seminal vesicle (T3b), or adjacent structures (as bladder neck, external sphincter, rectum, levatori ani or pelvic wall). This cancer confined to the prostate gland is in principle eradicated by RP. In the other cases, cancer is locally advanced and surgical treatment is not indicated.

How can we be sure that cancer is confined to the prostate gland? Rectal examination alone is inaccurate in up to 60% of cases, leading to both under- and overstaging. Rectal ultrasound does not offer any advantage over rectal examination with a sensitivity of 50% and a specificity varying from 40% to 70%. Number and percentage of prostate biopsies specimen involved by the tumor is a more accurate parameter but underestimates the presence and grade of PC in 30% of cases. Magnetic resonance imaging (MRI) is still in evaluation.

Despite the numerous diagnostic parameters used, the final report after RP is still disappointing, with surgical margins involved by tumor in 11% to 46% of patients [4]. Moreover, PC features have evolved over the past 20 years: palpable nodules have become less frequent (from 91% to 17%) and index cancer volume has decreased (from 5.3 to 2.4 cm^3) [20]. The widespread use of PSA testing associated with the extensive use of transrectal prostate biopsy have led to a spectacular stage migration of PC. Catalona [2] compared typical pathology diagrams of prostates with cancers in 1991 and 2005 (Fig. 7.1). The diagram shows what the typical PC looked like in the pre-PSA era as compared with today. A decade ago it was frequent to find a large (but probably incurable) index tumor. The PSA level correlated strongly with the size of the tumor. Today the dramatic decrease in the index tumor, despite the multifocality of the lesions, gives the PSA less importance in the staging of the cancer. The total tumor volume or the percentage of carcinoma in the RP specimen may have more prognostic value in the modern era. Although clinical and pathological stages correlate with outcome, a large percentage of patients thought to have organ-confined disease will have evidence of disease beyond the prostate identified at the time of surgery. This is due to our relative inability to accurately stage the cancer. Digital rectal examination is not reliable. Imaging modalities can identify tumor or metastatic lesions half a centimeter in diameter, but are not able to demonstrate microscopic foci of neoplastic cells that have migrated to lymph nodes or perivesical fatty tissue [26].

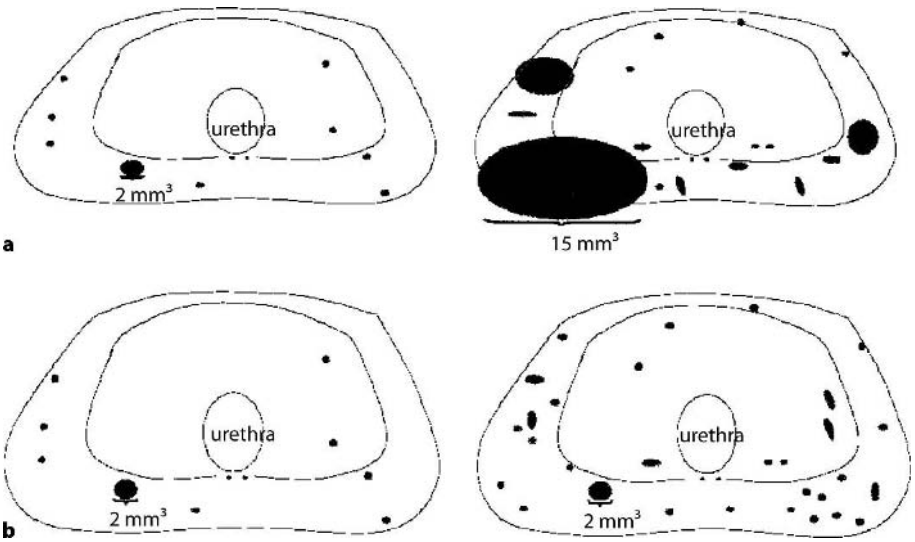

Fig. 7.1a, b Typical pathology diagrams of prostates with cancers in **a** 1991, compared with **b** 2005

"Low-" and "High-Risk" Tumors

The concept of a low- and high-risk tumor appears more appealing in the pretherapeutic period. Epstein [5] described in 1994 criteria predictive of organ-confined disease in nonpalpable prostate tumors (stage T1c). The criteria are based on Gleason grade (defining tumor differentiation), PSA density (level of PSA in relation to the size of the prostate gland) and the extension of tumor infiltration in prostate biopsies. A PSA density that is less than 0.1 ng/ml, the absence of a high-score tumor (Gleason score ≤7), the presence of tumor in no more than 3 out of 6 sampled biopsy specimens, and tumor infiltration that is less than 50% of each core biopsy correlates well with organ-confined disease.

Partin [15] in 1997 designed the "Partins table" evaluating a multi-institutional cohort of 4,000 patients who underwent RP. He compared the data known before the operation (PSA level, clinical stage and Gleason score from the biopsy specimen) with the final pathological stage of the prostate specimen in clinically localized PC. Let's give two examples of patients evaluated with Partin's table:

1. A 55-year-old patient underwent prostate biopsies because of a PSA increase from 2 to 4.5 ng/ml over a year, with a normal DRE (T1c): a Gleason score 8 tumor was found in 2 out of 6 biopsies.
   The risk for the patient to have an extraprostatic extension is 40%, seminal vesicle infiltration 6%, and lymph node involvement 1%. The chance for organ-confined lesion is 52% (41% to 63%).
2. A 65-year-old asymptomatic patient with a PSA of 7 ng/ml has normal DRE (T1c). Prostate biopsies show a Gleason score 7 (4+3) tumor. The chance for organ-confined lesion is 43% [35%–51%]. The risk for extraprostatic extension is 47%, seminal vesicle infiltration 8%, and lymph node involvement, 2%.

The chance for both patients to have localized PC are limited to 50%. Finally given the independent prognostic significance of pretreatment PSA, Gleason score, and stage, various algorithms have been developed to provide point-estimates of recurrence risk. Patients with a PSA of less than 10 ng/ml, Gleason 6, and T1 or T2a disease appear to be "low-risk patients" with a 6% to 20% of recurrence rate after local treatment. Such patients are likely to be cured with monotherapies such as external beam radiation therapy, brachytherapy, or prostatectomy.

Patients with a PSA exceeding 20 ng/ml, Gleason 8–10, and T3b disease are considered to be at "high risk," with recurrence rates of 50% to 100% after definitive local therapy.

Identifying patients with "low-risk" characteristics appears the better way to treat patients with organ-confined lesions according to Epstein who had already described in 1994 clinical and pathological criteria predictive of local extension in nonpalpable prostate tumors (stage T1c).

Criteria for Insignificant Localized PC

Examining the feature of cancers detected after RP, Epstein et al. [5] designed the criteria for insignificant PC: PC less than 0.2 cm^3, confined to the prostate with a Gleason sum less than 7. Ohori [14] is more flexible proposing for unimportant cancer, a tumor less or equal to 0.5 cm^3, confined to the prostate, with no primary or secondary Gleason pattern 4 or 5.

A careful evaluation of the pathologic profile of a patient diagnosed with a potentially "insignificant" cancer may help to distinguish those with a truly "insignificant" tumor—well differentiated (Gleason ≤6) of low volume (0.2–0.5 ml), manageable initially by surveillance—from those with a potentially life-threatening tumor requiring active treatment [25].

Localized PC is an entity situated between "potentially insignificant" cancer and what is already "non-organ-confined tumor."

How to Improve Diagnosis of Localized PC?

PSA is a valuable tool for detecting early stage PC and for staging men with newly diagnosed tumor. In the last few years it rapidly became obvious that men with higher PSA were significantly more likely to have higher clinical stages,

Table 7.1 Relationship of the prostate-specific antigen (PSA) level to the prevalence of prostate cancer and high-grade disease. High-grade disease was defined by a Gleason score of 7 or greater. The population was restricted to men with a PSA level of 4.0 ng/ml or less throughout the study. Used with permission [21]

PSA level	No. of men (n=2,950)	Men with prostate cancer (n=449)	Men with high-grade prostate cancer (n=67)	Sensitivity	Specificity
		No. of men (%)	No./total No. (%)		
1.1–2.0 ng/ml	998	170 (17.0)	20/170 (11.8)	0.75	0.33
2.1–3.0 ng/ml	482	115 (23.9)	22/115 (19.1)	0.37	0.73
3.1-4.0 ng/ml	193	52 (26.9)	13/52 (25.0)	0.12	0.92

higher grade cancers in the biopsy and final RP specimen, positive surgical margins, capsular penetration, seminal vesicle invasion, and lymph node metastasis [6]. The incidence of distant stage disease decreased at a dramatic rate since 1991 in the PSA era and today 75% of PC are discovered at a low stage. The 5-year survival rate is nearly 100% for local or regional disease and only 33.5% for distant stage disease [2].

After the PC Prevention Trial (PCPT) [21] it became obvious that, biopsy-detected PC, including high-grade cancers, is not rare (15.2%) among men with PSA ≤4.0 ng/ml, levels generally thought to be in the normal range (Table 7.1). A screening for PC at low PSA levels (<4.0 ng/ml) was suggested. Is it the solution to diagnose localized PC?

Using a Low PSA Level (<4.0 ng/ml) for Detecting Localized PC?

There is a debate about the optimal PSA cutoff for recommending prostate biopsy. It is well-documented that 7% to 27% men with PSA 1.0 to 4.0 ng have biopsy detectable PC and 14.9% have a Gleason score of 7 or higher [21]. However, recommending a lower PSA threshold for prostate biopsy to 2.6 ng/ml is not the right response according to Stamey [20], because this is precisely the range of serum PSA for benign prostatic hyperplasia currently (Table 7.2).

Schröder et al. [19] considered also that using a low PSA threshold (2.4 ng to 4.0 ng/ml) might detect clinically insignificant PC that would not pose a clinical threat to the patient (overdiagnosis).

If the best cutoff remains unknown, use of a normal threshold (4.0 ng/ml) risks missing clinically relevant cancers that are still curable, whereas the use of a lower threshold increases the number of unnecessary biopsies and the number of clinically insignificant cases. What about European Official Guidelines? According to the German Guidelines [18] the decision to undergo early PC detection needs to come from the patient. He should be thoroughly informed about what options he has after being advised about the risks and benefits. It seems medically warranted to stipulate a PSA cutoff at 4.0 ng/ml (5 biopsies needed to find 1 carcinoma). Reducing the cutoff to 3 ng/ml increases detection of curable tumors by only 2% (Table 7.2).

The EAU guidelines [1] confirm that the exact cutoff level of what is considered to be a normal PSA value has not yet been determined, but values around 2.5–3 ng/ml are often used for younger men (grade C recommendation).

Table 7.2 The probability of a positive biopsy and detecting organ-confined cancer can be correlated to PSA value (from Luboldt et al. [18])

0–4 ng/ml: case finding in 10%, ca. 90% are organ-confined malignancies
4–10 ng/ml: case finding in 25%, 70% are organ-confined malignancies
>10 ng/ml: case finding in 50%, 50% are organ-confined malignancies

What About Prostate Cancer Screening?

Screening for PC remains a controversial issue in spite of recent evidence of a decreasing PC mortality in geographic areas were screening is prevalent [19].

Criticism includes the financial burden of screening, the morbidity of prostate biopsy, the low positive predictive value of screening, the overtreatment of an indolent disease, and the lack of evidence demonstrating a mortality benefit due to screening. If the PSA era has brought great promise for improving the prognosis of PC, we have to improve PC screening to better select clinically significant localized PC [13].

PSA Velocity and PSA Doubling Time

A PSA velocity measurement is helpful because clinically significant PC is more likely to be found in men with a rapidly rising PSA. Recent studies suggest that for men with a total PSA higher than 4 ng/ml, a PSA velocity of 0.75 ng/ml per year is an indication for biopsy. However, in men whose total PSA level is lower than 4 ng/ml, a lower PSA velocity cutoff should be used, in the range of 0.1 to 0.5 ng/ml per year. More clinical research is needed to evaluate PSA velocity cutoffs for men with low PSA levels [2].

PSA doubling-time (DT) enhances prediction of the biological phenotype of the cancer. A PSA-DT shorter than 3 months has apparently a high predictive value for PC-specific mortality following surgery or radiation therapy in patients with clinically localized PC [23]. Moreover, in the pretreatment period a PSA-DT of less than 2 years appears to identify patients at high risk for local progression despite otherwise favorable prognostic factors. A patient with a PSA-DT of around 3 years has a high chance of remaining free of recurrence or progression for many years.

Can We Improve Management of Localized PC?

The situation today is a real paradox: men who underwent radical treatment (RP of radiotherapy) with curative intent for localized PC have a 20%—40% risk of 5-year biochemical recurrence; on the other hand, a relevant number of patients who are disease free at 5 years have probably been overtreated for clinically nonsignificant tumors.

What About Biochemical Failure After RP?

Most investigators consider the biochemical failure (PSA) after RP to be due to positive surgical margins, metastatic disease, and or local recurrence, but also to the presence of benign prostatic glands in the surgical margin. Positive cancer margins occur in 11% to 46% of patients after RP [4, 17] and biochemical or clinical recurrence appears for as many as 63% of patients in a 5-year follow-up.

The quality of life for men with PSA progression is definitely affected. Most patients with biochemical failure will experience clinical pelvic recurrence or even distant metastasis. Patients with PSA failure within the first 2 years carry the greatest risk of developing distant metastasis, and patients with a detectable serum PSA level immediately after surgery most probably had distant disease at the time of surgery. The PSA-DT is significantly associated with the time to PC-specific mortality and the time to overall mortality [23, 24].

Improving the technique to reduce positive margins is mandatory, but the risk of incontinence is high when dealing with apical tissue.

New Strategy with Active Surveillance and Selective Delayed Intervention Using PSA Doubling Time for Good Risk Patients

According to Klotz [10, 11] localized PC is overtreated, with some patients who have a favorable-risk disease not destined to experience PC death or morbidity undergoing radical therapy.

The Canadian Consensus Conference on PC defines good-risk PC as patients with a Gleason score 6 or less, T1c-T2a, and PSA of less than 10 ng/ml. In this group of patients, it is possible to estimate the biological aggressiveness of the tumor based on PSA-DT. Most patients who

understand the basis for this approach will remain on observation in the long term—PSA-DT varies widely and is not predicted by grade, stage, or baseline PSA. Of the patients in the series, 33% had a PSA-DT of more than 10 years—PSA-DT appears to be an excellent marker of cancer aggressivity in localized PC. A PSA-DT of less than 2 years identifies patients at high risk for local progression and who need active therapy. A PSA-DT of 3 years or more in cases of localized PC gives the patient a high probability of remaining free of progression for many years. It is likely that most of these patients will die of causes unrelated to PC. Active surveillance is clearly appropriate for elderly patients, patients with significant co-morbidity, or in the presence of favorable PC parameters.

Conclusion

Screening and early detection of PC in the PSA era have led to a greater proportion of early-stage PC at diagnosis and an increasing number of patients being offered definitive treatment with RP or radiotherapy. The recent experience from studies on watchful waiting and the results of randomized trials between surgery and active surveillance have clearly demonstrated that many localized PC are overtreated.

"Good risk" patients (with a Gleason score of 6 or less, PSA <10 ng and T1c–T2a tumors) now constitute 50% of newly diagnosed PC patients. The present challenge is to identify in this group of patients the prognostic criteria that might predict the degree of threat involved.

The assumption that localized PC at diagnosis warrants active treatment with a curative intent is now being challenged. In the group of patients with supposedly localized PC, clinically insignificant tumors coexist with aggressive life-threatening cancers sometimes associated with microscopic distant metastasis.

New screening and management strategies are required to target aggressive disease at an early stage while avoiding overdiagnosis and overtreatment.

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8 Staging of Prostate Cancer

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Recent Results in Cancer Research, Vol. 175

Introduction

Prostate cancer, with an incidence that is correlated to age, is the most common cancer tumor diagnosed among men older than 50 years, and an even higher incidence is found among patients older than 75. It is estimated that 234,460 men will be diagnosed during 2006 and 27,350 deaths will be attributed to prostate cancer in the United States. Thus, it is the 3rd most common cause of cancer-specific death, following lung cancer, in Western men (Jemal et al. 2006). The lifetime risk for prostate cancer is estimated to be one in six among countries with active screening programs. Since 1990 there has been a decline in prostate cancer death. Of the patients diagnosed from 1995 to 2000, around 90% were diagnosed during local or regional stages. The 5-year survival rate for those patients approached 100%, while the overall survival rate for all stages increased during the past 20 years from 67% to 99%, with a 10-year survival rate of 92%. Usually, the increase in survival rate for those patients is attributed to early diagnosis (American Cancer Society 2005). Many patients newly diagnosed with prostate cancer will be evaluated for curative treatment, according to age at diagnosis and comorbidities. Following histologic diagnosis of prostate cancer, staging is used to determine the extent of the patient's cancer to predict prognosis and to evaluate and select the appropriate treatment options. Accurate staging is helpful in assessing different treatment options and defining prognostic models.

Historically the staging of prostate cancer was based on the anatomical extent of the cancer determined during physical examination. The ability to better stage patients who are currently being diagnosed with prostate cancer continues to evolve because of improvements in imaging, defining, and detection of tumor markers, and creation of prediction tools based on currently available clinical variables. Such tools are used to better define the extent of cancer at time of diagnosis, the probability that the individual patient will clinically progress following local therapy, and the likelihood of prostate-related death. They are also used to evaluate the use of neoadjuvant and adjuvant treatment prior to or following local therapy.

Classification System

Since 1975 the UICC 2002 Tumour Node, Metastasis (TNM) classification system has been used by the American Joint Committee for Cancer Staging (AJCC). The AJCC classification is based on the extent of the primary tumor (T), the presence and extent of involved lymph nodes (N), and distant metastases (M). This system has replaced the previously used staging classification of Whitmore and Jewett, which was based on digital rectal examination (DRE) only and just described the extent of the tumor. The different classifications of the tumor included: class A [normal DRE, tissue obtained by transurethral resection of the prostate (TURP)], class B (palpable disease confined to the prostate), and class C (tumor extent beyond the prostate capsule) (Jewett 1975).

The 1992 version of the TNM system (International Union Against Cancer 1992), an effort by the AJCC and the International Union Against Cancer (UICC), included DRE, prostate-specific antigen (PSA), and transrectal ultrasound (TRUS) findings, and added a new classification—T1c, those tumors detected by prostate biopsy and triggered by elevated serum PSA. The proportion of tumors classified as T1c

was initially less then 10% of all cases (Ohori et al. 1994) and has increased significantly since then, accounting for more than 70% of all newly diagnosed prostate cancer cases (Draisma et al. 2003; Stamey et al. 2004). Nonpalpable disease identified by TRUS was classified as T2, similar to patients with palpable T2 disease; despite no difference in outcome compared with T1c with no visibility on TRUS (Ohori et al. 1994). Nonpalpable tumors compared with palpable tumors but had lower preoperative PSA (9.3 ng/ml vs 11.8 ng/ml), higher percentage of Gleason score 6 tumors (71.8% vs 52.5%), and reduced tumor involvement of the submitted tissue (14.3% vs 22.4%) (Augustin et al. 2003). Recent analysis of patients operated on from 1983 to 1998 showed no differences in presence of Gleason score of 7 and above, tumor volume, and presence of organ-confined disease at the radical prostatectomy (RP) specimen for patients with nonpalpable disease and no difference regarding biochemical failure between nonpalpable tumor with and without visible tumor by TRUS (Ohori et al. 2003). TRUS findings (T2a vs T2b vs T3c) did not predict freedom from biochemical failure. Only the group of patients classified as definitely having cancer, according to TRUS (group V vs groups I–VI), experienced an increased rate of progression following RP—76% vs 85%, respectively, at 5 years. Of the last 100 cases, only 4% were classified as group V according to TRUS findings. The percentage of low-volume palpable tumor (T2a) had similar progression-free probability compared with nonpalpable tumor with and without visible tumor by TRUS, suggesting that classifying patients with visible tumor by TRUS as T2a is not justified. The correlation between the TRUS-detected hypoechoic lesions and the pathology finding of RP is low. Many clinically significant tumors are not visible by TRUS, which diminishes the importance of the classification of nonpalpable tumor by TRUS finding (Garzotto et al. 2003). Other imaging modalities, such as endorectal probe magnetic resonance imaging (erMRI), might be more useful in staging nonpalpable tumors (Mullerad et al. 2005).

The 1997 edition of the TNM system (Fleming et al. 1997) combined the previous T2a and T2b classifications into T2a (tumor occupied only one lobe) and T3a and T3b to T3a (unilateral vs bilateral extracapsular extension of tumor). However, debate exists regarding the use of the 1997 classification vs the 1992 version, since the 1992 classification demonstrated differences in outcome in T2a vs T2b. The ability to differentiate between those groups was eliminated by the 1997 classification (Han et al. 2000). The 1992 classification was reported to predict better outcome following RP compared with the 1997 classification (Cagiannos et al. 2002). In 2002, the TNM staging was revised again. T2 lesions were classified as either "lesion with abnormal DRE without extracapsular extension (ECE) or seminal vesicle invasion (SVI)" or "hypoechoic lesion by TRUS." T3 lesions are subclassified to T3a and T3b based on the 1997 classification.

Evaluation of Local Disease and Presence of Metastatic Disease

The extent of local disease and biopsy variables are the most important variable used to define the natural history of prostate cancer and predict its progression, and to estimate response to definitive local therapy among patients with clinically localized prostate cancer. Treatment for locally advanced cancer in the presence of ECE, seminal vesicle invasion, and lymph node involvement definitely impact progression-free probability (measured by freedom from PSA recurrence), clinical progression, and death from prostate cancer. Patients with locally advanced cancer are not eliminated from potential curable treatments to control local disease and clinical progression. Several modalities are used to assess the local extent of the disease.

Digital Rectal Examination (DRE)

Used for more than 50 years, DRE represents the most accessible staging test for evaluating the local extension of prostate cancer (Jawet 1975). Staging systems and prognostic models rely on DRE for clinical staging of prostate cancer (Partin et al. 1997; D'Amico et al. 1998; Kattan et al. 1998). However, during the post-PSA period, more than 80% of tumors will be diagnosed

following elevated PSA, and more than 70% of those will have normal DRE. The probability of overstaging and understaging with use of DRE is significant, demonstrated by the discrepancy between DRE and pathology reports of RP specimens, and it is examiner-dependent. Organ-confined tumor (pT2) following RP was found among 59% to 77% of the patients classified as T1c. This staging upgrade was mainly due to the presence of ECE in 17% to 24% (Table 8.1).

Overstaging patients with prostate cancer can be estimated by evaluating the pathology report of RP specimens of patients classified as clinical T3 disease (either presence of ECE [T3a], SVI [T3b], or adjacent organ involvement [T4]). Clinical T3, based on preoperative physical examination, will be correct for 76% to 87% of patients. However, up to approximately 1/4 of the patients treated with RP as monotherapy will have pathological organ-confined disease following RP (Table 8.2).

DRE sensitivity in staging patients with prostate cancer is limited by the trend of using screening to identify clinically nondetectable small-volume tumor, areas of the prostate that are inaccessible to the examiner (DRE sensitivity of 59%–91%), and year of diagnosis and PSA level prior to cancer detection (Table 8.1). The specificity of DRE for local advanced tumors is reasonable, in the range of 76% to 87%. Only less than 25% of the patients who are considered by a urologist to have clinical T3 disease will present with organ-confined disease following RP (Partin et al. 1993; Van Poppel et al. 2000). Clinical T2a has similar tendencies for the presence of a positive surgical margin, ECE, and SVI compared with T1c disease. Researchers have suggested that the rate of biochemical failure for patients with T1c disease is comparable to that for patients with cT2a, according to the 1997 classification (Freedland et al. 2003b). Others have shown a difference in biochemical failure rates between T1c and T2a in a cohort of patients who were treated by RP (Kattan et al. 1998).

Table 8.1 Clinical T1c disease

	Years	N	OCD	ECE	SVI	LNI
Southwick et al. 1999[a]	1994–1996	268	71.6	23.9	2.2	0.7
Ohori et al. 2003	1983–1998	865	59			
Geltzer et al. 2002	1988–2000	1119	72.5			
Antenor et al. 2005a	1989–2001	2669	75.4	23.1	1.5	
Jack et al. 2002	1998–2000	228	77	17	4.3	1.3
Bastian et al. 2004	2000–2003	237	91.6	7.6	0.8	

ECE, extracapsular extension; LNI, lymph node involvement; OCD, organ-confined disease; SVI, seminal vesicle invasion

[a] Preoperative PSA level of 4 to 10 ng/ml

Table 8.2 Clinical T3 disease

	Years	N	OCD	ECE	SVI	LNI	T3
Partin et al. 1993		36	19				45
Lerner et al. 1995[a]	1966–1982	812	17				49
Amling et al. 1997			25			31	
Van Poppel et al. 2000		158	13	75	25		
Powell et al. 2002[b]	1993–1996	58	62		31	19	
Carver et al. 2006[c]	1983–2003	112	24	71	31	21	

[a] Neoadjuvant treatment in 491 cases (60%): external radiotherapy in 61 (7%), hormonal therapy 348 (43%) and both 82 (10%)

[b] Neoadjuvant hormonal therapy for all the patients (Goseralin and flutamide)

[c] No adjuvant therapy

Prostate-Specific Antigen (PSA)

Total

PSA was introduced to clinical urology less than 20 years ago and significantly changed the screening and follow-up process for patients with prostate cancer. PSA is 33-kDa serine protease of the kallikrein family, which includes 15 proteins; PSA is also known as human kallikrein 3. PSA is produced predominantly by the prostate epithelium, although it can be found in endometrium and breast tissue in limited amounts. PSA is secreted by the normal prostate epithelium to the seminal fluid, where the level of PSA reaches levels of milligrams per milliliter. Although traces of PSA can be found in endometrial and breast tissue by immunohistology assays, it is considered to be organ-specific. Every prostate disease, such as cancer, inflammation, trauma, infarct, and others, can cause PSA levels to rise. Differences in the expression and production of PSA by the different lobes of the normal prostate were reported, with the highest levels produced at the transitional zone. Therefore, the PSA level usually significantly decreases following surgery for benign prostate hyperplasia, with changes associated with the amount of removed prostatic tissue (Furuya et al. 2000).

The PSA level was found to have a negative correlation with Gleason score adjusted to tumor volume of patients treated by RP (Partin et al. 1990). However, since there is a correlation between tumor volume and increased rate of PSA release to the circulation with high-grade tumor, increased serum PSA level corresponds to the Gleason score (Stamey et al. 1987; Partin et al. 1997). Despite its limitation, PSA can provide useful information regarding pretreatment staging for prostate cancer.

Prediction of pathology stages as the presence of organ-confined disease, isolated capsular penetration, SVI, and lymph node metastases were associated with PSA level. Only 9% of patients with PSA above 50 ng/ml will have organ-confined disease compared with 64% of patients with PSA below 4 ng/ml. SVI and lymph node metastases were found among 3% and 1% and 32% and 27% of patients with PSA below 4 ng/ml and patients with PSA above 50 ng/ml, respectively (Partin et al. 1997).

The vast majority of patients diagnosed with prostate cancer in countries that perform PSA screening for prostate cancer will have a PSA level of less than 20 ng/ml (Draisma et al. 2003). Stamey et al. have demonstrated that serum PSA levels between 1999 and 2003 correlated primarily with prostate size, i.e., the amount of benign prostate tissue. In addition, PSA level was demonstrated to correlate with the volume of cancer. When taking into account prostate weight and cancer volume, no correlation was found between PSA level and ECE, SVI, and pathology percentage of Gleason 4/5 (Stamey et al. 2004).

Free-to-Total PSA Ratio

Using the free-to-total (f/t) PSA ratio has added information about patients presenting with normal DRE and elevated PSA (2.5–10 ng/ml) (Catalona et al. 1998). The role of the f/tPSA ratio for prostate cancer staging prior to RP is unclear. Among 76 patients undergoing RP, f/tPSA was significantly higher among patients with organ-confined versus those with non-organ-confined disease (11.9% vs 9.1%). A threshold of 11% in f/tPSA indicates organ-confined disease with a hazard ratio (HR) of 2.7 compared with f/tPSA below 11% (using monoclonal antibody immunoassay) (Tandem and Tandem-free PSA, Hybritech, Belgium) (Morote et al. 1999). Pannek and coworkers from Johns Hopkins demonstrated that using an f/tPSA ratio of 25% did not improve the prediction of non-organ-confined disease (Pannek et al. 1996). In a later study, the same group used monoclonal immunoassays for PSA and free (f) PSA for 255 patients prior to RP (Tandem and Tandem-free immunoassay, Hybritech, San Diego). A significantly lower f/tPSA ratio was detected among patients with non-organ-confined disease vs those with organ-confined disease (12.3% vs 15%) (Veltri et al. 2002). Similarly, 75% of patients with an f/tPSA exceeding 15% had a favorable pathology (organ-confined disease, Gleason score less than 7, and small tumors) compared with 34% when the f/tPSA was 15% or lower (Catalona et al. 2000). In contrast, the percentage of fPSA was associated with total

prostate and benign prostatic hyperplasia (BPH) volume among 256 patients who underwent RP, but was not associated with total cancer and Gleason 4/5 volume (Haese et al. 2003). Thus, there is still no clear answer regarding the utility of f/tPSA as a predictive variable when used with clinical DRE staging, and prostate biopsy results vs total PSA only.

PSA Velocity and Doubling Time

The dynamic characteristics of PSA changes can be described in terms of PSA velocity (PSAV), PSA slope, and PSA doubling time (PSADT). Those variables are calculated by using several PSA values over time and have been shown to be helpful in the prognosis and outcome of patients who failed biochemically following RP or radiotherapy (Pound et al. 1999; Roberts et al. 2001a; Dotan et al. 2005). Recently, PSAV and PSADT have proved to be important predictive factors for the probability of biochemical failure and prostate cancer-specific mortality (PCSM) after local therapy. PSAV of 2 ng/ml per year and above prior to RP was associated with increased probability of SVI compared with PSAV below 2 ng/ml per year (8% vs 3%), lymph node metastases (5% vs 0.7%), and a Gleason score of 8 to 10 at the final pathology (7% vs 3%) (D'Amico et al. 2004a). Those worsened characteristics translated to an increased rate of PCSM among patients with PSAV of at least 2 ng/ml per year, with an HR of 9.8, compared with patients with a PSAV below 2 ng/ml per year. Data for a large cohort of patients treated with RP confirm the additional predictive ability of preoperative PSAV and PSADT (Patel et al. 2005; Sengupta et al. 2005).

A similar effect was demonstrated for patients treated with external radiotherapy who were stratified by pretreatment PSAV. PSAV of at least 2 ng/ml per year prior to radiotherapy was associated with increased probability of biochemical failure (HR 1.8), PCSM (HR 12.0), and overall mortality (HR 2.1). PSAV provided prognostic information for PCSM after using known risk factors. Among low-risk patients stratified by PSAV of 2 ng/ml per year and above, PCSM at 7 years was 19% and 0%, while among high-risk patients the probability of PCSM was 24% and 9%, respectively (D'Amico et al. 2005a). The main limitation of using PSA dynamics prior to local treatment is the significant variation of PSA values at that time. PSA level has high variability among patients followed by PSA for prostate cancer screening. Of 40% to 55% of patients with an abnormal PSA level, repeated PSA testing showed normal levels during 4 years of follow-up prior to any treatment (Eastham et al. 2003). Conflicting data exist on the impact of PSAV on PCSM prior to RP (Bianco et al. 2004).

Prostate Biopsy

Prostate biopsy is the main procedure used to make an initial tissue diagnosis of prostate cancer, indicated by elevated PSA in the majority of cases. For less than 20% of patients, DRE is the only indicator for prostate biopsy. Among patients with suspicious DRE and low PSA (<2 ng/ml), the mean volume of tumors and Gleason score were less than 0.5 cc and 6, respectively (Schroder et al. 1998). Other procedures used to obtain prostate tissue that can be used to diagnose primary prostate cancer include: (1) surgery for clinically benign lesions of the prostate, such as TURP or open prostatectomy (classified as stage T1a/b), which contribute—since the introduction of PSA as a screening method for prostate cancer—less than 5% of newly diagnosed tumors (Stephenson et al. 2005); (2) prostate biopsy for patients who presented with metastatic disease of unknown origin. Thus, the majority of the patients with newly diagnosed prostate cancer will be diagnosed by prostate biopsy for clinically localized disease. Biopsy results including grading, estimation of tumor size, and tumor extent; presence of invasive components; and other factors provide important information regarding staging, treatment outcome, and survival.

A questionnaire filled out by experienced uro-oncologists estimated the data of prostate biopsy prior to performing RP. The following data were classified in a decreasing order of importance: Gleason score, percentage involvement of the core by cancer, presence of perineural invasion, number of involved cores by cancer, and the length of core involvement (Rubin et al. 2004).

Table 8.3 Probability of biochemical failure following radical prostatectomy according to pathology Gleason score (Partin et al. 1997)

Gleason score	OCD	ECE	SVI	LNI
2–4	68	30	2	0
5	54	44	1	1
6	59	34	3	4
7	29	51	8	12
8–10	29	33	10	28

Grading Prostate Cancer

The most common method used for grading prostate cancer is the Gleason grading system, which was first described in 1966 and adapted by the American College of Pathologists as the preferred method of prostate cancer grading (Gleason 1966; Bostwick and Foster 1999). Gleason grading is based on assigning a number between 1 and 5 to the two most common patterns following cancer diagnosis, creating nine different groups (2–10), to determine the Gleason score. Gleason grading is determined by the architectural patterns of the prostate cancer based on standard light microscopic interpretation of hematoxylin and eosin staining a tissue section (Epstein 2004). Gleason score is one of the most important variables for prostate cancer staging that correlates with the final pathology (Partin et al. 1997). An inverse correlation exists between Gleason score and outcome following local therapy (D'Amico et al. 1998; Kattan et al. 1998) and cancer-specific survival following observation only or androgen deprivation therapy (Albertsen et al. 2005).

The occurrence of organ-confined disease (lack of extra-capsular extension, seminal vesicle invasion, and lymph node involvement) inversely related to Gleason score (Table 8.3) (Partin et al. 1997). The correlation between biopsy Gleason score and the RP specimen's score is limited, and the differences between them were demonstrated in up to 64% of patients. Upgrading was noted in 46%, and downgrading in the remaining 18% (Noguchi et al. 2001). The differences were more pronounced with the low- and moderate-grade compared with high-grade biopsies (Bostwick et al. 1994; Steinberg et al. 1997). Among patients with biopsy Gleason scores of 5 or 6 on biopsy, only 64% correlated with prostatectomy specimen scores, while Gleason scores of 7 or higher correlated with 88% of the prostatectomy Gleason scores (Steinberg et al. 1997). In contrast, 45% of patients who presented with high-grade prostate biopsy (8–10) at Memorial Sloan-Kettering prior to RP demonstrated downgrade to Gleason of 7 or less on final pathology. Predictors for downstaging of pathology Gleason score were lower clinical stage and lower biopsy Gleason Score (8 vs. 9–10) (Donohue et al. 2006). The discrepancy between biopsy and final pathology can be caused by sampling bias, variability

Table 8.4 Probability of biochemical failure following radical prostatectomy according to pathology Gleason score

Gleason score	Han 2003[a]	Blute 2001[b]	Herman 2001[c]	Lau 2001[d]
2–4		89%		
5		85%		
6	88%	71%		
7	54%	69%		
8–10	29%	43%		
3+4			26%	33%
4+3			38%	46%

[a]Biochemical failure at 10 years (Han et al. 2003)

[b]Biochemical failure at 5 years, for T2–3N0

[c]Biochemical failure at 5 years

[d]Biochemical failure at 7 years

between pathologists, and borderline tumors (Epstein and Potter 2001).

An elevated Gleason score was also associated with increased likelihood of biochemical failure (Kattan et al. 1998; Blute et al. 2001; Han et al. 2001), metastases progression (Pound et al. 1999; Dotan et al. 2005), and PCSM (Freedland et al. 2005) following RP; however, most researchers used the pathology grading. Similarly, the impact of Gleason score was noted following external radiotherapy and brachytherapy. PCSM following radiotherapy among patients with Gleason scores of 7 and 8–10 according to pretreatment biopsy had HRs of 3.1 and 10.8, respectively, on multivariate analysis compared with patients with Gleason score lower than 6 (D'Amico et al. 2005b).

Among patients with a Gleason score of 7, the primary grade of 4 vs 3 was associated with a lower rate of advanced pathology characteristics—organ-confined disease (31.6% vs 48.6%), ECE (48.7% vs 37%), and SVI/LVI (17.6% vs 14.7%) (Makarov et al. 2002).

Estimating the Amount of Cancer According to Prostate Biopsy

Other prostate biopsy variables, such as the number of cores obtained at time of biopsy, number of involved cores, maximal length of cancer among all cores, and percentage of cancer in the submitted specimen can be used to estimate the final RP results and progression-free probability following local therapy.

The total number of biopsy cores was related to the accuracy of final pathology. RP Gleason score was better correlated with biopsy Gleason score according to the total number of cores obtained during prostate biopsy; among patients who had 10 or more cores, identical final score was found among 76% of the patients compared with 67% among patients with less then 10 cores (San Francisco et al. 2003). A similar pattern was seen when the cores numbered 6, 8, or 10; the use of 10 cores was a better predictor for the final Gleason score (Coogan et al. 2005).

The number of preoperative prostate biopsy cores containing cancer and/or percentage of cancer among the submitted cores correlated with presence of ECE (Ravery et al. 1994; Peller et al. 1995; Sebo et al. 2000; Lotan et al. 2004; Naya et al. 2004; Ohori et al. 2004; Antunes et al. 2005), SVI (Peller et al. 1995; Koh et al. 2003; Antunes et al. 2005) and positive surgical margin at the RP specimen (Cheng et al. 2005a). The number of preoperative prostate biopsy-positive cores seems to correlate with the tumor volume and, therefore, with the presence of non-organ-confined disease (Cheng et al. 2005a). Wills et al. reported that biopsy Gleason score and the number of involved cores predicted the presence of organ-confined disease (Wills et al. 1998). For patients with a Gleason score of 6 and below, 69% were organ-confined if only one to two cores were involved by sextant biopsy, while 48% of them had organ-confined disease if more then two cores were involved. That information should be taken into account when consulting the patient regarding treatment options, including nerve-sparing surgery. However, the main limitation of using the total number of involved biopsy cores is the lack of side-specific and area-specific (base vs mid gland vs apex) prediction of non-organ-confined disease, especially the presence of extracapsular involvement.

Preoperative clinical variables such as PSA, clinical stage, and pathology variables of prostate biopsy were used among patients with clinically localized prostate cancer to predict site-specific probability of ECE. Increased rate of ECE was found at the site of positive core with moderate- and high-grade tumor, compared with lower grade. Multivariate analysis revealed that the site-specific positive core related to the presence of ECE on the same side, with an HR of 3.17 (Taneja et al. 1999). However, the positive predictive value for the presence of ECE, according to the individually labeled positive core, and for the site-specific positive core was 8.9% and 12.9%, respectively. The authors concluded that labeling biopsy cores as "right side" or "left side" was not justified because of the low positive predictive value and the significant increase in the expanses for individually labeled cores. In contrast, the group from Memorial Sloan-Kettering developed a nomogram that can predict the side-specific location of ECE with better accuracy (Ohori et al. 2004). Of the 1,526 patients, 226 (30%) had ECE,

according to the RP specimen. Among them, 15% had bilateral ECE. Three different nomograms were developed using clinically available preoperative variables. The most extended model includes preoperative PSA, clinical stage on each side, Gleason score on each side, percentage of positive cores on each side, and percentage of cancer involvement of the submitted specimen, and better predicted the probability of ECE compared with the limited models. The areas under the curves for predicting side-specific probability of ECE was 0.788 and 0.806 for the limited and extended models, respectively. The authors recommended performing wider dissection of the neurovascular bundle around the lobe when there is a predicted ECE of more than 10%, and performing wide resection in the presence of positive DRE when there is an ECE estimation of 50% and above. With that approach one can decrease the rate of positive surgical margin to obtain a better progression-free probability (Graefen et al. 2001). Those recommendations need to be validated prior to their use. Predicting the probability of SVI can be done by evaluating preoperative data including site-specific prostate biopsy. According to a multivariate analysis preoperative PSA, primary Gleason score, and percentage of cancer at the base were correlated with presence of SVI. Presence of SVI was 12.8% and 1.2% among patients with positive and negative cores from the prostate base; none of the patients with negative base cores and PSA of less then 10 ng/ml had SVI (Koh et al. 2003).

Despite the association between preoperative biopsy results and final pathology results following RP, the following should be noted: surgical technique has an important impact on surgical margin beyond parameters such as ECE, SVI, and tumor volume (Ward et al. 2004; Swindle et al. 2005). The presence of extraprostatic disease is correlated with decreased probability of progression. However, the majority of patients with ECE and negative margin and about a third of patients with SVI will be free from disease at 5 years following RP (Han et al. 2001; Hall et al. 2003). In one study, the number of cores containing cancer was positive, and the percentage of cancer among the submitted cores was also correlated with progression-free probability following radical prostatectomy (D'Amico et al. 2000; Freedland et al. 2003a) and PCSM following external radiotherapy (D'Amico et al. 2004b). This suggested improvement in the prediction of the probability for biochemical failure following local therapy for prostate cancer.

Lymphovascular Invasion

Lymphovascular invasion (LVI) is known as a prognostic factor for biochemical, metastases progression, and disease-specific survival following RP (Herman et al. 2000). In addition, it can predict failure of salvage radiation for biochemical failure following RP (Brooks et al. 2005).

Despite the importance of LVI in long-term outcome prediction with RP specimens, we are unaware of any report predicting RP pathology and biochemical failure rate according to the presence of LVI at the prostate biopsy. One of the difficulties is the limited amount of tissue available at the time of prostate biopsy for assessment of LVI.

Predicting Insignificant Tumors

Since the use of PSA for diagnosing prostate cancer, the incidence of the disease has risen sharply in the United States compared with countries without active screening programs (Schroder 2004). One possible disadvantage of identifying tumors by PSA screening is the possibility of detecting clinically insignificant tumors. The definitions of clinically insignificant tumors vary and usually are based on the pathology report of the radical prostate specimen. The commonly usual criteria include lack of Gleason grade 4 to 5 and tumor volume of less the 0.5 cc (Epstein et al. 1994; Goto et al. 1996). However, validation of those criteria is still needed. A clear trend of decreased tumor volume and lower Gleason grade has been demonstrated since the clinical use of PSA screening. The presence of low-grade, small-volume tumors can potentially lead to different treatments and, therefore, the identification of those patients prior to treatment can be useful (Schmid et al. 1993; Epstein and Potter 2001; Carter et al. 2003; Patel et al. 2004; Albertsen et al. 2005). In a cohort of patients from

Johns Hopkins Hospital treated by RP, indolent tumors were found in up to 31% of T1c patients Accordy to preoperative estimation (Epstein et al. 1998). The preoperative criteria to determine the presence of indolent tumor according to biopsy were: less than three positive cores, less than 50% length involvement of each positive core, and lack of pattern 7 of the positive cores. The positive predictive value and negative predictive value of the model were 94.4% and 77.2%, respectively (Epstein et al. 1998). In a different cohort, 55 (16%) of 336 patients treated with RP had small tumors (<0.5 cc) at the final pathology. Predictive factors for small tumors were number of positive cores and highest percentage of cancer at any site (Cheng et al. 2005b). A nomogram for the determination of the probability of indolent tumor was constructed by Kattan et al. using preoperative variables, including the preoperative PSA, clinical stage, primary and secondary Gleason grade, prostate volume according to TRUS, and cancerous and benign tissue (length in millilitres) of all the biopsy cores. The model's ROC was 0.64 for the base model (preoperative PSA, primary, and secondary Gleason grade) and 0.79 when all the variables were used (Kattan et al. 2003a). All of the previously mentioned prediction models used the presence of indolent tumor as an endpoint, rather than the treatment outcome. Conducting a prospective study using the patient's co-morbidities, age, and life expectancy in addition to the tumor characteristics has been proposed. The recommendation for watchful waiting of patients with life-expectancies of 10 years or more is limited and should be used as part of a research protocol (Klotz 2005).

Imaging Modalities

The clinical variables used for prostate cancer staging include mainly the prebiopsy PSA level, biopsy results, and clinical stage as determined by DRE. The combination of those can be used to predict the presence of non-organ-confined disease and estimate biochemical recurrence following local therapy (Partin et al. 1997; D'Amico et al. 1998; Kattan et al. 1998; Partin et al. 1997; Kattan 1999; D'Amico et al. 1998b). However, significant variability is found between the prediction ability of those variables and the actual finding following surgical treatment by radical prostatectomy. To increase the pretreatment information regarding the location and extent of the primary tumor, to evaluate the presence of distant metastases, to help plan the different therapeutic options, and reduce postoperative short- and long-term complications, several imaging modalities were used following the diagnosis of prostate cancer, including TRUS, computed tomography (CT), MRI, bone scan, and positron emission tomography (PET).

Transrectal Ultrasound

TRUS is the most common imaging modality used to perform prostate biopsy. However, the use of TRUS for staging newly diagnosed prostate cancer is limited. The sensitivity and specificity of TRUS is low, and no significant change in predicting ECE and SVI was found between DRE and TRUS (Smith et al. 1997). More then 50% of prostate cancer cases would have been missed if a biopsy had targeted only prostatic lesions identified by TRUS (Flanigan et al. 1994). Tiguert et al. have suggested a change in the clinical stage of patients with nonpalpable disease by incorporating TRUS findings; they suggest classifying the patients with nonpalpable tumor but with a detected lesion by TRUS as T2 rather than T1c (Tiguert et al. 2000). However, analysis of more then 1,600 patients staged by TRUS prior to radical prostatectomy showed that although patients with nonpalpable and positive TRUS are at a more advanced pathology stage and have higher Gleason scores compared with T1c patients with invisible lesion of TRUS, no change in progression-free probability was found between the two groups. Comparison of patients with clinical T2 disease to patients with nonpalpable and visible lesion on TRUS showed better preoperative and postoperative findings for the latter group, with better biochemical outcome (Augustin et al. 2003). These data suggest that the classification of T1c disease by TRUS will not add significant information to the current AJCC TNM classification.

MRI and erMRI

The use of MRI in prostate cancer is of interest since the details obtained from abdominal ultrasound, TRUS, and CT are limited regarding the intra- and periprostatic anatomy—that is, zonal anatomy, prostate capsule, periprostatic soft tissue, and the relationship between the prostate and the urethra. Those details can be seen on T2-weighted images. The peripheral zone has higher signal intensity compared with the central and transitional zones. Distinguishing between the anterior aspect of the prostate and the anterior periprostatic space can be done by identifying the low-intensity signal anterior fibromuscular zone that is covering the anterior aspect of the prostate. The normal prostate capsule can be identified as the thin edge with a low-intensity signal surrounding the peripheral zone. The periprostatic soft tissue can also be rendered clearly by MRI. The venous plexus at the anterior (dorsal vein complex) and lateral aspect of the prostate (periprostatic venous complex) and the neurovascular bundle (NVB) at the posterolateral aspect of the prostate are captured by MRI. The advantages of MRI over CT are the ability to create images at different planes in addition to the axial plane, the potentially better resolution, the lack of a need for nephrotoxic contract material, and the lack of radiation exposure. Cancer can be seen as a low-intensity area among a high-intensity normal peripheral zone on T2 weighted images (Hricak 2005). However, the low-intensity area is not specific to cancer and can also be seen with hemorrhage, infection, and as a result of radiation or hormonal treatment. Delaying MRI by 4 to 8 weeks after prostate biopsy will lower the false-positive effect of hemorrhage secondary to biopsy (White et al. 1995). Also, MR spectroscopy imaging (MRSI) can be used. MRSI can identify metabolite levels at cross sections of the prostate and reveal the presence of cancer according to the ratio of choline and creatine to citrate [(choline+creatine)/citrate]. Citude is elevated in the absence of cancer. Elevated choline can be seen in the presence of cancer, especially with high-grade tumor (Hricak 2005). Resolution can be increased more effectively by using erMRI compared with using external surface coil, although no significant differences were observed when the diagnostic ability of the two methods were compared between patients with newly diagnosed prostate cancer (Kaji et al. 2002).

