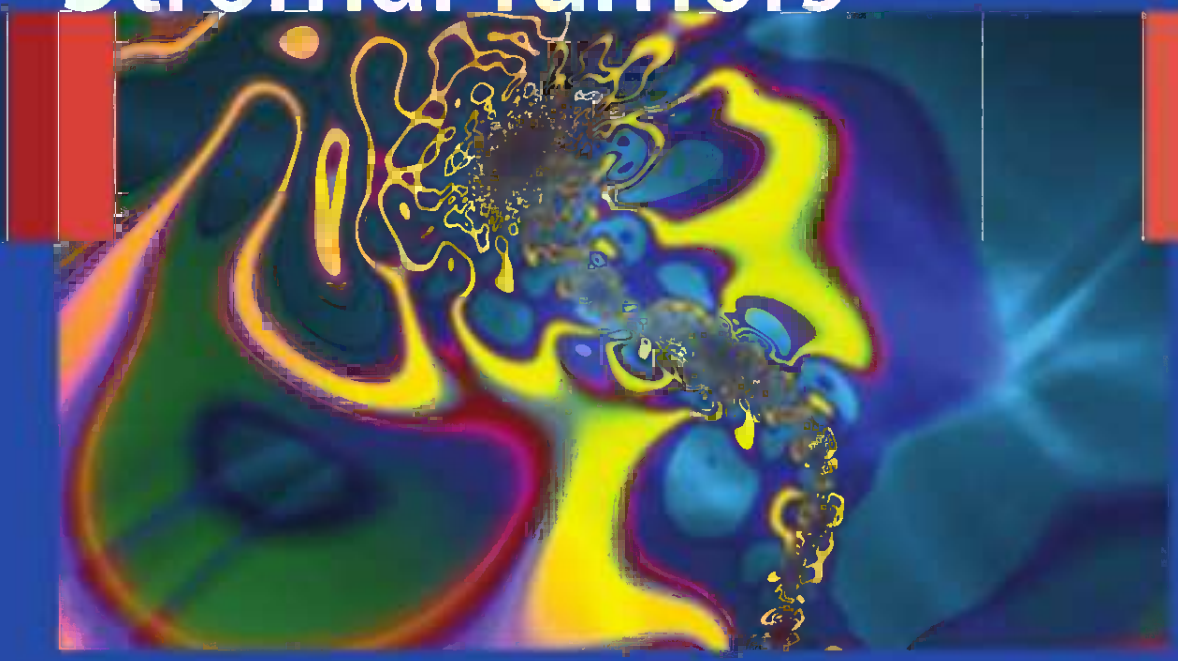
Elisabetta de Lutio di Castelguidone
Antonella Messina
Editors

GISTs – Gastrointestinal Stromal Tumors



Forewords by
Nicholas C. Gourtsoyiannis
Antonio Rotondo
Alfredo Siani

Springer

To Tommaso and Paolo, for the patient and loving support during the entire drafting.

Lilly

To Gianpiero, for the patient, loving and scientific support during the drafting.

Antonella

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Foreword

Gastrointestinal stromal tumors (GISTs) are a unique type of mesenchymal tumor that may occur anywhere in the GI tract, from esophagus to anus. They are exhibiting a wide spectrum of clinical behaviour, from benign, small, incidentally detected nodules to frank malignant lesions, widespread within the abdomen. Recent advances in molecular genetics allowed for a better understanding of the ultrastructural and immunophenotypic characteristics of these tumors, which resulted in the development of new strategies for their treatment. Hence the need for a precise morphological classification of the GISTs and an accountable evaluation of their response to treatment, both of which can only be obtained through imaging.

In this book Dr. E. de Lutio di Castelguidone and Dr. A. Messina, with authoritative contributions from keen experts in the field, convey a breadth and depth of experience and insight and enrich our understanding of GISTs, while providing a unique coverage of all current imaging techniques available for the study of these tumors.

Detailed descriptions and reviews on anatomic and clinical pathology, conventional radiography, ultrasound, including endoscopic, color-doppler and CEUS, endoscopy, computed tomography, magnetic resonance and PET/CT, are rounded off by chapters on medical and surgical treatment, strategic management perspectives and clinical governance of these tumors.

Illuminated with highly selected figures and some exquisite pathologic correlations the book will undoubtedly serve as both a detailed guide to clinical practice and as a standard reference source.

On top of its clinical relevance, this comprehensive volume is offered for multiple readings, as it additionally shows how central modern imaging has become to patient care and it emphasises the fundamental role of radiology within the multidisciplinary management teams.

I am convinced the book will meet with great success among specialists in all disciplines involved in the diagnosis and treatment of GISTs.

Crete, 2010

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Foreword

Gastrointestinal stromal tumors (GISTs) are the most common neoplasms arising from connective tissue in the gastrointestinal tract. GISTs have a distinct origin and well-defined clinical features. Treatment options for GISTs go far beyond surgery and conventional chemoradiotherapy, and include the use of selective protein kinase inhibitors.