The TNM staging system is based on imaging modality. For prostate cancer, no effective imaging modality had been established for clinical staging until recently, that is, the presence of ECE and SVI. erMRI has been shown recently to increase the accuracy of clinical staging compared with the use of DRE and PSA among 90 patients scheduled for RP. The use of erMRI proved to be better in detecting SV involvement and exhibited greater accuracy than DRE and TRUS for tumor localization at the mid-gland and base (Mullerad et al. 2005). Researchers evaluated the ability of erMRI to detect tumor localization and size and the extent of disease among 95 patients undergoing RP. Nakashima and associates compared erMRI findings with the prostatectomy pathology findings and found that the erMRI data correlated with tumors with diameters of 1 cm and above. The accuracy of erMRI was 74.7% for showing ECE and 75.8% for staging (Nakashima et al. 2004). Similar accuracy in detecting ECE was shown by the group from Memorial Sloan-Kettering that evaluated clinical variables including PSA, clinical staging, prostate biopsy variables, and erMRI results prior to RP. By multivariate analysis, serum PSA level, percentage of cancer in all core biopsy specimens, and erMRI findings were predictors of ECE; the areas under receiver operating characteristics curve (ROC) with and without erMRI findings were 0.838 and 0.772, respectively (p=.022) (Wang et al. 2004). Those reports indicate the ability of erMRI to detect tumor localization and predict the presence of ECE and SVI prior to RP. Similarly, erMRI was shown to be effective regarding treatment planning prior to intensive modulated radiotherapy and brachytherapy (Chen et al. 2004; Menard et al. 2004). In those series, the follow-up period and number of patients were small, and no data are yet available regarding the outcome of erMRI-based radiotherapy planning for prostate cancer. Does the use of erMRI lead to better patient selection for local therapy? Will the information obtained from erMRI lead to improvement in the surgical/radiation performance, and what will be the impact of it on the outcome of local therapy,

rate of biochemical recurrence, local recurrence, and metastases progression? The answers are still unknown. In addition, the criteria used for selecting patients for erMRI prior to local therapy are unclear, especially considering the expenses associated with the use of erMRI.

Computed Tomography

The use of CT for evaluating the extent of local disease in patients newly diagnosed with prostate cancer is limited. CT ability to image the prostate and the periprostatic soft tissue is significantly reduced compared with erMRI. The main potential advantage of CT is its use for detection of pelvic lymph node adenopathy (+PLN) prior to local therapy. However, the presence of +PLN in contemporary series is low and the majority of the positive lymph nodes represent microscopic involvement only (Meng and Carroll 2000; Bader et al. 2002).

Bone Scan

Bone scan is used frequently for patients newly diagnosed with prostate cancer. Metastatic prostate cancer has a tendency to spread to bones, predominantly in the axial skeleton, and the imaging of choice used to detect this is the radionuclide bone scan with ^{99m}technetium methylene diphosphonate (Dotan et al. 2005). The use of bone scan among patients with newly diagnosed prostate cancer is determined by their clinical stage, PSA level, biopsy results, and year of diagnosis. Oesterling found that PSA can be used to define the staging of newly diagnosed prostate cancer by bone scan. Only 3 of 561 patients had positive bone scan if their PSA was lower than 10 ng/ml, and none of them had PSA below 8 ng/ml (Oesterling et al. 1993). That observation was validated by others who found that positive bone scan rates for newly diagnosed prostate cancer was 0%, 4.5%, 8%, and 40% for PSA of less than 10, 10 to 20, >20 to 50 and >50 ng/ml, respectively (Levran et al. 1995; Gleave et al. 1996). Still others have suggested lower PSA thresholds for ordering bone scans (Wymenga et al. 2001). However, according to the CAPSURE database, the frequency of use of CT, MRI, and bone scan for newly diagnosed prostate cancer did not change from 1989 to 1997 (Kindrick et al. 1998). A recent meta-analysis of 23 studies concerning baseline bone scans of 8,644 patients stratified according to PSA level at diagnosis of prostate cancer showed that positive bone scans were found among 16% of the screened patients. PSA was the most commonly studied prognostic factor, whose detection rates for positive bone scan were 2.3%, 5.3%, 16.2%, 39.2%, and 73.4% among patients with PSA levels less than 10, 10–19.9, 20–49.9, 50–99.9, and 100 ng/ml or greater, respectively. These findings support the avoidance of bone scan in cases in which PSA is below 10 ng/ml and there is no bone pain prior to local treatment for newly diagnosed prostate cancer (Abuzallouf et al. 2004). Clinical stage and Gleason score were also important predictors for bone scan results. Noting the above data, the recommendation was to limit the use of staging bone scan for patients with either clinical stage T3 and above, PSA of 20 and above, and a Gleason score of 8–10.

FDG-Positron Emission Tomography

The use of 2-[fluorine-18]-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) for prostate cancer staging is limited because of its inability to differentiate between clinically localized prostate cancer and BPH secondary to low glycolytic rate and therefore low FDG uptake, its decreased sensitivity for detection of pelvic lymph node compared with CT and MRI, and its reduced detection of bone metastases compared with bone scan (Shreve et al. 1996; Yeh et al. 1996; Liu et al. 2001). In contrast, it plays a promising role in response to treatment of local advanced and metastatic prostate cancer in both animal models (Oyama et al. 2004) and with other isotopes such as C-11 acetate, and is still under investigation.

Combination Staging Methods

Clinically localized prostate cancer represents a heterogeneous disease. The natural history and outcome following different therapy options vary

according to known risk factors. Predictions of treatment outcome will change according to the chosen endpoint. In general, the preferred endpoint in oncology is a disease-specific survival rate, since it estimates the direct and indirect cancer-associated mortality rate of the specific disease (Welch et al. 2000; D'Amico 2002). The main limitation of estimating the rate of disease-specific survival among patients with localized prostate cancer is the relatively indolent natural history of prostate cancer, that is, only a limited number of patients will die of prostate cancer at 5 to 10 years from local treatment. Up to 1/3 of the patients will have detectable or rising PSA levels following RP (Dillioglugil et al. 1997; Roberts et al. 2001b; Han et al. 2003) and 15% to 57% will not reach a nadir below 1 ng/ml or will have rising PSA following a nadir caused by external radiotherapy, depending on their risk group (Pollack et al. 2003). In one study, disease-specific survival rates were 93%, 75%, and 55% at 5, 10, and 15 years from biochemical failure following RP (Freedland et al. 2005) and 85% from biochemical failure following radiotherapy at 5 years (Kwan et al. 2004). Comparison of any endpoints as progression-free probability, freedom from metastases, and disease-specific survival rates between patients following surgery and radiotherapy are beyond the scope of that chapter.

Multiple variables influence progression-free probability, freedom from metastases progression, and disease-specific survival rates for prostate cancer at different disease states. Using multiple variables or "combined modality staging" has the advantage of increasing the accuracy of prediction for prostate cancer patients. Combing the clinical stage according to the AJCC, pretreatment PSA, and Gleason score of the prostate biopsy and others has proved to be useful for staging clinical disease. Outcomes can be described as final pathology according to data obtained from patients undergoing RP, biochemical failure rate, metastases progression rate, and the PCSM rate following RP or radiotherapy.

Partin Tables

The estimation of final pathology was first described by Partin and predicted the probability of organ-confined disease, presence of ECE, SVI, and LNI according to clinical AJCC staging (T1a-c, T2a-c, T3a), biopsy Gleason score (2–4, 5, 6, 7, 8–10), and prebiopsy PSA (0–4.0, 4.1–10, 10.1–20, >20) (Partin et al. 1997). Data obtained from a nomogram can be used to consult the patient prior to choosing a local treatment for active surveillance, since the nomogram was externally validated and found to be accurate (Blute et al. 2000). An updated version, using the records of 5,089 patients treated since 1994 by RP with a median follow-up of 5.8 years, was recently published to improve the direction for current diagnosed patients (Partin et al. 2001). The nomogram was criticized for: (1) having endpoints that are the pathological findings of the RP specimen. The nomogram is useful for surgical planning but does not predict the clinical outcome following surgery. Although patients with local advanced prostate cancer (i.e., presence of ECE, SVI, and LNI) have increased probabilities of biochemical failure and clinical progression, the majority of patients with ECE and the major minority of patients with SVI will see no evidence of disease at 5 years from RP as monotherapy; (2) using an arbitrary preoperative PSA threshold (0–4, 4.1–10, 10.1–20, and >20) and, thus, creating heterogeneous groups (Diblasio and Kattan 2003); (3) having a limited ability to predict for patients with clinical stage T3–4 disease (Partin et al. 2001).

D'Amico Risk Classification

D'Amico has suggested classifying patients with clinical organ-confined disease by risk level and clinical stage, PSA, and Gleason score (GS) (low risk: GS≤6 and PSA≤10 and T1c/T2a; intermediate risk: GS 7 or PSA 10–20 or T2b; and high risk: GS 8–10 or PSA≥10 or T3–4) (D'Amico et al. 1998). The classification is popular because of its simplicity but, like the part in tables, was criticized for using of arbitrary thresholds (e.g., PSA <10, 10–20, and >20). It is also criticized for creating heterogeneous groups (Diblasio and Kattan 2003) and ignoring risk factors for different groups (e.g., ignoring the biopsy Gleason score and clinical stage when the prebiopsy PSA is >20 ng/ml) (Kattan 2003).

Kattan Nomograms

Kattan used a different approach for predicting outcome of patients with different solid tumors, namely, nomograms. Nomograms are developed based on Cox proportional hazard regression analysis and modified by restricted cubic splines. Hence, the variables are not assumed to have linear relations. For example, an increase in PSA level from 2 ng/ml to 4 ng/ml would represent the same significance as an increase from 302 ng/ml to 304 ng/ml (Diblasio and Kattan 2003). The use of variables in a continuous manner avoids the creation of heterogeneous groups in contrast to the grouping approach. A more accurate prediction is achieved with the prediction created for a specific patient rather than for his classification group (Diblasio and Kattan 2003). The nomogram uses multiple variables and each contributes to some extent to the prediction ability of the model. The variables are added according to their clinical importance, rather than according to their significance by multivariate analysis and, thus, add to the accuracy of the model. The impact of each variable on the model outcome is represented schematically by a vertical bar, and the summary of all the variables is translated to outcome probability at a specific time from treatment (e.g., freedom from progression at 5 years from RP).

Nomograms are evaluated according to their discrimination, calibration, and validation. Discrimination is the nomogram's ability to predict which patients will reach the desired endpoint. It is estimated by the concordance index (CI) and expressed by a number between 0 and 1; a value of 0.5 represents a flipped-coin probability. Calibration of the nomogram is the relationship between the prediction and actual outcome, and validation is the performance of the nomogram with respect to a different data set.

Applicability of the nomogram is limited to patient characteristics similar to those used for the nomogram development; for example, the pre-RP nomogram was developed with a cohort of 983 patients treated at a single academic institute by a single surgeon. Applicability of the nomogram to other populations at other academic institutes and community centers was validated by those cohorts. In addition, most of the nomograms used PSA relapse as an endpoint, except a nomogram predicting metastases progression following external radiotherapy (Kattan et al. 2003b) and the probability of bone metastases following biochemical failure after RP (Dotan et al. 2005). Comparison of PSA-based outcome according to local treatment is limited because of the different definitions of PSA failure after surgery vs radiotherapy (Gretzer et al. 2002).

Different nomograms are available for staging patients with prostate cancer prior to treatment. Those nomograms include the following:

a. RP—pretreatment nomogram
The nomogram was based on 983 patients treated by RP by a single surgeon from 1983 to 1996 with a median follow-up of 30 months and predicted the freedom from biochemical failure at 5 years following RP (Kattan et al. 1998). The variables used are prebiopsy PSA, clinical stage, and biopsy Gleason score; clinical stage was based on the 1992 classification. Freedom from biochemical failure for the entire cohort was 73%. The definitions of biochemical failure were PSA level of 0.4 ng/ml and above, 2nd treatment (radiotherapy and/or ADT), and patients for whom surgery was aborted because of lymph node metastases. The nomogram concordance index was 0.75. Validation was conducted by bootstrapping and by an external cohort of 168 patients treated by RP. External validation was performed with a cohort of 6,232 patients from seven academic centers in the United States and Europe treated with RP (Graefen et al. 2002). The CI was 0.75, and the prediction for the different risk groups matched well with the original nomogram. A cohort of 1,701 patients treated by RP from the CAPSURE database, which includes mainly community practices, was also used for validation (Greene et al. 2004). The CI was found to be slightly lower (0.68); reasons for that might include the lack of central pathology review and diversity of treating physicians (mainly community hospitals).

b. External radiotherapy—pretreatment nomogram
The nomogram was based on 1,042 patients treated with 3D conformal radiotherapy at

Memorial Sloan-Kettering Cancer Center from 1988 to 1998 with a median follow-up of 30 months and predicted the freedom from biochemical failure at 5 years following RP (Kattan et al. 2000). The variables used are prebiopsy PSA, clinical stage, biopsy Gleason score, use of ADT, and radiotherapy dose. The definition of biochemical failure was based on the 1997 ASTRO definition (American Society for Therapeutic Radiology and Oncology 1997). The nomogram CI was 0.73. The nomogram was externally validated by a cohort of 912 patients treated at the Cleveland clinic a CI of 0.76. The nomogram prediction was found to be superior to other grouping prediction models.

c. Transperineal interstitial permanent brachytherapy—pretreatment nomogram
The nomogram was based on 920 patients treated by permanent brachytherapy and predicted the freedom from biochemical failure at 5 years following RP (Kattan et al. 2001). The variables used are pre-biopsy PSA, clinical stage, biopsy Gleason score, and use of radiotherapy. Clinical stage was based on the 1997 classification and included patients categorized as T1c and T2 a/b. The definition of biochemical failure was based on the ASTRO definition (1997), the presence of clinical progression, and the use of ADT. The nomogram was externally validated with cohorts of 1,827 patients from Seattle and Arizona with CIs of 0.61 and 0.64, respectively.

d. Other—a nomogram that predicted the probability of the presence of indolent tumor, extracapsular extension, and seminal vesicle invasion was described in a previous part of the chapter.

Pelvic Lymph Node Dissection

Imaging modalities such as pelvic CT and MRI are relatively insensitive for detection of pelvic lymph node dissection, since the majority of the involved nodes at the PSA era have microscopic involvement only. The only accurate method of detecting lymph node metastases is lymph node dissection. Despite the high prevalence for treating prostate cancer with RP, the incidence of positive lymph node (+PLN) at pelvic lymph node dissection (PLND) and its indications, anatomical boundaries, and diagnostic and therapeutic outcomes are still debated.

An important question is, Who are the patients who can benefit from omitting PLND during RP without damaging the staging process? The potential morbidity of PLND was estimated to be 7% (Meng and Carroll 2000) and included more prolonged surgery, an increased rate of deep vein thrombosis, injury to major pelvic vessels and nerves, lower extremity lymphoedema, and additional surgery costs. Indications for PLND were determined according to the probability of +PLN and included probability of less than 1.5% for +PLN by Partin tables (Cagiannos et al. 2003); probability of +PLN of less than 18% (Meng and Carroll 2000); PSA less than 5 ng/ml or Gleason score of less than 6; or a combination of PSA less than 25, Gleason score of 7 or lower, and negative DRE (Rees et al. 1997).

The incidence of +PLN during PLND ranges between 1.1% and 24% and varies according to patient characteristics, extent of the performed PLND, pathological analysis of the submitted lymph node package, and year of surgery (Meng and Carroll 2000; Bader et al. 2002). The staging implications of PLND are clear, because patients with +PLN at the time of RP are associated with a significantly lower progression-free probability rate and an increased probability of death of prostate cancer (Cadeddu et al. 1997; Cheng et al. 2001; Hull et al. 2002; Zwergel et al. 2004). The therapeutic implications of PLND for prostate cancer in the setting of RP are still debated (Burkhard and Studer 2004). The treatment of patients with lymph node metastases at the time of RP is beyond the extent of the current review; however, reports with limited patient number and no randomization regarding treatment options have found prolonged disease-specific survival rates following RP and PLND as monotherapy in the range of 74% to 94% and 47% to 83% at 5 and 10 years, respectively (Cheng et al. 2001; Zwergel et al. 2004).

Despite potential advantages for cancer-specific survival seen with therapy combining hormonal treatment and RP (compared with hormonal therapy only; Ghavamian et al. 1999) and

for early hormonal therapy following RP (vs RP and late hormonal therapy; Messing et al. 1999), timing and the type of adjuvant therapy following RP for +PLN still inspire debate.

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9 Guidelines and Counselling for Treatment Options in the Management of Prostate Cancer

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Recent Results in Cancer Research, Vol. 175

Abstract

Prostate cancer is often a complex disease and one in which many aspects of the disease and the affected patient must be taken into consideration before decisions about diagnostic work-up, treatments, follow-up, etc. can be made. The current chapter reflects the current recommendations of the European Prostate Cancer Guideline Group made on the basis of criteria of evidence-based medicine after extensive review of the literature available up to December 2005.

Introduction

There are numerous treatment options with regard to the potentially optimal management of patients with organ-confined, locally advanced and metastatic prostate cancer (CaP), as has been demonstrated and extensively discussed in the previous chapters. However, the dilemma for many patients and even physicians is based on the fact that many treatment recommendations are merely based on subjective feelings due to the lack of valid prospective randomized clinical trials. This is especially concerning treatment decisions in men with clinically localized low-, intermediate- and high-risk CaP with the competing surgical, radio-oncological, medical and conservative therapeutic options. Even with regard to the important clinical scenario of prostate-specific antigen (PSA) recurrence following local treatment with curative intent, very few prospective randomized trials exists comparing different treatment options.

Clinical guidelines for the diagnosis and management of cancer are thought to somehow reduce the decision dilemma for both physicians and patients. Treatment decisions must be based on the available evidence which might form the basis for a consensus guideline delivering a clear proposal for diagnostic and treatment measures in the different stages of a given cancer and individual clinical situations. Evidence-based and national as well as European-wide guidelines were first established in the management of testicular cancer [1, 2]. Further studies have demonstrated that the clinical application of guidelines in the daily routine will help to reduce both over-treatment and treatment failure and/or relapse [3]. Evidence-based guidelines might serve as an internal quality control in institutions treating patients with any given type of cancer.

The new EAU guidelines on CaP are evidence-based, summarize the most recent findings in the management of CaP and put them into recent practice [4]. Therefore, integration of these guidelines will help physicians to objectively counsel their patients with regard to the most appropriate therapy in a given clinical situation.

This chapter summarizes the recent EAU guidelines which can be read in their entirety on Website for The European Association of Urology, www.uroweb.org.

In order for the reader to evaluate the quality of the information provided, the evidence levels and grade of each recommendation have been inserted in this updated guidelines text according to the general principles of evidence-based medicine (EBM) [5].

Classifications and Grade of Recommendations

The UICC 2002 Tumour Node, Metastasis (TNM) classification is used throughout these guidelines [6].The most commonly used system for grading

of adenocarcinoma of the prostate is the Gleason score [7]. The system describes a score between 2 and 10, with 2 being the least aggressive and 10 the most aggressive. This score is the sum of the two most common patterns (grades 1–5) of tumour growth found. To be counted, a pattern (grade) needs to occupy more than 5% of the biopsy specimen. Biopsy material (core biopsy or operative specimens) is required to be able to assess the Gleason score; cytological preparations cannot be used.

Prostate Cancer Screening

Population or *mass screening* is defined as the examination of asymptomatic men (at risk). Usually, screening takes place within the framework of a trial or study and is initiated by a screener. Contrary to that, *early detection* or *opportunistic screening* represents individual case findings. It is initiated by the screenee (patient) or his physician.

The trends in mortality from CaP show a wide variety from country to country all over the industrialized world [8]. A decrease in mortality rates due to CaP is currently seen in the United States and Austria, but also in the United Kingdom and France, which share a similar decrease in CaP mortality rates [8]. Similarly, in Sweden, the relative 5-year survival rates increased in the period from 1960 to 1988, which was attributed to increased diagnostic activities and the detection of more non-lethal tumours [9]. However, this trend could not be confirmed in a similar study from the Netherlands [10].

Currently, only a non-randomized screening project in Tyrol (Austria) may support the hypothesis that screening can be effective in reducing CaP mortality. The early detection programme in combination with the availability of free treatment was used as an explanation for the 33% decrease in the CaP mortality rate seen in Tyrol as compared with the rest of Austria [11] (level of evidence: 2b). Other studies have contradicted the positive findings attributed to screening, with a comparative study between the Seattle area (highly screened population) and Connecticut (seldom screened population) by Lu-Yao and coworkers [12] showing that, notwithstanding the very large diversity in PSA testing and in use of curative treatments, there was no difference in the reduction in the rate of CaP mortality (level of evidence: 2b).

Thus, at the present time there is a lack of evidence to support or disregard widely adopted, population-based screening programmes for early detection of CaP aimed at all men in a given population (level of evidence: 3). The use of PSA in combination with digital rectal examination (DRE) as an aid to early diagnosis in well-informed patients is less controversial and widely used in clinical practice [13] (level of evidence: 3). All patients, however, undergoing PSA screening should be informed intensively about the measures to be taken if a PSA serum value turns out to be suspicious for the presence of CaP.

Diagnosis and Staging of Prostate Cancer

The decision to proceed with further diagnostic or staging work-up is guided by which treatment options are available to the patient, taking age and comorbidity into consideration. Procedures that will not affect the treatment decision can usually be avoided.

An abnormal DRE result or elevated serum PSA measurement may indicate CaP. The exact cut-off level of what is considered to be a normal PSA value has not yet been determined, but values around 2.5–3 ng/ml are often used for younger men (grade C recommendation).

In younger men, aged 50–66 years, the CaP detection rate was 13.2% in the PSA interval 3–4 ng/ml; the majority of these cancers were judged to be clinically significant [14]. Even lower cut-off levels have been proposed by some authors, still with a relatively high detection rate [15]. The finding that many men may harbour CaP despite low levels of serum PSA has been underscored by the recent results from a United States prevention study [16]. The rate of CaP in relation to serum PSA for 2,950 men in the placebo-arm and with normal PSA-values is presented in Table 9.1. The age range at biopsy was 62–91 years.

The diagnosis of CaP depends on histopathological confirmation (grade B recommendation). Biopsy and further staging investigations are

Table 9.1 Risk of CaP in relation to low PSA values

PSA level (ng/ml)	Risk of CaP
0–0.5	6.6%
0.6–1	10.1%
1.1–2	17.0%
2.1–3	23.9%
3.1–4	26.9%

only indicated if they affect the management of the patient (grade C recommendation).

Ultrasound-guided transrectal 18G core biopsy has become the standard way to obtain material for histopathological examination. Sextant biopsies, as described by Hodge et al., have been used in the past. Lately, the standard way of obtaining sextant biopsies has been replaced by laterally directed sextant biopsies in order to optimize the CaP detection rate [17, 18]. Biopsy cores obtained this way include biopsies from the posterolateral aspect of the peripheral zone, the most common location for early CaP. The number of biopsies required for the optimal detection of CaP is controversial. Several studies have examined the detection rate with more biopsy cores at primary biopsy. Nearly all have shown a higher cancer detection rate in comparison with the standard sextant technique. Eskew and co-workers, for instance, demonstrated that the five-region biopsy protocol with 13 to 18 cores increased the detection rate by 35% when compared to standard, mid-lobar sextant biopsies [19]. Studies clearly show that the transition zone should not be the target area for a first set of prostate biopsies due to the consistently low cancer detection rate, which may be as low as 2% or less [20, 21].

If the first set of biopsies is negative, repeated biopsies can be recommended. In the second set of biopsies, a detection rate of about 10%–35% has been reported in cases with a negative first set of biopsies [22–24]. In cases where high-grade prostatic intraepithelial neoplasia (PIN) or atypical small acinar proliferation (ASAP) is present, as many as 50%–100% of prostates harbour a concomitant cancer, and re-biopsy is indicated [25, 26]. Djavan and co-workers found that two sets of biopsies detected the majority of clinically significant cancers [24]. Even patients who have undergone more extensive biopsies may still have a significant detection rate at repeat biopsy [22]. Today, we have no proven biopsy scheme that omits the need for re-biopsy in case of a persistent indication (level of evidence: 3).

With an increasing number of men undergoing more extensive biopsies at maybe two or even more occasions, the need for some form of analgesia has become more evident in clinical practice. Of the various methods examined, the use of a periprostatic injection with a local anaesthetic seems to combine high efficacy with easy application and low complication rates (best level of evidence: 1a).

Local staging (T-staging) of CaP is based on findings from DRE, transrectal ultrasonography (TRUS) and possibly magnetic resonance imaging (MRI). Further information is provided by the number and sites of positive prostate biopsies, tumour grade and level of serum PSA (grade C recommendation).

The most commonly used method for viewing the prostate is TRUS. However, only 60% of tumours are visible at TRUS and the remainder are not recognized due to their echogenicity. Thus, differentiation between T2 and T3 tumours should not be based on TRUS alone [27, 28] since multi-institutional large studies have shown that TRUS was no more accurate at predicting organ-confined disease than DRE [29, 30].

Both computed tomography (CT) and MRI are now of a high technical standard, but neither modality is sufficiently reliable to make it mandatory to use them to assess local tumour invasion. MRI of the prostate appears to be the most accurate non-invasive method of identifying locally advanced disease [31]. However, its routine use for the pre-treatment staging of CaP remains controversial and MRI is not always available. For dose planning before external-beam radiation, CT is most useful.

Lymph node status (N-staging) is only important when potentially curative treatment is planned for. Patients with Stage T2 or less, a PSA less than 20 ng/ml and a Gleason score of 6 or less have less than a 10% likelihood of having node metastases and may be spared nodal evaluation. The gold standard for N-staging is

operative lymphadenectomy, by either open or laparoscopic techniques (grade B recommendation). It is worth pointing out that recent studies with more extensive lymphadenectomy have shown that the obturator fossa is not always the primary site for metastatic deposits in the lymph nodes [32, 33]. Various studies have demonstrated recently that the use of Partin tables or other preoperative nomograms does not accurately predict the presence or absence of pelvic lymph node metastases. Both CT and MRI are considered of limited use due to their low sensitivity, which varies from 0% to 70% [34, 35]. Quite recently, high-resolution MRI with magnetic nanoparticles allows the detection of small and otherwise undetectable lymph node metastases in patients with CaP [36]. However, further prospective studies comparing MRI and extended lymph node dissection have to support these initial encouraging results.

For the identification of skeletal metastases, bone scintigraphy remains the most sensitive method, being superior to clinical evaluation, bone radiographs, serum alkaline phosphatase measurement and prostatic acid phosphatase (PAP) determination. Technetium diphosphonates are the optimum radiopharmaceuticals currently available due to their extremely high bone-to-soft-tissue ratio [37]. A semi-quantitative grading system based upon the extent of disease observed on the bone scan was found to correlate with survival [38]. This may not be indicated in asymptomatic patients if the serum PSA level is less than 20 ng/ml in the presence of well-, or moderately, differentiated tumours (grade B recommendation).

Treatment of Prostate Cancer

An overview of the primary treatment options in patients with prostate cancer is provided in Tables 9.2, 9.3, 9.4 and 9.5. It is usually impossible to state that one therapy is clearly superior over another, as there is a profound lack of randomized controlled trials in this field. Furthermore, it might be best to differentiate patients with low-, intermediate- and high-risk CaP with regard to the recommendation of specific treatment modalities. Based on the evidence of the available literature, some recommendations can be made. A summary, subdivided by stage at diagnosis, is found below.

Active Surveillance—Good Risk CaP

The term deferred treatment or active surveillance (WW) is used to describe a treatment strategy that includes an active standpoint to postpone treatment until it is required. The rationale for this type of treatment is based on the fact that for many good-risk patients defined by a Gleason score of 6 or less, a PSA of 10–15 ng/ml and cT1c–2a CaP the disease is indolent and slow-growing. The challenge is to identify those patients with aggressive disease and offer them curative treatment, while sparing other patients the morbidity of unnecessary treatment. Patients who are offered active surveillance must be followed-up carefully with serial PSA measurements and periodic prostate re-biopsies at 2, 5 and 10 years.

The earlier papers [39–44] describe cancer-specific survival and metastasis-free survival after 5 and 10 years of follow-up [1] (level of evidence: 2b). The importance of tumour grade is clear, with very low survival rates for grade 3 tumours. Even if the 10-year cancer-specific survival rate is equally good (87%) for grade 1 and 2 tumours, the latter have a significantly higher progression rate, with 42% of the patients having developed metastases. In another paper [45], the re-evaluation of all biopsy specimens using the more widely accepted Gleason score showed that the risk of CaP death was very high in Gleason 7–10 tumours (60%–87%), intermediate in Gleason 6 tumours (18%–30%), but low in Gleason 2–5 cancers (4%–7%) [45, 46] (level of evidence: 3). Quite recently, the results of a prospective phase II trial of active surveillance of 299 patients have been reported [47, 48]. At 8 years, overall actuarial survival was 85% and cancer-specific survival was 99%. A PSA doubling time of less than 3 years based on three consecutive measurements over 6 months has been identified as an indicator for the presence of aggressive disease, making a radical intervention necessary.

Table 9.2 Guidelines for the primary treatment of prostate cancer. Management of incidental prostate cancer

Stage	Treatment	Comment
T1a	Watchful waiting	Standard treatment for well-, and moderately, differentiated tumours and <10-year life expectancy. In patients with >10-year life expectancy, re-staging with TRUS and biopsy is advised (grade B recommendation)
	Radical prostatectomy	Optional in younger patients with a long life expectancy, especially for poorly differentiated tumours (grade B recommendation)
	Radiotherapy	Optional in younger patients with a long life expectancy, especially for poorly differentiated tumours. Higher complication risks after TURP, especially for interstitial radiation (grade B recommendation)
	Hormonal	Not an option (grade A recommendation)
	Combination	Not an option (grade C recommendation)

Table 9.3 Guidelines for the primary treatment of prostate cancer. Management of clinically localized prostate cancer

T1b–T2b	Watchful waiting	Asymptomatic patients with well-, and moderately, differentiated tumours and a life expectancy <10 years. Patients who do not accept treatment-related complications (grade B recommendation)
	Radical prostatectomy	Standard treatment for patients with a life expectancy >10 years who accept treatment-related complications (grade A recommendation)
	Radiotherapy	Patients with a life expectancy >10 years who accept treatment-related complications. Patients with contraindications for surgery. Unfit patients with a 5- to 10-year life expectancy and poorly differentiated tumours (combination therapy is recommended; see below) (grade B recommendation)
	Hormonal	Symptomatic patients who need palliation of symptoms and who are unfit for curative treatment (grade C recommendation). Antiandrogens are associated with poorer outcome compared to watchful waiting and are not recommended (grade A recommendation)
	Combination	NHT+radical prostatectomy: no proven benefit (grade A recommendation). NHT+radiotherapy: better local control. No proven survival benefit (grade B recommendation). Hormonal (2–3 years)+radiotherapy: better than radiotherapy alone for poorly differentiated tumours (grade A recommendation)

Table 9.4 Guidelines for the primary treatment of prostate cancer. Management of locally advanced prostate cancer

T3-T4	Watchful waiting	Option in asymptomatic patients with T3, well-differentiated and moderately differentiated tumours, and a life expectancy <10 years (grade C recommendation)
	Radical prostatectomy	Optional for selected patients with T3a and a life expectancy >10 years (grade C recommendation)
	Radiotherapy	T3 with a life expectancy >5–10 years. Dose escalation >70 Gy. Seems to be of benefit. If this is not available, a combination with hormonal therapy could be recommended (see below) (grade A recommendation)
	Hormonal	Symptomatic patients, extensive T3-T4, high PSA level (>25 ng/ml), unfit patients. Better than watchful waiting (grade A recommendation)
	Combination	Radiotherapy+hormonal treatment seems better than radiotherapy alone (grade A recommendation). NHT+radical prostatectomy: no proven benefit (grade B recommendation)

Table 9.5 Guidelines for the primary treatment of prostate cancer. Management of metastatic prostate cancer. (For more detailed information and discussion on second-line therapy, please see the full text version of the guidelines)

N+, M0	Watchful waiting	Asymptomatic patients. Patient driven. May have a negative influence on survival (grade C recommendation)
	Radical prostatectomy	No standard option (grade C recommendation)
	Radiotherapy	No standard option (grade C recommendation)
	Hormonal	Standard therapy (grade A recommendation)
	Combination	No standard option. Patient driven (grade B recommendation)
M+	Watchful waiting	No standard option. May result in worse survival/more complications than with immediate hormonal therapy (grade B recommendation)
	Radical prostatectomy	Not an option (grade C recommendation)
	Radiotherapy	Not an option (given for cure) (grade C recommendation)
	Hormonal	Standard therapy. Symptomatic patients should not be denied treatment (grade A recommendation)
	Combination	Not an option (grade C recommendation)

Combination, hormonal therapy given prior to and/or after radical prostatectomy or radiotherapy; hormonal, all forms of hormonal therapy; NHT, neoadjuvant therapy; TRUS, transurethral ultrasonography; TURP, transurethral resection of the prostate

Active Surveillance—Locally Advanced CaP

The literature reporting on deferred treatment for locally advanced CaP is sparse. There are no randomized studies that compare more aggressive treatments, such as radiation therapy or surgery, eventually in combination with hormones. Most patients whose disease progresses after deferred treatment of locally advanced CaP will be candidates for hormonal therapy. There are reports from non-randomized studies showing that hormonal treatment may safely be delayed until metastatic progression occurs, as no survival advantage was noted between patients treated with immediate orchiectomy compared with delayed treatment. However, when early and delayed treatments were compared in a large randomized trial carried out by the Medical Research Council (MRC), a survival benefit for immediate hormonal therapy was demonstrated [49] (level of evidence: 1b). Also, comparing placebo with bicalutamide 150 mg showed that in patients with locally advanced CaP, progression-free survival was better with early treatment [50] (level of evidence: 1b).

The SAKK 08/88 trial prospectively randomized 196 patients with CaP who, for any reasons, were no candidates for local treatment to receive either immediate or deferred orchiectomy on symptomatic progression [51]. Of the recruited men, 67% and 20% demonstrated T3–4 tumours and lymph node metastases, respectively. There was a slight benefit for patients with immediate treatment concerning cancer-specific, but not overall survival and progression-free survival. However, by careful follow-up, only 42% of the men with the deferred approach never needed any tumour-specific therapy (level of evidence: 1a).

Active Surveillance—Metastatic CaP

The only candidates for such treatment should be asymptomatic patients with a strong wish to avoid treatment-related side-effects (level of evidence: 4). The MRC trial highlighted the risk of

developing symptoms (pathological fractures, spinal cord compression) and even death from CaP, without receiving the possible benefit from hormonal treatment [49, 52] (level of evidence: 1b). If a deferred treatment policy is chosen for the patient with advanced CaP, there must be a possibility of close follow-up.

Radical Prostatectomy

Currently, radical prostatectomy (RP) is the only treatment for localized CaP that has shown a cancer-specific survival benefit when compared to conservative management in a prospective, randomized trial [53]. The retropubic approach, either by open surgery or laparoscopically, is more commonly performed, as it enables simultaneous pelvic lymph node assessment to be carried out. In men with localized CaP and a life expectancy of 10 years or more, the goal of a RP by any approach must be eradication of the disease and maintaining erectile function and continence [54]. In fact, there is no rigid age limit for RP and a patient should not be denied this procedure on the grounds of age alone [55].

Stage T1a-T1b CaP

Stage T1a CaP is an incidental histological finding of cancer in 5% or less of resected prostatic tissue during transurethral resection of the prostate (TURP) or open adenomectomy, while T1b is when more than 5% contains cancer, or when the tumour is poorly differentiated. Although the risk of disease progression of untreated T1a CaP after 5 years is only 5%, these cancers can progress in about 50% of cases after 10–13 years [56]. Thus, in younger patients with a life expectancy of 15 years or more, the chance of disease progression is real, requiring specific treatment.

In contrast, most patients with T1b tumours are expected to show disease progression after 5 years and aggressive treatment is often warranted [56]. Patients with T1b lesions are offered RP when they have a life expectancy of 10 years or more; however, external beam radiotherapy can be a valuable alternative treatment modality.

Stage T1c CaP

The clinically unapparent tumour identified by needle biopsy because of an aberrant PSA level has become the most frequent clinical stage in the actual RP population. In an individual patient it is difficult to differentiate between clinically insignificant and life-threatening CaP. Most reports, however, stress that PSA-detected tumours are mostly significant and should not be left untreated, since up to 30% of T1c tumours are locally advanced [57]. The proportion of insignificant tumours detected because of PSA elevation varies between 11% and 16% [58, 59].

While it might be reasonable to follow-up some patients whose tumours are most likely to be insignificant, RP should be advocated for most patients with T1c tumours, keeping in mind that significant tumours will be found in the majority of these individuals.

Stage T2 CaP

RP is one of the recommended standard treatments for patients with stage T2 CaP and a life expectancy of more than 10 years [60]. The prognosis is excellent when the tumour is confined to the prostate based on pathological examination [61, 62]. Although most poorly differentiated tumours extend outside the prostate, patients with high-grade tumours that are confined to the prostate at histopathological examination still have a good prognosis after RP [34], with a 10-year cancer-specific survival of 85%. T2a patients with a 10-year life expectancy should be offered RP since 35%–55% of them will have disease progression after 5 years if not treated. T2b cancer still confined to the prostate but involving more than half of a lobe or both lobes will progress in more than 70% of patients within 5 years [37]. These data have been confirmed by a large randomized trial comparing RP and watchful waiting that included mostly T2 CaP patients showing a significant reduction in disease-specific mortality [53]. In young men with localized CaP who are otherwise healthy, RP is an excellent option, and if an experienced surgeon performs it, the patient's subsequent quality of life (QoL) should be more satisfactory.

Stage T3 CaP

T3a cancer is defined as capsular perforation and T3b cancer as invasion of the seminal vesicles. In extracapsular tumours, RP often results in incomplete tumour excision. Whether or not T3 CaP should be considered an indication for surgical treatment remains unclear. The published reports on treatment outcomes in patients with clinical T3 are few.

Combination treatment with hormonal and radiation therapy is gaining popularity, although it has not been demonstrated that this approach is superior to surgical treatment. A randomized study on radiotherapy with hormones vs radiotherapy alone showed a clear advantage for the combination treatment, but did not show the superiority over RP [63]. Another problem is "contamination" by the additional use of either adjuvant radiotherapy or immediate or delayed hormonal treatment in most of the series that reported on the treatment of clinical T3 CaP.

In the absence of data from randomized clinical trials comparing possible options for definitive therapy in these patients, only single or multi-centre reports can be used to define the role of RP in this stage. Most studies have demonstrated that about 15% of all clinical stage T3 tumours were over-staged (cT3, pT2), while only 8% were under-staged (cT3, pT4).

For clinical T3 cancer, the overall PSA-free survival rate is about 20% after 5 years. The Gleason score of the tumour has a definite impact on progression, but there is not always a reliable correlation between the biopsy and the specimen Gleason score. On the other hand, seminal vesicle invasion, lymph node invasion, positive surgical margins and high PSA level are independent prognostic factors of PSA-free survival. Some authors have used a serum PSA level of 25 ng/ml as the discriminator for outcome [64, 65]. Others have shown that RP for clinical T3a cancer with a PSA below 10 ng/ml can achieve a 5-year PSA-free survival rate exceeding 60% [66]. Therefore, surgery has to be considered a therapeutic option for some patients with clinical T3a CaP. Not only clinically over-staged patients (pT2) but also individuals whose tumours actually are pT3a can benefit from this treatment option. RP for clinical T3 cancer necessitates sufficient surgical expertise in order to keep the level of morbidity acceptable, to improve oncological control and functional outcome, as has been described for the extended variant of RP [67].

Nodal Disease

Lymph node-positive (N+) disease will mostly be followed by systemic disease progression, and all patients with significant N+ disease will ultimately fail to be cured. Nevertheless, the combination of RP and simultaneous hormonal treatment has been shown to achieve a 10-year cancer-specific survival rate of 80% [68]. However, it is questionable whether or not these results could be obtained with hormonal treatment alone. The incidence of tumour progression is lower in patients with fewer positive lymph nodes and in those with microscopic invasion only.

N+ patients usually have significant nodal involvement and will be treated with hormonal manipulation only. In patients who prove to be pN+ after RP, adjuvant hormonal treatment can be advocated, but the benefits should be judged against side-effects of long-term hormonal therapy. PSA follow-up and hormonal treatment in case of PSA rise is therefore an acceptable option in selected cases.

Recently, an extended lymph node dissection comprising not only the obturator fossa but also the external and the internal iliac area with the presacral nodes has been advocated [32, 33], but this approach was not analysed in a prospective randomized fashion. Nevertheless, the limited value of a lymph node dissection as only a staging procedure without any therapeutic benefit is being increasingly challenged.

Neoadjuvant Hormonal Therapy and Radical Prostatectomy

Five prospective, randomized studies have shown a decrease in positive surgical margin rates, with the use of a short-term (6 weeks–4 months) course of neoadjuvant hormonal therapy (NHT). Follow-up of these randomized trials has indi-

cated that this has not resulted in any difference in PSA-free failure after 3–5 years of follow-up [69–72]. Since none of these studies was powered to study overall survival, the impact of neoadjuvant hormonal therapy (NHT) on overall survival remains unclear. The expectation had been that a longer duration of NHT could improve the PSA-free survival, but a well-designed randomized trial was unable to demonstrate any advantage of an 8-month vs a 3-month preoperative hormonal treatment [73]. With these results in mind, NHT cannot be recommended for routine clinical use prior to RP.

Summary of Guidelines for RP

Indications

- RP is indicated for patients with stage T1b–T2, Nx–N0, M0 disease and a life expectancy exceeding 10 years (level of evidence: 1b).

Optional Indications

- Patients with a long life expectancy and stage T1a disease (level of evidence: 3).
- Patients with stage T3a disease, a Gleason score exceeding 8 and a PSA of less than 20 ng/ml.

Comments

- Short-term (3 months) neoadjuvant therapy with gonadotrophin releasing-hormone analogues is not recommended in the treatment of stage T1-T2 disease (level of evidence: 1a).
- Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, Gleason score <7 and PSA <10 ng/ml or see Partin tables/nomograms) (level of evidence: 3).
- Unilateral nerve sparing procedures is an option in stage T2a disease (level of evidence: 4).
- The role of RP in patients with high-risk features, lymph node involvement (stage N1 disease) or as a part of a planned multimodality treatment (with long-term hormonal and/or adjuvant radiation therapy), has not been evaluated (level of evidence: 4).

Definitive Radiation Therapy

There are no randomized studies that compare RP with either external beam therapy or brachytherapy for localized CaP. In Europe, the 1990s saw the introduction of three-dimensional conformal radiotherapy (3D-CRT) and a growing interest in transperineal brachytherapy. At the onset of the third millennium, intensity modulated radiotherapy (IMRT) is gradually gaining ground in centres of excellence. After the appropriate assessment of tumour extension, the choice of treatment must be made based on a multidisciplinary approach, taking into account the 2002 TNM classification, Gleason score, baseline PSA, age of the patient, comorbidity, life expectancy and QoL. Obtaining a patient's consent is essential after providing exhaustive information regarding diagnosis, the therapeutic modalities and morbidity.

Localized CaP T1–2c N0, M0

Low-Risk Group

T1a–T2a N0, M0 and a Gleason score of 6 or less and a PSA of less than 10 ng/ml qualifies as low-risk. For external radiotherapy, up to 70–72 Gy is recommended as it offers the same results as dose escalation [74].

Intermediate-Risk Group

Intermediate-risk group patients, with T2b or PSA 10–20 ng/ml, or a Gleason score of 7, may benefit from dose escalation, as shown by two randomized trials. The MD Anderson Cancer Centre randomized study compared 78 Gy 3D-CRT to a 70 Gy conventional radiotherapy including 305 stage T1–3 patients with a pretreatment PSA level of more than 10 ng/ml (median follow-up of 40 months). A significantly higher 5-year free-from-failure rate was found in 75% of the patients who received 78 Gy vs 48%

of those who received 70 Gy (p=0.01) [75]. This study has been confirmed by the PROG 95-09 interim analysis that evaluated 393 T1b–T2b patients—75% of which had a Gleason score of 6 or less—and with a PSA less than 15 ng/ml. Patients were randomized to receive an initial boost to the prostate alone using conformal protons of either 19.8 or 28.8 Gy, then 50.4 Gy to a larger volume. With a median follow-up of 4 years, there was a significant decrease of the 5-year biochemical failure rate (p=0.00001) in favour of the patients assigned to the higher dose (79.2 GyE) vs those receiving a conventional dose (70.2 GyE) [76]. In daily practice, although a consensus has not been reached yet concerning the level of the dose escalation, 78 Gy seems to represent a good compromise.

High-Risk Group

For the high-risk group (T2c, or Gleason score greater than 7 or PSA greater than 20 ng/ml), external irradiation with dose escalation improves 5-year biochemical disease-free survival [75] but seems insufficient to cover the risk of relapse outside the pelvis. Many studies aim to evaluate the dose escalation with or without adjuvant hormonal therapy:

1. The MRC with neoadjuvant hormonal therapy comparing conventional radiotherapy of 64 Gy to high-dose (74 Gy) radical conformal radiotherapy [77]
2. The Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) comparing 70 to 80 Gy without hormonal therapy [78]
3. The European Organization for Research and Treatment of Cancer (EORTC) with dose stratification (70, 74 and 78 Gy) with or without neoadjuvant and concomitant hormonal therapy [79]

A prospective randomized trial, which included 206 patients with a PSA of at least 10 ng/ml (maximum 40 ng/ml), a Gleason score of at least 7 (range 5–10), or radiographic evidence of extra-prostatic disease, compared 3D-CRT alone or in combination with 6 months of androgen deprivation therapy (ADT). After a median follow-up of 4.5 years, patients randomized to receive 3D-CRT plus ADT had a significantly higher survival rate (p=0.04), lower CaP-specific mortality rate (p=0.02), and higher survival rate free of salvage ADT (p=0.002) [80].

Prophylactic Irradiation of Pelvic Lymph Nodes in Intermediate- or High-Risk Localized CaP

Nowadays, due to individual screening, comprehensive clinical work-up and new imaging modalities, the risk of pelvic lymph node invasion may be assessed by the Roach formula [81]. The Roach formula estimates the risk of pelvic lymph node involvement higher than 15%: positive lymph node=2/3 PSA+(GS-6)×10.

Innovative Techniques

Intensity Modulated Radiotherapy

IMRT enables radiation oncologists to homogeneously increase the doses up to 80 Gy within the target volume, while respecting the threshold doses in organs at risk. The Memorial Sloan-Kettering Cancer Centre has the largest experience with this technique, reporting on 772 patients treated between 1996 and 2001 with doses ranging from 81 to 86.4 Gy using an inverse planning approach. With a median follow-up time of 24 months (6–60 months), the 3-year actuarial likelihood of late grade 2 or higher rectal toxicity was 4%; the 3-year actuarial likelihood of grade 2 or higher urinary toxicity was 15%; and the 3-year actuarial PSA relapse-free survival rates for favourable-, intermediate- and unfavourable-risk group patients were 92%, 86% and 81% respectively [82]. The use of IMRT is opening the way to hypofractionated treatment, with a shorter duration for the overall treatment time, by delivering 70 Gy in 28 fractions over 5.5 weeks, with 2.5 Gy per fraction.

Transperineal Brachytherapy

Transperineal brachytherapy is a safe and efficient technique, which generally requires less than 2 days of hospitalization. There is a consensus on

the following eligibility criteria: stage cT1b–T2a N0, M0, a Gleason score of 6 of less assessed on a sufficient number of random biopsies, an initial PSA level of 10 ng/ml or lower, a prostate volume of 50 cm^3 or less and a good International prostatic symptom score (IPSS) [83].

In cases of permanent implants, iodine-125 in granule form is the radio-element of reference; palladium-103 may be used for less differentiated tumours with high doubling time. The dose delivered to the planning target volume is in the order of 160 Gy for iodine-125 and of 120 Gy for palladium-103. A Gleason score of 7 still remains a "grey zone", but patients with GS 4+3 show no difference in outcome [84]. In cases of intermediate or high-risk localized CaP, the combination with external irradiation [85] or neoadjuvant hormonal treatment [86] may be considered, but the potential positive impact of these treatments needs to be assessed with randomized trials. Non-permanent transperineal interstitial prostate brachytherapy using a high-dose rate iridium-192 stepping source and a remote after-loading technique can be applied with a total dose of 12 to 20 Gy in 2 to 4 fractions combined with fractionated external radiotherapy of 45 Gy [26].

Immediate Post-operative External Irradiation for Pathological Tumour Stage T3 N0, M0

Only one prospective randomized trial has assessed the role of immediate post-operative radiotherapy; The European Organisation for Research and Treatment of Cancer (EORTC) study 22911 compared immediate post-operative radiotherapy (60 Gy) to radiotherapy delayed until local recurrence (70 Gy) in patients classified as pT3 pN0 after retropubic RP. Immediate post-operative radiotherapy proved to be well tolerated with a risk of grade 3–4 and urinary toxicity of under 3.5% [88], without significant difference regarding incontinence and/or stricture of anastomosis. The study concludes that immediate post-operative radiotherapy significantly improves 5-year clinical or biological survival: 72.2% vs 51.8% $p<0.0001$. Consequently, for patients classified as T1–2 N0 (or T3 N0 with selected prognostic factors), pT3 pN0 with a high risk of local failure after RP due to rupture of the capsule, positive margins and/or invasion of the seminal vesicles, presenting with a PSA of <0.1 ng/ml 1 month after surgery, one of the following may be recommended:

- Immediate radiotherapy upon recovery of urinary function
- Clinical and biological monitoring followed by salvage radiotherapy, when the PSA exceeds 0.5 ng/ml

Locally Advanced CaP: T3–4 N0, M0, T1–4 N1 M0

The incidence of locally advanced CaP declined as a result of individual or mass screening. Pelvic lymph node irradiation is optional for N0 patients, due to the likelihood of infra-clinical disease and N1 patients (inter-iliac nodes). Results of radiotherapy alone are dismal. This is why, because of the hormone dependence of CaP [89], ADT has been combined with external irradiation with the dual objectives of:

- Reducing the risk of distant metastases by potentially sterilizing micrometastases already present at the moment of diagnosis
- Decreasing the risk of non-sterilization and/or local recurrence as a source of secondary metastases through the effect of radiation-induced apoptosis

Neoadjuvant Hormonal Therapy

The Radiation Therapy Oncology Group (RTOG) study 86-10 included 471 patients with stage T2-4N0-X M0. ADT was administered 2 months before irradiation and during irradiation, or, in the case of relapse, in the control arm. Of the patients, 32% were diagnosed as T2, 70% as T3–4 and 91% N0. The hormone treatment consisted of oral flutamide, 250 mg, 3 times daily and goserelin acetate (Zoladex) 3.6 mg every 4 weeks by subcutaneous injection. The pelvic target volume received 45 Gy and the prostatic target volume received 20–25 Gy. At 8 years, ADT was associated with an improvement in local control (42% vs 30%, $p=0.016$), disease-free survival (33% vs 21%, $p=0.004$) and biochemical disease-free survival [PSA <1.5 ng/ml, 24% vs 10% ($p<0.0001$)].

In patients with Gleason score 2–6, there was a significant improvement in survival: 70% vs 52% (p=0.015) [90].

Concomitant and Adjuvant Hormonal Therapy

The EORTC study 22863 recruited 415 patients diagnosed with T1–2 grade 3 WHO, T3–4 N0, M0 and compared radiotherapy with adjuvant ADT to radiotherapy alone. ADT was allowed in cases of relapse. Of the patients, 82% were diagnosed as T3, 10% as T4 and 89% as N0. The hormone treatment consisted of oral cyproterone acetate, 50 mg 3 times daily for 1 month, beginning 1 week before the start of radiotherapy, and subcutaneous injection of goserelin acetate 3.6 mg every 4 weeks for 3 years, starting on the first day of radiotherapy.

The pelvic target volume received was 50 Gy and the prostatic target volume was 20 Gy. With a median follow-up of 66 months, combination therapy compared with radiotherapy alone was significantly better for both survival (78% vs 62%, p=0.001) and survival without clinical relapse (78% vs 40%, p<0.001) [63]. The 5-year cumulative incidence of locoregional failure was 1.7% vs 16.4% in the radiotherapy alone arm (p<0.0001), and survival without clinical or biological failure (nadir of 1.5 ng/ml) was 81% for the combined treatment arm vs 43% in the radiotherapy alone arm (p<0.001).

Adjuvant Hormonal Therapy

The RTOG study 85-31 recruited 977 patients diagnosed with T3–4 N0-1 M0, or pT3 after RP. ADT was started in the last week of irradiation and continued up to relapse (group I) or started at recurrence (group II). Of the patients in groups I and II, 15% and 29%, respectively, had undergone RP, while 14% of the patients in group I and 26% in group II were pN1. Goserelin acetate 3.6 mg was administered every 4 weeks. The pelvis received 45 Gy and the prostatic bed received 20–25 Gy. Patients diagnosed with stage pT3 received 60–65 Gy. With a median follow-up time of 7.3 years, a statistical significance was reached for 5-year and 10-year overall survival in favour of the adjuvant hormonal therapy arm, 76% vs 71% and 53% vs 38%, respectively [44]. In this study, 95 of the 173 pN1 patients who received pelvic radiotherapy with immediate hormonal therapy had a significantly better survival rate without biochemical relapse at 5 years (PSA <1.5 ng/ml) than those in the arm with delayed hormonal therapy (p=0.0001) [92].

Neoadjuvant, Concomitant and Adjuvant Hormonal Therapy

The RTOG 92-02 trial closed in 1995 after accruing 1,554 patients. Statistically significant improvements were observed in biochemical non-evidence (bNED; actuarial biochemical freedom of disease) control, distant metastatic failure, local control and disease-free survival for patients receiving long-term ADT (before, during and 2 years after radiotherapy) compared with short-term treatment (2 months before, and during radiotherapy). With a median follow-up of 5.8 years, the long-term ADT arm showed significant improvement in all efficacy end-points except 5-year overall survival, 80% vs 78.5% (p=0.73), compared with the short-term ADT. In a subset of patients, who were not part of the original study design, with Gleason score 8–10 tumours, after 5 years the long-term androgen deprivation (LTAD) arm showed significantly better overall survival: 81% vs 70.7%, (p=0,04) [93].

Summary of Definitive Radiation Therapy

1. In localized CaP T1c-T2c N0 M0, 3D-CRT with or without IMRT, definitive radiation therapy is recommended, even for young patients who refuse surgical intervention. There is fairly strong evidence that intermediate-risk patients benefit from dose escalation (level of evidence: 2). For patients in the high-risk group, short-term ADT prior to and during radiotherapy may result in increased overall survival (level of evidence: 2a).
2. Transperineal interstitial brachytherapy with permanent implants may be proposed to patients cT1–T2a, a Gleason score less than 7

(or 3+4), a PSA of 10 ng/ml or lower, prostate volume of 50 ml or less, without a previous TURP and with a good IPSS (level of evidence: 2b).

3. Immediate post-operative external irradiation after RP for patients with pathological tumour stage T3 N0 M0 prolongs biochemical and clinical disease-free survival (level of evidence: 2a). An alternative option is to give radiation at the time of biochemical failure but before PSA reaches above 1–1.5 ng/ml (level of evidence: 3).
4. In locally advanced CaP, overall survival is improved by concomitant and adjuvant hormonal therapy (with a total duration of 2 to 3 years) with external irradiation (level of evidence: 1). For a subset of patients, T2c–T3 N0-x with Gleason score 2–6, short-term ADT before, and during, radiotherapy may favourably influence overall survival (level of evidence: 1b).

Experimental Local Treatment of Prostate Cancer

Besides RP, external beam radiation and/or brachytherapy, cryosurgery of the prostate (CSAP) and high-intensity focussed ultrasound (HIFU) have emerged as alternative therapeutic options in patients with clinically localized CaP. Whereas HIFU is still considered to be an experimental treatment, CSAP has been recognized as a true therapeutic alternative as recommended by the guidelines of the American Urological Association. Both techniques have been developed as minimally invasive procedures potentially resulting in the same therapeutic efficacy as the established surgical and non-surgical options associated with reduced therapy-associated morbidity.

The reader is referred to the full guidelines published at http://www.uroweb.org.

Summary of Experimental Therapeutic Options to Treat Clinically Localized CAP

1. CSAP has evolved from an investigational therapy to a possible alternative to treat CaP in patients unfit for surgery or in those with a life expectancy of less than 10 years (grade C recommendation).
2. All other minimally invasive treatment options, such as HIFU, RITA, microwaves and electrosurgery, are still experimental or investigational. For all of these procedures, a longer follow-up is mandatory to assess their true role in the management of CaP (grade C recommendation).

Hormonal Therapy

In 1941, Huggins and Hodges assessed the favourable effect of surgical castration and oestrogen administration on the progression of metastatic CaP, demonstrating for the first time the responsiveness of CaP to androgen deprivation [94]. Since their pivotal studies, androgen-suppressing strategies have become the mainstay for the management of advanced CaP, but recent years show an evolution towards increasing hormonal treatment of younger men with earlier (i.e. non-metastatic) stages of disease or recurrent disease after definitive treatment, either as primary single-agent therapy or as a part of a multimodality approach. Even if hormonal treatment effectively palliates the symptoms of advanced disease, there is no conclusive evidence at present that it can extend life.

Testosterone-Lowering Therapy (Castration): Bilateral Orchiectomy

Surgical castration is still considered the "gold standard" for ADT against which all other treatments are rated.

By removing the testicular source of androgens, a hypogonadal status with a considerable decline of testosterone concentrations is induced, though a very low level of testosterone (known as "castration level") does persist. Bilateral orchiectomy is a simple and virtually complication-free surgical procedure, which can easily be performed under local anaesthesia. The main drawback of orchiectomy is that it may have a negative psychological effect; some men consider it to be an unacceptable assault on their manhood.

Oestrogens

The most commonly used oestrogen was diethylstilboestrol (DES). In early studies by the Veterans Administration Co-operative Urological Research Group (VACURG) [95, 96], oral DES at a dosage of 5, 3 and 1 mg/day was tested, but the treatment was associated with high cardiovascular morbidity and mortality due to the first-pass hepatic metabolism with formation of thrombogenic metabolites.

Renewed interest in oestrogens can be ascribed to three main reasons. First, as a response to the number of deleterious side-effects and the high costs of long-term ADT with the currently widespread LHRH agonists: oestrogens suppress testosterone levels and do not seem to lead to bone loss and cognitive decline (97, level of evidence: 3). Second, oestrogenic compounds (DES, DES-diphosphate and the herbal supplement PC SPES) have been shown to induce PSA-response rates as high as 86% in phase II trials with patients diagnosed with hormone-refractory prostate cancer (HRPC). Third, a new oestrogen receptor-beta (ER-b), possibly involved in prostate tumourigenesis, has been discovered [98].

In conclusion, DES is one of the classic forms of hormonal therapy. Although its efficacy was demonstrated many years ago and recently reconfirmed in a meta-analysis as comparable to that of bilateral orchiectomy (99, level of evidence: 1a), the significant cardiovascular side-effects, even at lower dosages, remain a concern. Further data are needed before oestrogens will be readmitted in clinical practice as a standard first-line treatment option.

Luteinizing Hormone-Releasing Hormone Agonists

Long-acting luteinizing hormone-releasing hormone (LHRH) agonists (buserelin, goserelin, leuprorelin and triptorelin) have been used in advanced CaP for more than 15 years and are currently the predominant forms of ADT [100, 101]. Chronic exposure to LHRH agonists eventually results in down-regulation of LHRH-receptors, with subsequent suppression of pituitary LH and follicle-stimulating hormone (FSH) secretion and testosterone production. The level of testosterone decreases to castration levels usually within 2 to 4 weeks [19, 20]. However, approximately 10% of patients treated with LHRH agonist fail to achieve castration levels [21].

In a recent meta-analysis evaluating single-therapy ADT for advanced CaP, LHRH agonists have shown comparable efficacy to orchiectomy and DES (99, level of evidence: 1a). In addition, although only based on an indirect comparison, all seemed equally effective (99, level of evidence: 3). Today, LHRH agonists have become the "standard of care" in hormonal therapy because they avoid the physical and psychological discomfort associated with orchiectomy and lack the potential cardiotoxicity associated with DES. However, the main concerns associated with the administration of LHRH agonists are the potentially detrimental effects associated with the "flare phenomenon" in advanced disease, namely increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression and fatal cardiovascular events due to hypercoagulation status. A recent review [102] addressing these issues concluded that clinical flare needs to be distinguished from the more common biochemical flare (i.e. increasing levels of PSA) and even from asymptomatic radiographic evidence of progression, and that patients at risk for clinical flare are overwhelmingly those with high-volume, symptomatic, bony disease, accounting for only 4%–10% of M1 patients. Concomitant therapy with an anti-androgen definitely decreases the incidence of clinical relapse, but it does not completely remove the possibility of their occurrence. Based on pharmacokinetic considerations, it is recommended that administration of the anti-androgens should be started on the same day as the depot injection, and treatment should be continued for a 2-week period. However, for patients with impending spinal cord compression, alternative strategies for immediately ablating testosterone levels must be considered, such as bilateral orchiectomy or LHRH-antagonists.

LHRH Antagonists

In contrast to the agonists, LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. The effect is a

rapid decrease in LH, FSH, and testosterone levels without any flare.

This seemingly more desirable mechanism of action has made LHRH antagonists very attractive since their introduction, but practical shortcomings have limited clinical studies. Indeed, many of these compounds have been associated with serious and life-threatening histamine-mediated side-effects and, until recently, no depot formulation was available. Abarelix has recently been licensed by the United States Food and Drug Administration for clinical use, but its use is restricted to those patients with metastatic and symptomatic CaP for whom no other treatment option is available [103].

Anti-androgens

Anti-androgens compete with testosterone and DHT for binding sites on their receptors in the prostate cell nucleus, thus promoting apoptosis and inhibiting CaP growth [26]. These orally administered compounds are classified according to their chemical structure as steroidal [e.g. cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate] and non-steroidal or pure (e.g. nilutamide, flutamide and bicalutamide). Both classes act as competitors of androgens at the receptor level, but while this is the sole action of non-steroidal anti-androgens, steroidal anti-androgens additionally have progestational properties with central inhibition of the pituitary gland. As a consequence, non-steroidal anti-androgens do not lower testosterone levels, which remain normal or, conversely, slightly elevated.

Steroidal Anti-androgens

These compounds are synthetic derivatives of hydroxyprogesterone. In addition to peripherally blocking androgen receptors, they have progestational properties and inhibit gonadotrophin (LH and FSH) release and suppress adrenal activity. At high doses megestrol acetate is cytotoxic. Since steroidal anti-androgens lower testosterone levels, the main pharmacological side-effects are loss of libido and erectile dysfunction. The non-pharmacological side-effects are cardiovascular toxicity (4%–40% for CPA) and hepatotoxicity.

Cyproterone Acetate

There is only one randomized trial [104] comparing CPA to standard hormonal therapy (i.e. medical castration): patients in arm A (no contraindications to DES) were randomly assigned to CPA, goserelin or DES, while patients in arm B (contraindications to DES) were assigned to CPA or goserelin. In arm A, treatment with CPA was associated with significantly poorer median overall survival than goserelin only; adjusting for baseline characteristics did not account for this difference. The only comparative study on anti-androgens as monotherapy was recently published by EORTC protocol 30892 (a randomized trial of 310 patients comparing CPA vs flutamide in metastatic CaP), which showed no difference in cancer-specific and overall survival at a median follow-up of 8.6 years, though the study was underpowered (105, level of evidence: 1b).

Megesterol Acetate and Medroxyprogesterone Acetate

Very limited information is available on megesterol acetate and medroxyprogesterone acetate. The only prospective randomized trial evaluating medroxyprogesterone acetate as primary therapy in advanced (M0–1) CaP is the EORTC 30761 study mentioned above [106], in which 236 patients were assigned to receive CPA, DES or medroxyprogesterone acetate: While no difference in cancer-specific and overall survival was evident between CPA and DES, treatment with medroxyprogesterone acetate had a less favourable course with a shorter survival time and time to progression than any of the other two drugs tested.

Non-steroidal Anti-androgens

Non-steroidal anti-androgens have been promoted in monotherapy for QoL and compliance benefits over castration since they do not suppress testosterone secretion; it is claimed that libido, overall physical performance and bone mineral density are preserved.

Although no direct comparisons have been undertaken in a monotherapy setting, the three

available drugs do not appear to differ in the severity of pharmacological side-effects, namely gynaecomastia, breast pain and hot flashes. However, there are differences in the non-pharmacological side-effects, with bicalutamide showing a more favourable safety and tolerability profile than nilutamide and flutamide [107].

Flutamide

Flutamide was the first non-steroidal anti-androgen available for clinical use and has been studied as monotherapy for over 20 years, but no dose-finding studies against a currently accepted endpoint (e.g. PSA response) have been published. Flutamide is a pro-drug and the half-life of the active metabolite is 5 to 6 h, so it has to be administered three times daily to maintain therapeutic serum levels; the recommended daily dosage is 750 mg.

The main advantage shown in these studies was the preservation of sexual function, which was maintained in up to 80% of patients with no pre-treatment erectile dysfunction [108–111]. This rate has not been confirmed in the EORTC trial 30892 [105], where as few as 20% of the men treated with flutamide maintained sexual activity for up to 7 years. Only two phase III randomized trials comparing flutamide monotherapy to standard therapy (orchiectomy [112] and CAB [113]) for advanced CaP have reported survival data; both showed no significant difference in overall survival for flutamide or castration. Results are eagerly awaited from an on-going Swedish study in which 700 patients with M1 CaP have been randomized to flutamide 250 mg three times daily or CAB.

Bicalutamide

Early reports with bicalutamide monotherapy related only to the 50 mg dosage, which was the one licensed for use in CAB. An overall analysis of these studies showed that, although bicalutamide 50 mg/day had clinical benefits, it was inferior to castration in terms of overall survival (median difference 97 days) [114]. Subsequent dose-ranging studies established that bicalutamide 150 mg once daily achieved a PSA response similar to that seen with castration while maintaining a good tolerability profile [115].

As primary monotherapy, bicalutamide 150 mg/day has been compared to medical or surgical castration in two large prospective randomized trials with identical study design, including a total of 1,435 patients with locally advanced M0 or M1 CaP [115]. A pooled analysis showed:

- An improvement in overall survival with castration in M1 patients, although the difference in median survival between the groups was only 6 weeks; a further post-hoc analysis showed a survival benefit only for patients with higher PSA level (>400 ng/ml) at study entry.
- No significant difference was noted in overall survival in M0 patients.

In two smaller randomized trials, high-dose bicalutamide was compared to CAB. In the first trial (251 patients with predominantly M1 stage), no difference in overall survival was apparent [116]. In the second trial (220 patients with M0 and M1 stage), there was no difference in overall survival for well- or moderately well-differentiated tumours [117] (level of evidence: 1b), but both studies were underpowered.

As for the adjuvant setting, the on-going Early Prostate Cancer Programme including 8,113 patients worldwide was designated to evaluate the efficacy and tolerability of high-dose (150 mg/day) bicalutamide vs placebo given in addition to standard primary care (i.e. RP, radiotherapy and "watchful waiting") in localized or locally advanced CaP. The first combined analysis of the programme showed that, after a median follow-up of 3 years, adjuvant bicalutamide provided a reduction of 42% in the risk of objective disease progression compared to standard care alone [58]. After a median follow-up of 5.4 years, it was shown that the positive effects of bicalutamide were obvious in patients with locally advanced disease (stage M0), whereas for patients with localized disease survival appeared to be reduced as compared to those receiving placebo [50]. In conclusion, high-dose bicalutamide has emerged as an alternative to castration for patients with locally advanced (M0) and in highly selected, well-informed cases of M1 CaP, but should be avoided in patients with localized CaP.

Combination Therapies

Complete Androgen Blockade

A plethora of studies evaluating complete androgen blockade (CAB) over monotherapy have been carried out with contrasting results. From the most recent systematic reviews and meta-analyses it appears that at a follow-up of 5 years, CAB provides a small survival advantage (less than 5%) when compared to monotherapy ([119–123] level of evidence: 1a). It remains debatable whether this small advantage, if any, can be meaningful when applied to everyday clinical practice.

Minimal Androgen Blockade (or Peripheral Androgen Blockade)

In several phase II trials [124–128], the association of finasteride and flutamide, either in a concomitant or sequential regimen, has been evaluated in terms of PSA-response rate in patients with advanced or biochemically recurrent CaP. Notwithstanding the small sample and short follow-up, the overwhelming majority of patients experienced a substantial decline in PSA (by up to 96% compared to the level at entry). An update of one of these studies, at a long-term follow-up, reported on stronger endpoints, such as castration-free survival (median: 37 months), androgen-independent CaP-free survival (median: 48.6 months) and overall survival rate (65% at 5 years); the conclusion was that combination therapy can induce an overall period of hormone-responsive disease exceeding 4 years [129]. In all these trials, sexual function was reported to be preserved in the great majority (55% to 86%) of men.

The preliminary data make this treatment option most attractive in the management of patients for whom QoL is the primary issue. However, while awaiting the results of follow-up and larger controlled trials, the treatment is still regarded as investigational.

Intermittent Versus Continuous Androgen Deprivation Therapy

Several phase II trials have demonstrated the feasibility of intermittent androgen blockade (IAB) in metastatic or biochemically recurrent disease, with PSA-response rates and symptom improvement similar to that of CAB, but phase III prospective, randomized controlled trials are still underway and data on survival endpoints and QoL are not mature [130].

In conclusion, although IAB is at present widely offered to patients with CaP in various clinical settings, its status should be regarded as investigational.

Immediate Versus Deferred Androgen Deprivation Therapy

Evidence on immediate vs deferred ADT is provided by three systematic reviews of the literature (one of which is a meta-analysis). The Agency for Health Care Policy and Research report indicated that a possible survival advantage for early ADT existed in single studies where hormone treatment was the primary therapy, while the combined analysis showed no significant benefit. Furthermore, androgen suppression was shown to be most cost-effective if initiated after patients experienced symptoms from metastatic disease [131]. The Cochrane Library review extracted four good-quality randomized controlled trials {VACURG I & II studies [95, 96], the MRC trial [49] and the Eastern Cooperative Oncology Group (ECOG) 7887 study [133]}, which were all conducted in the pre-PSA era and included patients with advanced CaP who received early vs deferred ADT as primary therapy or adjuvant to RP, but not to radiotherapy. According to the analysis, early androgen suppression significantly reduces disease progression and complication rates due to the progression itself, but does not improve cancer-specific survival and provides a relatively small benefit in overall survival with an absolute risk reduction of 5.5%, which does not become evident until after 10 years [134]. Based on a systematic review of the literature, the recently published American Society of Clinical Oncology Guidelines on the initial hormonal

treatment for androgen-sensitive metastatic, recurrent or progressive CaP concluded that no recommendation can be made as to when to start hormonal therapy in advanced asymptomatic CaP until data from studies using modern diagnostic and biochemical tests and standardized follow-up schedules become available [135].

Summary of Guidelines of Hormonal Therapy

1. In advanced CaP, ADT delays progression, prevents potentially catastrophic complications and effectively palliates symptoms, but does not prolong survival (level of evidence: 1b).
2. In advanced CaP, all forms of castration as monotherapy (orchiectomy, LHRH and DES) have equivalent therapeutic efficacy (level of evidence: 1b).
3. Non-steroidal anti-androgen monotherapy (e.g. bicalutamide) is an effective alternative to castration in patients with locally advanced disease (level of evidence: 1b).
4. In advanced CaP, the addition of a non-steroidal anti-androgen to castration (CAB) results in a small advantage in overall survival over castration alone but is associated with increased adverse events, reduced QoL and high costs (level of evidence: 1a).
5. Intermittent and "minimal" ADT should still be regarded as experimental therapies (level of evidence: 3).
6. In advanced CaP, immediate (given at diagnosis) androgen suppression significantly reduces disease progression and complication rate due to progression itself compared to deferred (delivered at symptomatic progression) androgen deprivation (level of evidence: 1b).
7. Bilateral orchiectomy may be the most cost-effective form of ADT, especially if initiated after occurrence of symptoms from metastatic disease (level of evidence: 3).

Tables 9.6 and 9.7 summarize the guidelines for primary treatment of prostate cancer at different stages.

Follow-up of Prostate Cancer Patients

Patients diagnosed with prostate cancer are usually followed life-long or until high age makes follow-up superfluous. Determination of serum PSA and a disease-specific history supplemented by DRE are the cornerstones in the follow-up of prostate cancer patients. Routine imaging procedures in stable patients are not recommended and should only be used in specific situations. The follow-up intervals and necessary follow-

Table 9.6 Guidelines for follow-up after treatment with curative intent

1. In asymptomatic patients, a disease-specific history and a serum PSA measurement supplemented by DRE are the recommended tests for routine follow-up. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually (grade B recommendation)
2. After radical prostatectomy, a serum PSA level of more than 0.2 ng/ml can be associated with residual or recurrent disease (grade B recommendation)
3. After radiation therapy, a rising PSA level, rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease (grade B recommendation)
4. Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence (grade B recommendation)
5. Detection of local recurrence by TRUS and biopsy is only recommended if it will affect the treatment plan In most cases; TRUS and biopsy are not necessary before second-line therapy (grade B recommendation)
6. Metastasis may be detected by pelvic CT/MRI or bone scan. In asymptomatic patients these examinations may be omitted if the serum PSA level is less than 30 ng/ml, but data on this topic are sparse (grade C recommendation)
7. Routine bone scans and other imaging studies are not recommended in asymptomatic patients. If a patient has bone pain, a bone scan should be considered irrespective of the serum PSA level (grade B recommendation)

up tests have not been well-studied; often these need to be individualized. Table 9.6 outlines the guidelines for follow-up after therapy of curative intent; Table 9.7 summarizes follow-up after hormonal therapy. Patients initially managed by active monitoring (no active therapy) need individual follow-up, depending on the future aims of therapy and tumour characteristics.

Treatment of Relapse After Curative Therapies

Before reviewing treatments of relapse after curative therapy (Table 9.8), we need to define local and systemic failure after RP.

– Local failure following RP is predicted with an 80% probability by PSA increase more than 3 years after RP, a PSA doubling time

Table 9.7 Guidelines for follow-up after hormonal treatment

1. Patients should be evaluated at 3 and 6 months after initiating treatment. Tests should include at least serum PSA measurement, DRE and careful evaluation of symptoms in order to assess the treatment response and the side-effects of treatments given (grade B recommendation)
2. Follow-up should be tailored to the individual patient, according to symptoms, prognostic factors and the treatment given (grade C recommendation)
3. In patients with stage M0 disease with a good treatment response, follow-up is scheduled every 6 months, and should include at least a disease-specific history, DRE and serum PSA determination (grade C recommendation)
4. In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every 3–6 months. A minimal follow-up should include a disease-specific history, DRE and serum PSA determination, frequently supplemented with haemoglobin, serum creatinine and alkaline phosphatase measurements (grade C recommendation)
5. When disease progression occurs or if the patient does not respond to the treatment given, the follow-up needs to be individualized (grade C recommendation)
6. Routine imaging in stable patients is not recommended (grade B recommendation)

Table 9.8 Guidelines on second-line therapy after curative treatments

Recommendations	
Presumed local failure after RP:	Patients with presumed local failure only may be candidates for salvage radiotherapy. This should be given with at least 64 Gy and preferably before PSA has risen above 1.5 ng/ml. Other patients are best offered a period of watchful waiting (active monitoring) with possible hormonal therapy later on (grade B recommendation)
Presumed local failure after RT:	Selected patients may be candidates for salvage radical prostatectomy (or other curative efforts), although patients should be informed concerning the comparatively high risk of complications. Other patients are best offered a period of watchful waiting (active monitoring) with possible hormonal therapy later on (grade C recommendation)
Presumed distant ±/– local failure:	There is some evidence that early hormonal therapy may be of benefit in delaying progression and possibly achieve a survival benefit in comparison with delayed therapy. The results are not without controversy. Local therapy is not recommended except for palliative reasons (grade B recommendation)

Table 9.9 Guidelines for secondary hormonal, cytotoxic and palliative management in patients with hormone refractory prostate cancer

Hormonal manipulations
1. Castration levels of testosterone should be maintained also in hormone refractory patients (grade C recommendation)
2. Administration of all anti-androgens has to cease once PSA progression is documented (grade B recommendation)
3. After discontinuation of flutamide or bicalutamide, after 4 weeks and 6 weeks, respectively, the anti-androgen withdrawal (AAW) effect will become apparent (grade B recommendation)
4. The combination of ketoconazole and AAW results in significantly better PSA response rates and longer time to progression than AAW alone, but the side-effects of ketoconazole need to be taken into account (grade B recommendation)
5. No clear-cut recommendation can be made regarding the most effective drug for secondary hormonal manipulations since no data from randomized trials are available (grade C recommendation)
Cytotoxic therapy
1. In patients with a PSA rise only two consecutive increases of PSA serum levels above a previous reference level should be documented (grade B recommendation)
2. Prior to treatment PSA serum levels should be >5 ng/ml to assure correct interpretation of therapeutic efficacy (grade B recommendation)
3. Potential benefits of cytotoxic therapy and expected side-effects should be discussed with each individual patient (grade C recommendation)
4. In patients with metastatic HRPCA docetaxel at 75 mg/m2 every 3 weeks results in a significant survival benefit and represents the reference treatment (grade A recommendation)
5. In patients with symptomatic osseous metastases due to HRPCA either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable therapeutic options (grade A recommendation)
Palliative management
1. Bisphosphonates may be offered to patients with skeletal metastases (mainly zoledronic acid has been studied) to prevent osseous complications (grade A recommendation)
2. Palliative treatments such as radionuclides, external beam radiotherapy; adequate use of analgesics should be considered early on in the management of painful osseous metastases (grade B recommendation)

(PSADT) of 11 months or more, a Gleason score of 6 of higher, and stage being pT3a pN0, pTx R1 or earlier (Table 9.8 and 9.9).

- Systemic failure following RP is predicted with a greater than 80% accuracy by a PSA increase less than 1 year after RP, PSADT of 4–6 months, a Gleason score 8–10 and stage pT3b, pTxpN1.
- Local failure after radiation therapy is documented by a positive prostatic biopsy and negative imaging studies.
- Prostatic biopsy after radiation therapy is only necessary if local procedures such as salvage prostatectomy are indicated in an individual patient.

Diagnostic Procedure in Patients with PSA Relapse

1. Following RP, CT scans of the pelvis and abdomen are of low sensitivity and specificity in patients with PSA levels of less than 20 ng/ml or a PSA velocity of less than 20 ng/ml per year.
2. Endorectal MRI or PET scans may help to detect local recurrences if PSA is greater than 1–2.0 ng/ml, but this is not yet part of routine clinical use.
3. If available, the capromab pendetide scan shows a diagnostic yield of 60% to 80% independent of the PSA serum level.

4. Following radiation therapy, local recurrence is documented by a positive biopsy 18 months or later after the procedure.

Management of PSA Relapse After RP

- Local recurrences are best treated by salvage radiation therapy with 64–66 Gy at a PSA serum level at 1.5 ng/ml or less (grade B recommendation).
- Expectant management is an option for patients with presumed local recurrence unfit for, or unwilling to undergo, radiation therapy (grade B recommendation).
- PSA recurrence indicative of systemic relapse is best treated by early ADT resulting in decreased frequency of clinical metastases (grade B recommendation).
- LHRH analogues/orchiectomy or bicalutamide at 150 mg/day can both be used when there is indication for hormonal therapy (Table 9.7; grade A recommendation).

Management of PSA Relapse After Radiation Therapy

- Local recurrences may be treated by salvage RP in carefully selected patients (grade C recommendation).
- CSAP and interstitial brachytherapy are alternative experimental procedures in patients not suitable for surgery (grade C recommendation).
- ADT is an option in patients with presumed systemic relapse (grade B recommendation).

Guidelines for Second-Line Management After Curative Treatment

1. Presumed local failure after radical radiotherapy
   Only patients with presumed local failure may be candidates for salvage radiotherapy. This should be given with at least 64 Gy and preferably prostatectomy before PSA has risen above 1.5 ng/ml. Other patients are best offered a period of watchful waiting (active monitoring) with possible hormonal therapy later on (grade B recommendation).
2. Presumed local failure after RP
   Selected patients may be candidates for salvage RP after radiotherapy, although patients should be informed concerning the comparatively high risk of complications. Other patients are best offered a period of watchful waiting (active monitoring) with possible hormonal therapy later on (grade C recommendation).
3. Presumed distant
   There is some evidence that early hormonal therapy may be of benefit in local failure combined with distant occult metastases delaying progression, and such patients may possibly achieve a survival benefit in comparison with delayed therapy. The results are not without controversy. Local therapy is not recommended except for palliative reasons (Table 9.8; grade B recommendation).

Treatment of Relapse After Hormonal Therapy

Patients experiencing relapse after hormonal therapy (Table 9.9) are usually in a more advanced disease stage and will usually become symptomatic within a relatively short time after the start of PSA rise. *First PSA rise* following hormonal therapy refers to androgen-independent PCA being sensitive to secondary hormonal manipulations, including anti-androgen withdrawal and the addition of anti-androgens, oestrogenic compounds and adrenolytic agents, as well as other novel approaches [136]. *PSA progression* following secondary endocrine treatment refers to the state of true hormone refractory prostate cancer. Patients with hormone-refractory prostate cancer are not curable, and maintaining or improving QoL should be a main goal. In most cases the decision to treat or not to treat is made based on counselling of the individual patient, which limits the role of guidelines.

Secondary Hormonal Manipulations

Anti-androgen Withdrawal Syndrome

In 1993, Kelly and Scher [137] reported clinical and PSA responses in men who discontinued flutamide therapy upon development of progressive disease. Approximately one-third of patients respond to anti-androgen withdrawal as indicated by at least a 50% PSA decrease with a median duration of response of approximately 4 months. Anti-androgen withdrawal responses have also been reported after treatment with bicalutamide and megestrol acetate [138–140]. The availability and more favourable toxicity profile of secondary hormonal therapies allow the clinician to consider these drugs for the growing category of asymptomatic patients for whom chemotherapy is difficult to justify, but who, due to increasing serum PSA level, want treatment outside clinical trials. However, observation remains a viable choice for asymptomatic patients.

Approximately 10% of circulating androgen in humans is secreted by the adrenal glands. In androgen-independent states, some tumour cells must retain sensitivity to androgens, as a further decrease in circulating androgen levels by bilateral adrenalectomy or drugs that inhibit adrenal steroidogenesis can induce a clinical response. The simultaneous addition of ketoconazole to anti-androgen withdrawal, however, results in a significantly increased PSA response (32% vs 11%) and a longer time to PSA progression (8.6 vs 5.9 months) compared to anti-androgen withdrawal alone [141], as has been documented in a recent, prospective, randomized phase III trial including 260 patients with androgen-independent CaP. In a recent prospective randomized clinical phase II trial, ketoconazole was demonstrated to be significantly more effective than estramustine phosphate with regard to PSA response (67% vs 29%) and time to progression (7.9 vs 3.2 months).

Non-hormonal Therapy (Cytotoxic Agents)

Based on prospective randomized clinical phase III trials, several proven chemotherapeutic options are available for the management of HRPC with metastatic disease. In two recent phase III trials, a significant improvement in median survival of approximately 2 months could be demonstrated for docetaxel-based chemotherapy as compared to a combination of mitoxantrone and prednisone [143, 144]. In the TAX 327 study [143], 1,006 patients with metastatic HRPC were randomly assigned to mitoxantrone at 12 mg/m² every 3 weeks, docetaxel at 75 mg/m² every 3 weeks, or docetaxel at 30 mg/m² weekly for 5 of every 6 weeks. The median survival was 16.5 months in the mitoxantrone group and 18.9 months (p<0.001) and 17.4 months in the docetaxel 75 mg/m² every 3 weeks and docetaxel 30 mg/m² for 5 of every 6 weeks, respectively.

A 50% or greater PSA decline was achieved in 45% and 48% of men in the docetaxel-treated groups compared to 32% in the mitoxantrone group (p<0.001). Significant pain reduction was achieved in 22% of the patients in the mitoxantrone group compared to 35% (p=0.01) and 31% (p=0.08) in the docetaxel-treated groups. Adverse events were similar among the different treatment groups. However, QoL was significantly improved in both docetaxel-treated groups.

In the Southwest Oncology Group (SWOG) 99-16 trial [143], 674 patients with metastatic HRPC were randomly assigned to receive mitoxantrone at 12 mg/m² every 3 weeks or docetaxel and estramustine at 60 mg/m² every 3 weeks. In an intention-to-treat analysis, the median survival was 17.5 months and 15.6 months (p=0.02) in the docetaxel and the mitoxantrone groups, respectively. Also, the median time to progression was significantly longer in the docetaxel group with 6.3 months compared with 3.2 months in the mitoxantrone group (p<0.001). A PSA decline of 50% or more was achieved in 50% and 27% patients of the docetaxel and the mitoxantrone group, respectively. Pain relief was similar between both groups, though side-effects occurred significantly more often in the docetaxel group.

Despite these encouraging results, the time point to initiate a cytotoxic regime in patients with HRPC remains controversial. Although it appears evident that chemotherapy should be started in patients with metastatic HRPC, there are no data available with regard to the therapeutic efficacy of early chemotherapy in patients

with PSA rise only. There at least exists the recommendation that two consecutive increases in PSA over a previous reference value should exists and that the PSA level should exceed 5 ng/ml [135]. Therefore, the indication for the initiation of chemotherapeutic regimes has to made on an individual basis.

Mitoxantrone with corticosteroids [145, 146] has been extensively studied primarily in patients with symptomatic osseous lesions due to HRPC. In the Cancer and Leukemia Group B (CALGB) 9182 study [146], 244 patients with symptomatic metastatic HRPC were randomized to either receive mitoxantrone plus hydrocortisone at 12 mg/m² every 3 weeks or to hydrocortisone alone. Although no differences were observed with regard to survival, PSA response and median time to progression, QoL was significantly improved in the combination arm. In the other trial [30], 161 men with painful osseous metastases due to HRPC were randomized to receive mitoxantrone plus prednisone compared to prednisone alone. A significant benefit in terms of pain reduction was observed in the combination group (29%) compared to prednisone alone (12%, p=0.01); furthermore, duration of palliation was longer in patients who received mitoxantrone (43 vs 18 weeks, p<0.0001). There were no significant differences with regard to PSA response and median survival time. Although none of the studies demonstrated any survival benefit for the patients, QoL was improved significantly due to pain reduction.

Palliative Therapeutic Options

The majority of patients with HRPC have painful bone metastases. The two beta-emitting radioisotopes, strontium-89 and samarium-153, can partially or completely decrease bone pain in up to 70% of patients. Early use can make subsequent administration of chemotherapy more difficult because of myelosuppression [147, 148]. Critical issues of palliation must be addressed while considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression, which frequently occur (i.e. with palliative external beam radiation, cortisone, analgesics and anti-emetics).

Common complications due to skeletal metastases include bone pain, vertebral collapse or deformity, pathologic fractures and spinal cord compression. Recently, the use of bisphosphonates to inhibit osteoclast-mediated bone resorption and activity of osteoclast precursors has demonstrated a clinically significant effect in terms of prevention of skeletal complications and reduction of pain, or even total pain relief, in patients with HRPC. In the largest single phase III trial [149], 643 men with HRPC metastatic to the bone were randomized to receive zoledronic acid at 8 mg or 4 mg every 3 weeks for 15 consecutive months or placebo. At 15 months and at 24 months of follow-up, there was a significant reduction in skeletal-related events in the zoledronic acid-treated group as compared to the placebo group (44% vs 33%, p=0.021). The frequency of pathological fractures was significantly lower in the zoledronic acid group compared with the placebo group (13.1% vs 22.1%, p=0.015). Furthermore, the time to first skeletal-related event was significantly prolonged in the zoledronate group thereby significantly improving QoL. Currently, bisphosphonates could be proposed to patients with HRPC bone metastases in order to prevent skeletal complications.

Pain due to osseous metastases is one of the most debilitating complications of HRPC. Bisphosphonates have been proved to be highly effective with a response rate of 70%–80%, which, associated with a low frequency of side-effects, makes bisphosphonates to be an ideal medication for palliative therapy of advanced HRPC [150, 151]. Bisphosphonates should be considered early in the management of symptomatic HRPC.

Hormone refractory CaP is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is required with input from medical oncologists, radiation oncologists, urologists, nurses and social workers [90].

Summary on Treatment After Hormonal Therapy

– It is recommended to cease anti-androgen therapy once PSA progression is documented (grade B recommendation).

- Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal (AAW) effect will become apparent (grade B recommendation).
- No clear-cut recommendation can be made regarding the most effective drug for secondary hormonal manipulations since data from randomized trials are scarce (grade C recommendation).

Guidelines and Recommendations for Cytotoxic Therapy in HRPC

1. In patients with a PSA rise only, two consecutive increases of PSA serum levels above a previous reference level should be documented (grade B recommendation).
2. Prior to treatment, PSA serum levels should be greater than 5 ng/ml to assure correct interpretation of therapeutic efficacy (grade B recommendation).
3. Potential benefits of cytotoxic therapy and expected side-effects should be discussed with each individual patient (grade C recommendation).
4. In patients with metastatic HRPCA, and who are candidates for cytotoxic therapy, docetaxel at 75 mg/m² every 3 weeks has shown a significant survival benefit (grade A recommendation).
5. In patients with symptomatic osseous metastases due to HRPCA, either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable therapeutic options (grade A recommendation).

Guidelines for Palliative Management of HRPC

1. Patients with symptomatic and extensive osseous metastases cannot benefit from medical treatment with regard to prolongation of life.
2. Management of these patients has to be directed at improvement of QoL and mainly pain reduction.
3. Effective medical management with the highest efficacy and a low frequency of side-effects represents the major goal.

Recommendations for Palliative Management of HRPC

1. Bisphosphonates may be offered to patients with skeletal metastases (mainly zoledronic acid has been studied) to prevent osseous complications (grade A recommendation)
2. Palliative treatments such as radionuclides, external beam radiotherapy, adequate use of analgesics should be considered early on in the management of painful osseous metastases (grade B recommendation).

Summary

The present text represents a summary and for more detailed information and a full list of references, we refer to the full-text version. These EAU guidelines (ISBN 90-70244-27-6) are available at the website of the European Association of Urology: http://www.uroweb.org.

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10 Choices for Surgery

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Abstract

Surgical treatment of prostate cancer has seen many improvements in the past two decades, including laparoscopy, robotic surgery, and better assessment of quality of life and functional results. The limits of surgery for locally advanced disease and after failure of radiotherapy have been better defined, together with the roles of neoadjuvant and adjuvant treatment. Patients with clinically organ-confined prostate cancer, reasonable life expectancy, and little or no co-morbidity are the best candidates for radical prostatectomy. This chapter reviews the different technical options for the treatment of prostate cancer, with their respective indications and functional and oncological results.

Techniques of Radical Prostatectomy

Radical prostatectomy consists of removing the whole prostate gland and the seminal vesicles. Three approaches can be used: the retropubic approach, the perineal approach, and the laparoscopic approach.

Retropubic Prostatectomy

The retropubic approach is the reference technique. It is widely used and is described in detail elsewhere. The current "gold standard" technique, described by Walsh in 1983, has been combined with new nerve-sparing techniques giving better preservation of erectile function (Walsh et al. 1983). Blood loss has been limited by better control of the Santorini venous complex (Barre et al. 1999; Avant et al. 2000), and continence is now recovered sooner (Walsh and Marschke 2002).

Perineal Prostatectomy

Radical perineal prostatectomy was the surgical treatment of choice for localized adenocarcinoma of the prostate until the 1980s, when radical retropubic prostatectomy began to gain popularity. The perineal technique is extensively described in the literature (Weldon and Tavel 1988; Weldon 2002). Compared to the suprapubic approach, the perineal approach is associated with less bleeding, less pain, shorter hospitalization, and easier urethrovesical anastomosis (Weldon and Tavel 1988; Frazier et al. 1992; Walther 1993; Haab et al. 1994; Salomon et al. 1997; Weldon et al. 1997; Kahn et al. 1998; Lance et al. 2001; Ruiz-Deya et al. 2001; Korman et al. 2002). It seems to be at least as easy to learn as retropubic prostatectomy (Mokulis and Thompson 1997) and is less invasive.

The main problem with this approach is that lymph node dissection cannot be performed via the same incision, and some authors therefore advocate laparoscopic lymph node dissection prior to prostate surgery (Parra et al. 1994; Teichman et al. 1995).

In addition, the development of retropubic radical prostatectomy has permitted surgeons to better define the indications of the lymph nodes dissection according to the clinical stage, the prostate-specific antigen (PSA) level, and biopsy findings. Lymph node involvement is very rare when PSA is less than 10 ng/ml, rectal examination is normal, and the Gleason biopsy score is less than 7 (Bishoff et al. 1995; Bluestein et al. 1994). Lymph node dissection is optional for

such patients, and radical perineal prostatectomy is thus a good option. Nonetheless, this approach has not become as popular as the retropubic approach, and it is now being gradually discarded in favor of the laparoscopic approach.

Laparoscopic Prostatectomy

The laparoscopic approach to radical prostatectomy was gradually developed in the second part of the 1990s, initially by French surgeons. Abbou et al. (2000), Gaston et al. (Curto et al. 2006) and Guillonneau et al. (Guillonneau and Vallancien 2000) developed an intraperitoneal approach. The extraperitoneal approach was not very popular at the beginning of the epoch of laparoscopic prostatectomy, even if the technique was described approximately at the same time as the transperitoneal approach (Raboy et al. 1997).

Transperitoneal Laparoscopic Radical Prostatectomy

The transperitoneal approach requires a marked Trendelenburg position, and usually begins with seminal vesicle dissection via a direct approach above Douglas' sac. Dissection of the prostate is then usually performed by an antegrade approach from the seminal vesicles to the prostate apex (Guillonneau and Vallancien 2000; Hoznek et al. 2003; Curto et al. 2006), but retrograde dissection has also been described from the prostate apex to the seminal vesicles (Dubernard et al. 2003; Rassweiler et al. 2004).

Extraperitoneal Radical Prostatectomy

Abbou et al. (Hoznek et al. 2003) and others (Bollens et al. 2001; Stolzenburg et al. 2005) switched to the extraperitoneal approach for several reasons. First, it avoids abdominal complications such as gastrointestinal wounds, peritoneal urine leakage from the anastomosis, postoperative pain from the pneumoperitoneum, and occlusion secondary to incarceration of small ileal loops in front of the bladder. It also permits adjuvant radiotherapy sparing the gastrointestinal tract, and avoids possible dissemination of tumor cells into the peritoneal cavity. The Trendelenburg position can be avoided, and the technique reproduces the same approach as the open retropubic approach. In case of laparoconversion, the surgeon finds himself in a more familiar situation (Bollens et al. 2001; Hoznek et al. 2003; Stolzenburg et al. 2005). Normal feeding can resume more rapidly (Hoznek et al. 2003). Creation of the working space and the lack of initial dissection of the seminal vesicles may shorten the operation (Hoznek et al. 2003; Cathelineau et al. 2004), although this is still controversial for some authors (Erdogru et al. 2004). In case of gross obesity, previous abdominal surgery, or simultaneous inguinal hernia repair, the extraperitoneal approach is simpler than the intraperitoneal approach (Erdogru et al. 2004). No randomized studies have so far compared the two approaches, but the intraperitoneal approach does not seem to be associated with any significant advantages or disadvantages in terms of complications, functional outcomes, or carcinological results. Therefore, the choice of the laparoscopic approach will depend on the preference and experience of the individual surgeon (Cathelineau et al. 2004; Erdogru et al. 2004).

Robot-Assisted Radical Prostatectomy

One of the main difficulties associated with laparoscopic prostatectomy is the length of the learning curve. It has been suggested that at least 40 procedures are necessary to achieve an acceptable operating time and complication rate. Laparoscopic robotic assistance can restore two of the six degrees of freedom that are missing with standard laparoscopy. The feasibility and reproducibility of robot-assisted laparoscopic radical prostatectomy are now well-documented (Abbou et al. 2001; Binder and Kramer 2001; Pasticier et al. 2001; Rassweiler et al. 2001; Gettman et al. 2003; Menon et al. 2003). The largest published series comes from the Vattikuti Institute, where, compared to the laparoscopic technique, the use of the Da Vinci system was associated with less operating-room time, less estimated blood loss, and a shorter median time to urinary continence (Menon et al. 2005). For the surgeon, robotic as-

sistance offers a more ergonomic environment that might shorten the learning curve. This technology is still under active development, and future developments, including 5-mm instruments with enhanced articulation, the availability of a fourth arm (for solo surgery), arms installed in the roof, or three-channel optical systems allowing a panoramic view, may also help simplify and securitize the procedure. The main problem will be one of cost, especially for small centers. At least 10 robotically assisted radical prostatectomies would have to be performed every week to be cost-effective compared to open retropubic radical prostatectomy (Scales et al. 2005).

Differences Between Open and Laparoscopic Radical Prostatectomy

Only a few studies have prospectively compared the open retropubic approach to the laparoscopic approach, and none was randomized (Anastasiadis et al. 2003; Bhayani et al. 2003; Hara et al. 2003; Roumeguere et al. 2003).

The main advantages of the laparoscopic approach relative to the retropubic approach are a lower risk of bleeding and lesser analgesic requirements, with patients becoming active more rapidly (4 weeks instead of 6) (Bhayani et al. 2003; Hara et al. 2003; Farnham et al. 2006; Roumeguere et al. 2003). The main disadvantages are the longer operating time, the longer learning curve, and shorter oncological follow-up (the results are currently similar with the two approaches). The excision margins are the same, and no major differences in long-term oncological outcome are therefore expected (Bhayani et al. 2003; Hara et al. 2003; Roumeguere et al. 2003; Salomon et al. 2002; Anastasiadis et al. 2003; Hoznek et al. 2005). Likewise, no major differences in functional results have been observed. With the laparoscopic approach, some authors have reported more rapid recovery of continence (Anastasiadis et al. 2003) while other authors have found slower recovery (Roumeguere et al. 2003). Concerning erectile function, the laparoscopic approach has been linked to lesser sildenafil use (Roumeguere et al. 2003), but sexual dysfunction is still a problem with both approaches. There are probably no major differences between the laparoscopic and open approaches as regards recovery of potency, based on a series of patients with the same age in which the same principles and techniques were used (meticulous tissue handling and avoidance of electrocautery; Hoznek et al. 2005).

Complications of Radical Prostatectomy

Perioperative Complications

The surgical mortality rate is now below 0.5% in most studies, whatever the technique, all deaths being of cardiorespiratory origin (Lu-Yao et al. 1999; Anastasiadis et al. 2003; Bhayani et al. 2003; Hara et al. 2003; Roumeguere et al. 2003).

Hemorrhage is the most common intraoperative problem with open prostatectomy, but the proportion of patients who need blood transfusion has fallen from 30% to less than 5% (Barre et al. 1999; Avant et al. 2000). The use of the laparoscopic approach is associated with less bleeding: mean estimated blood loss is 250–500 ml, representing no more than two-thirds of the volume lost during retropubic approaches (Bhayani et al. 2003; Roumeguere et al. 2003; Farnham et al. 2006). Improved control of the Santorini plexus can nonetheless reduce blood loss to below 400 ml in open procedures (Barre et al. 1999; Avant et al. 2000). However, blood loss is difficult to estimate precisely, as blood is mixed with urine, and the blood transfusion rate is therefore a more reliable measure (even if some centers systematically reinfuse autologous blood collected before prostatectomy).

Rectal injuries are less frequent but can be responsible for significant morbidity when not diagnosed immediately. These injuries are more frequent with the perineal approach than with other approaches (Lance et al. 2001). The overall rates are approximately 1%–2% for the suprapubic and laparoscopic procedures, and 1%–6% for the perineal approach. Obturator nerve injury (<0.5%) and ureteral injury (0.1%) are other very rare intraoperative complications. The transperitoneal laparoscopic approach can also be associated with occasional gastrointestinal lesions. The perineal approach can be associated with hypesthesia of the lower limbs due to hyperflexion, and with pelvic cellulites.

Potential post-surgical complications include delayed bleeding (0.5%), lymphocele (3.4%), scar infection (1.5%), deep vein thrombosis (2.6%), pulmonary artery thrombosis (<0.5%), and myocardial infarction (0.6%). (Harpster et al. 1995; Haggman et al. 1996; Lu-Yao et al. 1999; Hoznek et al. 2001; Lance et al. 2001; Fichtner et al. 2003).

The risk of complications correlates with pre-existing comorbidity and with blood loss, but not with age or the length of the procedure. The surgeon's experience and skill are also key factors (Dillioglugil et al. 1997; Begg et al. 2002; Bianco et al. 2005).

Postoperative Complications

Urinary incontinence is common after surgery but usually resolves within 3 to 6 months. When incontinence is still present after 1 year it is unlikely to improve spontaneously. In a large series, 81% of patients did not need protection after 1 year, but the results can be worse in smaller centers (Murphy et al. 1994). Serious incontinence is reported in 3.4% of patients. The artificial sphincter is then a good option, with excellent long-term results (Elliott and Barrett 1998; Mottet et al. 1998). Risk factors for postoperative incontinence include older age, previous transurethral resection of the prostate, and postoperative anastomotic stricture. Postoperative anastomotic stricture may occur in 0.5%–9% of cases, and is more frequent in patients with major intraoperative bleeding, a transanastomotic fistula, or previous transurethral resection of the prostate (Dillioglugil et al. 1997).

Erectile dysfunction is also frequent after radical prostatectomy, whatever the approach used. Impotence is the rule unless a nerve-sparing procedure is used. The results obtained with nerve-sparing techniques are difficult to compare because of different definitions of erectile dysfunction and the use of different assessment methods. It seems that at least 18 months must elapse before erectile function can be reliably evaluated (Walsh et al. 2000; Kim et al. 2001). Many factors may influence the results, such as the surgical technique (unilateral or bilateral nerve-sparing technique, or none), the patient's age, and erectile status prior to surgery (Walsh et al. 2000). These factors explain why potency rates vary from 30% to 86% 12–18 months following surgery with a nerve-sparing technique (Stanford et al. 2000; Walsh et al. 2000; Kim et al. 2001; Hoznek et al. 2005).

Reduced penis size is another recently reported complication of prostatectomy (Fraiman et al. 1999; Savoie et al. 2003). Stretched penile length measured 3 months after radical retropubic prostatectomy diminished in two-thirds of patients, from 13 cm (median) to 12.5 cm. One in five patients had at least a 15% decrease in penis length (Savoie et al. 2003). The precise reasons for this decrease are unknown, but hypoxia and denervation could lead to apoptosis of penile erectile tissue cells and cause fibrosis or loss of cavernous smooth muscle cells (Klein et al. 1997); the latter was found in approximately 40% of patients with erectile dysfunction after radical prostatectomy (Ciancio and Kim 2000). However, no correlation between penile extensibility and the degree of smooth muscle fibrosis in the corpora cavernosa was found, making this explanation unlikely (Moreira de Goes et al. 1992). Other parameters like prostate volume, previous potency status, and nerve-sparing surgery were not related to penile size changes (Savoie et al. 2003).

Oncological Results

The oncological results of surgery for prostate cancer are best evaluated in terms of the percentage of patients who are still PSA-free after a defined period, for example 5 or 10 years. Biochemical recurrence after surgery is generally diagnosed when two or more PSA values are higher than 0.2 ng/ml. Global and specific survival rates compared to watchful waiting are discussed below, along with locally advanced disease and salvage prostatectomy. Comparison to radiotherapy is detailed in Chap. 11

Many factors may influence the risk of recurrence. The more advanced the tumor, the higher the risk of recurrence. Advanced tumors are more likely when preoperative PSA levels, clinical stage, pathological stage, and the Gleason score are high. Positive margins are also associ-

ated with a higher risk of recurrence. It is difficult to predict recurrence after prostatectomy, but nomograms or artificial networks adapted to each center may be of assistance (Partin et al. 1997; Crawford et al. 2000; Partin et al. 2001).

Globally, in the largest series, the 5-year PSA-free survival rate is 70%–84% and the 10-year rate is 52%–74% (see Table 10.1; Zincke et al. 1994; Han et al. 2001; Roehl et al. 2004).

Role of Lymph Node Dissection in Radical Prostatectomy

Advantages of Lymph Node Dissection

Lymph node dissection is the best way to assess node status in the patient with prostate cancer. Lymph node status is a prognostic factor in this setting (Cheng et al. 1999). Specific mortality correlates with the number of metastatic nodes (Smith and Middleton 1985; Golimbu et al. 1987; Bader et al. 2003). The prognosis is better for patients with microscopic rather than macroscopic node involvement. It is also likely that removal of the unique lymph node with microscopic involvement could have a curative effect when combined with local treatment (Golimbu et al. 1987; Steinberg et al. 1990; Bader et al. 2003).

When Is Lymph Node Dissection Indicated?

Lymph node dissection is recommended at the same time as radical prostatectomy, unless the risk of finding lymph node involvement is very low. The latter risk obviously correlates with the extent of lymph node dissection, and with the patient's oncological characteristics (more advanced disease is more likely to have spread to the lymph nodes).

The probability of finding metastatic lymph nodes can be assessed with the help of nomograms and artificial networks (Partin et al. 1997; Crawford et al. 2000; Partin et al. 2001). Because the chances of finding a metastatic lymph node is very low when the stage is below T2a, the PSA is less than 10 ng/ml, the Gleason score is below 7 (with grade 4<50%), and the CT shows no evidence of lymph node enlargement, lymph node dissection is optional in such cases.

Table 10.1 Oncological results of radical prostatectomy

Study	Number of patients	Mean follow-up (months)	5-year PSA-free survival (%)	10-year PSA-free survival (%)
Roehl et al. (2004)	3,478	65	80	68
Zincke et al. (1994)	3,170	60	70	52
Han et al. (2001)	2,404	75	84	74

When Is Frozen Section Analysis of Removed Lymph Nodes Necessary?

Frozen section analysis of lymph nodes is usually done systematically, as surgery cannot cure metastatic prostate cancer. However, the sensitivity of the procedure is only about 67%. False-negative results can occur, especially in patients with nonpalpable micrometastases (Davis 1995).

Therefore, when lymphadenectomy is performed during an open procedure, frozen section analysis is optional when there are no macroscopic signs of lymph node involvement.

Extent of Node Dissection

Lymphadenectomy is currently performed in one of two ways. Removal of the obturator and external iliac nodes is known as the modified way, and removal of both the internal and external iliac nodes is known as the extended way. The modified way has been the reference for more than 20 years (Stone et al. 1997; Brendler et al. 1980). The internal iliac nodes are most often involved, and 20%–30% of node metastases involve only these nodes; modified lymphadenectomy may therefore fail to identify such involvement (Stone et al. 1997; Heidenreich et al. 2002; Bader et al. 2003; Brenot-Rossi et al. 2005). The extent of lymphadenectomy does not appear to affect the outcome of prostate cancer in node-nega-

tive patients, and extended lymphadenectomy might thus be of limited interest when there is a low probability of node metastasis (DiMarco et al. 2005).

Complications of Lymph Node Dissection

Lymph node dissection itself is associated with increased morbidity and a longer operating time (Heidenreich et al. 2002; Kavoussi et al. 1993; Dillioglugil et al. 1997; Link and Morton 2001). Compared to open procedures, laparoscopic node dissection is associated with more vascular and colonic injuries, but with less nerve damage, lymphocele, infections, deep venous thrombosis, and bowel occlusion. Altogether, laparoscopy is associated with only about half the morbidity of the suprapubic procedure (Kavoussi et al. 1993; Link and Morton 2001). However, according to the number of lymph nodes removed, laparoscopic node dissection is generally less extensive than open procedures.

Extended node dissection was associated with a complication rate of 10%–20% in series published before the 1990s (Dillioglugil et al. 1997), but in recent series published by experienced teams the difference with limited dissection is not significant (Heidenreich et al. 2002). The complication rate of pelvic lymphadenectomy is around 7%, symptomatic lymphocele being the most common complication (Dillioglugil et al. 1997).

To prevent complications, lymphatics lateral to the external artery should be preserved, the distal ends of the lymphatics should be either ligated or clipped, drains should be placed in each side of the pelvis, and heparin should be used to prevent venous thrombosis.

Mini-invasive techniques (mini-open surgery or laparoscopy) have been developed for removing the external and obturator nodes, with results comparable to those of the open technique.

These procedures may be less promising than first thought, as the current trend is toward extended lymph node dissection, which can discover up to 30% of additional metastatic lymph nodes.

Radical Prostatectomy for Locally Advanced Disease

Prostate cancer is locally advanced when the prostate capsule has been breached or the seminal vesicles have been invaded, but without evidence of metastasis. This stage is associated with a higher risk of undetectable lymph node involvement (Boccon-Gibod et al. 2003) in an estimated 30%–50% of cases (Peneau et al. 1998). Prostate cancer staging prior to surgery is inaccurate, however, and 9%–27% of cT3 patients are over-staged (Peneau et al. 1998; van den Ouden et al. 1998; Ward et al. 2005b). These over-staged patients could probably be cured by surgery alone, and small pT3 cancers may also be cured by radical prostatectomy if the tumor and prostate are completely removed (van den Ouden and Schroder 1998; Van Poppel et al. 2000). Radical prostatectomy is thus a possible first-line treatment for suspected locally advanced disease in selected patients (Aus et al. 2005). Surgery is also more effective than nonsurgical therapies at reducing local morbidity associated with invasion of surrounding structures. As is the case with other local treatments performed alone, radical prostatectomy results are often disappointing for locally advanced prostate cancer, and hormone treatment is either added or used alone (Meraney et al. 2005).

Indications

For patients with clinical T3 stage disease, surgery can be proposed when the PSA is less than 10 ng/ml (up to 20 ng/ml for some authors), when seminal vesicle invasion is absent, when the Gleason score is below 8, and when life expectancy is more than 10 years (van den Ouden and Schroder 2000; Van Poppel et al. 2000; Van Popple 2005).

Neoadjuvant Hormone Therapy

The large number of locally advanced prostate cancers that turn out to be metastatic has led many physicians to use hormone therapy prior to or after surgery in these cases. Neoadjuvant

hormone therapy for 3 months reduced prostate size and the surgical margins rate, but had little impact on the T stage and no effect on the PSA recurrence rate at 3 years. (Cher et al. 1995; Soloway et al. 1995; Goldenberg et al. 1996; Hugosson et al. 1996; Rabbani et al. 1998; Bono et al. 2001). Surgery was reported to be more difficult, but no increase in blood loss, the transfusion rate, or the length of the procedure was observed (Van Poppel et al. 1992; Soloway et al. 1995; Hugosson et al. 1996).

These initial reports on 3-months neoadjuvant hormone therapy were disappointing, and longer treatments lasting 4–8 months were therefore proposed. The results were at least as good as with neoadjuvant hormone therapy combined with radiotherapy (Powell et al. 2002), with a decrease in the T stage and specific survival rates of 76%, 55%, and 32%, respectively, at 5, 10, and 15 years.

Adjuvant Hormone Therapy

Many randomized studies have shown that early adjuvant hormone therapy improves survival in patients with locally advanced prostate cancers, with or without lymph node involvement. When lymph node involvement is present, Messing et al. have shown that, relative to delayed hormone treatment, immediate hormone treatment is associated with better overall and specific survival after 10 years of follow-up (Table 10.2; Messing et al. 1999, 2006). These results confirmed those of Seay et al., who reviewed the files of 790 patients with pTxN+ prostate cancer who underwent radical prostatectomy with or without hormone treatment (Seay et al. 1998).

Table 10.2 Survival rates after immediate and delayed hormone therapy in men with pTxN+ prostate cancer (Messing et al. 2004)

	Overall survival	Specific survival
Immediate hormone therapy	74.4%	87.2%
Delayed hormone therapy	49%	56%

More recently, bicalutamide 150 mg daily has been compared with a placebo in a randomized study, after local treatment of pT1b-T4NxM0 prostate cancer (Iversen et al. 2004). After 5 years of follow-up, the bicalutamide group had a 43% lower risk of disease progression. There was also a significant improvement in overall survival among men with locally advanced prostate cancer. The Early Prostate Cancer Program, with 8,000 patients, gave similar results after 5 years of follow-up, confirming the significant improvement in progression-free survival among men with locally advanced prostate cancer, but with no evidence of a beneficial impact on overall survival (See et al. 2003; Wirth et al. 2005). It had also been shown that adjuvant bicalutamide is not appropriate for patients with localized disease.

Adjuvant Chemotherapy

Adjuvant chemotherapy has proved effective on progression-free survival in many studies. Estramustine (Akduman and Crawford 2003), mitoxantrone (Wang et al. 2000), epirubicin (Pummer et al. 1997), and, more recently, docetaxel (Petrylak et al. 2004; Tannock et al. 2004) are effective on locally advanced prostate cancer. In hormone-refractory prostate cancer, docetaxel increases overall survival. Nonetheless, it is not yet possible to predict which patients will respond to chemotherapy. Some studies have shown that patients with muc1 gene overexpression in the tumor have a higher risk of recurrence, and that patients with AZGP1 gene overexpression have a lower risk of recurrence, regardless of the Gleason score and PSA level (Lapointe et al. 2004). It should eventually be possible in the future to associate different molecular profiles with treatment responsiveness, as in breast cancer (van 't Veer et al. 2002) and some lymphomas (Lossos et al. 2004).

Technical Aspects

The success of radical prostatectomy for locally advanced prostate cancer is due to more radical excision and extensive lymph node dissec-

tion. Locally advanced prostate cancers are more likely to extend into the posterolateral and rectal periprostatic tissue, especially in the caudal area. As the lymph ducts of this area drain into the lymph nodes of the sacrum and the promontory (Gil-Vernet 1996), it is recommended to perform extensive resection, including the internal lymph nodes (Heidenreich et al. 2002). For the same reasons, the neurovascular bundles are usually widely resected, especially on the side of the cancer. The contralateral bundle can be spared in some men with small unilateral T3 prostate tumors. To reduce the risk of positive surgical margins, the posterior plane of resection should be deep enough under Denonvilliers' fascia so that both layers of the fascia are completely excised. It is also recommended to fully transect the puboprostatic ligaments in order to permit proper apical dissection, to avoid positive apical margins, and to perform bladder neck resection with reconstruction when the cancer is not localized to the apex (Ward and Zincke 2003; Van Popple 2005).

Complications and Results

The outcome of radical prostatectomy in men with locally advanced prostate cancer is well documented in the Mayo Clinic series (Ward et al. 2005b), which is the largest single-institution experience in the management of cT3 prostate cancer with a mean follow-up of more than 10 years.

Morbidity was similar to that in men with clinically localized disease. Erectile dysfunction was observed in 75% of cases, but nerve-sparing techniques were used in only 26% of cases. Urinary continence at 1 year was achieved in 79% of men staged cT3, and only 6% of men had severe urinary incontinence (≥2 pads/day). No significant difference in complication rates was reported by other authors (Davidson et al. 1996). At 10 and 15 years after radical prostatectomy for cT3 disease, respectively 43% and 38% of patients were free of biochemical recurrence (vs 61% and 52% for stage cT2). Among patients with T3/4N0 disease, 60% received adjuvant or salvage hormone therapy and 40% received adjuvant or salvage radiotherapy. The 10- and 15-year overall survival rates (76% and 53%) and cancer-specific survival rates (90% and 79%) among patients with cT3 disease were only moderately lower than in patients with cT2 disease (82% and 61%, and 96% and 92%, respectively).

Surgery is an effective treatment for locally advanced disease, as a significant number of patients are at stage pT2 despite clinical signs of stage T3 disease, and radical prostatectomy can cure both T2 tumors and small pT3 tumors. In more advanced cases, radiotherapy is still possible and more accurate information could be delivered to patients using that strategy.

Salvage Radical Prostatectomy

After failure of radiotherapy, salvage radical prostatectomy is the only potentially curative for men with evidence of persistent localized prostate cancer (Stephenson et al. 2004b; Ward et al. 2005a). Showing that the cancer is still localized is thus crucial for the success of the procedure, and so is the management of complications.

The oncological results of salvage radical prostatectomy after 5 years follow-up are comparable to those of first-line radical prostatectomy for a given pathological stage (Stephenson and Eastham 2005). The probability of localized prostate cancer is higher when the PSA level is less than 10 ng/ml, and when biopsies of the prostate are positive at least 1 year after radiotherapy. To be eligible for salvage radical prostatectomy, patients must also have no evidence of metastasis, and must have a life expectancy of at least 10 years (Stephenson et al. 2004a; Ward et al. 2005a). Patients with troublesome radiation cystitis might be considered for bladder removal as well. When these recommendations are respected, 70% of patients are progression-free at 5 years (Stephenson et al. 2004a; Ward et al. 2005a).

Nonetheless, this technique is challenging, and surgeons encounter major complications, especially at the beginning of their experience (Rogers et al. 1995; Stein et al. 1992; Cheng et al. 1998). Blood transfusion (up to 73% of patients), rectal injury (up to 15%), anastomotic strictures (up to 32%), and reoperation (up to 15%) are more frequent than with first-line radical prostatectomy, and the salvage procedure is associated

with longer hospital stays. Incontinence is much more frequent (up to 64%) and the potency rate is low (less than 16%).

However, with experience, the frequency of some of these complications can become acceptable, especially that of rectal injuries, blood transfusion, and reoperation (Stephenson et al. 2004a). The complication rate also seems to be lower after external beam radiotherapy than after interstitial radiotherapy. Continence increased with experience, with an incontinence rate of 61% to 44% after 5 years (Stephenson et al. 2004a; Ward et al. 2005a). The high risk of urinary incontinence is probably the biggest hindrance to salvage radical prostatectomy. The potency rate can be increased by nerve-sparing techniques, but not by nerve-grafting procedures. At 5 years, Stephenson et al. reported a potency rate of 28% with nerve-sparing techniques, and 45% in previously potent patients (Stephenson et al. 2004a).

Laparoscopic techniques have also been used by Vallancien and colleagues for salvage radical prostatectomy, with encouraging results on the first 7 patients after 11 months of follow-up (Vallancien et al. 2003). No major complications were observed, the mean operating time was 190 min, mean blood loss was 400 ml, and 5/7 patients remained continent.

Patient qualifying for salvage radical prostatectomy should be informed of the increased incidence of complications associated with this procedure. There must be strong evidence that the prostate cancer is still localized to the prostate, and life expectancy should be more than 10 years. Many complications can occur, including urinary incontinence. Nonetheless, experienced teams can expect to obtain acceptable complication rates.

Watchful Waiting

Unlike other cancers, prostate cancer is indolent in a significant proportion of men. No impact on longevity or health is observed for many years when the cancer is diagnosed early. Watchful waiting strategies have thus been developed, with the introduction of hormone treatment only when clinical signs occur. Given the mean age at diagnosis (between 65 and 70 years in Western countries) there is a significant chance that the patient will die from another cause. The benefits of prostate cancer screening and radical treatment are therefore linked to the patient's life expectancy and to the characteristics of his prostate cancer.

It is now well established that patients with nonlocalized prostate cancer do not benefit from local treatment, except for some patients with locally advanced disease (see preceding section).

In men with localized prostate cancer, the Scandinavian Prostatic Cancer Group Study 4 has published the first randomized controlled trial to compare watchful waiting with radical prostatectomy (Holmberg et al. 2002; Steineck et al. 2002), and the data were recently updated with a median follow-up of 8.2 years (Table 10.3; Steineck et al. 2002). The trial randomized 695 men with a mean age of 64.7 years, localized disease, a mean PSA level of 13 ng/ml, and a Gleason score below 7 in 68% of cases. The trial showed a small advantage in terms of global survival and a strong advantage in terms of disease-specific mortality among patients who had radical prostatectomy.

The benefits of radical prostatectomy were largest in patients under 65 years. It must be underlined that the study population probably differed from the general population of

Table 10.3 Comparison of mortality rates after radical prostatectomy and watchful waiting, with 10 years of follow-up (Bill-Axelson et al. 2005)

	Radical prostatectomy group	Watchful waiting group	Relative risk	p-value
Prostate cancer mortality	9.6%	14.9%	0.56	0.01
Overall mortality	27.0%	32%	0.74	0.04

men identified by prostate cancer screening. In the Scandinavian population, only 11.7% of the patients were T1c, and 18.7% had a PSA above 20 ng/ml. Screening populations generally have less advanced disease, and radical treatment should therefore give better oncological results and less specific mortality. Ongoing randomized trials are addressing this issue (Schroder et al. 1999; Donovan et al. 2003; Andriole et al. 2005).

As regards quality of life, compared to prostatectomy, watchful waiting is associated with less erectile dysfunction (45% vs 80%), less urine leakage (21% vs 49%) but more urinary obstruction (44% vs 28%) (Steineck et al. 2002). The respective benefits and disadvantages of radical prostatectomy and watchful waiting must be fully explained, so that patients can make an informed choice.

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11 Radiation Therapy in Prostate Cancer

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Abstract

Adenocarcinoma of the prostate is one of the most frequently diagnosed cancers of men in the Western hemisphere and is second only to lung cancer for male cancer mortality. Most patients are diagnosed in the early/clinically localized stage, which can be treated curatively with radiation therapy alone. Innovative methods such as brachytherapy, three-dimensional conformal radiotherapy (3D-CRT), and IMRT (intensity modulated radiotherapy) are able to deliver very high tumoricidal doses to the diseased prostate, with minimal side effects to the surrounding tissue. Radiation therapy combined with hormonal treatment can be curative in locally advanced disease. Radiation therapy is also very effective in alleviating symptoms of metastatic prostate cancer (bone metastases, spinal cord compression, and bladder outlet obstruction).

History of Radiation Therapy in Prostate Cancer

In the 1930s, Smith and Peirson (1930) described the therapeutic value of 200 kV percutaneous roentgen therapy in prostate cancer. Widman (1934) followed them in his 1934 study with reasonable results using radium and roentgen (X-ray) therapy, even in advanced-stage disease. However, the further use of radiotherapy did not gain popularity because of the poor skin-sparing effect and the insufficient dose depth properties of the kilovoltage equipment.

As the limitation of hormonal treatment became apparent in the early 1950s, radiation therapy (RT) was rediscovered. The development of megavoltage equipment and improved physical properties contributed to the re-implementation of RT in localized early prostate cancer. A pioneering study conducted at MD Anderson Hospital in Houston, Texas, between 1966 and 1974 showed the effectiveness of radiotherapy for localized prostate cancer, although 8% developed major complications, including severe proctosigmoid injury, necessitating diverting colostomies (Hussey 1980).

Radiobiological Parameters of Prostate Cancer

Read (1959) and Lea (1955) quantified biologic response to irradiation in terms of a linear dose coefficient (α) and a coefficient for the square of the dose (β), according to the formula that effect is proportional to αD+βD2. The linear component (αD) of this dose survival relationship dominates response at low doses; with a dose per fraction in the order of 2 Gy, it has major significance. The lower the α/β ratio, the lower the dose per fraction below which the sparing effect of dose fractionation is lost.

The dose range over which the linear component dominates in a linear quadratic relationship depends on the relative value of α and β, and the α/β ratio defines the dose at which cell killing by linear and quadratic components are equal. If the α/β coefficient is low, the survival curve will go down after a relatively small initial linear region, and there will also be a marked sparing effect at dose fractionation on cell survival.

Prostate tumors have the slowest natural turnover rates of all tumors. The average t_{pot} (potential cell number doubling time, before any cell loss factor) measured before treatment is 40 days (range, 15 to >60 days), compared with 5 days

for many other types of tumor (King 2000). The fractionation sensitivity of prostatic carcinoma, as quantified by the α/β ratio, is low comparable to that for late-responding tissue (1.5 Gy) and shows a large fractionation effect.

Generally speaking, hypofractionation regimens for prostate cancer, in addition to their economical and logistic advantages, would be expected to result in less acute sequelae and late effects for a given level of tumor control and probability. Estimated values of α/β ratios for prostate cancer are 1.2 Gy, 1.5 Gy, or 1.49 Gy. These estimated values are clearly lower than for most other tumors and are comparable to those of adjacent late-responding normal tissues (Brenner and Hall 1999; Brenner et al. 2002).

The consequences might be that, in prostate cancer patients, appropriate hypofractionation schemes using intensity modulated RT (IMRT) or high-dose radiotherapy (HDR) should produce tumor control and late sequelae that are as good as or better than those currently achieved with conventional fractionation, and may even give reduced rates of early sequelae. According to Fowler et al. (2001, 2003), a satisfactory tumor response might be expected from a 5–25 fraction scheduled external beam RT (EBRT) or HDR brachytherapy. These authors showed that 10 fractions, each of 4.4 Gy, should give the same biochemical control as 75 Gy in 2-Gy fractions, with the same rate of late complications expected from 66 Gy in 2-Gy fractions. Such appropriately designed schedules using approximately 10 large fractions can result in absolute increases of 15%–20% in biochemical control with no evidence of disease and with no increase in late sequelae (Brenner and Hall 1999; Logue et al. 2001).

In conclusion, hypofractionation will increase the therapeutic ratio between tumor control and late sequelae, provided that the α/β ratio for prostate cancer is lower than that for complications. However, hypofractionation given in an unusually short overall time, without proper phase I testing of the toxic effect of such a schedule, might result in unexpected and severe rectal complications. It should be emphasized that the high fraction-size modality must be used with appropriate reduction of total dose.

External Beam Radiotherapy in Prostate Cancer

EBRT alone or in combination with other treatment modalities, such as hormonal therapy or brachytherapy, has become an alternative treatment to radical prostatectomy in patients with low-risk tumors. Yet the long natural history often observed in these patients makes an accurate assessment of the impact of any therapy on survival more difficult.

The local failure rate following conventional RT is likely to be due in large part to tumor-related factors [lymph node involvement, more advanced stages, extracapsular involvement, perineural and vascular invasion, high Gleason score, high initial prostate-specific antigen (PSA) level] and partly to technical factors related to the delivery of the radiation (older equipment, inaccurate planning and verification, insufficient total dose, inadequate coverage of the target volume). These have been identified to be of importance with respect to prognosis. In an analysis by Roach et al. (1999), the Gleason score was the single most important predictor of death in the first 10 years after therapy. Another example is the study of de Crevoisier, which raised the question of local failure with regard to patient treatment preparation. They found strong evidence that rectal distension on the treatment-planning CT scan decreased the probability of biochemical control, local control, and rectal toxicity (de Crevoisier et al. 2005).

A number of retrospective and prospective studies support the long-term efficacy of EBRT in the management of clinically localized and locally advanced prostate cancer. It has become widely accepted that overall dose is crucial to tumor recurrence. Long-term treatment results after EBRT show that an insufficient dose compromises efficacy. The value of dose escalation has been clearly demonstrated by several nonrandomized and randomized trials (Pollack et al. 2000, 2004, 2005; Peeters et al. 2005). Regarding failure-free survival, there was an advantage to a higher total dose, in particular for patients with intermediate- and high-risk tumors. Unfortunately there was also some increase in rectal toxicity with rising radiation doses. The results of these studies initiated important future de-

velopments. First, there is a need for improved quality assurance protocols concerning patient preparation, treatment planning and treatment verification (i.e., image guided radiotherapy). Second, there is a need for safer dose escalation with the growing use of sophisticated radiation techniques, such as IMRT (Ashman et al. 2005).

Standard Radiotherapy

Standard (non-conformal) RT was based mainly on estimations of the anatomic boundaries of the prostate defined by plain X-ray or a single computed tomography (CT)-slice radiography. Guidelines for treatment planning were based on the location of the pelvic bones (mainly the pubic bone), insertion of a bladder catheter balloon, and the use of bladder and rectal contrast media Standard RT used open squares or rectangular fields. It typically involved the initial use of a "4-field box" (box technique) followed by a boost to the prostate using a bilateral 120° arc on the 4-field box technique for the entire treatment or brachytherapy. These methods limited the ability of the radiation therapist to deliver biologically active high doses to the clinically estimated extension of the tumor without causing acute and long-term damage to sensitive organs (urinary bladder, rectum, femoral heads, urethra, penile bulb) in the immediate vicinity of the prostate. The later use of conformal blocking was an attempt to optimize the dose distribution to correspond to the shape of the target volume (Ten Haken et al. 1989).

Information about pelvic lymph node involvement could be obtained by imaging studies (only macroscopic lymph nodes) or by performing a lymph node dissection. The latter procedure was not commonly performed, but the available imaging studies were not able to decrease uncertainties regarding the risk of involvement.

With the help of the so-called Roach formula [2/3 PSA+10×(Gleason score−6)] (Woo et al. 1988; Seaward et al. 1998), the risk of lymph node involvement may be estimated, thus accelerating decision-making. If pelvic irradiation is regarded as necessary, simulation should be performed when the patient is in the prone or supine position. Some institutions used rigid immobilization devices (Kneebone et al. 2003) and performed an urethrogram to identify the inferior extent of the prostate apex. The superior field border was L4/L5 or L5/S1 junction, and the inferior border was set 1 cm inferior to both ischial tuberosities. The lateral margins are approximately 1–2 cm lateral to the bony margin of the lateral pelvic wall. The posterior field border was placed at the S2–3 junction. Appropriate corner blocking was used to decrease the dose to the femoral heads, small bowel, bladder, and the posterior wall of the rectum. Following delivery of the appropriate pelvic dose, the initial field size can be reduced to a field encompassing the prostate (plus margins) only. Total dose to the pelvic field used in standard radiotherapy was generally 45–50 Gy with 1.8–2.0 Gy per fraction, followed by a boost to the prostate of 15–20 Gy. The rationale and results of combined radiotherapy and hormonal treatment for intermediate- and high-risk prostate cancer patients are depicted below.

Results of Conventional External Beam Radiation Therapy

Accumulating data indicate that conventional (non-3D) techniques yield 10-year cause-specific survival rates for T1, T2, T3, and T4 tumors of 79.0%, 66.0%, 55%, and 22%, respectively (Duncan et al. 1993). These results were confirmed by Perez et al. (1993a,b). One of the EBRT studies with the longest follow-up is the retrospective study of a cohort of 136 patients treated with 60 Gy EBRT between 1964 and 1973 with a median follow-up of 25.6 years for surviving patients. Disease-free survival curves never reached a plateau and tumor recurrences still occurred after 20 years (Swanson et al. 2004). The authors concluded that results from studies with a median follow-up of less than 10 years must be regarded as preliminary. Furthermore, results from these studies indicate that more than 25% of all tumor recurrences occur after more than 10 years (Swanson et al. 1994). For locally advanced disease with higher risks of extracapsular tumor extension or seminal vesicle involvement, data demonstrate poor local control and long-term survival following standard radiotherapy.

It became obvious that radiotherapy with standard dose levels in the range of 60–70 Gy would not be sufficient to completely eradicate local prostate cancer in a significant proportion of patients. Furthermore, the delivery of higher radiation doses would result in an increased rate of genitourinary and gastrointestinal (GI) toxicities. Dearnaley et al. and Koper et al. compared radiation-induced side effects of conventional vs three-dimensional conformal RT (3D-CRT). Both studies demonstrated a reduction in toxicity, mainly rectal toxicity, by using 3D-CRT. Dose volume histogram (DVH) analysis demonstrated a statistically significant dose reduction. For instance, the treated anal volume and thus anal toxicity were markedly reduced by the 3D conformal treatment (Dearnaley et al. 1999; Koper et al. 1999). Hence, delivering higher doses without increasing toxicities promoted 3D-CRT.

3D Conformal Radiation Therapy

Nowadays, 3D-CRT may be considered standard treatment in most institutions. Using multileaf-collimators (MLC) that are mounted on the treatment machine, the photon beam may be shaped irregularly according to the shape of the target volume.

3D-CRT allows delivery of higher doses of radiation to the target volume while sparing the surrounding normal tissues. This is achieved by CT scans of the treatment volume, which are used to delineate target structures as well as organs at risk. There are convincing data that favor the use of additional imaging modalities such as magnetic resonance imaging (MRI), as it provides superior soft tissue visualization compared to CT (McLaughlin et al. 2005a, 2005b). Compared to MRI, CT leads to a larger volume than that derived by MRI, which also facilitates a more precise definition of the prostate apex (Kagawa et al. 1997; Sannazzari et al. 2002).

Guidelines for the organs at risk and target volume definitions are the International Commission on Radiation Units and Measurements (ICRU) 50 and ICRU 62. Standard terms of both classifications are summarized in Table 11.1 (ICRU 1993, 1999). Currently the European Organisation for Research and Treatment of Cancer (EORTC) is preparing guidelines for target and organs at risk definitions in prostate radiotherapy. Today most institutions use delineation procedures that depend on the individual patient's risk profile. After a 3D calculation of the dose, modern planning systems are able to calculate dose volume histograms that allow different techniques to be compared and rated. Digitally reconstructed radiographs (DRR) serve as virtual simulation images and may be used for verification procedures.

Since their first publication, the "Partin tables" have evolved into the major prognostic prediction tool in radiotherapy. The latest publication comprises the results of more than 4,000 men with prostate cancer (Khan and Partin 2003). These tables are not only useful for predicting the probability of transcapsular tumor spread or

Table 11.1 Volume definitions

1. Gross tumor volume (GTV)	Tumor only, no margins. Gross extent of tumor as determined by palpation or imaging studies. GTVp (primary tumor) should be distinguished from GTVn (nodal areas)
2. Clinical target volume (CTV)	Includes margins around the GTV for regions of microscopic risk (subclinical involvement)
3. Planning target volume (PTV)	Includes margins around the CTV accounting for beam penumbra, patient and organ movement, daily set-up inaccuracies
4. Dose-volume histograms	A method to evaluate the entire amount of dosimetric data obtained by using a 3-D-CRT treatment plan. It presents the data in an understandable format and shows minimal, maximal and mean doses, the percentage volume receiving greater than or equal to the prescription dose for target volumes, and the percentage volume receiving greater than or equal to the established tolerance dose

seminal vesicle or lymph node involvement, they are also of outstanding importance for target definition during radiotherapy treatment planning. The question of whether or not to irradiate pelvic lymph nodes may be further clarified by recent studies on new imaging modalities, which provide evidence that pelvic nodal radiation portals should be based on vascular rather than on bony anatomy landmarks, because of the localization of nodal metastases in prostate cancer along the major pelvic vasculature. These results were obtained by lymphotropic nanoparticle enhanced MRI (LNMRI) which has proved to be useful in the detection of minimal disease in normal-sized nodes at high sensitivity and specificity (Brassell et al. 2005; Shih et al. 2005; Will et al. 2006).

The efficient implementation of conformal techniques into prostate cancer treatment has been promoted by systematic and accurate evaluation of internal organ motion, proper patient preparation and positioning, and treatment verification procedures. Currently there is no patient preparation procedure that can be regarded as "standard." Although recent publications have clarified some obscurities, controversies remain about many issues, such as bladder filling, feet fixation, etc. Patient immobilization devices significantly reduce errors in patient positioning, especially in the prone position. The question of patient positioning has been an issue of controversy for some years. Currently there is only one prospective randomized trial comparing supine and prone position. Bayley et al. found a significant advantage in the supine treatment position with respect to prostate movement, number of set-up corrections, patient comfort and radiation therapist convenience as well as for all dose levels for small bowel, rectal wall, and bladder wall doses (Bayley et al. 2004).

Another issue in clinical quality assurance is treatment verification. In recent years verification procedures have been established that provide improved patient set-up accuracy, such as ultrasound localization systems, X-ray imaging systems, cone beam CT scanners and implanted gold markers. These systems offer the possibility of visualizing the prostate (or markers within the prostate) immediately before treatment to assure optimal target positioning. This procedure is called image-guided radiotherapy (IGRT).

Results of 3D-Conformal Radiation Therapy

Retrospective dose escalation studies using 3D-CRT provide clear evidence for a dose–response relationship in various subgroups of patients with prostate cancer. Two phase III randomized trials and several retrospective analyses have confirmed the advantage of dose escalating conformal RT for patients with localized prostate cancer. Hanks et al. (1996) found that doses ranging from 66–79 Gy in patients treated with 3D-CRT alone showed a clear dose response in intermediate- and high-risk cohorts, along with an acceptable toxicity profile. These results were confirmed in 2002. With a median follow-up of more than 9 years, Gleason score, palpation T-stage, pretreatment PSA levels between 10 and 20 ng/ml, and radiation dose were significant predictors of biochemical control. GI late toxicity grade 2 was the only factor that significantly increased with dose (Hanks et al. 2002). They furthermore demonstrated that patients with a PSA level of 10–20 ng/ml showed a benefit with a radiation dose exceeding 75.6 Gy compared to less than 71.5 Gy (84% vs 19% at 5 years, p=0.0003). Pollack and colleagues demonstrated a significant improvement for intermediate-risk patients with respect to biochemical failure when the radiation dose was escalated to 76 Gy or greater (Pollack et al. 2004). Zelefsky and Eid (1998) published their experience at Memorial Sloan-Kettering Cancer Center in New York. A total of 743 patients with prostate cancer classified as T1c–T3 were treated with 3D-CRT. Doses ranged from 64.8 Gy up to 75.6 Gy and 81 Gy. They found a minimal incidence of severe late complications. Multivariate analysis showed that doses exceeding 75.6 Gy, a history of diabetes mellitus, and acute GI symptoms were independent predictors of grade 2 or higher late toxicity. The phase I/II RTOG 9406 trial is investigating changes in toxicity with increasing radiation doses. In their latest report there is no significant difference in acute and late toxicity up to the highest dose level of 79.2 Gy (Michalski et al. 2005). The vast majority of 3D-CRT studies showed a direct relationship between high doses and no biochemical evidence of disease. In his study using high doses, Zelefsky et al. (2001) found that a radiation dose level exceeding or equal to 75.6 Gy had a significant im-

pact on PSA relapse-free survival, mainly in the intermediate group. Pollack et al. (2000) found that dose escalation (78 Gy vs 70 Gy) benefited mainly patients with initial PSA counts higher than 10 mg/ml. Updated data continued to indicate that improvement in freedom from failure is most significant for patients with intermediate disease. It is noteworthy that the role of dose escalation remains undefined for low- and high-risk patients. For the latter group, the combined effects of dose escalation, pelvic radiation, and adjuvant hormonal±chemotherapy are currently under investigation.

The step-by-step process of 3D-CRT is depicted in Table 11.2. Generally, the prescription isodose (100%) covers the PTV with an acceptable under- and over-dosage of 5% and 7%, respectively. Specific dose constraints are derived from toxicity studies. Treatment plans should be evaluated with respect to these constraints to prevent increasing rates of late toxicities. The dose to 25% of the rectum, for instance, should be limited to 70 Gy to prevent rectal bleeding. Maximal dose to the femoral head is limited to less than 60 Gy; maximum dose to the large bowel is less than 60 Gy; maximal dose limit to the small bowel should be kept below 50 Gy (Michalski et al. 2000; Blanco and Michalski 2003).

Sequelae of Conventional External Beam Radiation Therapy

External beam RT is generally well-tolerated; the most common side effects are grades 1–2 acute rectal morbidity: discomfort, tenesmus, diarrhea, and urinary symptoms (frequency, dysuria, urgency, nocturia) requiring conservative medication. Serious persisting complications that require corrective surgical intervention are rare. Late chronic urinary sequelae (cystitis, hematuria, urethral stricture, bladder contracture) or chronic intestinal sequelae (rectal bleeding, chronic diarrhea, perineal pain, proctitis, fistulas, rectal/anal stricture, rectal wall ulcer) have been described in 1%–3% of cases. Less than 1% of treated patients demonstrated bowel obstruction or perforation. Most complications occur in the first 3–4 years after treatment, and the rate of fatal complications is about 0.2%. The risk of

Table 11.2 Process of 3D-CRT

i	Patient positioning and immobilization (i.e., specific mold)
ii	Supine position. Semi-filled bladder and empty rectum
iii	Establishing patient reference marks system
iv	Set-up and simulation
v	Acquisition/input CT (MRI or other imaging data) into 3D radiation therapy treatment planning system
vi	Anatomy definition; definition of volumes/surfaces of organs at risk, target volume (e.g., rectum contoured from the anal region to the level of the inferior border of the sacroiliac joint)
vii	Dose prescription for the PTV and dose tolerance for the organs at risk. Dose specification (ICRU 50 Report)—the PTV should be covered by 95% isodose
viii	Determination of beam arrangement, field shape (blocks, multileaf collimation), beam modifiers, beam weighting
ix	Generating digitally reconstructed radiographs
x	Plan evaluation
xi	Dose-volume histogram analysis and estimation of normal tissue complication probability (NTCP) and tumor control probability (TCP)
xii	Plan review and documentation (before implementation)
xiii	Implementation
xiv	Verification (monitoring treatment alignment, at least weekly port films or electronic portal imaging)

complications is increased when doses exceed 70 Gy. The risk of rectal or urinary bladder toxicity has been correlated with the volume of the anterior rectal wall or urinary bladder exposed to the high dose (Leibel et al. 1984; Hanks et al. 1995).

Liu et al. (1997) reported low acute GI and genitourinary toxicities in elderly (>70 years of age) patients who were treated by conventional whole pelvic irradiation (total dose 45 Gy), followed by a cone-down and a final boost, to a total dose of 72 Gy. Comorbidities, in decreasing order of frequency, such as hypertension, hemorrhoids, diabetes mellitus, cardiovascular disease, diverticulitis/diverticulosis, and Crohn's disease, were associated with a higher rate of GI toxicity.

Late Sequelae of High-Dose 3D Conformal Radiation Therapy

Rectal Toxicity

There is a significant correlation between the percentage of the rectum treated to 70 Gy or higher and the likelihood of late rectal toxicity (bleeding, rectal wall ulcer, severe diarrhea, incontinence). In the dose volume histogram studies described by Storey et al. (2000), patients with more than 25% of the rectal wall treated to 70 Gy or a higher dose had a 37% risk of grade 2 rectal toxicity compared to 13% in patients who had less than 25% of the rectal wall exposed to this dose. Michalski et al. (2000) found that the relative risk of developing a late bowel complication increased if the total rectal volume on the planning CT exceeded 100 cc.

On the other hand, Zelefsky et al. (1998, 1999) found a much lower incidence of grade 2 or 3 late toxicities in their series. Their multivariate analysis identified doses at 75.6 Gy or higher, a history of diabetes mellitus, and the presence of acute GI symptoms during treatment as independent predictors of grade 2 or higher late GI toxicity. In their dose-escalation modality for patients treated to a dose of 81 Gy, a separate boost plan was initiated after 72 Gy, which blocked the anterior rectal wall in all fields. Other authors (Roeske et al. 1995; Zelefsky et al. 1999) used tighter PTV margins at the prostate-rectal interface or recommended the addition of rectal shielding or the routine use of the prone position in an attempt to reduce the rectal volume included in the irradiated field.

Identifying diabetes mellitus as an independent predicting factor for late grade 2 proctitis after 3D-CRT supports the notion that radiation-induced proctitis is an ischemic phenomenon that affects the rectal mucosa due to ischemic events in the microvascular system.

Bladder Toxicity

In the preliminary report of toxicity encountered in the 3DOG/RT0G 9406 study, Michalski et al. (2000) described two major predicting factors for acute bladder toxicity: more than 30% of the bladder receiving doses of 65 Gy or higher and neoadjuvant hormonal treatment (because of rapid volume shrinkage and more normal tissue exposed to irradiation). In addition, the relative risk of developing late bladder complications (bleeding, strictures) also increased as the percentage of the bladder receiving 65 Gy or more of radiation increased. Zelefsky et al. (2001, 2002) used a dose volume histogram to ensure that no more than 50% of the bladder wall received a maximum dose of 75.6 Gy. They also found that prior transurethral resection of the prostate (TURP) did not increase the incidence of late grade 2 urinary complications. However, Sandhu et al. (2000) found a 4% incidence of stricture development after 3D-CRT treatment in patients who previously had undergone TURP.

Potency

Potency was defined as the ability to achieve erectile function adequate for penetration. The rates of erectile dysfunction after external beam RT range from 6% to 84%. With a median follow-up of 34 months, Mantz et al. (1997) found that actuarial potency rates at 1, 20, and 60 months were 96%, 75% and 53%, respectively. Zelefsky et al. (1998, 1999, 2002) reported that 39% of their pre-treatment potent patients became impotent, and the 5-year actuarial risk of potency loss was

60%. Multivariate analysis demonstrated that the most significant predictors of impotence were doses exceeding or equal to 75.6 Gy, followed by androgen deprivation treatment, while younger age or prior history of TURP were not identified as predictors. There are other causative factors for erectile dysfunction that may be present in this aging population (ischemic diseases, diabetes mellitus, high blood pressure), which may add to an accelerated deterioration of erectile function (Zelefsky et al. 1998).

Guidelines for Treatment Planning and Set-Up

The standard terms recommended by the ICRU (ICRU 50) for defining target volumes during treatment planning appear in Table 11.1.

Androgen Deprivation Therapy as an Adjunct to Radiation Therapy

It has been postulated that the biological activity of prostate-specific hormonal treatment may lead to various classes of molecular effects when combined with RT and may rapidly accelerate tumor destruction.

Androgen deprivation results in significant tumor volume reduction, enhancing response by decreasing the total number of viable clonogenic cells or by improving blood flow, with a decrease in tumor cell hypoxia, rendering the remaining cell more sensitive to RT. Androgen deprivation can eradicate microscopic tumor deposits that lie outside EBRT portals. Androgen-dependent cytoreduction results from a triggered, irreversible, cascade response to a variety of agents leading to programmed cell death (apoptosis). RT, through DNA damage, may lead to alternative pathways for apoptosis that might have an additive effect (Joon et al. 1997; Lawton 2003).

The use of endocrine therapy in conjunction with EBRT has been explored in two main directions: as neoadjuvant cytoreductive therapy in patients with bulky, locally advanced (including pelvic lymphadenopathy) prostate cancer or as adjuvant therapy with EBRT in patients with a high risk for occult metastatic disease [high PSA and Gleason score levels; early (T1, T2) grade 3 tumors (high-grade, poorly differentiated carcinoma)].

Several prospective, randomized trials of neoadjuvant androgen deprivation therapy (ADT) strongly support this approach. In most studies, the neoadjuvant approach has consisted of several months of ADT with the luteinizing hormone-releasing hormone (LHRH)-agonist goserelin acetate (Zoladex, 3.6 mg subcutaneously every 4 weeks); in some studies, flutamide (Eulexin) 250 mg po three times daily, was also given. All patients received pelvic irradiation ranging from 45 to 50 Gy and an additional prostate boost of 20–25 Gy (Pilepich et al. 1997; Lawton et al. 2001).

The majority of phase III randomized trials comparing EBRT alone to EBRT with neoadjuvant ADT or neoadjuvant and concurrent ADT demonstrated the benefit of the addition of ADT. All these studies demonstrated greater local control, disease-free survival, and overall survival than with EBRT alone (Hanks et al. 2003; Roach et al. 2003).

The Radiation Therapy Oncology Group (RTOG 8610) (Pilepich et al. 2001) report was the landmark study that demonstrated a survival benefit with neoadjuvant (2 months prior to RT) and concurrent hormonal therapy combined with RT, as compared to RT alone. This study demonstrated that the benefits of short-term hormonal therapy consisting of combined androgen suppression therapy were limited to patients with bulky disease and Gleason scores of 2–6. The study also showed a decreasing incidence of distant failure, longer biochemical, and actuarial disease-free survival. Although there was no significant difference in overall survival in the two groups, there was a highly significant improvement in survival in patients with a Gleason score 2–6 compared to higher (7–10) Gleason score patients. Treatment was well-tolerated, no grade 4–5 toxicity from RT was observed, and preservation of sexual potency was similar for both treatment groups.

Further support for the use of adjuvant hormone manipulation came from the EORTC study (Bolla et al. 1997) on a group of 415 patients with locally advanced prostate cancer. Eligible patients were those whose disease was T1T2 N0,

MX, with World Health Organization grade 3 histology or T3T4 disease without any radiological or surgical evidence of involved lymph nodes. Patients received treatment to the whole pelvis using a 4-field technique (L5-S1 upper border, ischial tuberosities lower border, 1 cm beyond the maximum width of the bony pelvis laterally) to a total dose of 50 Gy, with a 20 Gy boost to the prostate plus seminal vesicles. Hormonal therapy consisted of goserelin starting on the first day of RT and continuing for 3 years, along with the steroidal antiandrogen cyproterone acetate 150 mg po for 1 month.

With a median follow-up of 45 months, the overall survival at 5 years for the combined modality group was 79% vs 62% (p=0.001) for the RT alone group. The authors also noted statistically improved disease-free survival (85% vs 48%, p<0.001) and local control. An update of this trial (Bolla et al. 2002) showed there to be continued statistically significant improvement in survival (78% vs 62%, p=0.0002) and clinical disease-free survival (74% vs 62%, p=0.0001) with a median follow-up of 66 months and a 5-year specific survival of 94% vs 79%. Another EORTC study conducted by Bolla et al. compared EBRT in combination with 3-year LHRH-agonist treatment vs EBRT and 6 months of hormonal therapy. The results of this study are not yet available, as follow-up has been too short.

The RTOG protocol 9413 (Roach et al. 2003a) addressed the timing of hormonal manipulation. Eligible patients were those with adenocarcinoma of the prostate whose estimated risk of pelvic lymph node involvement was greater than 15% or patients with T2C–T4 and a Gleason score of 6 or higher. Randomized patients had a mean PSA of 22.8 mg/ml, 67% had T2C–T4 clinically staged disease, and 72% had a Gleason score of 7–10. Patients were randomized between whole pelvis RT plus a boost to the prostate vs RT to the prostate only, and between neoadjuvant hormone manipulation (LHRH agonist plus an antiandrogen) for 2 months before and during RT or the same hormonal manipulation for 4 months after RT. With a median follow-up of 59.3 months, patients treated with neoadjuvant hormonal manipulation and radiation had a 4-year progression-free survival of 53% vs 48% for the adjuvant hormone arm (p=0.33). Patients treated with whole pelvis RT plus boost had a 4-year progression-free survival rate of 56% vs 46% for the prostate-only RT (p=0.014). An improved progression-free survival rate was also noted in the whole pelvis RT plus neoadjuvant hormonal treatment group, compared to other arms of the study. Overall survival was not statistically different for any of the arms.

The update of the RTOG study 9413 (Roach 2003) proved that the intermediate risk subpopulation (T3, Gleason score 6, or T1–2, Gleason score 7) will benefit from neoadjuvant concurrent hormone treatment in combination with EBRT, while high-risk patients (bulky disease, Gleason score 7 or higher, PSA >30 mg/ml) require the addition of long-term adjuvant hormone therapy.

D'Amico et al. (2004), from the Brigham and Women's Hospital, conducted a phase III trial evaluating the role of ADT in clinically localized prostate cancer. They introduced neoadjuvant/concurrent androgen deprivation plus EBRT and continued ADT for 6 months vs EBRT alone. With a follow-up of 4.5 years, they found a significantly improved 5-year overall survival (88% vs 78%), 5-year cause-specific survival (100% vs 94%), and 5-year biochemical NED (79% vs 55%) in favor of the combined modality group, especially in the intermediate-risk patients.

In conclusion, based on the extensive scientific work that has been carried out regarding the potential benefit of neoadjuvant hormonal manipulation and RT for patients with prostate carcinoma, it is clear that there are benefits to the combination therapy. Both the potential for cytoreduction as well as potential control of micrometastatic disease have been documented. Patients with nonmetastatic, intermediate-risk disease represent a group that benefits from neoadjuvant and concurrent hormonal cytoreduction for at least 3–4 months. The addition of short-term androgen deprivation confers no benefit for high-risk patients who should receive neoadjuvant and concurrent androgen deprivation and long-term adjuvant treatment (for at least 2 years).

Several groups have prospectively evaluated the role of adjuvant ADT in combination with EBRT. The RTOG described the results of RTOG 85-31 (Lawton et al. 2001) in determining the

advantage of androgen deprivation as adjunctive therapy following standard EBRT in locally advanced prostate cancer. A total of 977 patients were randomized to receive radiation only (androgen deprivation started at disease relapse) or radiation plus adjuvant goserelin. There was a statistically significant decrease in local and distant failure rates in favor of the combination arm. The local failure rate at 8 years was 23% for the combination-therapy arm and 37% for the radiation-alone arm ($p<0.0001$). The distant metastasis rate in the combination arm was 27% and 37% in the radiation-alone arm ($p<0.0001$). The disease-free survival favored the immediate androgen deprivation arm, but overall survival was not statistically different between the two groups. These results were confirmed by Pilepich et al. (2005).

An evidence-based oncology study (Pilepich et al. 2005; Roach 2005) summarized the results of several American hospitals in the treatment of poor prognosis prostate cancer patients, including T1 and T2 stage patients with radiographic or histological evidence of lymphadenopathy, treated with adjuvant androgen suppression with radiotherapy or radiotherapy alone (minimal target dose 60–70 Gy, 1.8–2 Gy daily fractions), followed by LHRH-agonist (goserelin 3.6 mg subcutaneously) at relapse. Participants in the adjuvant goserelin arm received goserelin for the last week of radiotherapy until disease progression. It was demonstrated that radiotherapy plus adjuvant goserelin significantly and statistically increased the 10-year absolute disease-free survival (49% vs 39%; $p=0.002$), 10-year disease-free survival (37% vs 23%; $p<0.0001$), reduced 10-year disease specific mortality (16% vs 22%; $p=0.005$), and decreased both the 10-year local failure rate (23% vs 38%; $p<0.0001$) and 10-year incidence of distant metastases (24% vs 39%; $p<0.0001$) compared to radiotherapy alone followed by goserelin at relapse. Several important issues remain unresolved about:

1. What is the best use of adjuvant hormonal therapy in higher risk patients, e.g., subpopulations of high-risk patients who do not need long-term adjuvant hormone therapy or subset of intermediate-risk patients for whom long-term adjuvant hormonal therapy should be considered?
2. What about considering neoadjuvant hormonal therapy in addition to adjuvant hormonal therapy?
3. Most importantly, what is the optimum duration of adjuvant hormone therapy use?

The long-term findings of RTOG 8513 have answered some questions but many more remain to be addressed.

Radiation Therapy Following Radical Prostatectomy

Radical prostatectomy is widely used as the primary treatment for clinically localized prostate cancer. The role of postoperative RT is still controversial. Some patients with pathological T2N0 and clear surgical margins enjoy long-term progression-free survival, ranging from 84% to 98%, without a need for RT (Kupelian et al. 1996). On the other hand, if disease extends beyond the prostatic capsule (pT3) or is present at the surgical margins, disease-free survival rates are lower because of the subclinical disease burden. For these high-risk patients, RT plays an important role (Valicenti et al. 2003).

Postoperative RT can be delivered in an adjuvant setting or as a salvage modality in the setting of a rising PSA. In the EORTC Trial 22911, Collette et al. (2005) demonstrated that immediate postoperative RT significantly improved biochemical disease-free survival compared to a wait-and-see policy until relapse or pathological risk factors appeared in pT2–3 patients after radical prostatectomy. Their risk model revealed that positive margins, seminal vesicle invasion, World Health Organization differentiation grade, preoperative PSA (>10–20 ng/ml), and a postoperative (3 weeks) level of greater than 0.2 ng/ml were independent factors for biochemical disease-free survival in a wait-and-see group. In the majority of studies, the most consistent predicting factors for disease recurrence and overall survival were penetration of the prostatic capsule, the presence of tumor at the inked surgical margins, lymph node involvement, preoperative PSA level, and surgical Gleason score. According to D'Amico et al. (1998), who used multivariate analysis, a pretreatment PSA of 10 mg/ml or

higher and a Gleason score of 7 or higher were adverse prognostic factors when biochemical control was used as an endpoint. These high-risk patients may benefit from the use of RT.

The main goal of adjuvant RT is the eradication of microscopic residual tumor in the periprostatic tissues or adjacent pelvic lymph nodes. Using total doses in the range of 55–65 Gy showed a 55% and 48% clinical or biochemical disease-free interval at 10 and 15 years, respectively, compared with 37% and 33%, respectively, for radical prostatectomy alone. Paulson et al. (1990) and Anscher et al. (1995) showed that patients receiving postoperative RT have a marked reduction in mortality, significantly better 10-year disease-free survival rates and fewer incidences of distant metastatic disease in T3–T4 disease. In their randomized study, Leibovich et al. (2000) demonstrated that patients with pT2N0 disease and a single positive margin, who received postoperative RT (without androgen deprivation treatment) had higher 5-year clinical and biochemical disease-free survival rates compared to patients not receiving RT (88% vs 59%). None of their patients treated with postoperative irradiation had local or distant recurrence. Most beneficial effects of irradiation were evident in patients with positive margins either at the base or apex.

Irradiation techniques include the pelvis up to the bifurcation of the common iliac vessels with the "box" technique (antero-posterior/postero-anterior and right/left lateral field) to a dose of 45–50 Gy (1.8 Gy per fraction). The prostate bed and margins should then be supplemented with the same box technique or with a bilateral 120° arc rotation with a boost of 15–20 Gy in 2 Gy daily fractions. These doses are effective when postoperative PSA levels are less than 2 ng/ml. Higher PSA levels are less likely to benefit from higher irradiation doses alone and should be considered for additional hormonal treatment. The most effective total dose is controversial. Median doses reported for both salvage and adjuvant irradiation are between 60 Gy and 64 Gy; according to Valicenti et al. (1998), 64.8 Gy or above should be used for appropriately selected patients after radical prostatectomy.

Bolla et al. (EORTC Trial 22911) (2005) performed a randomized controlled trial to compare RP alone to RP patients irradiated in an immediate setting for pT3 or positive surgical margins patients. Patients were irradiated to a dose of 50 Gy/25 fractions/5 weeks (volume encompassing surgical limits from the seminal vesicles to the apex with margins to include subclinical disease in the periprostatic area) with a 10 Gy boost in 5 fractions over a week to reduced volume circumscribing the previous landmarks of the prostate with reduced security margins. Biochemical progression was defined as an increase of more than 0.2 μg/l over the lowest postoperative value measured on three subsequent occasions. Biochemical disease-free survival was significantly improved in the irradiated group (74% vs 52.6%). Clinical progression-free survival was also improved in the irradiated group. Severe late toxic effects (grade 3 or higher) were rare but the side effects were more frequent in the irradiated group. The EORTC will soon activate a trial in which all pT3 patients will receive immediate irradiation following RP. Patients will be randomized between EBRT alone vs EBRT combined with hormonal therapy.

The RTOG recently completed accrual to a phase 3 trial (RTOG 96-01), comparing salvage RT alone vs salvage RT plus 2 years of androgen deprivation treatment in pT2–T3 patients and/or positive surgical margins. These patients, who must have had a rising PSA from 0.2 ng/ml to 4 ng/ml, were randomized to receive hormonal monotherapy (Casodex, 150 mg daily) or a placebo for 2 years. All patients receive irradiation to the prostatic bed to a dose of 64.8 Gy. The RTOG is also carrying out a study to evaluate the value of adjuvant therapy in high-risk prostatectomy patients prior to biochemical progression. RTOG P-0011 is a randomized study to test whether adding androgen deprivation to RT (total dose of 63–66 Gy) leads to a better outcome than each modality used separately. Poor-risk factors were defined as capsular penetration and surgical Gleason scores of 7 or higher, positive surgical margins, or seminal vesicle invasion. Eligible patients must have had a postoperative PSA below 0.2 ng/ml before randomization. Endpoints included overall survival, disease-free survival, freedom from distant metastases, and biochemical disease-free failure.

Most side effects are mild or moderate in severity: urinary stress incontinence, cystitis, and proctitis, which can be treated successfully with conservative management. Urethral stricture was observed in approximately 5%–10% of these patients. Incidence of impotency (erectile dysfunction) increased even in patients who retained potency after nerve-sparing radical prostatectomy.

In conclusion, determining postoperative PSA levels might serve as the best indicator for irradiation in low-risk patients. Patients with intermediate-risk disease can benefit from pelvic and prostatic bed irradiation to a total dose of 55–60 Gy. Replacing conventional external irradiation with conformal radiotherapy can promote dose escalation up to 64–66 Gy. Appropriate patients for immediate irradiation are those with high-risk factors (positive margins, seminal vesicle invasion, Gleason score>6 or PSA>20 ng/ml). On the other hand, Hayes and Pollack (2005) established well-defined prognostic factors that should be used to select patients appropriately for salvage RT: a positive margin, no seminal vesicle invasion, PSA doubling time exceeding 10 months, pre-radiation PSA level of less than 1.0 ng/ml, and a post-surgical Gleason score of less than 7. All these factors suggest possible late local or locoregional recurrence without metastatic disease.

Hormone-Induced Gynecomastia Prophylaxis

Gynecomastia occurs in about 90% of patients receiving estrogens or flutamide, but only in 8% of patients undergoing orchiectomy. In patients treated with combined androgen blockade on high-dose antiandrogens, some 3%–15% developed gynecomastia (Kirschenbaum 1995). Others (Di Lorenzo et al. 2005; Kuten et al. 2004) described gynecomastia with breast tenderness in 61%–85% of patients treated with bicalutamide (Casodex) monotherapy vs 19%–22% in patients treated with LHRH agonist goserelin and the antiandrogen flutamide. Breast tenderness alone was noted especially in the bicalutamide group (13.1% vs 4.4%).

Prophylactic RT should be completed 2–3 days before the initiation of hormone therapy. RT can be given with orthovoltage irradiation: appositional 9- to 12-MeV electrons or Co-60 or 4 MV photon beams (tangential portals); or a single dose of 9 Gy or a total dose of 12–15 Gy in 4–5 Gy fractions. With these methods, gynecomastia can be prevented in up to 50% of patients (Tyrrell et al. 2004; Kuten et al. 2004). Painful gynecomastia developing after estrogen or nonsteroidal antiandrogen therapy could be relieved with RT to a total dose of 20 Gy (5 fractions), 40 Gy (20 fractions), or 8–15 Gy (single fraction). In these cases, pain relief was obtained for an average of 3.6 months (Chou et al. 1988; Tyrrell et al. 2004).

Some recent studies suggest that adding tamoxifen (an antiestrogen) to the hormonal treatment might prevent/reduce gynecomastia or alleviate pain in a significant number of patients (Di Lorenzo et al. 2005).

History of Brachytherapy in Prostate Cancer

Implantation techniques have evolved from intraurethral insertion of temporary radioactive sources in the early decades of the last century. In 1917, Pasteau described the use of interstitial radium (Pasteau and Degrais 1917) and, in 1917, Barringer combined radioactive radon (222Rn) as permanent interstitial therapy with external radiation. In 1965, radioactive iodine (125I) was introduced for permanent implantation (Hilaris et al. 1977). Flocks et al. (1952) described the direct insertions of radioactive colloidal gold (198Au) into the prostate or the tumor bed with good results. During the early 1970s and early 1980s, retropubic implants with 125I became popular but this method was later partly abandoned in favor of transperineal methods. Prostate brachytherapy entered the modern era with a preliminary report in 1983 by Holm et al. (1983) who described the use of transrectal ultrasonography to guide transperineal insertion of needles into the prostate to permanently deposit 125I sources into the gland.

In clinical practice, brachytherapy for prostate cancer can be performed either by temporary or permanent implants. Temporary implants are small radioactive sources surgically implanted

directly into the prostate or tumor bed. Most common is iridium-192 (192Ir) which has a 73.8-day half-life and a dominated β-decay. Its photon spectrum includes characteristic X-rays and gamma rays ranging from 63 KeV to 1.4 MeV. Its average energy is 0.397 MeV. It is used in low- and high-dose rate implants (Nag et al. 1999).

Permanent implantation of iodine-125 (125I) has been used for 35 years, and palladium-103 (103Pd) has been available for more than a decade. 125I is available in the form of seeds. Its half-life is 59.6 days and its average energy is 0.028 MeV. It decays by electron capture producing a cascade of 27- to 32-KeV characteristic X-rays. It is actually an X-ray emitter, and it has therapeutic advantage in slow-growing prostate carcinoma (Gleason score 2–6). 103Pd has a half-life of 17 days. Its average energy is 0.020 MeV (X-rays) and is presented in the form of seeds. Due to its short half-life, 103Pd should theoretically show better cell kill in rapidly proliferating tumors (Gleason score>6) (Nag et al. 1999; Ponholzer et al. 2005). Generally, despite differences in physical properties of these two isotopes, no differences have been established in clinical outcome (e.g., effectiveness or complications).

Necessary investigational steps before conduction of temporary brachytherapy include history of pelvic surgeries, recurrent urinary tract infections, and transurethral procedures. Generally, the volume of the gland should be smaller than 60 cm^3 and be more than 5 mm from the rectal mucosa. Ultrasound should assess initial prostate volume. Urodynamic studies to measure maximum urinary flow rate and postvoidal residual urine are vital, especially in patients with lower urinary tract infections. The symptom score before treatment is an important predictor of urinary morbidity after treatment.

Systemic staging, initial PSA level, pathology, and Gleason score are mandatory before any decision is made. Transrectal ultrasound should image the exact zonal anatomy within the gland, evaluate extracapsular extension, and detect pubic arch interference. CT scan, MRI with rectal coil, and surgical lymph node staging are not mandatory (Kovacs et al. 2005).

Brachytherapy can be used as monotherapy, mainly for low-risk patients with smaller prostate volumes. The 192Ir dosage is as high as 60 Gy. Combined EBRT, followed by a temporary brachytherapy (BT) boost, is effective in low-risk patients (T2a, initial PSA <10 ng/ml, Gleason score<6), but these patients also do well with permanent BT alone. The greatest advantage of EBRT plus temporary BT (total dose of 20–25 Gy) seems to be in intermediate- and high-risk patients (T1b–T3b or PSA>10 ng/ml or Gleason>6) (Borghede et al. 1997; Kovacs et al. 2005).

Hormonal treatment has a role in reducing prostate volume before treatment ("downsizing"), due to reduced benign prostate hyperplasia (BPH) of the gland. The role of a short course of neo-adjuvant hormonal therapy combined with EBRT and temporary BT is under investigation. So far, there is no clearly significant advantage of short hormonal treatment observed in dose escalating studies (total biologic effective dose >70 Gy) with regard to long-term results (Kovacs et al. 2005). On the other hand, Stock et al. (2004) demonstrated that trimodality therapy (androgen deprivation, brachytherapy and external beam RT) for high-risk patients (Gleason scores 7–10, PSA levels >10–>20 ng/ml, T2b–T3) resulted in excellent biochemical and pathologically confirmed local control.

Implantation is almost always performed as out-patient surgery under general or spinal anesthesia. A needle guide template is mounted against the perineum. With the patient in the lithotomy position, the template acts as a guide for needle placement. This allows for control over the entire prostate target volume and specification of source placement at any point within the gland. The position of the needle is checked with transrectal ultrasound and/or fluoroscopy.

If the prostate is imaged as a 3D ellipsoid within the pelvis, any point within the prostate can be given a unique set of coordinates (*x*-, *y*-, and *z*-axes). The images of the prostate are used to calculate the approximate total radiation dose needed for target coverage, by using nomograms based on the orthogonal dimension of the prostate. Images are taken along the prostate at 5 mm intervals.

Modern treatment planning computers can use this planning target volume to develop a pattern for the most ideal radioactive source placement that will deliver the desired (prescribed)

dose. The three orthogonal dimensions are used to calculate the total activity needed to achieve a minimal peripheral dose (MPD). They can generate dose-volume histograms for target volume, rectum, and urethra. If areas are found to be underdosed or higher urethral doses are observed on the images, appropriate adjustments are made. High central doses may lead to urethral damage. Postoperative dosimetry must be performed to assess the adequacy of implantation and to determine the actual dose received by the prostate and normal surrounding tissues. The planning and execution of the implant is evaluated using 3D CT-based reconstruction of the prostate to optimally assess the dose coverage of the gland.

For the treating brachytherapist, there are some guidelines and definitions which are of crucial importance for successful treatment of the tumor. The MPD is a dose enclosing a volume equal to the target volume, indicating the lowest dose received within the prostate volume. Physically, it is the minimum dose to the periphery of an ellipsoid with the same average dimensions of the prostate. D90 is a dose covering 90% of prostate volume and V100 is the percentage of prostate volume receiving prescription dose. A urethral dose of less than 10 Gy/fraction, a rectal dose less than 6 Gy/fraction, and a dose less than 50 Gy delivered to 50% of the penile bulb are generally tolerable. It is also advisable to define different target areas within the gland as CTV1 (prostate CTV), CTV2 (tumor in the peripheral zone), and CTV3 (visible tumor infiltration areas) (Kovacs et al. 2005).

Because of the low α/β ratio (<2 Gy) of prostate cancer, it might be appropriate to give treatment with a high-fraction size. However, it should be kept in mind that delivering the total dose in a very few high-dose fractions has also radiobiological disadvantages, such as inadequate tumor re-oxygenation and normal tissue damage. On the other side, there are some important advantages of high-dose rate brachytherapy which have gained popularity:

1. As efficacious as standard protraction
2. More convenient for the patient, both in terms of logistics and acute morbidity
3. Less resource-intensive than standard protraction
4. Loss of therapeutic differential between the slow-responding tissue and tumor
5. Less early morbidity
6. Less radiation exposure to personnel

Conformal high-dose rate brachytherapy (C-HDR BT) is an alternative means of precise dose escalation that offers similar tumoricidal effects as 3D conformal EBRT. By placing HDR after-loading needles directly into the prostate gland, a steep dose gradient between the prostate and adjacent normal tissues can be generated that is unaffected by organ motion and edema or treatment set-up uncertainties. The ability to control the amount of time the single radioactive source dwells at each position along the length of each brachytherapy catheter further enhances the conformity of the dose (Kestin et al. 2000).

At the William Beaumont Hospital (Martinez et al. 2002), HDR BT was used to boost patients with locally advanced prostate cancer (>T2b, PSA≥10, Gleason score≥7). External beam RT (pelvic irradiation) amounted to 46 Gy, and 3 HDR implants of 5.5–6.5 Gy each were given, to a total dose of 16.5–19.5 Gy. With a median follow-up of 4.4 years, the biochemical control rate was 74%, with 91.6% overall survival and no chronic grade 3 GI toxicity. Other authors (Vicini et al. 2003) gave, in addition to EBRT, an HDR boost of 20–25 Gy, 6.5 Gy per fraction in 3–4 fractions, to intermediate- and high-risk patients. The low-risk group (T1b–c, T2a, Gleason score≤6, PSA≤10) was boosted with a total dose of 18–24 Gy, 5.5–6 Gy per fraction in 3–4 fractions.

In the William Beaumont and other hospitals' series, patients experienced between 1.5% and 7.4% urethral stricture, 5%–7% moderate frequency/urgency, and 2% severe urgency. There was a very low incidence of chronic grade 3 GI complications, 1.6%–3% rectal bleeding. 1.7% recto-vesicle fistula, and less than 2% rectal wall necrosis.

Permanent brachytherapy offers several practical and theoretical advantages over EBRT in selected patients. Due to the physics of radiation emanation from the implanted radio-isotopes, there is dose escalation within the prostate, with a rapid dose fall in surrounding normal tissues.

125I is given as monotherapy (145 Gy) to patients with stage T1a–2a, Gleason score 2–6, and PSA of less than 10 ng/ml, and as a boost (110 Gy) to EBRT (40–45 Gy) in clinical stage T2b–2c or Gleason score 8–10 or PSA>20 ng/ml.

Exclusion criteria for permanent brachytherapy are: short life expectancy (<5 years); poorly healed TURP defect; distant metastases and unacceptable operative risks. Exclusion criteria for temporary brachytherapy include: volume exceeding 60 cm^3; TURP within 6 months; infiltration of the external sphincter of the bladder neck; significant urinary obstructive symptoms; severe pubic arch interference; rectum–prostate distance on TRUS of less than 5 mm; and lithotomy position not possible or high-risk patients for general anesthesia.

Relative contraindications for brachytherapy are: risk of developing complications or technical difficulties leading to inadequate dose coverage (Anscher et al. 1995); large/prominent median lobes (Ashman et al. 2005); previous pelvic irradiation/multiple pelvic surgeries (Barringer 1917); severe diabetes mellitus (Bayley et al. 2004); previous transurethral resection of prostate (TURP) (Beyer 1999); gland size greater than 60 cc at time of implantation (Beyer 2001); and involved seminal vesicles (Beyer 2003; Nag et al. 1999).

Brachytherapy can also be used for recurrent prostate cancer after RT. Indications include the following parameters: histologically confirmed local recurrence (Anscher et al. 1995); no distant metastases (Ashman et al. 2005); adequate urinary function (Barringer 1917); 5- to 10-year life expectancy (Bayley et al. 2004); prolonged disease-free interval (>2 years) from primary RT (Beyer 1999); long PSA doubling time (>6–9 months) (Beyer 2001); Gleason score of 6 or less and a PSA count below 10 ng/ml at the time of recurrence (Beyer 2003). Grado et al. (1999) implanted a median of 31.76 mCi 125I or 126 mCi 103PD to deliver a median-matched peripheral dose of 160 Gy and 120 Gy, respectively. At 3 and 5 years, the biochemical disease-free survival was 48% and 34%, respectively, for patients who reached a PSA nadir of less than 0.5 after salvage brachytherapy. Urinary complications were observed in 30% of the patients and included urethral strictures requiring TURP (14%), incontinence (6%), hematuria (4%), and dysuria (6%). Rectal ulcers were observed in 4% of patients, and one patient required a colostomy for therapy-resistant proctitis. Using lower doses of 125I and 103PD, Beyer (1999) achieved 53% biochemical disease-free survival and 93% prostate cancer-specific survival at 5 years. PSA level and Gleason score at the time of salvage are the best predictors of outcome. The most likely to respond are patients with PSA counts below 10 ng/ml and a Gleason score of 6 or less.

Some authors reported an increase in the severity and duration of acute morbidity after salvage brachytherapy. However, with the introduction of transperineal ultrasound-guided techniques and the use of lower activity 125I and 103PD sources, the reported risks have diminished. Most side effects include pelvic/penile pain, hematuria, and urinary incontinence. Rectal complications include proctitis and bleeding or necrosis leading to colostomy at rates ranging between 0% and 5%.

Side Effects

Transient urinary morbidity related to radiation-induced urethritis or prostatitis are the most common side effects of brachytherapy. Irritative and obstructive lower urinary tract symptoms may develop over the first few weeks as a result of implant trauma. These side effects are of a temporary nature. In addition to the urethral dose, the presence of obstructive symptoms secondary to preexisting benign prostatic hypertrophy before brachytherapy has been correlated with an increased incidence of acute symptoms, including urinary retention.

Late side effects—such as incontinence, chronic cystitis, urinary retention, dysuria, and frequency and late grade 3 urinary complications—that require medical or surgical intervention may occur in approximately 2%–5% of patients, with stricture reported in 2%–3% of patients. Combined modality (with EBRT) can cause about 20% of patients grade 2 and 8% grade 3 toxicity.

Late rectal complications, including proctitis with diarrhea, perineal pain, tenesmus, or rectal

bleeding may occur in 2%–19% of patients. Isolated cases of rectal fistula formation have been also reported. A combined modality (EBRT and BT) cause about 23% of the patients grade 2 rectal toxicity (Beyer 2001).

Compared to other standard RT modalities, permanent brachytherapy has been reported to give better preservation of potency. However, with a continuous follow-up (>2 years), gradually declining erectile function has been reported. Ponholzer et al. (2005) found, in early prostate cancer patients treated with 103-palladium implantation and using the International Index of Erectile Function-15 (Cappelleri et al. 1999), a high prevalence of preexisting erectile dysfunction among his patients; albeit, 57% of men fully potent or with mild erectile dysfunction before brachytherapy had lost no function 30 months after the therapy. In a multivariate analysis, age, preoperative PSA level, prostate volume, D90, hormonal treatment, diabetes, smoking, or hypertension were not predictive of preserving potency (p>0.05). Zelefsky et al. (2000) reported impotence rates of 21% and 42%, respectively, at 2 and 5 years after transperineal implantation.

The following parameters were generally found to be significant predictors of erectile dysfunction after brachytherapy: D50 to the penile bulb, high dose delivered to the neurovascular bundles, postimplantation prostate CT volume, patient age, vascular disorders, and diabetes mellitus.

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12 Cryoablation and High-Intensity Focused Ultrasound

Chris D'Hont

Recent Results in Cancer Research, Vol. 175

Abstract

The fight against prostate cancer goes beyond radical prostatectomy, radiation therapy, and hormonal therapy. Temperature can also kill cells and proves to be highly successful in this war on prostate cancer. There is no known insensitivity to extremely low or extremely high temperatures.

Targeted CryoAblation of the Prostate

Targeted cryoablation of the prostate (TCAP) [1–12] brings low temperature inside the prostate through transperineal hollow, closed needles (same set-up as in brachytherapy). Everything is controlled by transrectal ultrasound. By sending argon gas through those needles the Thomson-Joule effect produces very low freezing temperatures of 180 °C or lower at the tip of each needle, resulting in freezing the surrounding tissue. Conic ice balls (1–2 cm) arise at the tip of each needle, and by confluencing these ice balls the entire gland—or part of the gland—can be frozen. The critical freezing point to kill the cells is at −40 °C and should be reached all through the capsula of the prostate for sufficient tumor control. The temperature gradient from −180 °C in the center of each ice ball to 0 °C at its periphery and the warming up of the frozen tissue by sending extra blood supply from the periphery into the prostate (normal protective body reaction against freezing) may compromise killing temperatures all through the capsula. Therefore temperature monitoring during freezing is absolutely mandatory for efficient tumor kill. A double freeze (argon gas)/thaw (helium gas) cycle is usually recommended, and pullback of the probes to treat the apical area is usually necessary with two extra freezing cycles. The limitations are the size of the prostate and the high cost of the single-use material. Nerve sparing procedures are possible in highly selected cases but may result in lower tumor control [9, 10]. The treatment can be repeated in case of local recurrence, TCAP can also be done after irradiation failure [3, 7, 12]. A urethral warming catheter seems to be absolutely necessary to protect the urethra. Impotence rates are very high, incontinence rates similar to those after radical prostatectomy, and rectal fistula are seen because of freezing the rectal wall (hence, again, we emphasize the importance of temperature monitoring—since shape of the ice ball is opposite to the shape of the posterior prostate capsula). Patients can leave the hospital within 24 h.

Main complications are perineal edema and numbness, sloughing, and impotence [5, 6, 8–11]. Within 3–6 months the necrotic tissue is transformed into firm fibrotic tissue around a normal urethra, and the size of the prostate usually shrinks to less than 10 cc. Endocare and Galil Medical are the main suppliers, and all machines have a similar approach in that the use of liquid nitrogen has been abandoned. Importantly, the learning curve is greater than 50 cases, and knowledge of transrectal ultrasound is mandatory. TCAP is a minimally invasive treatment, but still it:

1. Requires multiple punctures of the perineum (cryoprobes) with a risk of bleeding and cracking of the prostate during the freezing cycle
2. Allows for no exact freezing control
3. Will require posttreatment catheterization for 2–3 weeks.

TCA can also be used for liver tumors and kidney tumors by introducing the freezing needle directly into the tumor tissue (via sur-

gery). Other variations and applications of cryoablation (with skin, lung tumors) are well known.

High-Intensity Focused Ultrasound

High-Intensity focused ultrasound (HIFU) [13–45] kills the tumor cells by heat [14, 15, 21, 44]. By focusing ultrasound waves through the rectal wall a heat wave arises from the buildup of acoustical pressure at the focus point coming down toward the rectal antenna, which destroys the prostate tissue in a very tiny and controllable area at temperatures of 85°C–95°C. This can be compared to the shockwave in ESWL, focusing energy and destroying prostate tissue without damaging the interlaying rectal wall. With Ablatherm this heat wave kills by thermonecrosis and controlled cavitation, and the single lesion expands from the anterior to the posterior wall of the prostate with a variable focus distance of 1.9–2.4 cm and a with of 1.7–2 mm (resulting in a killing zone of 20–30 by 2 mm per lesion). The safety distance from the rectal wall can also be adjusted between 3 and 6 mm, and the entire treatment is fully automated [15, 18–21, 25, 40, 42]. With the Sonablate the lesions are only 1 cm in length and killing results from thermonecrosis alone. Manual repositioning of the rectal antenna is necessary with Sonablate [27, 32, 46]. By reproducing these lesions, one next to the other in one layer and then again in the next layer, the urologist can truly shape the killing area to the exact contour of the prostate or of the target area. Theoretically a more focused approach becomes possible—a nerve-sparing procedure resulting in high potency preservation rates. Comorbidity is extremely low. HIFU can be done after a transurethral resection of the prostate (TURP), in case of local recurrence after any former therapy [radical prostatectomy (RP), external beam radiotherapy (EBRT), brachytherapy, cryotherapy, etc.] and patients can also be safely retreated with HIFU in case of local recurrence. The rectal wall is protected by a continuous cooling (5°C), and a specific software design in the Ablatherm system guarantees safe and efficient, automated treatment under real-time powerful transrectal ultrasound control.

The advantages of HIFU are the minimal invasive approach, relatively low cost of the single-use material (compared to TCAP and brachytherapy), excellent results on tumor control [low and stable prostate-specific antigen (PSA) counts and negative biopsy rates while preserving quality of life (QoL)], and the excellent shaping possibilities of following the exact shape of the prostate, even at the level of the rectal wall (resulting in very low comorbidity and extremely rare fistula rates). Potency preservation is high and incontinence rates are extremely low. Specific software programs guarantee safe re-treatment after irradiation (EBRT or brachytherapy). Patients leave the hospital within 24 h after treatment and can get back to normal activity very shortly after. Within 3–6 months the necrotic tissue is transformed into firm fibrotic tissue around a normal urethra and the size of the prostate usually shrinks to less than 5–10 cc. A short learning curve (5–10 cases) is involved, and knowledge of transrectal ultrasound is mandatory. HIFU is done by a truly minimal invasive transrectal approach (no transperineal needles). Practicioners get precise lesion control, and there is a limited need for post-HIFU catheterization 3–10 days.

Immune Response?

There are indications that killing prostate cells by TCAP or by HIFU produces an immune (T cell stimulation) reaction that in some reported cases seems to have led to disappearance of metastases [36]. These, however, are case reports and no scientific studies have confirmed these findings so far.

Long-Term Results?

Results over more than 10 years have been published on cryotherapy from a limited number of centers. There is a difference in outcome between centers that systematically apply TCAP under temperature monitoring (better results by expanding the ice ball until killing temperatures are reached throughout the target area) and centers that rely only on the transrectal ultrasound im-

age of the posterior wall of the ice ball (shadowing the rest of the prostate). The results are very operator-dependent [5, 6, 8–11].

Only two centers (Lyon and Munich) have results on Ablatherm-HIFU covering more than 10 years (newer technology), but they confirm the durability of the short-term results over a long follow-up period. Several short-term results have been reported. They generally conform across all the different centers (>65 so far), showing the procedure to be less operator-dependent. Lots of very promising results are being published and have been presented at international urology meetings from many new centers with follow-ups dating back up to 5 years [19–21, 25, 28–35, 38–46].

Both TCAP and HIFU, however, are very promising and show advantages over radiotherapy and brachytherapy. Both can be repeated in cases of local recurrence, are possible after irradiation failure, show very promising results as primary therapy in patients who cannot or do not want to have radical surgery, and show good results in low- and high-risk PCA patients and in all Gleason scores.

Ablatherm-HIFU has the advantage of being less operator dependent, more automated, and less invasive and safer for the patient (specific software programs for specific conditions, fully automated computer safety control of all parameters prior to each individual lesion).

Further clinical follow-up will have to confirm these promising results and define the definite place of these new technologies in prostate cancer managing.

Results

Results TCAP

Although different reports highlight different study interests and outcomes, the overall results of TCAP seem to be very similar to classical alternatives for radical prostatectomy (Tables 12.1 and 12.2).

A quick lowering of the PSA to reach nadir within 1–3 months, with fairy long-term results, seems to be the overall outcome of TCAP. DFS rates around 65%.

Results HIFU

A Multicenter European study shows very high negative biopsy rate of more than 85% after a single HIFU treatment. The rate climbs to more than 95% with a second HIFU treatment, which is indicated for a proven local recurrence (Table 12.3) [31].

Multiple single center reports show similar results on disease-free survival and success rates, a quick lowering of the PSA with very low nadir PSA usually reached within 1–3 months after HIFU treatment, and negative biopsy rates of 80%–93% with stable DFSR (Table 12.4).

PSA stabilizes around the nadir value of less than 0.5 ng/ml for more than 75% of HIFU patients for the entire follow-up period (Tables 12.5 and 12.6) [42].

Comparing the outcome of the different treatment options for localized PCA, the results of HIFU prove to be at least as good as those of any other classical treatment option (Table 12.7).

Complication rates with HIFU are extremely low, as fistula have not been seen with the current Ablatherm software and rectal cooling. These extremely low comorbidity data favor HIFU over all other treatment options (Table 12.8).

With HIFU a more focal treatment is technically possible. Nerve sparing treatments in well-selected patients offer potency preservation to more than 75% of patients along with full tumor control (Table 12.9).

HIFU can be repeated without additional comorbidity, any other local treatment remains possible after HIFU treatment in case of local recurrence. Local recurrences after HIFU are rare and show no upgrade in tumor aggressiveness.

HIFU also proves to be a good salvage treatment for local recurrences after radiotherapy. With the development of specific software parameters for re-treatment after radiotherapy (EBRT or brachytherapy) with the Ablatherm equipment, HIFU seems to offer a safe second line treatment option for those formerly lost patients. Negative biopsy rates in the Gelet series are around 80%, and comorbidity is low and very much acceptable (Table 12.10).

Fewer results are published with Sonablate, with short follow-up periods. Success rates are around 76% biological disease-free survival rate

Table 12.1 Therapies for localized prostate cancer. Treatment options for local PCA 2005–2006

	RP	RXT	Brachy	TCAP	HIFU
Min.inv	No	Yes	Yes?	Yes?	Yes!!!
Repeatable+choices	No	No	No	Yes	Yes
1 day	No	No	Yes	Yes	Yes
Biopsy neg	Yes	No?	No?	Yes	Yes
PSA<0.5	Yes	No?	No?	Yes	Yes

HIFU, high-intensity focused ultrasound; Min.inv, minimal invasive procedure; RP, radical prostatectomy; RXT, radiotherapy; Brachy, brachytherapy; TCAP, targeted cryoablation of the prostate

Table 12.2 Results TCAP

		Bahn, Lee [10]	Chinn [2]	Chin, Paulter [7]	Prepelica, Katz [13]	De la Taille [3]
Number		590		118 ebrt fail	65	43 ebrt fail
mfolow_up		5.43 years	5 years	18.6 months	35 months	21.9 months
						3-month MAB
PSA<0.5	Low	61%	76%			
	Med	68%	72%			
	High	61%	40%			
				34%		37%
PSA<1	Low	87%	96%			
	Med	79%	91%			
	High	71%	49%			
					35%	
ASTRO	Low	92%				
	Med	89%				
	High	89%				
					83%	66%
POSBX		13%	15%	3.10%	12.50%	
2°TCAP	PSA<0;5	68%				
	PSA<1	72%				
	ASTRO	91%				
Fistula		0%		3.30%		

Table 12.3 European multicenter HIFU [31] study Thüroff-AUA/WCE 2002

	Negative biopsy rate
Overall T1–2	85.7%
Low risk	92.4%
Interm. risk	84.4%
High risk	72.1%

Table 12.4 Results HIFU [21, 26, 29, 31, 33, 38, 34, 42]

	Thüroff	Chaussy	Poisonnier	Vallencien	Blana	D'Hont	Gelet	Conti
Nb	402	271	120	30	146	350	245	146
M nadir PSA	1.8	0.8	0.9	0.9	0.07	0.5	0.9	0.07
Neg bx %	87.2	87.7	86	80	93.4	ND	86	93.4

Nb, number; Neg bx, negative biopsies

Table 12.5 PSA post HIFU [42]

Mean PSA (mPSA) per risk group [42]									
		PSAO	PSA1	PSA 3	PSA12	PSA18	PSA24	PSA30	PSA36
Low	Full	6.4	0.3	0.2	0.5	0.6	0.6	0.9	0.8
	NS	6.4	0.7	0.5	0.5	0.3	0.6	0.7	0.6
	Mean	6.4	0.55	0.35	0.5	0.45	0.6	0.75	0.7
Interm.	Full	8.2	0.6	0.4	0.6	1.3	1	1.2	1.1
	NS	7.7	0.7	0.6	0.6	1.6	1	0.1	0.5
	Mean	7.95	0.7	0.5	0.6	1.45	1	0.65	1
High	Full	12.8	0.7	0.8	1.3	1.5	1.5	1.7	1.6
	MS	16.2	0.4	0.4	0.8	0.2	0.2	0.3	0.5
	Mean	14.5	0.55	0.6	1.05	0.85	1	1.2	1.05
T3a		15.4	2.5	1.5	1.5	1.4	1.3	1.7	1.8

Table 12.6 PSA less than 0.5 ng/ml post HIFU [42]

	PSA<0.5 ng/ml			
Low	F	82%	86%	88%
	NS	84%	84%	82%
Interm.	F	75%	83%	68%
	NS	83%	84%	81%
High	F	63%	60%	60%
	NS	74%	70%	74%
T3a	F	67%	60%	47%

PSA less than 1 ng/ml at 6 months: low risk, 100%; intermediate risk, more than 90%; high risk, more than 80%; T3 cancer, more than 70%

Table 12.7 Adapted outcome after Katz and Newcastle [11]

Biochemical disease-free survival bDFS						
Katz and Newcastle [11]						Gelet [20]
	RP	Cryo	Brachy	3DCRT	XRT	HIFU
Low	76%–98%	60%–92%	78%–89%	76%–87%	81%–86%	84%
Moderate	37%–77%	61%–89%	66%–82%	51%–58%	26%–60%	68%
High						46%

Table 12.8 Complications post HIFU [42]

Risk	Treat	Numb.	Loc rec	Micro meta	Urge	Stress I	Stress II	TUR/ strict	Fistula	Death follow-up
							>3 months	Mini		Not rltd
Low	Full	29	0	0	1	1	0	7	0	0
	NS	33	1	0	1	2	0	2	0	0
									0	
Interm.	Full	56	0	4	1	10	0	8	0	1
	NS	41	3	4	1	5	0	4	0	0
									0	
High	Full	65	6	5	2	7	1	9	0	0
	NS	21	2	1	0	2	0	3	0	0
									0	
	T3	82	8	13	2	3	1	8	0	3
Total		327	20	27	8	30	2	41	0	4
%			6.1	8.2	2.4	9.1	0.6	12.5	0	1.2

Distant tumor activity, rise in PSA, biopsies negative after HIFU; Loc rec, local recurrence proved by positive biopsy(s) after PSA-rise: all had successful 2° HIFU treatment; NS, nerve sparing; rltd, related; Strict, stricture; TOT, total; TUR, transurethral resection

Table 12.9 Potency preservation after HIFU [42]

Risk	Full/nerve sparing	Pot. Pros.
Low	F	32%
	NS	78%
Interm.	F	25%
	NS	73%
High	F	35%
	NS	75%
T3a	F	8%

Table 12.10 Salvage treatments of prostate cancer relapse after definitive EBRT (Gelet [37])

	Procedures			
	Surgery	Cryo	Brachy	HIFU
	Amiing et al.	Chin et al.	Grado et al.	Gelet et al.
Patients (n)	108	118	37	106
DFSR	43%	40%	34%	40%
Incontinence	51%	20%	6%	21%
Obstruction	21%	8.5%	14%	16%
Rectal injury	6%	9%	6%	5%–0%*

*New specific software program on Ablalherm

(BDFSR) at 2 years, with negative biopsy rates of 68% (Uchida et al).

Conclusion

Both TCAP and HIFU use temperature to kill prostate cells. Freezing below −40 °C or heating the prostate over 50 °C each seem to be an effective method to control PCA and kill off prostate cells. Both are performed under transrectal ultrasound control.

TCAP is more aggressive, since perineal puncture is needed to stick the cryoprobes into the prostate tissue; temperature monitoring seems to be best way to obtain optimal results. The learning curve is long and the results are very much operator-dependent.

HIFU is less aggressive and is performed transrectally. No puncturing of the perineum or the prostate is needed to obtain good tumor kill. With Ablatherm (for which we have the most publications and the largest documented experience) most of the results are standardized thanks to the fully automatic computer-controlled treatment, with fully automatic safety checks before each lesion and rectal cooling stage. There are also specific software programs for safe re-treatment. Thermonecrosis and controlled cavitation are at the basis of good HIFU treatment. The learning curve is extremely short for a urologist experienced in transrectal ultrasound. Comorbidity is extremely low, and reconvalescence extremely short. Therefore, HIFU seems to be taking over TCAP very quickly, ensuring its position in the treatment of localized PCA.

Both treatments have proved their value killing tumors in PCA and therefore no longer need to be called experimental treatments. Their results have been established in numerous single and multicenter studies, with clinical follow-up dating back over 10 years.

Long term follow-up needs to confirm these very promising data, but once that happens, both treatments can be repeated and leave an opening for any other second-line curative option in case of local recurrence, which has not been the case to date with any of the more classical treatments.

Both HIFU and TCAP are sure to play a role in the future as less aggressive approaches to fighting PCA, preserving quality of life without compromising the chances for a cure to this all-too-common malignancy.

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13 The Role of Hormonal Treatment in Prostate Cancer

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Abstract

In 1941 Huggins and Hodges published for the first time the favorable effects of surgical castration and estrogen treatment on the progression of metastatic prostate cancer. However, this hormonal therapy is not without side effects. Since this pioneering milestone in history of prostate cancer, a further tremendous innovation did not take place. Today, due to intensive clinical, biochemical, nuclear–biological and molecular–biological research, many hormone active treatment variations are available. Besides traditional hormonal therapy, surgical or chemical castration, maximal androgen blockade, nontraditional forms of hormonal therapy, intermittent hormonal therapy, antiandrogens, 5-α-reductase inhibitors, and their combinations, we discuss options toward creating an increased number of side effect-oriented offers of hormonal treatment options, guaranteeing a longer and more comfortable exhaustion of the individual hormonal period of response and probably a longer survival. The prerequisite is a closer-than-ever monitoring by tumor marker and an early observation of symptomatic changes.

Abbreviations

AD	Androgen deprivation therapy (surgical or chemical castration)
DES	Diethylstilbestrol
DHT	Dihydrotestosterone
HT	Hormonal therapy
IHT	Intermittent hormonal therapy
HRPC	Hormone-refractory prostate cancer
MAB	Maximal androgen blockade
NHT	Neoadjuvant hormonal treatment
PSA	Prostate specific antigen
RP	Radical prostatectomy
RT	Radiotherapy
T	Testosterone

History

The introduction of hormonal therapy (HT) in the treatment of prostate cancer (PC) by Huggins and Hodges (1941) in the 1940s was like a thunderbolt. However, despite intensive basic research on the field of hormonal receptors and of testosterone (T) bioconversion and a better understanding of the endocrine mechanisms of action and inhibition in endocrine-active organs, a further pioneering development has not been achieved. The first-line standard option in virginal metastatic PC remains the androgen blockade achieved today with minimal side effects using luteinizing hormone-releasing hormone (LHRH) analogs. Low-priced, equally effective alternatives to hormone deprivation such as orchiectomy with the disadvantage of morbidity and irreversibility had to give way to the demand for a better quality of life (Fowler et al. 2002; Potosky et al. 2002). Due to their high rate of cardiovascular and hepatogenic complications, estrogens had fallen out of favor until recently. Today a renaissance may be expected as the transdermal form of parenteral applications, avoiding hepatic first-pass metabolism, seems to be as effective as LHRH analogs, prevents andropause symptoms, improves quality of life scores, and increases bone density. It could be shown recently that this estrogenic compound induces a prostate-specific antigen (PSA)-response in patients with hormone-refractory PC (HRPC). It is important to mention that the

transdermal application of estradiol costs a tenth of current therapy (Ockrim et al. 2004, 2005). In the last few years, survival and quality of life have improved due to modern hormonal treatment options consisting of many endocrine-active drugs, closer monitoring of tumor markers, early observation of symptomatic changes, and use of different hormone-active substances in a secondary and even tertiary setting before non-hormonal treatment is indicated. In the case of metastatic PC, the average duration of response to castration was between 18 and 24 months 20 years ago. Further survival was rarely longer than 6 months. Nowadays these patients survive twice as long on average (Sharifi et al. 2005). Therefore, delaying the onset of a true hormone-refractory state and exhausting all possible forms of hormonal manipulations before starting effective chemotherapy is a reasonable strategy. Today PSA values are followed more closely in actively treated patients. Early change from a treatment that effectively has been exhausted to one that may be by now of benefit is possible. In this paper we give a summarized report of today's treatment options for patients with locally confined PC, for patients in PSA progress after curative treatment, for those with locally advanced PC, for those with distant metastases, and for those progressing in hormonal relapse.

Locally Confined Prostate Cancer (T1–2 N0 M0)

In T1/T2 PC, curative treatment is indicated. Especially in young patients, radical prostatectomy (RP) is the first treatment option. In pT1 and pT2 tumors, no further therapy is needed. There is no place for adjuvant androgen deprivation therapy (AD) or maximal androgen blockade (MAB) because, due to the side effects, survival may even worsen. Recently, the members of the Early Prostate Cancer (EPC) program (Wirth et al. 2004; Iversen et al. 2004; Iversen 2005) reported experiences with patients with localized and locally advanced PC. The EPC program comprised three randomized, double-blind, placebo-controlled trials. Altogether 8,113 patients had RP (55%), radiotherapy (RT) (17%) or watchful waiting (25%) as standard care, and thereafter they were randomized into a bicalutamide 150 mg/day arm (n=4,052) or a standard care only arm (placebo; n=4,061). Bicalutamide led to a significantly improved progression-free survival in the overall population. Overall survival was similar in the bicalutamide and placebo groups, across the program, and in each trial. However, in the patients primarily treated with watchful waiting, overall survival appeared to be reduced in patients with localized tumors treated with bicalutamide. The authors concluded that there is no indication for RP and adjuvant HT in patients with localized disease and with low risk.

RT is also a curative treatment option. In low-risk T1a–T2b N0 M0 PC patients (Gleason score<7, PSA<10 ng/ml), the recommendation is for external RT up to 70–72 Gy. In intermediate-risk T2b PC patients (Gleason score 7, PSA 10–20 ng/ml), dose-escalating RT up to 76–81 Gy becomes necessary. Additive adjuvant HT does not improve the outcome (Wirth et al. 2004; Iversen et al. 2004; Tyrrell et al. 2005). However, the high-risk tumor T2c and upward (Gleason score>7, PSA>20 ng/ml) often has not been treated sufficiently by dose escalating RT alone. Adjuvant HT is of significant benefit when there is a possibility of a not-yet-detectable lymph node involvement, or tumor spread outside the pelvis (Aus et al. 2005). D'Amico et al. (2004) reported a survival benefit in a randomized controlled study for the management of high-risk patients with clinically localized PC treated with 70 Gy three-dimensional conformal RT in combination with 6 months of HT. Eligible patients included those with PSA at least 10 ng/ml, a Gleason score of at least 7, or radiographic evidence of extraprostatic disease. After a median follow-up of 4.52 years, patients randomized to receive RT plus HT had a significantly higher survival (p<0.04), a lower PC-specific mortality (p<0.02), and a higher survival free of salvage HT (p<0,002). Granfors et al. (1998) confirmed the above findings. In a prospective randomized study they compared orchiectomy and external RT versus RT alone for nonmetastatic PC with or without pelvic lymph node involvement. There were 91 patients enrolled. Patients with early stage and well or moderately well differentiated T1–2 N0 tumors were excluded from the study. After a median follow-up of 9.3 years, clinical

progression was seen in 61% of the control group and 31% of the hormone group ($p<0.005$). The overall mortality was 61% and 38% ($p<0.02$), and cancer-specific mortality was 44% and 27% ($p<0.06$), respectively. The differences in favor of combined therapy were mainly observed in lymph node-positive tumors. For node-negative tumors there was no significant differences in survival rates. The two above-cited studies clearly demonstrate that there is no benefit of adjuvant HT after RT in locally confined PC. These statements were recently confirmed by Tyrrell et al. (2005) who presented an exploratory analysis of the subgroup of the EPC program consisting of 1,065 patients with T1–2 PC. The patients received RT and were later randomized in a bicalutamide treated arm and RT only arm. No benefit was seen in the bicalutamide arm.

The first randomized studies assessing the impact of immediate HT alone in men with locally confined PC was reported by the Veterans Administration Cooperative Urological Research Group (VACURG) in 1972 (Byar 1972). The studies found higher mortality in patients receiving 5 mg/day diethylstilbestrol (DES) as compared to those receiving placebo. Cardiovascular complications induced by DES caused the high mortality rate. Due to this concern, the use of DES had fallen out of favor until recently (Aus et al. 2005; Ockrim et al. 2004, 2005). A less morbid form of HT using an antiandrogen alone has been examined by the EPC program in a large, ongoing, randomized trial (Wirth et al. 2004; Iversen et al. 2004; Iversen 2005). The program design is described above. The authors confirmed again a trend toward a reduction of overall survival in patients with localized PC treated with bicalutamide. This contention was especially derived from the Scandinavian subgroup of the EPC program (Iversen et al. 2004). In this trial, 1,218 patients were enrolled, of whom 81% were given primarily standard care with watchful waiting. Of the participants, 60% had stage T1–2 tumors, 38% T3 PC; 43% had a Gleason score in the 2–4 range, and 44% a Gleason score of 5–6. The authors calculated that the relative effect of bicalutamide as compared to placebo on overall survival was dependent on baseline prognostic factors showing statistical significance. Low-risk patients characterized by low baseline PSA and localized disease showed a decrease in overall survival when treated with bicalutamide. On the other hand, patients with locally advanced disease and high baseline PSA showed trends toward an improved survival. They concluded that watchful waiting remains a valid treatment option in low-risk patients with localized PC.

To date there is no indication for starting HT alone or in combination with RP or RT in T1/T2 PC. In patients with poorly differentiated, aggressive tumors showing contraindications for RP such as advanced age, comorbidity, or refusal of RP, combination therapy consisting of any form of HT and RT can be indicated, especially when there is a suspicion of lymph node metastasis or tumor spread outside the pelvis.

EUA comment (Aus et al. 2005):

- *For patients with localized PC T1c–T2c N0 M0 with high-risk short-term AD prior to, and during, radiotherapy may result in increased overall survival (level of evidence: 2a).*
- *LHRH or bicalutamide at 150 mg/day can both be used when there is an indication for hormone therapy (grade A recommendation).*

Prostate Cancer in PSA Progress After Curative Treatment

PSA has dramatically altered the epidemiology of PC. For one, the incidence of PC has increased. PC is detected at an earlier stage and in younger men. Consequently there is a remarkable shift toward curative treatment procedures such as RP and RT. After a follow-up of about 10 years, 25% to 40% of patients who undergo RP or RT will have biochemical recurrence, as detected by early PSA monitoring. In the favorable early stage of low tumor burden, the crucial question is: Which is the best treatment strategy? PSA doubling time after recurrence, Gleason score, and time to early PSA relapse are helpful markers on which to base the decision whether curative treatment is still possible, or if hormonal manipulations with the goal of palliation have to be recommended (Pound et al. 1999; D'Amico et al. 2003). Curative RT is indicated in case of local recurrence in the prostate bed. This situation can be expected in case of a PSA increase after more than 2 years, PSA doubling time of more

than 10 months, and a Gleason score below 7. Otherwise HT is indicated, raising new questions: What kind of strategy is effective, cost-efficient, and can be performed with acceptable side effects? When is the optimal time to start? Decisions concerning treatment options have to consider the experiences at Johns Hopkins Hospital (Pound et al. 1999) demonstrating a median time of 8 years up to the onset of metastases in patients with early PSA progress and a median time to death after development of metastases of 5 years. Gleason grade 8 to 10, PSA relapse 2 years or less after surgery, and PSA doubling time of less than 10 months are adverse factors that decrease metastase-free survival. Due to this long natural history of cancer, patients have to be fully informed about improvement of survival on the one hand, and loss of quality of life (and sexuality) caused by treatment on the other hand. Today, patients have to play an active role in the treatment decisions.

Watchful Waiting

Duration of survival, quality of life, and cause of death are considered important questions for therapeutic decisions. If one remembers that patients with PC treated by RP have a life expectancy of more than 10 years, it must be considered that the natural history of PC after PSA relapse may be longer than 10 years (Pound et al. 1999). So after the decision for palliative treatment, two forms of HT appear to make sense and be convenient: the watchful waiting strategy with deferred hormone therapy beginning at the time of symptomatic progression, or the intermittent hormonal therapy (IHT) at the time when PSA reaches values of an average of 5 ng/ml. Elderly men frequently die from other comorbidities than cancer. So if the patients' life expectancy at the time of PSA progress is less than 10 years, watchful waiting is a convincing option.

EUA comment (Aus et al. 2005):

– *Expectant management is an option for patients with presumed local recurrence unfit for, or unwilling to undergo, radiation therapy (grade B recommendation).*

Radiation Therapy

Patients with a long life expectancy are candidates for salvage RT with curative intention, when the possibility of either residual or recurrent tumor confined to the prostate bed is given. In the first case, PSA levels often do not reach normal values after operation. The second case is characterized by a PSA relapse after more than 2 years, a PSA doubling time of more than 10 months, and a Gleason score below 7. In this situation there is no indication for HT. This step should be reserved as second-line treatment for men progressing despite salvage RT. A consensus panel report (American Society for Therapeutic Radiology and Oncology, ASTRO) recommended that patients should receive salvage RT with at least 66 Gy to the prostatic fossa before PSA is greater than 1.5 ng/ml (Cox et al. 1999).

EUA comment (Aus et al. 2005):

– *Local recurrences are best treated by salvage radiation therapy with 64–66 Gy at a PSA serum level <1.5 ng/ml (grade B recommendation).*

Hormonal Therapy

Patients whose PSA postoperatively never decreases to undetectable levels are generally considered to have either metastatic disease or residual tumor. In the latter, a decision for RT is advisable, when there is the probability that PC is confined to the prostate bed. Otherwise and when there is a suspicion of metastatic spread, HT is recommended. Furthermore, systemic progress must be supposed when initially undetectable PSA levels increase in a period of less than 2 years, when the PSA value doubles in less than 10 months, and when the Gleason score is 8–10. In case of systemic progress, HT is the first option (D'Amico et al. 2003). No consensus has been reached regarding the optimal time to begin HT. Moreover, which kind of HT should be administered? At which PSA level HT should be initiated? Should patients be treated as soon as possible, or at higher PSA levels such as 10, 20, or even 50 ng/ml? The favorable natural history of PC in patients with early PSA progress after RP raises the question of whether early hormonal therapy will improve the outcome?

Today it must be accepted that long-time results of studies aimed at cancer-free survival, overall survival, and time to hormone resistance are missing, and so definite treatment recommendations cannot be given. Therefore one should attempt to work up the most effective strategy by extrapolation of older trials with comparable questions. Furthermore, new studies and the interim reports of running trials dealing with hormonal treatment in early PSA relapse should be considered.

Traditional Hormonal Therapy

Since the 1980s, many authors have discussed the effectiveness of MAB (Bertagna et al. 1994; Caubet et al. 1997; Bennett et al. 1999). The extent of disease is seen as a prognostic factor for overall survival with MAB, and some (Eisenberger et al. 1994; Soloway et al. 2000), although not all authors (Eisenberger et al. 1998), reported better survival in patients with minimal metastatic disease. Meta-analyses (McLeod et al. 1997; Postate Cancer Trialists' Collaborative Group 2000) with the intention to evaluate the clinical benefit of MAB for advanced PC ranged from no significant survival benefit, up to 22% benefit. Some authors demonstrated an advantage for patients with minimal metastatic disease. In performing an extrapolation of these results to treatment options for PC in early PSA relapse, they concluded that there might be a benefit of MAB in this stage as well.

Recently a randomized study from the British Medical Research Council (MRC) compared immediate versus delayed HT in 938 patients with newly diagnosed local advanced PC (M0) or with asymptomatic metastatic disease (M1). A significant advantage for the immediate treatment group could be seen in the lower progression rate from stage M0 to M1 and in lower cancer-specific mortality. This advantage was most pronounced in those with M0 disease (Medical Research Council Prostate Cancer Working Party Investigators Group 1997). These results led to the assumption that immediate HT in men with early PSA relapse may be advisable. However, the patients with M0 disease in this study had a more advanced disease than patients with early PSA recurrence after curative treatment. In a prospective, randomized study, the Eastern Cooperative Oncology Group demonstrated significant advantages in case of immediate AD compared with delayed treatment in 98 patients who underwent RP and pelvic lymphadenectomy and who were found to have nodal metastases. After a median follow-up of 7.1 years, clinically staged recurrence-free survival was significantly better in the immediately treated group than in the observation group (p<0,001). Overall survival was significantly better among the men in whom AD was initiated immediately, than among those with delayed treatment (p<002) (Messing et al. 1999). If an extrapolation is possible it can be speculated that there may be a benefit of early HT for men with PSA-only recurrence after curative treatment. According to Moul (2000), an extrapolation of these results to patients with PSA recurrence makes sense.

In a retrospective study of a large observational multicenter database conducted by Moul et al. (2004), 1,352 patients with PC in PSA relapse after RP (PSA>0.2 ng/ml) were enrolled. Of the cohort, 355 received early HT (PSA level<10 ng/ml). They were compared with 997 patients with delayed HT (PSA level>10 ng/ml). Of the 1,352 patients with PSA relapse, clinical metastases developed in 103 (7.6%). The interim results demonstrated that early AD delayed the metastatic progress in the patients with high-risk (PSA doubling time<1 year or Gleason score>7). However, by analyzing all patients, there has been no difference so far concerning time to clinical metastases. A longer follow-up will be needed to evaluate whether there is a benefit for cancer-free or overall survival. In some patients, low PSA levels after curative treatment could be caused by benign prostate cells, which remain in the prostate bed after operation. These cells could produce low and stable PSA levels over the time and falsely manipulate the history of PC under trial conditions (Ravery 1999; Djavan et al. 2000).

At the time PSA levels start to rise, patients are often young and healthy, and quality of life plays an important role. This has to be considered in the design of the individual treatment strategy. IHT starting at a low PSA level is one option to reduce adverse events. Furthermore, it aims at delaying the onset of androgen-independent PC cells. Recently Kurek et al. (1999) reported on 44

patients treated in an IHT pilot study. Patients with a PSA of more than 3 ng/ml were treated for 9 months with continuous MAB. All reached a PSA nadir of less than 0.5 ng/ml. When PSA increased again to more than 3 ng/ml, HT was restarted for a new 9-month cycle. At a mean follow-up of 48 months the average duration of HT was 26.6 months. Due to the short duration of the study, the results were good, as expected. No patient progressed to hormone refractory disease. Peyromaure et al. (2005) stated that IHT for biochemical recurrence after RP achieves satisfactory oncologic results. In his series of 57 men, most were at high risk, explaining the 15.8% rate of metastatic progression and the cancer-specific mortality rate of 12.3%. The group of Peyromaure had started their first treatment phase (the "on" phase) with an antiandrogen alone. They explained the favorable results reported by Kurek et al. (1999) by the use of MAB and/or by the longer period of the first on-phase. Sciarra et al. (2000) also mentioned that Gleason score was important for the outcome. Of 12 patients with early PSA progress after RP with Gleason scores of 8 or higher, 9 failed to respond to IHT and all developed metastatic and/or local failure. No case with a Gleason score below 7 failed to respond. Prapotnich et al. (2003) reported comparable results. There were 90 patients with early PSA relapse after RP or RT who were initially treated with MAB. After a median follow-up of 35 months, a metastatic progression rate of 23% and a cancer specific mortality of 4% were found. Pain (2.5%) and urinary complications remained limited in patients with PSA relapse. It is remarkable that, overall, patients spent 32% of their time in the treatment phase (on-phase) and 68% in the surveillance phase (off-phase). Ongoing large multicenter, randomized trials (AUO AP 17, 19, 20, SWOG 9346, NCIC PR7) have to confirm these encouraging results.

EUA comment (Aus et al. 2005):

Relapse after RP or RT:

- *PSA recurrence indicative of systemic relapse is best treated by early AD resulting in decreased frequency of clinical metastases (grade B recommendation).*
- *LHRH/orchiectomy or bicalutamide at 150 mg/day can both be used when there is indication for hormone therapy (grade A recommendation).*

As endpoint studies concerning survival benefit in early PSA progression are missing, the real advantages of early or delayed HT with MAB, AD, or IHT have not been proved. Hence, benefits regarding these approaches are so far purely speculative. Since the natural history of PC can be calculated as extending up to 13 years, HT, beginning at the time when PSA levels begin to rise, will generally run for more than 10 years, and the advantage of long-term treatment needs to be questioned. The burdens of long-term treatment—loss of libido, impotency, hot flashes, depression, lack of drive, cognitive decline, malaise, mild anemia, fatigue, and long-term concern for osteoporosis with risk of bone fracture and decreased muscle mass—are distressing for the still young and otherwise healthy patients (Wei et al. 1999; Potosky et al. 2001). One solution is the above-mentioned IHT, and other options include single forms of nontraditional HT options that are currently receiving increasing amounts of attention and acceptance by patients.

Nontraditional Hormonal Therapy

Nontraditional HT includes nonsteroidal antiandrogens (bicalutamide, flutamide, nilutamide), 5-α-reductase inhibitors (finasteride or dutasteride) and their combinations. These drugs do not block the T synthesis in the testes, so that longtime side effects of MAB or AD including PADAM (partial androgen deficiency in the aging man) do not occur. Therefore, most patients should retain libido, potency, muscle mass, erythropoiesis, and their psychological status. However, if gynecomastia and breast tenderness or pain occur, prophylactic RT of the mammillary glands can reliably prevent these side effects.

The growth of PC is regulated primarily by dihydrotestosterone (DHT), which is converted in the prostatic cells out of T by 5-α-reductase. A 5-α-reductase inhibitor blocks this enzymatic reaction. DHT has a higher binding affinity for the intracellular androgen receptor than T. Antiandrogens occupy the cytoplasmatic DHT receptor in the PC cell by competitive binding. In case of adequate concentration of antiandrogens, DHT cannot find a binding place at the receptor. In this case there is no stimulating effect on

PC cells growth by DHT. Both agents inhibit the action of androgens secreted from the adrenal glands and from the testes. Remarkably, they do not decrease serum T.

Nonsteroidal Antiandrogens

Nonsteroidal antiandrogens (bicalutamide, flutamide, nilutamide) given alone in the treatment of metastatic PC are currently not accepted as standard therapy. While flutamide has a relatively short half-life and must be administered three times per day, both nilutamide and bicalutamide are given once daily. None of these agents causes a decrease in luteinizing hormone (LH) production. Thus, serum T levels remain normal or may slightly increase, and potency is spared when these agents are used as monotherapy.

Bicalutamide given alone in a dose of 50 mg once daily in patients with metastatic PC showed a lower efficacy in the time to treatment failure, time to progression, and survival as compared to castration (Bales and Chodak 1996). Subsequently, it was administered in a higher dose of 150 mg. In this dose the effect of bicalutamide as compared to castration was examined in two large studies with M1 and M0 PC. In 805 patients with M1 PC at a median follow-up of 1.9 years, bicalutamide was not as effective as castration. It is interesting to mention that especially in the subgroup of patients with a PSA count of more than 400 ng/ml the castration effect was dominant, whereas in the M1 cancer group with PSA below 400 ng/ml bicalutamide and castration had a comparable efficacy. In patients with M0 disease (n=480 patients) at a median follow-up of 6.3 years, no statistical difference was found between the two forms of HT (Tyrrell et al. 1998; Iversen et al. 2000; Kaisary et al. 2001). It is still unknown whether the results of these stages of M1 PC with pretreatment PSA value of below 400 ng/ml or of M0 disease can be extrapolated to prove a benefit of bicalutamide monotherapy in patients with PSA relapse. However, bicalutamide monotherapy guarantees an acceptable quality of life to a high degree.

In the ongoing EPC program, bicalutamide was given 150 mg once daily as an adjuvant treatment to standard care consisting of RP, RT, or watchful waiting. In a total of 8,113 men with localized or locally advanced PC, effectiveness was compared with standard care alone (See et al. 2001). Primary endpoints were objective progression-free survival and overall survival. Although the two treatment arms did not differ with respect to overall survival, a significant benefit of bicalutamide versus standard care in progression-free survival could be demonstrated at a median follow-up of 5.4 years. Analyzing the subgroups, overall survival appeared to be improved with bicalutamide in patients with locally advanced disease, whereas in those with localized disease survival was reduced with bicalutamide (Wirth et al. 2004). These results were confirmed recently by Iversen in his third analysis at a median follow-up of 7.4 years. The EPC trial provides results on adjuvant bicalutamide treatment. Patients definitively cured by RP or RT are part of the statistical analysis, and therefore conclusions applied to PC patients in early PSA progress may be trend-setting but still speculative. It should be noted that this is a trial dealing with a well-staged T1–2 PC population, as less than 2% of the patients had lymph node metastases. Nevertheless, bicalutamide in a dose of 150 mg daily has not yet been extensively evaluated in patients with early PSA progress, and therefore there is need for randomized clinical trials. The trend in the analyses toward a reduced overall survival after a follow-up of 5.4 years (Wirth et al. 2004) and 7.4 years (Iversen 2005) of bicalutamide treatment underlined the reservations of some authors to begin any form of HT immediately at the time of early PSA relapse. For flutamide monotherapy the published data are rare and inconclusive. The reason may be the many side effects caused by its gastrointestinal- and hepato-toxicity.

EUA comment (Aus et al. 2005):

- *Bicalutamide at 150 mg/day can be used when there is indication for hormonal therapy (grade A recommendation).*

5-α-Reductase Inhibitor

The 5-α-reductase inhibitor finasteride reduces the enzymatic intraprostatic bioconversion of T to DHT. Andriole et al. (1995) published the first

randomized trial dealing with this treatment option. In the first year, orally administered finasteride in a dose of 10 mg daily versus placebo was given to 120 men with PSA only recurrence after RP. Thereafter all patients were treated with finasteride for a further year. The drug was well-tolerated. A delayed marginal decrease in PSA levels could be demonstrated. However, no significant benefit concerning recurrence rates could be calculated for finasteride as compared to placebo. From a biochemical point of view, a complete inhibition of DHT synthesis is not possible. In our opinion there is no place for finasteride monotherapy in early PSA progress. A stimulating effect of PC growth due to the still persistent DHT concentration cannot be excluded. On the other hand, the combination of finasteride with an antiandrogen seems worth examining. Consideration should be given to the fact that this treatment is not inexpensive.

Combination Therapy of Nonsteroidal Antiandrogen Plus 5-α-Reductase Inhibitor

Combination therapy of nonsteroidal antiandrogen plus 5-α-reductase inhibitor is also named minimal androgen blockade or peripheral androgen blockade. The biological mechanisms of action of each drug is described above. Additional synergistic effects were reported by Wang et al. (2004). They performed experiments with an established hormone-dependent PC cell line (LNCaP). Due to the more complete inactivation of the androgen receptor, a diminished ability of the receptor to mutate and so to generate androgen-independent clones is discussed in this section.

In two studies recruiting 71 (Barqawi et al. 2003) and 36 (Moul et al. 1998) patients, combination therapy was conducted with a low-dose flutamide application of 2×125 mg plus 2×5 mg finasteride daily in patients with early and only PSA progress after RP or RT. In the first study, 58% of patients reached a PSA nadir below 0.1 ng/ml after a median time of 7.9 months. In 21 patients progress was found; 6 of them (28%) did not reach the nadir of less than 0.1 ng/ml. Comparable results are reported by Moul et al. (1998). A change in libido or potency was not seen. Breast tenderness (90%), breast enlargement (72%), nipple tenderness (33%), gastrointestinal disturbance (22%), elevated liver function tests (9%), and chronic fatigue (10%) were found. Kirby et al. (1999) conducted a randomized multicenter phase II study in patients with M1 PC comparing a combination of finasteride (2×5 mg, daily) and flutamide (250 mg, t.i.d.) with two other arms. The second arm consisted of 3.6 mg goserelin, administered monthly in combination with 250 mg flutamide, t.i.d. and a placebo, daily, instead of 2×5 mg finasteride. A third arm consisted of 3.6 mg goserelin, monthly in combination with finasteride, 10 mg (2×5 mg) daily and a placebo (t.i.d.) instead of flutamide. The reduction in concentration of serum PSA at 24 weeks was the endpoint of interest. Baseline PSA of the patients in the three groups were very similar. At the end of the study there were no statistical differences in terms of PSA behavior and decline between the centers nor among the three treatment arms. WHO performance status and pain score did not differ between the groups. Comparable clinical results were reported for the combination of finasteride and bicalutamide in patients with advanced PC (Tay et al. 2004). Longer follow-up of patients treated with oral combination therapy is needed, and a randomized phase III trial in early PSA recurrence cases is warranted. Combination therapy is not inexpensive. Therefore it should be clarified at the beginning whether or not there is any advantage in combination treatment compared to nonsteroidal antiandrogen alone.

It can therefore be summarized that in case of early PSA progression after curative treatment, a proven advantage of early or delayed HT has not yet been documented. To date no randomized trial has confirmed the effectiveness of early HT. Any benefit regarding the best timing and treatment options such as MAB, AD, IHT, or a nontraditional hormonal therapy with antiandrogens or antiandrogens plus 5-α-reductase inhibitor is currently purely speculative. Nevertheless, the increasing application of nontraditional HT underlines the claim that it will improve quality of life in younger and mostly healthier patients who are seeking nerve-sparing procedures. In cases of early PSA progress, such patients pursue an intention to preserve their potency.

Locally Advanced Prostate cancer (T3–4 NO/N1 M0)

The incidence of locally advanced PC declined as a result of PSA screening. Men with locally advanced clinical T3 PC are generally offered active treatment, consisting of RP, RT, HT alone, or HT in combination with RP or RT. The goals of treatment are cure, longer survival, or metastasis-free survival, as well as improvement of quality of life. Watchful waiting and deferred treatment seem dangerous and are not optimal options since local and systemic progression occurs within 36 months in 87% and 100% of such cases, respectively (Allison et al. 1997). The watchful waiting strategy is only acceptable in patients with low-grade disease and with short life expectancy (Aus et al. 2005). However, there is no option for patients with intermediate or high risk and with long life expectancy. Here local therapy is warranted.

Radical Prostatectomy

According to the EAU guidelines, small unilateral T3 tumors with a PSA lower than 20 ng/ml, a Gleason score lower than 8, and a life expectancy of more than 10 years demand more radical tumor extirpation including: an extensive lymph node dissection, clean apical dissection, neurovascular bundle resection, and often a large resection of the bladder neck (Aus et al. 2005). RT in combination with HT should no longer be considered as the treatment of choice for all T3 PC, as recently reported data of the EPC group presented at the ECCO in Paris 2005 confirmed that after a median follow-up of 7.4 years in terms of overall survival, there was no statistical difference between the combined arm consisting of RP and adjuvant bicalutamide as compared to the RP-only arm. However, overall survival could be statistically prolonged by the addition of bicalutamide to RT compared with RT alone (Iversen 2005; Tyrrell et al. 2005). So the first option for T3 PC is RP (Hsu et al. 2005), and in case of pT3 N0 adjuvant HT is not appropriate. However, it is accepted today that the advanced T3 tumor cannot be cured by surgery alone, and therefore a combination of hormones and/or RT is advocated. For more effective tumor treatment, neoadjuvant HT before RP, and adjuvant HT after RP are controversial. The primary goal of treatment is to extend a progression-free time and the overall survival. Concerning T4 PC, there is no indication for any attempt at active curative treatment.

EUA comment (Aus et al. 2005):

- *Optional: patients with stage T3a disease, a Gleason score of >8, and a PSA of <20 ng/ml.*
- *The role of radical prostatectomy in patients with high-risk features, lymph node involvement (stage N1 disease), or as part of a planned multimodality treatment (with long-term hormonal and/or adjuvant radiation therapy), has not been evaluated (level of evidence: 4).*

Neoadjuvant Hormonal Treatment

The shortcoming of RP is that nonlocalized PC is often found after the operation. This situation is associated with a high rate of recurrence. For this reason, the goal of neoadjuvant hormonal treatment (NHT) is the improvement of operability of the tumor, better local cancer control, and longer survival of the patients. It is clear that this setting lowers the pathological stage and reduces positive margins (Labrie et al. 1994). An effect of downgrading has not yet been convincingly proved (Van Poppel et al. 1995; Paul et al. 2001). Due to reduction of prostate size and tumor mass, an operation may be easier after NHT, giving the surgeon better local control. On the other hand, fibrosis could be induced and may complicate surgery. Furthermore, pathological evaluation of the Gleason score and subsequent prediction of a patient's prognosis is more difficult. Although Soloway et al. (2002) found significantly decreased positive margins in patients treated 3 months before RP with NHT, there was no significant difference in terms of the biochemical recurrence rates in the neoadjuvant-treated group (64.8%) compared to the control group (67.6%) (p=0.663) after a follow-up of 5 years. Other authors confirmed these findings and agreed that NHT neither improved the time to clinical progression nor the rate of survival (Aus et al. 1998; Schulmann et al. 2000). A randomized study was conducted by Gleave et al. (2001)

with the hypothesis of a better and maximal effect of AD after 8 months of NHT prior to RP. In a recent abstract, he reported that there was no advantage of an 8-month over a 3-month NHT (Gleave et al. 2003). Therefore, neoadjuvant treatment cannot be recommended in locally advanced PC.

Adjuvant Hormonal Treatment

There is no need for adjuvant HT in the pT3 N0 M0 R0 PC. This could be clearly confirmed in a comprehensive EPC study with an enrolment of 8,113 patients. These men underwent a standard care consisting of RP (55%), RT (17%), and watchful waiting (25%). Thereafter the patients were randomly assigned to receive oral bicalutamide 150 mg/day or standard care alone. Less than 2% of the patients had a lymph node involvement. After a median follow-up of 5.4 years (Wirth et al. 2004) and 7.4 years (Iversen 2005) there was a significant improvement in progression-free survival in the overall population, but no advantage could be demonstrated in terms of overall survival.

In case of lymph node metastasis, there is a clear-cut treatment option. A randomized study performed by Messing et al. (1999) beginning immediately after RP with HT using orchiectomy or LHRH-agonists, demonstrated that adjuvant HT in case of positive lymph nodes significantly increases patients' survival. Of 98 men with N+PC randomized 12 weeks after RP, AD was begun immediately in one arm and compared with the other arm that was treated with delayed HT. After a median of 7.1 years of follow-up, 7 out of 47 men who received immediate HT had died, as compared to 18 out of 51 men in the observation group (p=0.02). The cause of death was PC in 3 patients in the immediately treated arm and in 16 patients in the observation arm (p<0.01). At the time of the last follow-up, 36 patients in the immediately treated arm (77%) and 9 patients in the observation arm (18%) were still alive (p<0.001). The findings of Messing confirm the results of several uncontrolled reports of the Mayo Clinic group (Myers et al. 1992; Seay et al. 1998). Here only patients with N+ tumors bearing DNA diploid cells, and treated immediately after RP with AD, had shown a survival benefit after a minimum of 10 years of therapy. If RP was not performed because of lymph node infiltration of the tumor and the decision was made for HT, Wijburg et al. (1999) reported a rise in the cancer-caused death rate compared to delayed HT. Altogether, the consequences of this procedure appear to be worse than those after RP, despite lymph node involvement and immediately started HT. Cheng et al. (2001) underlined the advantage of RP and adjuvant HT in stage pT3 N1–2 tumors. In relation to the extent of lymph node involvement, they reported a 10-year cancer-specific survival rate of 74% after RP and pN+ status. In case of minimal lymph node involvement there is only a slight improvement in survival compared with patients without lymph node involvement. These data are in agreement with those of Bader et al. (2003) who report that some patients with minimal metastatic disease found by meticulous pelvic lymph node dissection remained free of PSA relapse for more than 10 years after RP without any adjuvant treatment. In summary, there are good reasons to recommend RP and lymphadenectomy followed by immediate HT in case of pN+. Since only less than 2% of the 8,113 patients enrolled in the EPC program have had lymph node involvement, the efficacy of bicalutamide-only treatment in N+ PC is not yet convincingly shown. The wait-and-see strategy can be recommended only in a minimal N1-disease clearly documented by meticulous pelvic lymph node dissection. There is no need for adjuvant HT after RP and pT3 N0 PC.

EUA comment (Aus et al. 2005):

- *In advanced PC, all forms of castration as monotherapy (orchiectomy, LHRH-analogs and DES) have equivalent therapeutic efficacy (level of evidence: 1b).*
- *Nonsteroidal antiandrogen monotherapy (e.g., bicalutamide) is an effective alternative to castration in patients with locally advanced disease (level of evidence: 1b).*

Radiation Therapy

In clinical trials the evaluation of the stage-related prognosis in clinical staged cT3 tumors is difficult. In case of RT the cT3 PC may consist of a mixture of T2 to T4, N0 to N2 tumors. Ward et al. (2005) found an overstaging in 27% (cT3 to

pT2), an understaging in 8% (cT3 to pT4), and an additional lymph node involvement in 27%. Even when applied in high doses, RT appears to have a limited curative potential in patients with locally advanced PC. The results of RT can be improved by combining RT with HT. Nowadays, this is the "gold standard" in RT of T3 PC (Lawton et al. 2001; Bolla et al. 2002). Still, it could not be shown that combined radio-hormonal therapy was superior to surgical treatment either in monotherapy or in combination with postoperative RT or HT (Van Poppel 2005; Iversen 2005). Pelvic lymph node irradiation is optional for N0 patients due to the possibility of occult N1 disease. However, in this stage the outcome of radiotherapy alone is dismal (Bagshaw et al. 1988). AD therapy in combination with RT is recommended in order to kill clinically undetected micrometastases, because of the hormonal dependency. In addition, the risk of early progression caused by not completely sterilized tumor cells in the pelvic lymph nodes can be decreased. In this situation a supra-additive apoptotic response depending on the timing of HT and RT could be seen (Zietman et al. 1997; Joon et al. 1997). However, the real extent of the contribution of RT to the patients' outcome in case of combination therapy with hormones is still unknown, since an HT-alone arm is missing in reported studies. For this reason, the recently conducted NCIC/MRC/SWOG PR.3/PR07 International Intergroup trial is comparing HT alone with HT combined with RT. The trial started 1995, has been expanded to 1,200 patients, and is expected to release survival data from 2008 onwards.

Neoadjuvant Hormonal Therapy

In the Radiation Therapy Oncology Group (RTOG) study 86-10, 471 patients were recruited with stage T2–T4 N0-x, M0 PC. All patients received RT. In the neoadjuvant treated arm 3.6 mg goserelin acetate was given every 4 weeks for 2 months before RT and during RT. In the control group, HT was started in case of relapse. After 8.6 years the update of the neoadjuvant-treated arm as compared to the control arm showed a significant improvement in local control (42% versus 39%, p=0.016), in disease-free survival (33% versus 22%, p=0.0004), and in biochemical disease-free survival (PSA<1.5 ng/ml; 24% versus 10%; p=0.0001). Still, a significant advantage in survival (70% versus 52%; p=0.015) was only seen in patients with favorable Gleason 2–6 PC (Pilepich et al. 2001). The main conclusion of this trial is that there is no significant benefit for survival especially in the intermediate and high-risk groups. However, studies with a longer period of hormonal therapy for 8 months prior to RT are missing. In contrast to NHT performed prior to RP, where no advantage in NHT could be demonstrated when comparing 3-month with 8-month-HT (Gleave et al. 2003), there may be an advantage in case of RT. Pilepich et al. (2005) discussed that tumor debulking caused by HT leads to a better tumor control by RT. Up-to-date randomized studies have not been conducted that deal with a reduction in radiation dose and radiation field caused by NHT as the prostate is downsized. So RT could be milder and more protective as the radiation field decreases. A decrease of acute complication rates could be expected. Finally, it is important to know if, after NHT, a reduction in radiation dose is at all acceptable, as dose escalation in the high-stage and -grade PC is indicated.

Concomitant and Adjuvant Hormonal Treatment

The European Organisation for Research and Treatment of Cancer (EORTC) study No. 22863 included 415 patients with either T1–2 G3 cancer or with a T3–4 tumor of any histological grade, and with or without nodal involvement. In the first arm patients received 50 mg cyproterone acetate 3 times daily for 1 month and 3.6 mg goserelin acetate every 4 weeks at the beginning of RT. In the control group patients received RT alone. Of the patients, 82% were staged as T3, 10% as stage T4, and 89% as N0. HT was finished after 3 years. This study included men with higher risk. After a median follow-up of 5.5 years, there was a significant advantage for the combination therapy concerning overall survival (78% versus 62%, p=0.001), clinical disease free-survival (74% versus 40%, p<0.0001), locoregional progression (1.7% versus 16.4%), metastatic progression (9.8 versus 29.2%), and survival without clinical or biochemical progress (PSA<1.5 ng/ml; 81% versus 43%, p=<0.001) (Bolla et al. 2002). Compa-

rable results concerning overall survival in combination therapy consisting of only 6 months of AD and three-dimensional conformed RT of high-risk patients are reported by D'Amico et al. (2004). A further, much smaller study of HT (n=91 patients) conducted by Granfors et al. (1998) supports these findings. The study was designed to include up to 400 patients, but after an interim analysis it was closed to further recruitment due to high frequency of disease progression in patients treated with RT alone, especially in the group with positive lymph nodes. All patients underwent bilateral lymphadenectomy. Positive lymph nodes were found in 43% of the subjects. Excluded from the study were patients with early-stage, well-differentiated, or moderately well differentiated lymph node-negative tumors. In the hormonally treated group patients underwent orchiectomy about 3 weeks after staging lymphadenectomy. RT was started 5 weeks later. In the control group, RT started 5 to 6 weeks after lymphadenectomy. After a median follow-up of 9.3 years, clinical progression was seen in 61% of the control group and 31% of the hormone group (p<0.005). The overall mortality was 61% and 38% (p<0.02) and cancer-specific mortality 44% and 27%, respectively (p<0.06). The differences in favor of combined therapy were mainly caused by lymph node-positive tumors. For node-negative tumors there was no significant difference in survival rates.

Adjuvant Hormonal Treatment

In the RTOG study 85-31 (Pilepich et al. 1997), 977 patients with stage T3–4 N0–N1 Mo or pT3 patients after radical prostatectomy showing capsule penetration or involvement of the seminal vesicles were enrolled. In the first arm, indefinite AD therapy (Goserelin in a dose of 3.6 mg given every 4 weeks) started in the last week of RT. In the control arm, HT was delayed, beginning at the time of recurrence. Of the patients, 15% in the hormone group and 29% in the control arm had undergone RP, while 14% of the patients in the hormone arm and 26% in the control arm had had pN1 PC. After a median follow-up time of 7.3 years, statistically significant differences were found in the hormone arm versus the control arm concerning local progression rates of 5 years in 15% versus 30% and of 10 years in 23% versus 39%, respectively (both p<0.0001). Concerning metastatic progression, the ratios were 15% versus 29% and in 25% versus 39%, respectively (both p<0.0001). Overall survival of 5 years was found in 76% versus 71%; there was survival of 10 years in 49% versus 38% (p<0.002). An advantage concerning overall survival was seen especially in patients with a Gleason score of 7 to 10. In a subset of the study, 95 patients of 173 with pN1 PC and immediately administered hormonal therapy in the last week of radiation therapy had a significantly better survival rate without biochemical relapse at 5 years (PSA<1.5 ng/ml) compared to the control arm (p=0.0001) (Pilepich et al. 2001, 2005; Lawton et al. 1997). Tyrrell et al. (2005) presented an analysis of the preplanned subgroup of the EPC program consisting of 305 patients who received RT with curative intent in order to determine the efficacy of bicalutamide as adjuvant setting. After a median follow-up of 5.3 years, bicalutamide significantly increased progression-free survival by 53% and reduced the risk of disease progression by 42% (p<0,0035). Objective tumor progression was experienced by 33% versus 48.6% in the control group. On the 13th European Cancer Conference in Paris, 31 October 2005, Iversen (2005) confirmed these findings and underlined that after an actual follow-up of 7.4 months the overall survival was prolonged by the addition of bicalutamide among men with locally advanced PC as compared to those who had received RT alone. In this context it must be stressed that less than 2% of the patients in this study have had lymph node involvement. It could be concluded that in this well-staged subgroup the antiandrogen bicalutamide is an effective antiandrogen when given immediately in an early stage of T3–4 PC.

Duration of Hormonal Treatment

Current studies do not give a clear indication for the optimal duration of HT in combination with RT. Is indefinite therapy (such as surgical castration) necessary? Is long-term treatment over 2 to 3 years more effective than short-term treatment only around the time of radiation? There are few

facts available; most questions are still open to speculation. Today most data support the assumption that there is an advantage of long-term over short-term HT (Horwitz et al. 2001). Two studies dealing with this issue are running comparing long-term HT (2 years=RTOG 92-02 (97) and 2.5 years=EORTC 22961) with short-term HT (up to 6 months) at the time of RT. Preliminary data showed that tumor grade is apparently a stratification parameter, as there are significant gains for long-term treatment concerning survival in patients with Gleason score 8–10 PC (Hanks et al. 2003). However, the favorable results of RT combined with HT limited to 2–3 years could have been only due to the reduction in the size of the primary tumor and the entire prostate gland, which would thereby improve the efficacy of RT. So we must reflect that, especially in high-risk subgroups and those with clinically undetected metastases, an indefinite HT may be most effective. Furthermore, we have to consider that the complications and side effects caused by indefinite or long-term AD influence the overall survival. Therefore the benefit of these traditional forms of HT in low-risk patients must be evaluated. Consequently, the question is raised again for the use of nontraditional HT (see page 216) and again data given of the EPC program blaze a trail to antiandrogen only treatment (Wirth et al. 2004; Iversen 2005).

EAU comment (Aus et al. 2005):

- *In locally advanced PC, overall survival is improved by concomitant and adjuvant hormonal therapy (with a total duration of 2 to 3 years) with external irradiation (level of evidence: 1).*
- *For a subset of patients, T2c–T3 N0-x with Gleason score 2–6, short-term AD before, and during, radiotherapy may favorably influence overall survival (level of evidence: 1b).*

Hormonal Therapy Alone

The MRC (Medical Research Council Prostate Cancer Working Party Investigators Group 1997) PR03 study conducted in men with locally advanced or asymptomatic metastatic PC recruited 938 patients between 1985 and 1993. In all, 500 patients had a nonmetastatic disease. The effect of immediate and deferred HT was investigated. According to patients' preference, orchiectomy or LHRH agonists were accepted. The first analysis in August 1996, after 74% of the patients had died, showed that 30% of the immediately treated patients and 22% of the patients with deferred treatment were still alive ($p<0.02$). In patients with nonmetastatic disease at the beginning of the study, survival was 41% in the immediately treated group as compared to 30% in the deferred treatment group. In a new analysis undertaken in 2000, when 86% of the patients had died, the results continued to show significant overall and disease-specific survival. In the subgroup of patients with nonmetastatic disease at study entry however, no significant difference could be demonstrated (Kirk 2000). However, patients with immediate therapy benefited in terms of reduced bone pain and risks of bone metastatic progression, thus diminishing the risk of complications such as pathological fracture and spinal cord compression, as well as systemic progression resulting in distant metastases and urinary flow obstruction. The Cochrane Library review analyzed four randomized controlled studies of the pre-PSA era (Byar 1973; Medical Research Council Prostate Cancer Working Party Investigators Group 1997; Jordan et al. 1977; Messing et al. 1999) comparing immediate versus delayed HT and concluded that immediate HT significantly reduces cancer progression and progression-caused complications. An improvement of cancer-specific survival could not be demonstrated, but a slight benefit in overall survival could be seen. Recently in the EPC program (Iversen et al. 2004) it was calculated that the relative effect of 150 mg/day bicalutamide on overall survival when given immediately as compared to placebo was dependent on the baseline prognostic factors PSA and tumor stage. Patients with locally advanced disease and high baseline PSA showed trends toward improved survival. On the other hand, in carefully reviewing the literature, the American Society of Clinical Oncology (ASCO) guidelines state that no recommendation could be made about when to start HT in advanced asymptomatic PC (Loblaw et al. 2004).

The time to start HT in patients with locally advanced and asymptomatic PC remains a matter of debate. However, because of the reduction of disease progression and above-mentioned

complications, immediate hormonal therapy may be recommended in locally advanced PC (T3–4, NO/N1 M0). There is a difference concerning overall survival between N0 and N1 PC. Due to the side effects of longtime or indefinite treatment, AD plays a more remarkable role than previously expected. Therefore considerations concerning treatment options such as nontraditional HT, as discussed on page 216, appear worthwhile. The second analysis of the bicalutamide EPC program (Wirth et al. 2004) supported the assumption that there is an advantage of early HT with bicalutamide (150 mg) in patients with locally advanced PC after a follow-up of 7.4 months. At the 13th European Cancer Conference in Paris, 31 October 2005, Iversen (2005) actually underlined in his third analysis the advantage of early HT with bicalutamide 150 mg/day. Although less than 2% of the patients were N+, a prolongation of overall survival could be demonstrated in patients treated with bicalutamide as compared to those with watchful waiting alone. It remains difficult to predict the best timing and the appropriate form of HT for asymptomatic advanced disease.

In summary, it can be stated that the first option for locally advanced PC is RP. There is no need for adjuvant HT after RP and pT3 N0 PC. The advanced T3 tumor cannot be cured by surgery alone. If a decision is made for RP, no benefit in terms of survival can be expected by performing NHT. Adjuvant HT is clearly indicated when lymph node metastases are proved. The wait-and-see strategy can be recommended only in a minimal N1 disease clearly documented by meticulous pelvic lymph node dissection.

After a decision for RT, data suggest the combination with HT. Patients with locally confined PC and low-risk disease (Gleason 2–6) might benefit from NHT and short-time adjuvant HT. Patients with intermediate or high risk (Gleason 7–10) need definitive RT and adjuvant long-term HT. In this subset NHT is not effective.

If curative options are not sought, the advantage of early HT in all its forms is not really proved in cT3 N0 M0 PC. Due to its minimal adverse events, bicalutamide is of advantage for prolongation of overall survival. In case of lymph node involvement (cT3 N+) early and long-term HT is recommended. In this stage an advantage of bicalutamide-only treatment has not yet been proved. Watchful waiting and deferred HT is only acceptable in asymptomatic patients with low-grade disease and without lymph node metastases.

EAU comment (Aus et al. 2005):

- *In advanced PC, all forms of castration as monotherapy (orchiectomy, LHRH-analogs and DES) have equivalent therapeutic efficacy (level of evidence: 1b).*
- *In advanced PC, AD delays progression, prevents potentially catastrophic complications and effectively palliates symptoms, but does not prolong survival (level of evidence: 1b).*
- *Nonsteroidal antiandrogen monotherapy (e.g., bicalutamide) is an effective alternative to castration in patients with locally advanced disease (level of evidence: 1b).*

Metastatic Prostate Cancer

Hormone Therapy Alone: Immediate Versus Deferred Hormone Therapy

The most appropriate time to begin HT is controversial. There is agreement that symptomatic metastatic PC needs to be treated immediately by HT. The clinical benefits include a reduction of bone pain, an improvement in performance status, and a reduction of urinary obstruction. Considerable debate remains about the impact of HT in men with asymptomatic metastases. Properly conducted randomized and controlled studies with convincing data outlining a clearly defined stage and hormonal treatment schedules are missing. So the real outcome in terms of survival and quality of life is still unclear. There are single studies demonstrating an advantage in survival for the immediately started HT. However, in the meta-analyses no significant benefit could be demonstrated. Furthermore, four randomized controlled studies of the pre-PSA era (Byar 1973; Jordan et al. 1977; Medical Research Council Prostate Cancer Working Party Investigators Group 1997; Messing et al. 1999) comparing immediate versus delayed HT were analyzed by the Cochrane Library review with the conclusion that immediate HT significantly reduces cancer progression and progression-caused com-

plications. An improvement of cancer-specific survival could not be demonstrated, apart from a slight benefit in overall survival (Schmitt et al. 2000). After a careful review of the literature, the ASCO guidelines state today that no recommendation can be given as to when to start HT in advanced asymptomatic PC (Loblaw et al. 2004).

EAU comment (Aus et al. 2005):

– *In advanced PC, immediate (given at diagnosis) androgen suppression significantly reduces disease progression and complication rate due to progression itself compared to deferred (delivered at symptomatic progression) androgen deprivation (level of evidence: 1b).*

Maximal Androgen Blockade or Castration Alone

MAB is the combination of surgical or chemical castration effectively preventing testicular androgen synthesis (95%), and of antiandrogens blocking the activation of the androgen receptor in the prostate cells caused by the persistent adrenal androgens (5%) due to their competitive binding affinity at the receptor level. Another important effect of antiandrogens consists of the blockade of the receptor by growth factors and other ligand-independent activators (Kuil et al. 1995). The latter mechanism plays an important role in receptor activation in the androgen-depleted environment of the prostate caused by castration.

The discussion concerning the benefit of MAB began in the middle of the 1980s (Labrie et al. 1985). There remain some vestiges of controversy by the advocates of MAB. Steroidal antiandrogens (cyproteronacetate) are considered to be of no advantage due to their cardiovascular and hepatotoxic side effects. Meta-analyses and systematic reviews of large trials using nonsteroidal antiandrogens document a benefit of MAB only in a small group of younger men with defined small burdens of metastatic disease over pharmacological or surgical castration alone (Seidenfeld et al. 1999; Schmitt et al. 2000; Prostate Cancer Trialists' Collaborative Group 2000). Recently Klotz et al. (2004) spoke about a reassessment of the role of MAB for advanced PC after calculating an estimated benefit of 20% in favor of MAB treatment using bicalutamide as compared to castration alone. The background is that bicalutamide is said to be a more effective antiandrogen than both flutamide and nilutamide due first to its clinically effective anticancerous properties, and second to its better-tolerated side effect profiles. Data on bicalutamide are missing for inclusion in the metaanalyses, as bicalutamide was not available when most combined versus monotherapy studies were conducted. In in vitro binding studies, Bicalutamide has shown a 2–4 times higher binding affinity for the human androgen receptor than flutamide and a two times higher affinity as compared to nilutamide (Kolvenbag et al. 1998). As a consequence, bicalutamide is much more potent in reducing the mass of intact ventral prostates of the rat. Furthermore, nonsteroidal antiandrogens differ in their interaction with the androgen receptor. For instance, bicalutamide activates the nuclear androgen receptor co-suppressor N-CoR and inhibits the co-activator SRC-1, resulting in inhibition of cell growth signals by activated androgen receptors. In contrast, flutamide activity is much more muted in this system (Hu and Lazar 2000). There are important biological differences between the nonsteroidal antiandrogens in the androgen-depleted environment. Bicalutamide is superior to flutamide and nilutamide in delaying androgen-independent progression. Bicalutamide appears to be more favorable than other antiandrogens in MAB, but its real advantage remains to be proved. Nevertheless, recently reported information about cardiovascular side effects caused by electrocardiographically proved QT-prolongation in men subjected to MAB have to be taken into consideration when a decision is made in favor of MAB. Patients with a baseline QT interval exceeding 450 ms or those taking class IA or III antiarrhythmics have to be excluded from AD plus bicalutamide, as they are at risk of sudden death by arrhythmias (Garnick et al. 2004).

The minimal advantage in survival using nonsteroidal antiandrogens (bicalutamide, flutamide, nilutamide) in the everyday clinical practice does not justify the costs this treatment generates in patients with metastatic PC. MAB is not recommended as standard therapy, since there is no general benefit to patients with metastatic disease as suggested originally by Labrie et al. (1985).

EAU comment (Aus et al. 2005):

– *In advanced prostate cancer, the addition of a nonsteroidal antiandrogen to castration results in a small advantage in overall survival over castration alone but is associated with increased adverse events, reduced QoL and high costs (level of evidence 1a).*

Intermittent Hormone Therapy

The reversibility of chemical castration, the reduction of morbidity caused by long-term HT, the amelioration of quality of life, the possibility of monitoring the course of PC by PSA, and at least the theoretical possibility of delaying hormone resistance as underlined by experimental data of IHT in murine models (LNCaP and Shionogi) (Bruchovsky et al. 1990; Sato et al. 1996) were convincing facts for beginning trials with IHT. In summarizing details of five phase II studies, Goldenberger et al. (1999) reported that the initial AD should last 9 months on average, that some on/off cycles can generally be carried out, and that quality of life in the AD-free off-phase is clearly improved as compared to the on-phase. Furthermore, we have learned that patients with initial bulky tumors, with numerous lymph nodes or bone metastases, initial serum PSA greater than 100 ng/ml, a rapid PSA progression slope of more than 5 ng/ml per month or severe pain are apparently poor candidates for IHT, since they frequently achieve only a partial or short-term response (Prapotnich et al. 2003).

Encouraging results were reported by Lane et al. (2004). They recruited 75 patients in an open, nonrandomized study initiated 10 years ago and treated them with IHT. Of the patients, 86% remain alive at a median of 134 months (11 years) after initial histological diagnosis. The authors calculated the survival time and the time to hormone resistance (from first cycle of HT). A median survival time of 95 months (8 years) was found in patients with localized or locally advanced PC. In patients with metastatic disease they reported a median survival time of 87 months (7 years). The median time to hormone resistance was calculated as 83 months in the group of localized and locally advanced PC and as 50 months in those with metastases. A 100% 5-years actual survival rate was found for those with localized and locally advanced PC and a 70% 5-years actual survival rate for patients with metastatic disease. The authors' opinion is that IHT is safe and effective and they suggest an apparent survival advantage related to a delay in the onset of androgen resistance.

After having treated 72 men with localized, advanced, or metastatic PC, De La Taille et al. (2003) recommend IHT for PC patients aged more than 70 years with localized PC and a Gleason score of 7 or lower. The 24 patients with biochemical progression were younger than those with no biochemical progression and had a statistically higher Gleason score. Sciarra et al. (2000) also mentioned that the Gleason score is an important variable. Of the 12 cases with a Gleason score of 8 or higher, 9 failed to respond to IHT and all developed metastatic and/or local failure. No case with Gleason score below 7 failed to respond.

Strum et al. (2000) pointed out that hormone-naive patients who achieved and maintained an undetectable PSA level for at least 1 year during HT might anticipate a prolonged off-phase. Achievement of long, undetectable PSA levels may serve as an in vivo sensitivity test of a patient's tumor cell population and allow for a better selection of patients best suited for IHT.

The first randomized phase III trial was conducted by de Leval et al. (2002). They compared the efficacy of total IHT (35 patients) with continuous MAB (33 patients). The study suggested that IHT could maintain the androgen-dependent state of advanced PC at least as long as continuous MAB.

Another interesting option of IHT is the so-called intermittent triple androgen blockade, reported by Leibowitz and Tucker (2001). There were 110 patients with T1 to T3 PC treated with a three-drug androgen blockade regimen, consisting of an LHRH agonist, an antiandrogen, and finasteride, followed by finasteride maintenance therapy in the off-phase. The long-term experiences were encouraging. In all patients PSA levels declined to 0.1 ng/ml or less in a median time of 3 months. After a median follow-up of 36 months after initiation of treatment, PSA levels have remained stable in 105 of 110 patients. No patient has received a second cycle of hor-

mone blockade. Recently Eggener et al. (2005) illustrated the theoretical background. In contrast to DHT, T is a weak inducer of proliferation and a more potent inducer of tumor differentiation. Finasteride increases T and decreases DHT during the off-phase and enhances the efficacy. The authors reported on experiments in which they established LNCaP tumors in nude mice. Finasteride administered in the off-phase of IHT provided the most favorable tumor growth kinetics and survival when compared to MAB or standard IHT.

The use of IHT is increasing, but despite theoretical advantages in terms of possible delay of hormonal resistance and of quality of life, randomized clinical trials with large patient cohorts, long follow-up, and comparable study designs have to prove its superiority to continuous HT. The available studies document the feasibility of IHT in the treatment of patients with metastatic disease, as well as of those with locally confined PC with PSA relapse after RP or RT. Nevertheless, until more data regarding its safety and impact on survival are available, IHT should be considered experimental, and results of running phase III prospective, randomized controlled studies must be awaited. We need clear therapeutic strategies and trigger points guided by PSA (Pether and Goldenberger 2004).

EAU comment (Aus et al. 2005):

- *Intermittent AD should still be regarded as experimental therapy (level of evidence: 3).*
- *In advanced PC, all forms of castration as monotherapy (orchiectomy, LHRH and DES) have equivalent therapeutic efficacy (level of evidence: 1b).*
- *Bilateral orchiectomy may be the most cost-effective form of AD, especially if initiated after occurrence of symptoms from metastatic disease (level of evidence: 3).*

Hormone Refractory Prostate Cancer

The stage of the illness following progression after AD or MAB is termed hormone-refractory disease. The median overall duration of response to HT in patients with metastasizing PC is only 18 to 36 months, even when AD is given in combination with long-term antiandrogens.

The following EAU criteria of HRPC must be fulfilled (Aus et al. 2005): (1) serum castration levels of T; (2) three consecutive rises of PSA 2 weeks apart resulting in two 50% increases over the nadir; (3) antiandrogen withdrawal for at least 4 weeks (either antiandrogen withdrawal, or one secondary hormonal manipulation should have been done); (4) PSA progression, despite secondary hormonal manipulations; (5) progression of osseous or soft tissue lesions.

In defining the status of HRPC, we must distinguish two forms. (1) The androgen-independent, but hormone-sensitive HRPC implies that disease progression occurs despite castration. However, the tumor remains sensitive against further different forms of HT due to its tremendous heterogeneity. Small et al. (1997) could demonstrate that certain hormone refractory cases retain hormonal sensitivity even after progression following antiandrogen withdrawal or change in antiandrogen application (second-line hormonal therapy; duration 6–10 months) making possible an effective further treatment with ketoconazole, aminoglutethimide, glucocorticoids, or estrogens (third-line hormonal therapy; duration 4–8 months). Finally, PC will uniformly become "hormone refractory" (Ryan and Small 2005). (2) The second form is the true HRPC from the outset. This tumor is resistant to all hormonal manipulations.

Different forms of cancer resistance developing at different unpredictable time intervals can be attributed to the heterogeneity of PC cells. Reasons discussed are multifactor mechanisms such as mutation and amplification of the androgen receptor gene, deregulation of apoptosis, loss of microtubule integrity, and loss of autocrine stimulation of growth factors (Visakorpi et al. 1995; Taplin et al. 1995; Fenton et al. 1997; Isaacs 1999). The estimated natural mean survival of patients with HRPC is 18–20 months in case of asymptomatic disease and high PSA level in patients with no metastasis. With minimal metastases it is 14 months, and with extensive metastases 9–12 months. If metastases become symptomatic, natural mean survival declines to 9 months in men with minimal metastases and to 6–8 months in men with extensive metastases (Aus et al. 2005). However, primary androgen resistance does not mean that PC is resistant a

priori to further androgen stimulation. At the time of androgen relapse some hormonal-sensitive clones may still exist. From the therapeutic point of view it is advisable to continue AD treatment, for example with LHRH agonists during the following treatment schedules, since after a withdrawal of AD, DHT and T levels return to normal after a median of 16.6 weeks (Gulley et al. 2005). In this case, PC growth accelerates and reduces survival (Taylor et al. 1993).

A valid therapeutic response is defined by the following EAU guidelines (Aus et al. 2005): PSA decline of more than 50% maintained for 8 weeks; assessment according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria in case of nonosseous metastases; in patients with advanced symptomatic metastatic HRPC, therapeutic response can be best assessed by improvement of symptoms.

Each period of response may be short and may last only a few months. Therefore it is important to establish an effective long-term strategy for HRPC. Despite the recently reported promising outcome of a docetaxel-based regimen showing a significant effect on survival, toxicity is grave and hardly tolerated in elderly patients. The challenge is to better understand the multifactor endocrinological, immunological, and genetic correlations in the PC cells that make it possible to open new pathways for effective combination strategies and to develop better means to avert a total hormone refractory PC.

Second-Line Hormonal Therapy

In case of hormone relapse after simple AD, additive treatment with antiandrogens is indicated before starting second-line HT. However, flutamide (Fossa et al. 1990) as well as bicalutamide (Joyce et al. 1998) administration in patients previously untreated with antiandrogens have a modest response. Joyce reported a response rate of only 6% for those patients treated with 150 mg bicalutamide after simple primary androgen deprivation failed. The mean duration of response lasts 4 to 6 months on average.

Progression Under Maximal Androgen Blockade

When progression occurs, the therapy must be switched. If initial MAB was performed using flutamide as antiandrogen, a substitution of flutamide with high-dose bicalutamide is advisable. Scher et al. (1997), McLeod (1993), and Joyce et al. (1998) reported that bicalutamide is a stronger and more effective antagonist of the native androgen receptor than flutamide. Furthermore, a 3 to 4 times higher dose (150 up to 200 mg daily) should be applied to maximize androgen receptor blockade. If this maneuver fails, a further promising step of second-line HT is the withdrawal of antiandrogens after long-term MAB. Approximately one-third of patients will respond to antiandrogen withdrawal as indicated by a decline of PSA exceeding 50%. The mean duration of response amounts to 5 to 6 months (Scher and Kelly 1993).

The androgen receptor activation may occur by stimulation of hormones or antihormones (Culig et al. 1993). These observations, taken together with the fact that the androgen receptor continues to be expressed and is often overexpressed in PC metastases (Visakorpi et al. 1995), have led to the hypothesis that continued stimulation of the androgen receptor pathway may still be critical for cancer cell survival. There must be a change in receptor function. How can we explain the paradoxical form of hormonal therapy in HRPC in which 25%–40% of patients after having profited for a long time from antiandrogen application with the aim of killing PC cells, will suddenly reverse and respond with temporary tumor remission caused by antiandrogen withdrawal (Scher and Kelly 1993)?

The mechanisms explaining the positive effects of antiandrogen withdrawal are not known with certainty. But it must be assumed that long-term treatment of antiandrogens e.g., flutamide, directly stimulates tumor cell growth in some patients with androgen-independent PC due to androgen receptor gene mutations and/or its amplification, supporting the paradoxical antiandrogen cancer stimulation. For instance, LNCaP cells developed from a patient with androgen-independent disease provide a possible paradigm for the flutamide withdrawal response. Due to

an androgen receptor mutation, these cells are stimulated in vitro by flutamide as well as estradiol and progesterone (Olea et al. 1990; Joyce et al. 1998). Patients who have been treated with flutamide or bicalutamide over a long period of time are better responders to antiandrogen withdrawal. In case of flutamide, clinical impact can be expected after a few days, in case of bicalutamide in a few weeks (Schellhammer et al. 1997).

EAU comment (Aus et al. 2005):

- *It is recommended to cease antiandrogen therapy once PSA progression is documented.*
- *Four to 6 weeks after discontinuation of flutamide or bicalutamide, an eventual antiandrogen withdrawal effect will become apparent (Grade B recommendation).*

Progression After Antiandrogen Withdrawal

In addition to the above-described possibility of androgen receptor mutation, it was found that some mutant androgen receptors capable of being stimulated by flutamide were paradoxically inhibited by the structurally different antiandrogen bicalutamide or vice versa. Joyce et al. (1998) observed a dramatic response rate of 43% exclusively in patients treated with long-term flutamide as part of a MAB when administering bicalutamide at 150 mg a day. Comparable results were reported by Scher et al. (1997). They discussed that bicalutamide may be a more effective antagonist of the native androgen receptor than flutamide, which has weak agonist activity for the wild-type receptor (Wong et al. 1995; Fenton et al. 1997). Even if flutamide withdrawal is not effective in progressive androgen-resistant PC, bicalutamide may succeed. If flutamide withdrawal is successful, bicalutamide treatment is recommended in case of a new relapse. Flutamide was administered after a first relapse of MAB using bicalutamide and after a relapse of bicalutamide withdrawal (Miyake et al. 2005). A 22% response rate was reported with a median interval of response of 6 months. In this series, nonresponders tended to have a higher incidence of bone metastases and a shorter response period to first-line therapy than responders. Kojima et al. (2004) have reported better results with a 50% response. However, this report was based on only 10 patients. Bicalutamide and flutamide are not completely cross-resistant, and therefore their alternative use in MAB or as second-line HT after MAB relapse may be reasonable in some cases (Joyce et al. 1998).

The first two small retrospective studies that evaluated the efficacy of nilutamide as a second-line therapeutic tool were presented by Desai et al. (2001) and Kassouf et al. (2003). They reported a PSA level decrease of more than 50% in 50% and 43% of patients, with a median response duration of 11 and 7 months, respectively. In another retrospective study, nilutamide appears to work as second-line hormonal therapy, after bicalutamide or flutamide failed in 40% of patients. The median time to progression was 4.4 months. In this study some patients benefited from nilutamide even when it was used as fifth-line hormonal therapy (Nakabayashi et al. 2005). However, a recently published prospective phase II study of nilutamide in men with PC after failure of flutamide or bicalutamide was discontinued after an interim analysis because nilutamide had no apparent effect (Davis et al. 2005). Randomized clinical trials are necessary in order to clarify these controversies and to assess whether nilutamide offers any survival benefit.

Antiandrogens share a comparable common chemical structure required for interaction with the androgen receptor. Despite functional similarities, each antiandrogen appears to interact uniquely with the androgen receptor as shown in vitro in androgen-dependent LNCaP cells (Olea et al. 1990). Compared to flutamide and bicalutamide, nilutamide has a unique interaction with the ligand-binding domain of the receptor when analyzed by three-dimensional crystal structure. An Asn705 residue in the ligand-binding domain of the androgen receptor is crucial in anchoring flutamide and bicalutamide, but has not such a role in the case of nilutamide (Marhefka et al. 2001). This may be the reason why nilutamide is discussed as the antiandrogen of choice when other antiandrogens have failed (Nakabayashi et al. 2005). Nilutamide side effects are: mild and reversible visual changes (light-to-dark adaptation), fatigue, alcohol intolerance, and respiratory symptoms.

Third-Line Hormonal Therapy

The adrenal glands are the second source of androgen production in man. The androgens androstenedione and dehydroepiandrosterone are converted in a first step to T in peripheral tissues and in the prostate gland, and converted in a second step to DHT. This androgen production makes up approximately 5% of total androgens. In HRPC some tumor clones remain sensitive to these hormones even after progression following antiandrogen withdrawal or change in antiandrogen medication. An elimination of the androgen production in the adrenal glands and a blocking of stimulation of these tumor clones is possible using aminoglutethimide, ketoconazole, estrogens, and glucocorticoids.

Aminoglutethimide together with hydrocortisone has a reported average response rate of 10% (Dawson 1993). More favorable response rates could be achieved when aminoglutethimide was administered after flutamide withdrawal (Sartor et al. 1994). Fatigue, sickness and nausea, erythema, orthostatic hypertension, and ataxia were noted as side effects.

Ketoconazole blocks the testicular and adrenal production of androgens. A direct cytotoxic effect on PC cells is discussed in Rocklitz et al. (1988). Response rates of ketoconazole and hydrocortisone of 15%, lasting 6 to 9 months are reported, when 400 mg oral ketoconazole is administered every 8 h and 20 mg oral hydrocortisone each morning plus 10 mg orally each evening (Small et al. 1997). In a recently published randomized prospective study, Small et al. (2004) reported a significant advantage of the combination therapy consisting of antiandrogen withdrawal and additive ketoconazole application, as compared to ketoconazole alone. Furthermore, ketoconazole is effective, especially when given to patients who have responded to antiandrogen withdrawal. According to Wilkinson and Chodak (2004), the daily ketoconazole dose in combination with 30 mg oral hydrocortisone can be reduced to 600–800 mg with comparable effectiveness. Ketoconazole is better tolerated than aminoglutethimide. Toxicity is mild and includes nausea, sickness, fatigue, edema, hepatotoxicity, and rash.

Glucocorticoids and estrogens caused a decrease of the adrenal androgen production as regulated over the feedback mechanism. A response rate after administration of glucocorticoids can be expected in 10% of the cases (Tannock et al. 1996; Kantoff et al. 1996). The role of estrogens in the treatment of HRPC is discussed anew. The rationales are interesting as well as speculative. However, a positive effect has been reported only in single case experiences. On the one hand, estrogen receptors are found in PC cells and they can be upregulated by castration in the animal model. On the other hand, Taplin et al. (1995) demonstrated in vitro an activation of a mutated androgen receptor isolated from hormone-independent PC cells when estrogens were added. These findings offer different therapeutical options for the HRPC. In a pilot study, Horton et al. (1988) reported response rates of 10% after administration of antiestrogens. An estrogen withdrawal may also be effective in some cases. Finally, a high dose of intravenously applied estrogen push therapy is an established polypragmatic therapeutic tool in the painful stage of metastatic HRPC. The mechanism of palliation remains unclear. The most frequently discussed explanation is a direct cytotoxic effect caused by mitotic arrest (Ferro et al. 1989).

EAU comment to substitution of antiandrogen and third-line HT (Aus et al. 2005):

– *No clear cut recommendation can be made regarding the most effective drug for secondary/tertiary hormonal manipulations since data from randomized trials are scarce (grade C recommendation).*

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14 Androgen-Independent Prostate Cancer

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Abstract

Androgen-independent or hormone-refractory prostate cancer (AIPC) is prostate cancer that progresses after primary androgen-ablation therapy—either orchiectomy or a gonadotropin-releasing hormone (LHRH) agonist, followed by addition and subsequent withdrawal of an antiandrogen. In the majority of patients, AIPC appears after a median time of 18 months of hormone deprivation. Patients with AIPC have a median survival between 10 and 20 months and the prognosis can be defined by using nomograms. Standard treatment is continued castration by LHRH agonists in combination with docetaxel-containing chemotherapy. Other treatment options to palliate symptoms are hormones, other chemotherapeutic agents, radioisotopes or radiotherapy and bisphosphonates. New targeted drugs and vaccination strategies are evaluated in the treatment of AIPC.

Epidemiology

Androgen-independent or hormone-refractory prostate cancer (AIPC) is defined as prostate cancer that progresses after primary androgen-ablation therapy by either orchiectomy or a gonadotropin-releasing hormone (LHRH) agonist, followed by addition and subsequent withdrawal of an antiandrogen (Scher et al. 1995).

At diagnosis, AIPC is observed in less than 20% of patients with advanced prostate cancer (Mahler and Denis 1995). In the majority of patients, AIPC appears after a median time of 18 months of hormone deprivation. Patients with AIPC have a median survival between 10 and 20 months.

Pathophysiology

Androgens are the primary regulators of cell growth and proliferation of prostate cancer cells. When androgens are ablated or withdrawn, apoptosis is observed in a proportion of cells, while those that survive remain in the G1 phase of the cell cycle. Clinical progression is the result of regrowth of cells that are primarily resistant to androgen ablation or which, after a period of growth arrest, adapt to the low-androgen environment and resume proliferation (Scher and Sawyers 2005).

Androgen Receptor-Related AIPC

The androgen receptor (AR) plays a critical role in the development of AIPC. The androgen-receptor gene is the only gene that is consistently upregulated during tumor progression in different AIPC experimental models, and it seems that tumor progression despite androgen deprivation is associated with an active AR signaling pathway.

In patients with AIPC, a number of changes in the AR signaling pathway have been described (Scher and Sawyers 2005; Fig. 14.1):

- Changes in the level of ligand(s) in tumor tissue
- Increased levels of the AR protein due to gene amplification or altered messenger (m)RNA expression
- Activating mutations in the receptor that affect structure and function
- Changes in coregulatory molecules including coactivators and corepressors
- Factors that lead to activation of the receptor independent of the level of ligand or receptor by kinase crosstalk

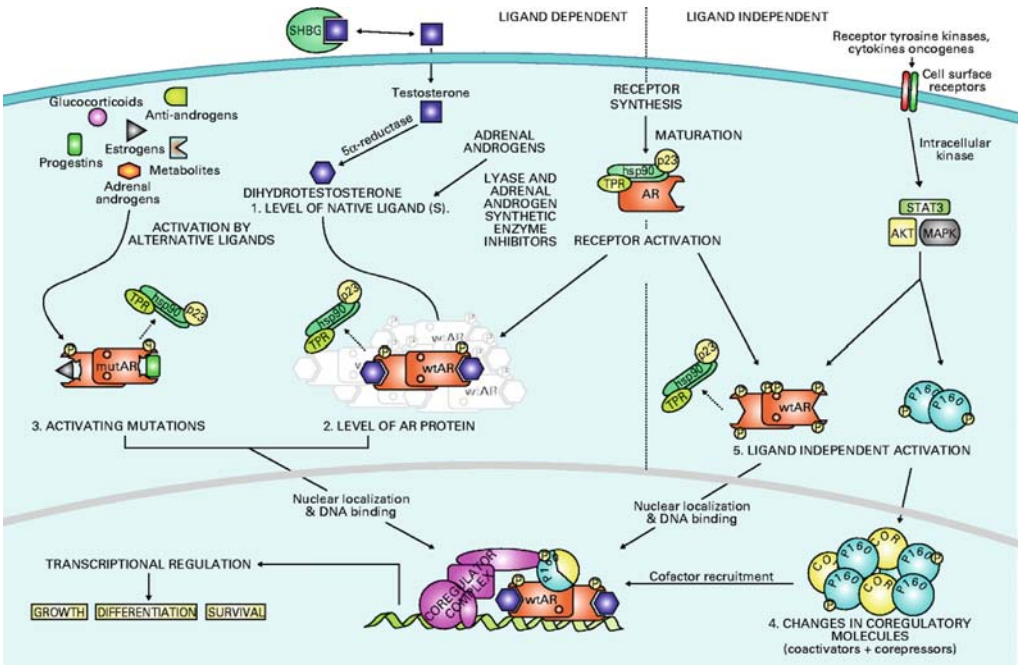

Fig. 14.1 Classification of mechanisms associated with continued signaling through the androgen-signaling axis despite castration

Incomplete Blockade of AR Ligand Production

Medical and surgical therapies that ablate production or androgen action do not result in undetectable androgen levels in tumor tissue. Intratumoral testosterone levels in patients with castration-resistant disease are similar to untreated benign prostatic disease, and the level of dihydrotestosterone is sufficient to maintain AR signaling and expression of prostate-specific antigen (PSA). Intratumoral androgens may come from an adrenal source or from direct synthesis within the tumor by an intracrine mechanism. Therefore, prostate tumors rarely encounter a completely androgen-depleted environment.

Increased Levels of AR Protein Without Mutation

Amplification of the *AR* gene has been documented in 20%–25% of both castration-resistant metastatic and recurrent primary tumors. The increase in AR protein sensitizes prostate cancer cells to respond to low levels of ligand.

AR Mutations

AR mutation rates in human prostate cancer range from 5%–50% depending on tumor status (primary versus metastatic, pre- versus post-androgen ablation) and prior therapy. The majority of mutations are in the ligand-binding domain, and most of the mutations are associated with gains as opposed to a loss of function and produce a receptor that is more sensitive to native ligand, or that can be activated by other steroid hormones and/or by the specific antiandrogen.

Indirect Mechanisms of AR Activation

Coactivators that enhance or corepressors that reduce receptor function mediate the transcriptional activity of the *AR*.

Coactivator proteins such as ARA54 and ARA70 can selectively enhance the activity of the receptor to alternative ligands such as estradiol and hydroxyflutamide, can sensitize the receptor to lower concentrations of native and non-na-

tive ligands, or allow ligand-independent activation by receptor tyrosine kinases (RTKs) such as HER2.

Decreased expression of corepressors such as nuclear receptor corepressor (N-CoR) and silencing mediator of retinoid and thyroid receptors (SMRT), which mediate, in part, the antagonist action of bicalutamide, flutamide, and mifepristone, may contribute to the agonist activity that can be observed with these agents.

A change in the coactivator-to-corepressor ratio can alter AR transactivation activity in the presence of low concentrations of dihydrotestosterone. Conversely, the corepressors SMRT and N-CoR can inhibit AR function in a ligand-dependent manner.

Alterations in the coactivator-to-corepressor ratio can explain the paradoxical agonist effects of antiandrogens and other steroid hormones on prostate cancer growth. Coactivators may play a role in castration-resistant disease.

HER-2/*neu*, a member of the epidermal growth factor receptor (EGFR) family of RTKs is consistently overexpressed at a higher frequency in castration-resistant as opposed to hormone-naïve primary tumors. HER2, and other growth factors such as keratinocyte growth factor, insulin-like growth factor-1, and epidermal growth factor, and cytokines such as interleukin-6, can activate the AR and minimize or possibly even negate the requirement for ligand. HER-2/*neu* is thought to promote DNA binding and AR stability through activation of mitogen-activated protein kinase (MAPK) and Akt, which can also bind directly to the receptor.

Androgen Receptor-Independent Mechanisms

Neuroendocrine cells are present in prostate stem cells and increase in AIPC. Neuroendocrine cells have a low rate of proliferation, which permits them to survive many different types of treatment. In addition, neuroendocrine cells secrete neuropeptides such as serotonin and bombesin, which can increase the proliferation of neighboring cancer cells, thereby allowing progression of AIPC. Neuroendocrine cells are present in 40%–100% of patients with AIPC (Debes and Tindall 2004).

Another pathway that bypasses the AR involves the deregulation of apoptotic genes. The tumor-suppressor gene *PTEN* and the antiapoptotic gene *Bcl-2* play important roles in AIPC. PTEN inhibits the phosphatidylinositol 3-kinase pathway in normal cells. Activation of this pathway stimulates a protein called Akt, which inactivates several proapoptotic proteins, thus enhancing cell survival.

In the normal prostate, PTEN allows cells to undergo apoptosis, whereas in cancer cells and in AIPC the loss of PTEN increases Akt activity and blocks apoptosis. Loss of PTEN function is infrequent in androgen-dependent prostate cancer. Inactivation of PTEN is considerably more likely to occur in AIPC. One of the primary targets of Akt, when it is blocking apoptosis, is Bcl-2. Activated Akt frees Bcl-2 (which is bound to a protein called Bad), allowing it to increase cell survival. Overexpression of Bcl-2 has been implicated in the progression to AIPC (Gleave et al. 2002).

Evaluation

A patient is having AIPC if there is disease progression after treatment with a standard hormonal regimen with androgen-ablation therapy (usually orchiectomy or LHRH agonist), followed by addition and subsequent withdrawal of an antiandrogen. He should be treated with this regimen for at least 4 weeks and his serum testosterone level should be below 30 ng/ml (Small et al. 2004).

Baseline studies should include a complete blood cell count, alkaline phosphatase, serial PSA levels (Bubley et al. 1999; Sartor et al. 1999), lactate dehydrogenase, albumin, testosterone level, chest X-ray, plain radiographs of painful bony sites, bone scan, and imaging of disease (e.g., abdominal CT scan in case of retroperitoneal lymph node metastases).

In addition, quality of life [e.g., European Organisation for Research and Treatment of Cancer (EORTC), QLQ-C32, and a module of ten questions specific for metastatic prostate cancer] and symptom measures (e.g., pain, including present pain intensity, visual analog scale), comorbid conditions and a geriatric assessment should be included in the evaluation of patients with AIPC (Curran et al. 1997).

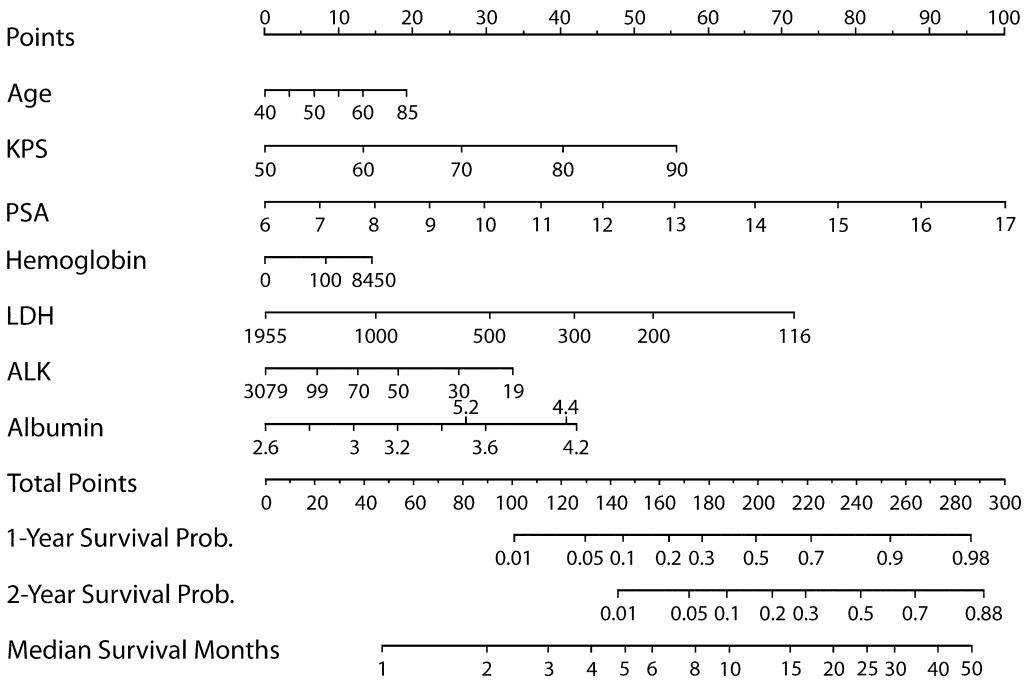

Fig. 14.2 Nomogram for survival of patients with progressive castrate metastatic disease

Prognosis of AIPC

There are several prognostic models that are predictive of survival in men with AIPC.

- In the model of Berry et al., a short survival is seen in patients with an age exceeding 65 years, severe bone pain, poor performance status, presence of soft tissue metastases, anemia, and elevated levels of lactate dehydrogenase (LDH), acid phosphatase, alkaline phosphatase, and prolactin (Berry et al. 1979).
- In the model developed by Emrich et al., identified factors that were predictive of survival in order of importance were previous hormone response, anorexia, elevated acid phosphatase, pain, elevated alkaline phosphatase, obstructive symptoms, tumor grade, performance status, anemia, and age at diagnosis (Emrich et al. 1985).
- Kantoff et al. (1999) identified the following prognostic factors: alkaline phosphatase, LDH, baseline PSA, and hemoglobin.
- Other factors identified in other studies were greater than 50% decline in PSA, changes in PSA after therapy, weight loss, extent of bone metastasis, pretreatment serum testosterone level, and any decline in PSA. Biologic markers such as plasma and urine vascular endothelial growth factor and reverse transcriptase polymerase chain reaction for PSA have been identified as statistically significant predictors of overall survival in patients with AIPC.
- There have also been developed pretreatment nomograms to predict survival in patients with AIPC (Figs. 14.2 and 14.3) (Smaletz et al. 2002; Halabi et al. 2004).

Treatment

Standard treatment options for patients with AIPC include secondary hormonal therapies or chemotherapy. In patients without prior orchiectomy, castration with an LHRH agonist is maintained. The treatment choice depends on the

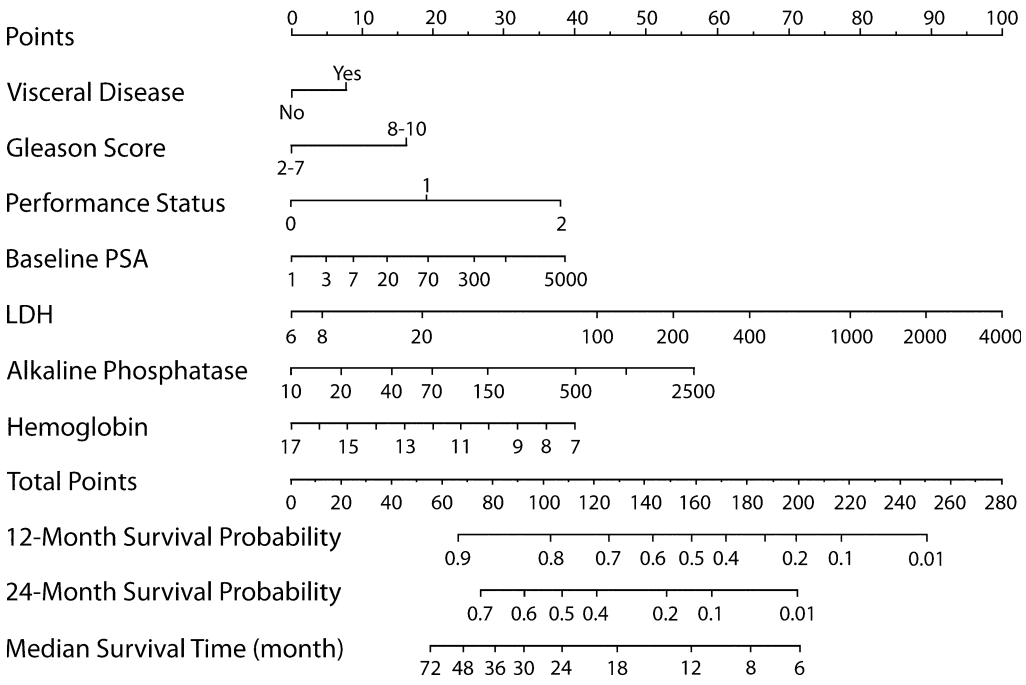

Fig. 14.3 Pretreatment nomogram predicting probability of survival. Instructions to physicians: Please start from the *second top axis* by identifying the disease measurability. Draw a vertical line to the points axis (*top line*) to represent the number of prognostic points the patients will receive for measurable disease. Do the same for the other prognostic variables. Once all prognostic points for the predictors have been determined, add up the prognostic points for each prognostic variable. You can determine the 12-month survival probability by drawing a vertical line down from the "total points axis" (*fourth from the bottom*) to the 12-month survival probability axis (*third line from the bottom*). The same process can be done to estimate the 24-month survival probability

impact of the disease on the quality of life, the expected beneficial effect, and the general condition of the patient.

In patients with painful bone metastases, external radiotherapy, radionucleotides, and bisphosphonates may be beneficial.

Hormonal Manipulation

For patients that progress on both an LHRH agonist and antiandrogen, the withdrawal of antiandrogen therapy results in a response in 25%–50% of patients.

In patients with a frail condition and/or slowly progressing disease, hormonal manipulations may be useful. These hormonal manipulations include prednisone or other glucocorticoids, ketoconazole, and estrogens such as diethylstilbestrol. Although secondary hormonal manipulation may produce a subjective response in approximately 25%–50% of patients, it is short-lived (approximately 4 months).

Prednisone and Dexamethasone

Glucocorticoids may lead to PSA responses or relief of symptoms (or both) in patients with late-stage prostate cancer. Corticosteroids depress adrenocorticotropic hormone secretion leading to suppression of adrenal androgen release. A randomized EORTC phase III study comparing flutamide with prednisone in patients with prostate cancer who were progressing symptomatically after androgen ablative therapy found similar PSA response rates (±20%), and prednisone was superior in terms of pain control

and overall quality of life (Fossa et al. 2001). In most patients who have been treated with first-line chemotherapy, corticosteroids are added; the potential benefit in these patients is therefore probably minimal.

Ketoconazole

Ketoconazole is an inhibitor of steroid synthesis and must be administered with hydrocortisone or prednisone. It may increase the probability of an antiandrogen withdrawal response, although this does not result in improved survival. When used after prior chemotherapy it is associated with occasional PSA responses, although these responses are usually transient (Berthold et al. 2005).

Estrogens

Estrogens, such as oral diethylstilbestrol (DES) have been shown to be associated with PSA responses and improved symptoms in several small trials when used after failure of other hormonal measures. However, they must be used with caution since they may cause thrombosis and cardiovascular events. These side effects are usually not a major problem if the dose of DES is at or below 3 mg/day (Berthold et al. 2005).

Chemotherapy

Several clinical trials have evaluated the role of both single agent and combination chemotherapy in the treatment of AIPC. Some of these trials have demonstrated encouraging results in disease control, PSA response, radiological responses, overall survival, and improvement in quality of life. At the moment, the combination of docetaxel and prednisone is considered as the standard treatment in men with AIPC.

Estramustine

Estramustine is a 17-β-estradiol phosphate derivative linked to a nor-nitrogen mustard molecule and binds to microtubule-associated proteins (MAPs) in the nuclear matrix and inhibits microtubule assembly and disassembly.

As a single agent, estramustine has shown an overall response rate of 14%–48%, with subjective improvements in pain and performance status. The addition of estramustine to other spindle poisons such as vinblastine, vincristine, and paclitaxel improves the response rates compared to these agents alone, although there is no improvement of overall survival. Common side effects of estramustine are nausea, vomiting, and thrombosis secondary to the high estrogen content (Goodin et al. 2002).

Vinca Alkaloids

Vinblastine, an agent that binds to tubulin and prevents microtubule assembly, is active in patients with prostate cancer and has a response rate of 21% when used as a single agent in continuous infusion. In combination with estramustine, the response rate, as measured by PSA, has varied from 40%–54% while several studies showed an improvement in pain control. Vinorelbine, a newer vinca alkaloid, has shown a clinical benefit in 40% of 15 patients in a phase II study. Studies combining vinorelbine with other agents are ongoing (Goodin et al. 2002).

Topoisomerase II Inhibitors

Etoposide is a topoisomerase II inhibitor that acts at the nuclear matrix and has a synergistic effect with estramustine. In phase II studies, a response rate of 39%–50% was seen with this combination, but some of the regimens were associated with major toxicities including grade 3 or 4 leukopenia and nausea in 25% and 29% of patients, respectively.

Doxorubicin is another a topoisomerase II inhibitor; it has a single agent activity of 5%–84% in prostate cancer, depending on response criteria. Combinations of doxorubicin with either ketoconazole (response rate 45%) or cyclophosphamide (response rate 33%–46%) have been reported in phase II trials. These combinations led to substantial hematologic toxicity (Goodin et al. 2002).

Mitoxantrone in combination with prednisone was approved for the treatment of AIPC based on palliative endpoints in randomized phase III trials (Tannock et al. 1996; Kantoff et al. 1999). Patients with AIPC were given prednisone, 10 mg orally each day alone or in combination with mitoxantrone, 12 mg/m² intravenously every 3 weeks. Patients who received mitoxantrone plus prednisone achieved a statistically significant greater palliation of symptoms, including pain, compared with those who received prednisone alone (29% versus 12%, p=0.01) along with a significantly longer duration of symptom palliation (43 versus 18 weeks, p <0.0001). Toxicity was mild, with the exception of a decreased left ventricular ejection fraction in the mitoxantrone group. There was no difference in survival between the groups.

Taxanes

Docetaxel induces apoptosis by interfering with the microtubule formation during mitosis and inhibiting Bcl-2. Docetaxel phosphorylates Bcl-2 at serine residues, which inactivates this protein and leads to the activation of the caspase cascade and apoptosis. Docetaxel also inhibits the growth of Bcl-2-negative tumors by inducing overexpression of the cell cycle inhibitor p27, which is frequently lost in AIPC.

Docetaxel treatment has become the new standard treatment in patients with AIPC, replacing mitoxantrone based on the results of two independent phase III trials showing that taxane-based chemotherapy led to a survival benefit in men with AIPC (Tannock et al. 2004; Petrylak et al. 2004).

In a large international trial, two schedules of docetaxel and prednisone were compared to mitoxantrone and prednisone in 1,006 men with AIPC. They were randomly assigned to docetaxel 75 mg/m² every 3 weeks, docetaxel 30 mg/m² once weekly for 5 weeks, or mitoxantrone 12 mg/m² every 3 weeks. All patients also received 5 mg oral prednisone twice daily. The 3-week schedule of docetaxel increased survival by 24% as compared to mitoxantrone. The median survival was 18.9 months in the every-3-week docetaxel group, 17.4 months in the weekly docetaxel group, and 16.5 months in the mitoxantrone group. Pain reduction was most pronounced in those that received docetaxel every 3 weeks (35% compared with 31% on weekly docetaxel and 22% on mitoxantrone) (Tannock et al. 2004).

Another trial compared docetaxel and estramustine to mitoxantrone and prednisone. Of the 674 patients eligible for the trial, 338 received docetaxel (60 mg/m² every 21 days) and estramustine (280 mg three times daily over 5 days). The other 336 received mitoxantrone (12 mg/m² every 21 days) and prednisone (5 mg twice daily). In an intention-to-treat analysis, the median overall survival was longer for patients receiving docetaxel and estramustine than with mitoxantrone and prednisone, with a 20% reduction in the risk of death in favor of the docetaxel group. Median survival in the docetaxel and estramustine arm was 17.5 months, compared to 15.6 months. The median time-to-progression was 6.3 months compared to 3.2 months. PSA declines of at least 50% occurred in 50% of the patients treated with the docetaxel-based regimen, compared to about 25% of patients in the mitoxantrone group. Grade 3 or 4 neutropenic fever, nausea and vomiting, and cardiovascular events were more common among patients receiving docetaxel and estramustine than among those receiving mitoxantrone and prednisone (Petrylak et al. 2004).

These studies show that a docetaxel-based regimen can improve survival by a median of 2 to 2.5 months and reduce the risk of death by 20% to 24% in comparison to mitoxantrone. In addition to an improvement in survival, docetaxel was linked to an increase in time to disease progression, PSA declines, and quality of life.

Epothilones

Epothilones have significant antitumor activity in *in vitro* and *in vivo* models insensitive or resistant to taxanes. They induce microtubule bundling, formation of multipolar spindles, and mitotic arrest. Although reversible neurotoxicity is the predominant toxicity, an advantage is that no corticosteroid premedication is required.

Ixabepilone is a new epothilone and has potent cytotoxic effects on paclitaxel-sensitive and insensitive cells, and in taxane-resistant tumor cell lines overexpressing P-glycoprotein. It is given in an intravenous dose schedule of 40 mg/m² every 3 weeks and induces PSA responses in patients with AIPC of ±40%.

The response rate increases when ixabepilone is combined with estramustine with responses in ±70% of patients with AIPC. Neutropenia and neuropathy are the main adverse events, with 9% of patients having a grade 3–4 thrombotic event (Berthold et al. 2005).

Platinum Compounds

Several older phase II trials showed a moderate activity of cisplatin and carboplatin as single agents or in combination with other chemotherapeutic agents, with response rates varying between 14%–30%. The newer agent oxaliplatin induced a PSA response rate of 8% with a clinical benefit in 32% of patients.

Satraplatin is an orally bioavailable platinum compound, and in an EORTC Genitourinary Tract Group trial, a PSA decrease of more than 50% was seen in 8.7% on prednisone versus 33.3% on satraplatin, with better progression-free survival on the satraplatin arm (Sternberg et al. 2005).

Based on these data, docetaxel treatment in combination with prednisone should be considered first-line standard treatment in patients with AIPC. Currently, it is unclear how the effectiveness of mitoxantrone is affected when it is used as second-line treatment after docetaxel compared with the results seen in first-line studies.

Overall, the PSA response rate to docetaxel after initial treatment with mitoxantrone seems similar to that achieved with first-line treatment (response rate 44%–85%), whereas a relatively low proportion of patients respond to mitoxantrone after first receiving docetaxel (response rate 6%–15%). Tolerability seems to be somewhat worse than for first-line chemotherapy, with about 45%–65% of patients requiring a delay, dose reduction, or cessation of chemotherapy in the second-line setting (Berthold et al. 2005).

The role of the newer cytotoxic agents should be evaluated in randomized clinical trials.

Targeted Therapies

Several new agents based on translational research are being tested in patients with AIPC.

Oblimersen

Bcl-2 is an important pro-survival regulator of apoptotic cell death. Oblimersen is a phosphorothioate antisense oligonucleotide complementary to the Bcl-2 mRNA and a potent inhibitor of Bcl-2 expression, which in pre-clinical testing can significantly enhance the therapeutic effect of chemo therapy, hormones, and radiation therapy. The antisense oligonucleotide directed to BCL-2, oblimersen sodium (Genasense, Genta, Berkeley Heights) lowers Bcl-2 level (Chi 2005).

Thalidomide

Thalidomide and its analogs modulate the immune system in various ways. Some of these immunomodulatory activities, together with the antiangiogenic, antiproliferative, and proapoptotic properties, are believed to mediate antitumor responses in some tumors. A randomized phase II trial combining docetaxel with thalidomide resulted in an encouraging PSA decline rate. At 18 months, overall survival in the docetaxel plus thalidomide group was 68.2% compared to only 42.9% in the docetaxel alone group (Dahut et al. 2004).

Atrasentan

Endothelin-1, acting via the endothelin-A receptor, has been implicated in metastasis and progression of prostate cancer, particularly in bone.

Atrasentan is a potent, oral, selective endothelin-A receptor antagonist. A meta-analysis of two large randomized placebo-controlled studies of atrasentan in men with metastatic AIPC showed that atrasentan resulted in a significant

reduction in disease progression, attenuation of the rise of the biomarkers PSA and bone alkaline phosphatase, delay in time to biochemical progression, decrease in time to bone pain and incidence of bone pain, and disease-specific quality of life benefit (Vogelzang et al. 2005).

Vaccine Therapy

Prostate cancer cells express many unique differentiation-associated antigens that allow for development of organ-specific targeted vaccines. APC8015 utilizes prostatic acid phosphatase (PAP), which is highly expressed in more than 90% of prostate tumors. It is an immunotherapy cellular product consisting of autologous peripheral blood mononuclear cells enriched for the dendritic cell fraction pulsed with a PAP-GM-CSF construct. Patients with asymptomatic metastatic AIPC were randomized (2:1) to receive APC8015 (n=82) or placebo (n=45) every 2 weeks for 6 weeks, and at 3 years 34% of those vaccinated were alive compared to 11% in the placebo arm. In a subset analysis, treatment with APC8015 resulted in a 6.4-month survival advantage in patients with Gleason scores of less or equal to 7 (Small et al. 2005).

Bisphosphonates

Bisphosphonates act by decreasing the rate of bone turnover, reducing the number of osteoclasts, their recruitment, lifespan, and activity. Bone complications in prostate cancer occur as a result of skeletal metastases, long-term treatment with androgen withdrawal, and radiotherapy. Bisphosphonates have been shown to reduce bone pain in prostatic cancer for 2–3 weeks after a single intravenous infusion, in up to 30% of patients.

Promising results were observed with zoledronic acid, and in phase III trials there were fewer skeletal events compared with placebo (44.2% vs 33.2%, p=0.02) after a 15-min infusion of zoledronic acid every 3 weeks. However, renal function should be monitored carefully, and osteonecrosis of the yaw may occur with the use of bisphosphonates (Goodin et al. 2002).

Radiotherapy

External radiotherapy may be useful for perineal pain, bleeding, or bone pain.

A single fraction of external local radiotherapy is effective for pain relief in symptomatic bony metastases in up to 76% of patients. It may, however, take several weeks for it to take effect.

Hemibody irradiation is utilized where a large treatment field is required, usually encompassing the pelvis and upper femurs. However, this frequently results in diarrhea and nausea.

Strontium-89 is a β-emitter and is used as an intravenous injection for pain control in widespread bone metastases. It may be associated with an initial pain flare, but approximately 10% of treated patients do experience a complete resolution of pain. However, the presence of any critical metastases potentially able to cause spinal cord compression must be excluded, as strontium may cause edema at these sites. In addition, the treatment commonly produces prolonged myelosuppression, particularly thrombocytopenia, and in patients with already depleted marrow reserves, either due to disease or treatment, this can be problematic. It may also limit future use of chemotherapy.

In two randomized phase III studies, strontium-89 was shown to give better and more durable relief of pain than limited field radiotherapy, while in a recent study this effect could not be confirmed (Bauman et al. 2005; Oosterhof et al. 2003).

Newer radiopharmaceuticals e.g., Samarium-159, are being tested for the treatment of painful bone metastases in patients with AIPC.

Conclusions

The evaluation and treatment of patients with AIPC should be performed by an integrated multidisciplinary approach to allow optimal symptomatic control. Recent advances in the understanding of the molecular mechanisms implicated in prostate cancer progression may lead to new therapies.

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15 Prostate Cancer Treatment and Quality of Life

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Abstract

Prostate cancer is detected today at earlier stages and in younger men than ever before. A lot of men are asymptomatic and also physically and sexually active at diagnosis, and most of them are being treated by curative procedures. These trends have led to increasing numbers of patients undergoing disease management for longer periods of time. For many patients quality of life (QoL) may be just as important as survival. Thus, QoL considerations may well be the critical factor in medical decision-making for most of them. Widespread interest in studying patient-centred outcomes has led to the development of methods for health-related QoL measurements. In fact, many questionnaires have been introduced in clinical practice to assess the impact of QoL in patients (SF-36, CARES, FACT, EORTC QLQ-C30, GRISS, UCLA PCI, PCOS). Herein we evaluate the impact of QoL on patients affected by prostate cancer and treated with watchful waiting, radical prostatectomy, radiotherapy and hormonal therapy; we have also considered the role of supportive care, including the administration of analgesics, antidepressants, corticosteroids, bisphosphonates, antiemetics and stool softeners, together with psychological support. The ultimate goal of QoL research should strongly improve medical care and concretely assist patients and physicians in treatment decision-making.

Introduction

Prostate cancer is the most common cancer in men in Western countries and it is the second leading cause of cancer death [1]. In 2002 there were an estimated 189,000 new cases of prostate cancer in the United States, with 30,200 deaths caused by the disease [2]. Each year the American Cancer Society estimates the number of new cancer cases and deaths expected in the United States in the current year and compiles the most recent data on cancer incidence, mortality and survival based on incidence data from the National Cancer Institute and mortality data from the National Center for Health Statistics. Incidence and death rates are age-standardized to the 2000 standard million population of the United States. A total of 1,372,910 new cancer cases and 570,280 deaths are expected to have occurred in the United States in 2005. Regarding prostatic cancer, 232,090 new cases and 30,000 estimated deaths are expected in the same period [3].

Prostate-specific antigen (PSA) testing has led to prostate cancer being detected at earlier stages and in younger men than was previously the case (low-stage migration). A lot of men are asymptomatic and also physically and sexually active at diagnosis and more of them are being treated by curative procedures [4]. These trends have led to increasing numbers of patients undergoing disease management for longer periods of time.

Traditionally, the primary endpoints in prostate cancer treatment have been cure and survival. The advent of the medical outcomes movement and the worldwide effort to contain the rizing costs of care, however, have underscored the importance of patient-centred outcomes, such as health-related quality of life (QoL). This trend is relevant in patients with prostate cancer, who often live for years after diagnosis. Because of the long survival time, even modest changes in QoL may have a significant impact on the patient. For many patients, therefore, QoL may be just as important as survival.

When making treatment choices, patients with early prostate cancer must weigh the benefits, such as delay in time to progression and an extended period without pain, against any adverse events than may affect QoL. In the light of evidence that survival outcomes may be similar for the various treatment options of the subgroups [5], QoL considerations may well be the critical factor in medical decision-making for some men with prostate cancer.

QoL Assessment

The impact of health-related QoL on therapeutic decision-making is now considered so important that some investigators consider a clinical cancer trial incomplete without QoL assessment [6, 7]. Consequently, appropriate QoL questionnaires have been introduced into large multi-centre trials [8, 9]. A contemporary interpretation of health-related QoL is based on the WHO's definition of health as a state of complete physical, mental and social well-being and not merely the absence of disease [10]. Since prostate cancer and its treatment can influence many aspects of QoL, a wide spectrum of the components of well-being must therefore be addressed when treating patients with cancer.

Health-related QoL encompasses the physical, emotional and social well-being of the patient and will be influenced by the psychological and physical effects of the disease, as well as its treatment [11, 12]. The psychological impact of being diagnosed with prostate cancer, even when asymptomatic, could have a marked impact on QoL.

During recent years, widespread interest in studying patient-centred outcomes has led to the development of a rigorous set of methods for health-related QoL measurement. The clear lesson from this work is that researchers and clinicians need to ask, in a standardised manner, about disease-specific impairments such as erectile dysfunction (ED) and urinary incontinence. These are complex qualitative variables that are not easy to standardize; in order to quantify such subjective phenomena, data are collected from health-related QoL surveys, with so-called 'instruments'. They contain questions, or items, that are organized in scales, each scale measuring a different aspect, or domain, of QoL. For example, items of a particular instrument may address a patient's ability to have an erection and his satisfaction with ejaculation, both of which might be included in a sexual domain. Some scales comprise many items, while others include only one or two. Each item contains a stem, which may be a question or a statement, together with a response set. Instruments are best when they are self-administrated by the patient himself, but if the assistance of an interviewer is required it must be conducted from an impartial position. In order to compare treatment efficacy in relation to health-related QoL, contemporaneous longitudinal studies with randomized controls provide not only an effective study, but also the most valid results. Health-related QoL instruments must be shown to exercise reliability, validity and responsiveness [13].

The Medical Outcomes Study Group Short-Form Health Survey (SF-36) determines both 'function' and 'bother' in patients with prostate cancer [14] and probably constitutes the 'gold standard' generic tool. Nevertheless, cancer-targeted instruments such as Cancer Rehabilitation Evaluation System (CARES) Short-Form, the functional Assessment of Cancer Therapy-General (FACT-G) form and the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire (EORTC QLQ-C30), have been found to be more sensitive to relevant changes in patients treated for localized disease [15, 16, 17]. It is a 20-item questionnaire, covering bowel, urinary and sexuality symptoms, which has been validated in men with localized [18, 19] and metastatic [20] disease. Certain tools designed to assess the existence and severity of sexual problems, such as the Golombok Rust Inventory of Sexual Satisfaction (GRISS) [21], have been used in studies of anti-androgen therapy for patients with prostate cancer [22, 23].

Several questionnaires have been designed specifically for prostate cancer, the validated Functional Assessment of Cancer Therapy-Prostate (FACT-P), for example, addressing weight loss, appetite and urinary and erectile disorders on a 12-item scale [24], whereas the University of California, Los Angeles Prostate Cancer Index (UCLA PCI), a validated 20-item questionnaire,

quantifies 6 separate domains, essentially urinary function, urinary bother, sexual function, sexual bother, bowel function and bowel bother [17, 25–27].

Lower rates of impotence in groups of men who had nerve-sparing versus non-nerve-sparing radical prostatectomy and, moreover, lower rates of potency and continence in older versus younger patients who had undergone surgery were characterized in the Prostate Cancer Outcomes Study (PCOS), using a modified type of UCLA PCI questionnaire. Using the same tool in a different group of patients from the PCOS, men taking luteinizing hormone-releasing hormone (LH-RH) agonists as primary therapy fared worse in several domains compared with men who had been surgically castrated, although similar rates of sexual function were identified [28].

When comparing androgen-deprivation therapy with no treatment of patients with newly diagnosed prostate cancer, significantly higher rates of impotence and reduced vitality were found in the former group. Despite this, patients on androgen-deprivation therapy were significantly more likely to be satisfied with their treatment decision than the latter group [29].

More comprehensive tools that include a hormonal domain with specific questions on breast tenderness and gynaecomastia have been created by expanding the UCLA PCI (Expanded Prostate Index Composite, EPIC) [30, 31].

The components of QoL often thought to be of greater concern to patients are impotence and incontinence. Treatment choice surveys show that only a minority of men are willing to accept a treatment that has a greater than 50% risk of impotence [32], and importantly, men will often accept a certain degree of reduced life expectancy in return for preserved potency [33, 34]. Consequently, for treatments with similar outcomes in terms of survival or time to progression, a QoL tool that includes determinants of both impotence and incontinence is, therefore, an important endpoint to consider. QoL issues assume greater importance as treatment for longer duration becomes more widely used and increasing numbers of men manifest fewer symptoms.

QoL Following Watchful Waiting

Although watchful waiting avoids the immediate harmful side-effects of early intervention, an impact on QoL is often experienced by men with untreated prostate cancer, who experience troublesome local and systemic symptoms that affect their daily routine [35]. The worst consequence of deferring active treatment is that the cancer might progress beyond curability and eventually kill the patient. This possibility cannot be excluded for any individual patient, but to date there are few data that document this risk. Regarding QoL, these patients appear to have the same degree of sexual dysfunction and urinary and bowel symptoms as do age-matched controls [32, 36]. In one particular study [36] the overall QoL was similar in patients on observation as in age-matched controls; in another study [37] it did not change during the first year of follow up. Patients on watchful waiting seem to have similar psychological morbidity as patients subjected to radical prostatectomy, when assessed 3 and 10 years after treatment [38]. A deferred treatment option, with active monitoring and periodic evaluation, can provide an appropriate solution for well-informed patients who wish to minimize the short-term risks of immediate therapy and who accept the consequent risks. For men with a short life expectancy, active monitoring may be appropriate for any stage of cancer in the absence of symptoms, or signs of impending morbidity from the disease. For those with a life expectancy of 10 years or longer, active monitoring is an option for intermediate-risk cancer. What is important is providing the correct information to the patient with regard to his decisions and his possible anxiety.

QoL Following Radical Prostatectomy

Radical prostatectomy may result in a loss of sexual function and incontinence, whereas radiotherapy can be associated with a loss of sexual function and gastrointestinal side-effects [39]. Operative time, transfusion rates, admission to the intensive care unit, patient length of hospital stay and major and minor complications, as well as the mortality rate of radical prostatectomy,

have all decreased over time [40]. The more recent mortality rate ranges from 0.16% to 0.66%, rising with increasing age and co-morbidity [41]. In centres of excellence, operative mortality occurred in only 11 (0.29%) of 3,834 reported patients [40]. Although perineal and laparoscopic prostatectomy are associated with a much lower blood loss and fewer transfusions, severe bleeding can occur and complicate recovery [42]. Rectal injury occurs in less than 1% of patients. Previous pelvic irradiation, rectal surgery and transurethral resection of the prostate (TURP) have all been cited as predisposing factors. Deep venous thrombosis and pulmonary embolism occur in approximately 1.1% of perineal prostatectomies and 1.2% of laparoscopic prostatectomies, respectively [40]. Concerning the later complications, urinary incontinence and ED are the most important. Nation-wide surveys using validated patient-reported questionnaires reveal 'severe' incontinence in 8% of men of all ages after radical prostatectomy [43, 44]. In centres of excellence, complete continence is reported in 92%–95% of patients, with severe stress incontinence requiring an artificial urinary sphincter in less than 1% [43, 45]. The preservation of sexual potency is possible in the majority of patients, depending on age and the extent of nerve sparing [46]. Older patients are less likely to experience an adequate recovery of sexual potency after surgery and clearly, unilateral is less effective than bilateral nerve preservation [46]. Anastomotic stricture has been reported in 0.5%–9% of patients, with one recent survey finding patient-reported stricture in 15% of 337 patients during the first year after surgery [47]. Previous TURP, excessive intraoperative blood loss and urinary extravasation at the anastomotic site may contribute to stricture development [48].

QoL Following Radiation Therapy

The most widely applicable outcomes information on the effect of radiation therapy on urinary, bowel and sexual function has recently been reported by the Prostate Cancer Outcomes Study Group [49–51]. The reported risk of patients needing to wear pads to stay dry following external beam radiation therapy ranged from 2% to 7% and was lowest following three-dimensional (3D) conformal external beam radiotherapy (EBRT). The risk of bowel urgency following conventional EBRT was 35.7% [49], and 22% following 3D conformal EBRT. The percentage of patients bothered by bowel dysfunction was lower following 3D conformal EBRT (4%) than following conventional EBRT (8%). When 3D conformal EBRT included 46.8 Gy to the pelvic lymph nodes, the risk relative to prostate-only irradiation, of bowel urgency and frequent bowel movements was 1.8 [51].

The identification of patients who will not benefit from pelvic lymph node irradiation will therefore raise long-term health outcomes. From the recently reported Radiation Therapy Oncology Group (RTOG) protocol 94-13, patients with high risk localized disease who were treated with whole pelvis and prostate radiation therapy had a significantly higher 4-year progression-free survival than those randomized to treatment with prostate-only radiation [52]. Recently, Talcott and colleagues [53] reported long-term treatment-related complications for men with localized disease receiving EBRT or brachytherapy [53]. Patient-reported rates of diarrhoea or frequent watery bowel movements were 6% following brachytherapy alone, 12% following EBRT and 15% after brachytherapy together with EBRT. The prevalence of a need for absorbent pads for urine leakage, again reported by patients, was 5% following EBRT, 18% following brachytherapy alone and 13% after brachytherapy together with EBRT. The percentage of patients having an erection inadequate for intercourse was 70% following EBRT, 51% following brachytherapy alone, and 67% after brachytherapy and EBRT. Treatment by brachytherapy causes few rectal symptoms, but does significantly increase urinary incontinence.

Physician-assessed toxicity depends upon the scoring system used, which includes the RTOG, SOMA–LENT (subjective, objective, management, analytic/late effects on normal tissue) and FC-LENT (Fox Chase modified LENT) scales [54–56]. Other available questionnaires are the general RAND SF-16, the general cancer-related FACT-G and disease-specific questionnaires such as FACT-P, American Urological Association (AUA) symptom index, UCLA PCI and the more recent five-domain EPIC [14, 30].

QoL Following External Beam Radiation Therapy

Late rectal toxicity appears to be the limiting factor in dose escalation trials. Using generous safety margins of 15 mm around the prostate, patients experienced FC-LENT grade 2 and 3 late rectal toxicity in 34% and 5% of cases at 75 Gy, and 55% and 13% at 80 Gy, respectively. Consequently, the rectal dose was limited to 72 Gy by additional rectal shielding. The dose effect relationship to bladder toxicity is far less clear, which to some extent can be explained by its decreased radiosensitivity and also a longer median latency period of 23 versus 14 months for late rectal toxicity [59, 60]. Of great interest for future dose escalation trials are the long-term follow-up data from the randomized proton trial, which shows a continually rising incidence of RTOG, with a greater than grade II bladder toxicity reaching 59% at 15 years. ED following EBRT can vary from 6% to 84% because of the absence of validated measuring instruments [61]. Men who are sexually active before EBRT have the better chance of remaining potent after treatment [62]. The International Index for Erectile Function (IIEF), recently introduced as a validated [63] instrument for measuring ED, has already been used in a brachytherapy series [64] and will offer reliable comparisons of different treatment modalities. The time point of assessment of ED after EBRT is equally important, since it increases further between 1 and 2 years following EBRT [65]. Its aetiology after EBRT is believed to be mainly arteriogenic [66], and the radiation dose to the bulb of the penis may be the cause [67]. Bowel dysfunction with cramps, bleeding, diarrhoea and bowel urgency is reported in up to 20% of patients after EBRT [68, 69].

QoL Following Three-Dimensional Conformal RT

Side-effects are related to both the dose and volume of irradiated normal tissue [70]. 3D-conformal radiotherapy (3D-CRT) techniques attempt to spare normal surrounding and juxtaposed tissue by providing a dose distribution that closely approximates the planning target volume. Several studies have reported low toxicity rates after 3D-CRT [71, 72] and further improvement can be expected from intensity-modulated radiotherapy (IMRT) [73, 74]. However, 3D-CRT alone is no guarantee against complications. The ability of 3D-CRT to spare healthy tissues is limited by the borders of the planned target volume, which includes a normal tissue safety margin around the clinical target to account for set-up error, prostate motion and dosimetric build-up [75].

QoL Following Prostate Brachytherapy

In one of the first analyses of the QoL of men treated with prostate brachytherapy (PB), Brandeis [76] compared generic and disease-specific QoL in men treated with PB (with and without EBRT) after radical prostatectomy. Generic QoL did not differ greatly between the two groups, with only the physical function of the QoL domain in the SF-36 showing differences; the radical prostatectomy patients scored higher than the PB group. Disease-specific QoL measures were very different. Urinary function, essentially leakage and bowel function, were worse in the PB group, while sexual function and bother did not differ in the two groups.

QoL data were reported [77] for men treated with either PB alone or EBRT and radical prostatectomy for clinically localized prostate cancer. Examination of the urinary, bowel and sexual function indicated that men treated with PB had better results. Significant differences were identified [78] in sexual, urinary and bowel QoL parameters between the treatment of 842 patients treated with PB and EBRT, or by radical prostatectomy, with better sexual and urinary function as well as less sexual bother in the former. Men treated with PB or EBRT, however, reported significantly worse bowel function, bowel bother and urinary bother than men treated with radical prostatectomy.

Results from 1,000 patients [79] treated with RP, PB or EBRT between 1995 and 1999 and using the EPIC instrument, a specific questionnaire, showed the PB group to have the worse urinary, bowel and sexual QoL compared to controls. A comparison of QoL scores in men, at least 1 year from completion of therapy, found

that the PB group had significantly worse urinary, bowel and sexual symptoms than the RP or EBRT groups. When patients who had received EBRT were excluded from the PB group, sexual QoL parameters were similar to the EBRT group and superior to the RP. Lee and colleagues [25] reported a prospective study examining QoL in a group of patients treated with PB, RP or EBRT. Men treated with PB or RP experienced a greater depreciation in QoL at 1 month than men treated with EBRT, although there were no differences at 1 year. In a recent report [81] a significant improvement in QoL was seen after high dose rate prostate brachytherapy (HDR-PB) at 1 year of follow up.

QoL Following Hormonal Therapy

Hormonal therapies vary with respect to their side-effect profiles with QoL influenced by effects on physical and sexual activity, sexual interest, anaemia, bone mineral density, gynaecomastia and breast pain [82, 83].

The treatment benefits observed with anti-androgen therapy require consideration in relation to morbidity associated with long-term therapy. Cyproterone acetate (CPA) is associated with a high incidence of loss of libido and impotence, whereas sexual interest and function are generally preserved using non-steroidal anti-androgens [84]. In addition, CPA is associated with adverse effects associated with the cardiovascular system and hepatotoxicity [84]. The principal pharmacologic effects of treatment with non-steroidal anti-androgens are gynaecomastia and breast pain [85]. Differences also exist between the non-steroidal anti-androgens with respect to non-pharmacologic effects such as gastrointestinal symptoms, hepatotoxicity and pulmonary events [86]. Diarrhoea, for example, is more common with flutamide than with either bicalutamide or nilutamide. Clinically significant hepatotoxicity is rare with bicalutamide and nilutamide, whereas the incidence with flutamide has been estimated to be 3/10,000 [86]. Interstitial pneumonitis and visual disturbances are unique adverse effects of nilutamide [85]. Bicalutamide seems to have a more favourable tolerability profile than the other non-steroidal anti-androgens and CPA.

Bicalutamide monotherapy has been shown to offer improved health-related QoL compared with castration in patients with locally advanced non-metastatic disease (M0) (Fig. 15.1). Using a brief, self-administered, patient questionnaire covering 10 domains of health-related QoL [87], data from two large studies showed that bicalutamide was favoured in 8 of 9 evaluable parameters, with statistic significance associated with both sexual interest (p=0.029) and physical capacity (p=0.046),

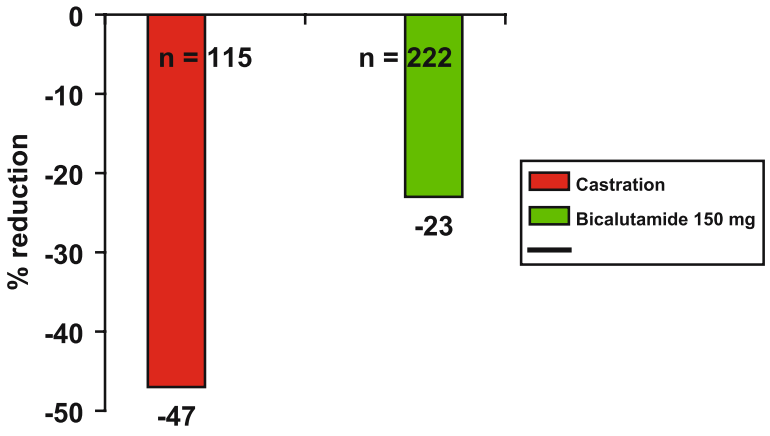

Fig. 15.1 Percentage reduction from baseline in sexual interest after 12 months of treatment with bicalutamide or castration (M0 patients) [22]

evidence suggesting that this treatment may benefit patients with early disease [22, 88].

In the Scandinavian arm (SPCG-6) of the on-going bicalutamide EPC programme, sexual function, assessed using the GRISS [21], was found to be retained in 74.9% of the bicalutamide (150 mg) group, compared to 85% of the standard care-alone group.

In early prostate cancer, where many patients are asymptomatic, gynaecomastia and breast pain causes significant bother to patients, problems that are greater with anti-androgen as monotherapy. In the bicalutamide EPC programme, the main side-effects of bicalutamide (150 mg) were gynaecomastia and breast pain (53%), breast pain alone (20%) and gynaecomastia alone (13%), although these were mild to moderate in more than 90% of cases (Table 15.1) [89]. Withdrawals due to breast pain and/or gynaecomastia were 15.6% in the bicalutamide

Table 15.1 Adverse events following treatment with bicalutamide 150 mg or placebo of patients with localized or locally advanced prostate cancer who have previously had no prior treatment or treatment of primary curative intent (median follow-up was 2.6 years) [89]

	Bicalutamide 150 mg % (n=1,798)	Placebo % (n=1,805)
Gynaecomastia alone	17.4	5.3
Breast pain alone	17.6	3.1
Gynaecomastia plus breast pain	47.5	2.1
Vasodilatation	9.3	4.6
Flu syndrome	8.6	9.5
Back pain	8.2	10.9
Impotence	8.0	5.3
Urinary tract infection	7.9	6.4
Constipation	7.8	5.7
Hypertension	7.5	7.1
Abdominal pain	7.3	6.7
Asthenia	7.2	6.1
Arthralgia	7.1	8.6
Pharyngitis	6.9	6.0
Infection	6.9	5.3
Urinary incontinence	6.3	5.1
Rash	6.3	4.8
Urinary tract disorder	5.8	7.1
Weight gain	5.6	2.6
Pain	5.4	6.7
Diarrhoea	5.1	6.3
Hernia	5.1	6.2
Bronchitis	5.1	4.8
Somnolence	5.1	3.1
Pelvic pain	5.0	5.2
Haematuria	3.9	5.8

(150 mg) group, compared to 0.7% in the standard care-alone group [90], although withdrawals due to objective disease progression were 2.6% and 9.3% in the two groups, respectively [91]. The use of anti-oestrogens, radiotherapy and surgery for the prophylaxis and/or treatment of gynaecomastia and breast pain [92] have been suggested, although these side-effects are reversible if therapy is withdrawn within a few months of the onset of symptoms [31]. In future trials of anti-androgen therapy in early prostate cancer, it may be desirable to assess QoL using a tool such as EPIC, which evaluates the patient's own perception of breast tenderness and gynaecomastia.

The introduction of gonadotropin-releasing hormone (GnRH) analogues and anti-androgens, especially in combination, has greatly increased the economic and biological costs of prostate cancer without any concomitant decrease in overall mortality.

An EORTC group concluded from their study of QoL in patients with newly diagnosed M1 prostate cancer that the physician's rating does not accurately reflect the functional health and symptom status of their patients [94]. The long-term impact of androgen withdrawal on QoL is not well-defined and it can be difficult to differentiate effects of the disease from those of the treatment. In EORTC trial 30853, an overall improvement in QoL was reported [94] following androgen withdrawal therapy, specifically lower urinary tract symptoms, although other outcomes were difficult to assess. During hormonal treatment many patients reported a reduction of sexual activity, although this was not consistently related to overall QoL and many patients suffered from ED before they started hormonal therapy. Non-specific symptoms, such as fatigue and loss of energy, can occur following androgen deprivation as well as slight anaemia and loss of muscle mass, although the potential impact of androgen withdrawal on central nervous system function and cognition is uncertain.

Use of androgen deprivation at the time of biochemical relapse following primary therapy and for locally advanced disease is increasing, and the cumulative impact of the side-effects is likely to be higher the longer the duration of therapy. Whereas a meta-analysis of 21 trials found a slight advantage of complete androgen blockade on 5-year survival [95], it remains unclear whether the minimal survival benefit equates to a QoL improvement. The side-effects and the rate of withdrawal from complete androgen blockade are more prevalent than with castration alone.

The Southwest Oncology Group (SWOG) trial (INT 0105) showed [96] that patients randomized to complete androgen blockade reported more problems than those assigned medical castration. One non-randomized study showed that patients prefer treatment with a GnRH analogue to orchiectomy for psychological reasons [97], with the reversibility of this approach, avoidance of surgery and the patient's self-esteem underlying this preference.

Hot flashes, a prevalent side-effect of hormonal therapy, decreased the QoL of a large number of patients who are often in a palliative situation. As many as 75% of men treated with either LH-RH agonists or non-steroidal anti-androgens, or by castration, experience hot flashes and sweats. Several classes of drugs, from antidepressants to oestrogens, have been assessed and advocated as treatment of hot flashes.

Osteoporosis is another important and debilitating side-effect of many prostate cancer therapies, although precise estimates of the incidence, degree and cost of osteoporosis are not completely known. Bone mineral density loss can be as much as 3% to 5% yearly during the first few years of androgen deprivation therapy [98]. An emerging approach to control bone loss, including that induced by treatment for prostate cancer, is the use of intravenous bisphosphonate therapy to block tumour-promoted osteoclast activity. Patients with bone metastases often suffer from morbid skeletal-related events, such as pain, pathologic fractures, radiation therapy, surgery to bone and changes due to anti-neoplastic therapy for the management of bone pain. Unfortunately, advanced prostate cancer responds poorly to current anti-neoplastic treatment and, as skeletal disease progresses, patients may be left with significant disability and loss of mobility and independence. When patients with advanced or recurrent cancer and bone metastases were randomised [99] to leuprolide and pamidronate, or leuprolide alone, bone mineral density did not change significantly in men treated with both drugs for 48 weeks. It was concluded that pamidronate prevents bone loss in the hip

and lumbar spine in patients receiving treatment with LH-RH agonist.

More recently, a new bisphosphonate, zoledronic acid, has been introduced into clinical practice with good results [100, 101]. Intravenous bisphosphonates, including zoledronic acid, are generally well-tolerated and can be administrated safety. The most common side-effect is a transient flu-like syndrome characterized by fever, arthralgias, myalgias and chills. Nausea, fatigue and headache are among the other more common adverse events. Bisphosphonate administration may also be associated with impairment of renal function related to the precipitation of calcium-bisphosphonate complexes in the kidney and also mandibular osteonecrosis.

Anaemia is a common problem for men being treated for metastatic disease, due to various causes, including invasion of the disease into the bone marrow, side-effects of cytotoxic drugs, radiation therapy and bisphosphonate therapy. Epoetin-α therapy (10,000 IU, three times weekly), is associated with a significant increase in haemoglobin level and decrease in transfusion use within 4 weeks after initiation of therapy [102].

Supportive Care

Supportive treatment includes the administration of analgesics, anti-depressants, corticosteroids, anti-emetics and stool softeners, together with psychological support [103, 104]. Pain management is a multidisciplinary concept. Bisphosphonates are potent inhibitors of osteoclasts [105], and zoledronic acid, a new generation of nitrogen containing bisphosphonates, is 100- to 1,000-fold more potent than the previous generation. It has been shown to be important in the control and reduction of skeletal-related events and pain in a variety of cancers, including prostate cancer [106–109]. A recently completed, multicentre, randomized, placebo-controlled trial of zoledronic acid in hormone-refractory prostate cancer with bone metastases provided evidence [110, 111] of significant clinical benefit in reducing the risk of pathologic fractures and other skeletal-related events (Figs. 15.2 and 15.3). The current recommended treatment with zoledronic acid is 4 mg infused over 15 min every 3 or 4 weeks. A better dosage should be done in consideration of the creatinine clearance, however, because the major risk in its use includes a

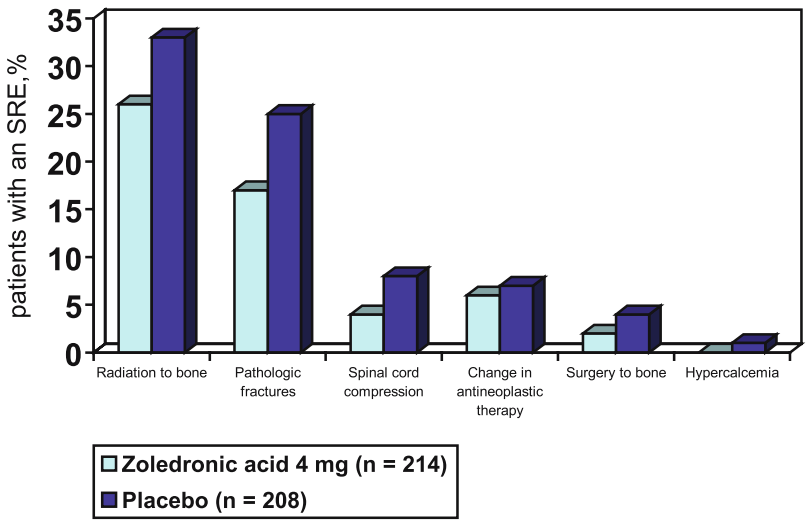

Fig. 15.2 Treatment with zoledronic acid reduces all types of skeletal-related events (SREs) compared with placebo in men with hormone-refractory prostate cancer metastatic to bone. Zoledronic acid (4 mg every weeks for 24 months) reduced the percentage of patients with SREs compared with placebo. SREs included radiation to bone, pathologic fractures, spinal cord compression, antineoplastic therapy, surgery to bone, and hyperkalemia. Adapted by Saad et al. [111]

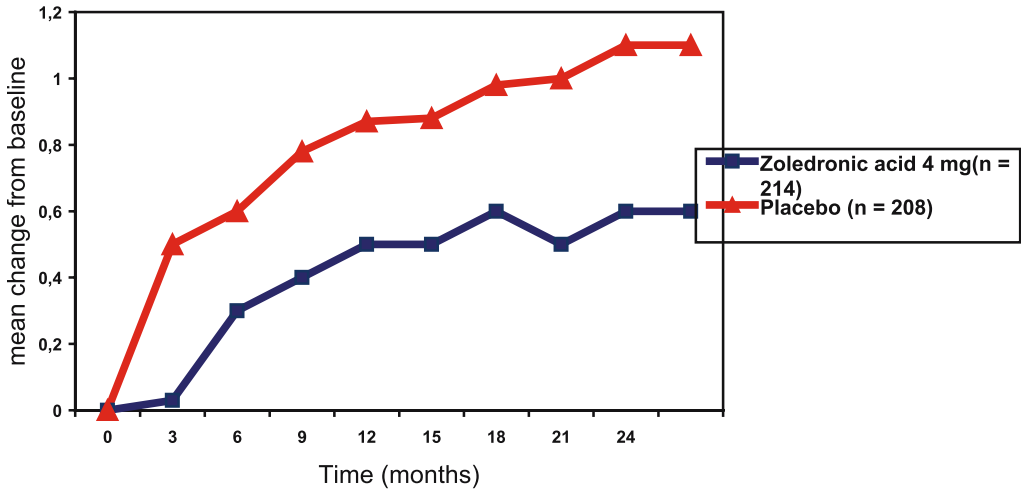

Fig. 15.3 Treatment with zoledronic acid significantly reduces pain scores compared with placebo in men with hormone-refractory prostate cancer metastatic to bone. Zoledronic acid (4 mg every weeks for 24 months) consistently reduced pain scores compared with placebo throughout the course of the study. Graph depicts mean change from baseline pain scores after initiation of treatment. *Asterisks* indicate significant differences at months 3 (p=0.003), 9 (p=0.030), 21 (p=0.014) and 24 (p=0.024). Adapted by Saad et al. [112]

low incidence of renal insufficiency, and serum creatinine should therefore be checked prior to each dose.

Conclusions

The increased popularity of QoL measurements in prostate cancer clinical trials has led to improvements in the quality of patient care. When physicians are attuned to the QoL concerns of their patients, care is more comprehensive at the bedside and in the clinic. As QoL studies are extended to the screening environment, we may learn that QoL is affected by anxiety in the prediagnosis phase. This factor must be considered in assessments of the value of screening programmes. Beyond the descriptive analysis, QoL outcomes must be compared in patients undergoing different modes of therapy. General and disease-specific QoL must be measured to facilitate comparison with patients treated for other common chronic conditions.

The ultimate goal of QoL research must be to improve medical care and assist in medical decision-making. The QoL research objectives are to assess overall treatment efficacy, including subjective morbidity, help to determine whether the goals of treatment have been met, educate patients and clinicians about the full spectrum of treatment outcomes, facilitate medical decision-making and provide the defining issue if treatments are otherwise equivalent.

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16 Europa Uomo: The European Prostate Cancer Coalition

Tom Hudson, Louis J. Denis

Recent Results in Cancer Research, Vol. 175

Abstract

Europa Uomo is a patient-led, non-governmental association (NGO), launched formally in Milan in 2004 with a legal base in Antwerp. As a coalition of prostate cancer patient groups with representation in 18 European countries, the NGO focusses on awareness, early detection, optimal treatment, multi-professional care and, above all, quality of life and patient advocacy.

In the majority of European countries prostate cancer is the most commonly diagnosed cancer affecting men beyond middle age. The incidence and substantial mortality rises with age, peaking in the seventh decade. Standards of diagnosis and treatment vary across Europe and attitudes differ. Information about the early detection and awareness of prostate cancer available to the public leaves much to be desired.

Since 2002, involved individuals, patient support groups, patients, family members, physicians, urologists, oncologists and nurses joined in the formation of an independent, international, non-profit association of patient-led prostate cancer support groups from European countries known as Europa Uomo, the European Prostate Cancer Coalition. This Coalition was legally established as an NGO in June 2004 in Milan with the headquarters and secretariat in Antwerp, Belgium.

Its membership represents 18 countries by the national or regional groups listed in Table 16.1 with their respective contact persons. The coalition is led by a steering committee under the control of the annual general assembly. The steering committee members and their co-ordinates are listed in Table 16.2.

Scientific advice is given by a scientific committee chaired by Prof. H. Van Poppel as the liaison officer with the European Association of Urology (EAU). The support for EAU guidelines appears on the Web site and will be linked to all members in their own language (www.cancerworld.org/europauomo).

The goals and activities of Europa Uomo have been condensed in a series of slides at the request of the Eurocan+Plus collaboration to facilitate international collaboration. These slides have been listed in Tables 16.3, 16.4 16.5, 16.6, 16.7, 16.8, 16.9, 16.10, 16.11, 16.12, 16.13 and 16.14.

It should be noted that membership includes supporting activities for patients and adherence to our 10 objectives listed in the manifest (Tables 16.4–16.6). The bottom line is that the coalition focuses on peer-to-peer support, information and education, as well as partnership with professional associations.

We in Europa Uomo hope to see the decrease in over-treatment and mortality of prostate cancer by the clinical activities, trials and research of the professional organizations. We have the great opportunity to be supported and sponsored by the European School of Oncology (ESO) and its director Dr. A. Costa. The European Society of Medical oncology (ESMO), the International Consultation of Urological Diseases (ICUD) and the International Prostate Health Council (IPHC) support our advice on scientific data.

It is quite natural that all of our members have joined the European Cancer Patients Coalition (ECPC) to speak for all European patients with one voice.

We are a young association but ambitious enough to launch several projects in addition to the Web site, such as the Prostate Passport, a global coalition of patient support organizations, and a series of patient symposia. In this way we are able to show our support and collaboration

Table 16.1 Europa Uomo's groups

Country	Group	Contact person
Austria	Selbsthilfe Prostatakrebs	E. Buechler
Belgium	Wij Ook België—US TOO Belgium	L. Denis
Czech Republic	Arcus—Onko Centrum	J. Kozelska
Denmark	PROPA	E.P. Pyndt
Finland	PROPO	H. Tavio
France	ANAMACaP	R. Muntz
Germany	Bundesverband Prostatakrebs Selbsthilfe e.V.	C. Ligensa
Ireland	Men Against Cancer	T. Hudson
Italy	Europa Uomo Italy	F. Sereni
Norway	PROPO Norway	J. Christie
Poland	Gladiator	T. Wlodarczyk
Portugal	Associação Portuguesa dos Doentes da Próstata	A. Pereira Pinto
Romania	Institute of Oncology Bucharest	S. Colovai
Slovak Republic	Europa Uomo Slovakija	V. Koprda
Spain	Fefoc	E. Valverde
Sweden	Prostatacancerförbundet	L. Eliason
The Netherlands	US TOO Forum	T. Eggenhuizen
	SCP	A. van der Linden
United Kingdom	PCaSO	M. Lockett

Table 16.2 Steering committee legends

Name	Title	Street address, etc.
T. Hudson	Chair	Cullahill Killiney Road, Killiney Dublin, Ireland Tel: 00353 1 2852859 Fax : 00353 1 2852859 E-mail : rlthudson@eircom.net
C. Ligensa	Vice chair	Römerstrasse 20 56412 Niederelbert, Germany Tel: 00492602–2433 Fax: 00492602–2013 E-mail: ligensa@t-online.de
H. Tavio	Vice chair	Haukikuja 3B 02170 Espoo, Finland Tel: +358 40 765 3228 (mobile) E-mail: hannu.tavio@cancer.fi
L. Denis	Secretary	Lange Gasthuisstraat 35–37 2000 Antwerpen, Belgium Tel: +32 3 223.53.54 Fax: +32 3 223.53.52 E-mail: louis.denis@skynet.be
F. Sereni	Treasurer	Instituto di Pediatrica e Neonatologia dell Universita Degli Studi Via della Commenda 9 20122 Milano, Italy Tel: +39 02 57 99 28 49 E-mail : fabio.sereni@unimi.it
R. Muntz		Rue des Carrières 11 B.P. 51 57400 Sarrebourg, France Tel: +33 614 88 36 67 Fax: +33 387 03 34 60 E-mail: muntzr@sarre-moselle.com
L. Eliason		Ekdungen 13 443 42 Grabo, Sweden Tel: +46 302 40 598 E-mail: lars@eliason.se

Table 16.3 Europa Uomo's mission

The Coalition wants to mobilize the support and solidarity of men towards better public and professional education, early detection and optimal physical and psychological treatment of prostate diseases and prostate cancer in particular, to raise public awareness and promote research on all aspects of these diseases
Keywords: awareness, education, peer support, partnership, research

Oncology Centre Antwerp (OCA) 2006

Table 16.4 First three of the ten objectives of Europa Uomo (I)

1. To find ways and means to promote quality of life for prostate cancer patients and their families
2. To promote the dissemination and exchange of evidence-based information on prostate cancer
3. To promote prostate awareness and appropriate diagnosis and prognosis

OCA 2006

Table 16.5 Further objectives of Europa Uomo (II)

4. To emphasize the need for appropriate early detection
5. To campaign for provision of and access to optimum treatment
6. To ensure quality supportive care throughout and after treatment
7. To promote multi-professional quality care and appropriate medical infrastructure

OCA 2006

Table 16.6 Ten objectives Europa Uomo (III)

8. To acknowledge good clinical practice and promote its development
9. To ensure that all men fully understand any proposed treatment options, including entry into clinical trials and their right to a second opinion
10. To promote the advancement of prostate cancer research

OCA 2006

Table 16.7 Health policy

The coalition will promote initiatives at all government and professional levels (global to local) to give appropriate priority to prostate diseases (with emphasis on the specifics of prostate cancer) while respecting cultural differences
The coalition aims to act as a clearinghouse of evidence-based information in partnership with the professional organizations to provide access to new treatments and clinical trials
Keywords: appropriate priority, centre of objective information, access to drugs and trials

OCA 2006

Table 16.8 Prevention

The coalition promotes the unity of primary and secondary prevention including population screening based on facts. The right to early detection is an individual right preceded by complete information on pros and cons confirmed by informed consent. Survival vs quality of life is the choice of the patient
Keywords: primary and secondary prevent research, complete information and consent

OCA 2006

Table 16.9 Treatment and care

The coalition aims towards promotion of the provision and access to optimal treatment with emphasis on the holistic approach towards the patient and an effective multi-professional treatment
The quality care with emotional support has to be continued after initial treatment. Men in support groups and clinical trials receive optimal care
Keywords: holistic and multi-professional treatment, access to support groups and clinical trials

OCA 2006

Table 16.10 Cancer research

The coalition promotes basic and clinical research. Causes of prostate cancer may derive from oestradial 17 beta and/or chronic infection, while clinical research should include the psycho-oncology and emotional aspects of patient and family
Keywords: basic and overall clinical research including psycho-oncology

OCA 2006

Table 16.11 Training

The coalition supports appropriate medical infrastructure and emphasizes the needed communication skills for all health personnel towards the patient. The outcome results of any given treatment should be available to the patient with appropriate emphasis on side-effects and their treatment
Keywords: appropriate functional good clinical practice, outcome results

OCA 2006

Table 16.12 Dissemination of information

There should be factual, up-to-date and evidence-based information provided in simple, clear messages and treated as strategic communication towards public, patients and health workers. Professional advice is needed to reflect expert authority
Keywords: factual updated and evidence-based information, strategic to different cohorts

OCA 2006

Table 16.13 Clinical trials

The coalition supports the patients‘ full understanding of a clinical trial; the consent form is a basic right, while access to trials should be made available for the patients that meet the inclusion criteria
Keywords: consent and access are patient rights

OCA 2006

Table 16.14 Europa Uomo membership

Only legally existing and active associations led by patients are accepted as full members; individual members (without voting rights) are reserved for professionals in the scientific council, advisers or sponsors
Keywords: support groups led by patients

OCA 2006

with all health workers, including nurses, social workers, nutritionists and psychologists.

We like to conclude this contribution with a list of questions to the experts from our participation in the 6th International Consultation of Urological Diseases (ICUD) symposium in Paris (Hudson et al. 2006).

Why?

Clearly there are many questions yet to be answered. Europa Uomo found when researching and preparing the presentation for Paris that there were many pressing questions; some of them had been discussed and others needed to be revisited. The conclusion was that there is a series of questions that need to be posed to you the professional. From the patients' perspective, therefore, and to summarize what we had been talking about in Paris:

- If early detection is important for effective treatment, why not develop better patient-specific early detection guidelines?
- This is both in your hands and ours, as an organization; we need to work with you and, if necessary, remind you that this is urgent,
- If evidence suggests patients are over-treated, why not develop better treatment protocols?
- If patients are faced with so many different choices, why not provide better education for the patient and the public?
- This is something that we as Europa Uomo aim to do, but we can only do it in consultation with you because we need your guidance; we would like to tap into your knowledge to ensure that the information that we are passing on to the patient and the public is accurate, and we can only get that in consultation with you.
- If prostate cancer represents different diseases, why not increase the use of multi-professional teams and a more holistic patient outlook?
- If treatments change so rapidly, why not increase the use of centres of excellence in complicated cases?
- If evidence shows age-based treatment decisions can be effective, why do physicians continue to routinely suggest invasive treatments on so many men over the age of 65?
- This comes down to the quality-of-life issue, which you are well aware of.
- If patients control the choices they must make, why are they largely uninformed about the wide range of available treatment options?
- If prostate cancer involves a slow-growing tumour, why are patients often not given the *time* to absorb the diagnosis, get other opinions and evaluate the correct course to take?

These questions can be well-addressed if patient and physician groups work together. This is the key. We believe that by finding the time to work together we will be able to make positive progress for everybody's benefit.

Changes in Policy and Protocols Alone Can Positively Save Lives

We hope to see most of these questions answered in the future, as only optimal care should be the standard of treatment and greatly facilitate our dream of having each patient enjoy patient-centred and truly holistic care.

References

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