Diagnostic imaging of GISTs is focused not only on identification, diagnosis and staging, but also on formulating rational strategies for the use of different imaging techniques to monitor the effects of therapy.

In recent years, the radiology team resident in IRCCS Fondazione Pascale has made a worthwhile cultural and scientific contribution to the study of GISTs related to the prestige of the Institute, which continues to be a reference center in the Campania region (and beyond) for the diagnosis, treatment and follow-up of non-epithelial tumors of the gastrointestinal system.

The evident quality of the content of this book is thanks to the ability and care of E. de Lutio di Castelguidone and A. Messina, who were able to assemble a group of important experts from different centers to create an easy to read and manageable text for those who wish to study GISTs for the first time.

The information provided ranges from the epidemiology of GISTS, their diagnosis, to issues encountered within the clinic, as well as exploring fields such as molecular biology and surgical techniques, knowledge of which is essential to the understanding of therapeutic option and expected results.

The book begins with a comprehensive chapter on the pathology and clinical characteristics of GISTs, continuing to the heart of the volume - a precise and accurate review of all the current radiological techniques that can and must be employed in the diagnosis of GISTs.

The section begins with conventional radiography, explaining its history and the role of single and double contrast-barium studies in the assessment of different intestinal segments. The classical semeiotic criteria for non-epithelial tumors in gastrointestinal system are explained, as are the main features of GISTs in different sites.

The section about conventional radiography is a preamble to a second, equally interesting, chapter, focusing on endoscopic and echo-endoscopic techniques, and showing how a multidisciplinary approach is now the strategy of reference for the proper management of ‘niche’ diseases or , rather, of patients with rare diseases.

This is followed by three chapters on sectional radiography (US, CT and MRI) that underline how the participation of specialists culturally dedicated to specific problems could be useful to clinicians but especially to patients giving them access to a range of precious and irreplaceable semeiotic aspects in the management of their disease. Once

again it stresses the co-operation with radiologists which can of course serve more accurately to define the best treatment strategies and provide more conclusive data for the diagnosis and follow-up of these tumors.

Also, as part of the multidisciplinary approach, radiologists with expertise in different sectors (nuclear medicine and medical imaging physicians) should cooperate so that morphological and functional findings are properly considered in the rational diagnostic process. There should be a comprehensive and cumulative assessment of all the information that modern imaging techniques provide.

Undoubtedly valuable is the final section of the book detailing pharmacological and surgical treatment options for the radiologist who manages follow-up of patients and who needs information on how to integrate and categorize his therapeutic outcomes, as it is extremely necessary, in a time when medicine is increasingly the medicine of evidence, being a reference for the communities and coordinated centers, such as the GISTs' units.

Thanks to the experience, dedication and critical thinking skills that have always guided them, de Lutio and Messina have produced an invaluable and interesting work, bringing together the highest national and international experts. Through their participation and contribution, they have created a comprehensive text that will become a treasured part of the libraries of experienced radiologists who want to delve more deeply into the topic, while the concise and easy to consult approach will also make it an essential part of the cultural growth of the new generation of specialist and trainee radiologists.

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Section I
Clinical Pathology

Anatomic and Clinical Pathology

1

Annarosaria De Chiara and Angelo Paolo Dei Tos

Abstract Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the GI tract. These tumors derive from Cajal cells or their precursors. The oncogenic drivers are tyrosine kinase enzymes (KIT) and, to a lesser degree, platelet-derived growth factor receptor alpha (PDGFRA), both of which become constitutively activated following certain primary mutations. These mutations are mostly in the *c-KIT* gene and rarely in *PDGFRA*.

The diagnosis relies on morphological and immunohistochemical features; most of the tumors show KIT (CD117) or DOG1 positive cells. In negative cases, a mutational analysis is recommended. The introduction of imatinib mesylate – a potent and selective tyrosine kinase inhibitor (TKI) – and the understanding of GIST biology have made the tumor a paradigm for molecularly targeted therapy. The discovery of new mechanisms of resistance to TKIs has resulted in the development of new strategies for treatment. These different options demand exact morphological classification and risk assessment.

Keywords GIST • Epidemiology • Histology • Metastasis • Mutational Analysis • Multifocality • Syndromic

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal (GI) tract, even though they account for less than 1% of all primary neoplasms at that site. The incidence of GISTs is ~15 cases/million/year [1]. The origin from interstitial cells of Cajal, the pacemaker cells of the GI tract, or their stem cell-like subset, has been postulated.

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1.1 Epidemiology

The real incidence of GISTs could be much higher if one considers that retrospective studies have shown the presence of small GISTs (max. 10 mm) in ~20% of individuals, mostly in the proximal stomach and the gastroesophageal junction, less frequently in the small and large bowel [2, 3]. Many of these "micro-GISTs" harbour mutations of *KIT* or *PDGFRA* genes, although with a different frequency than that observed for larger GISTs [2, 4]. Most micro-GISTs tend to regress or do not progress to clinical GISTs. They may represent preneoplastic lesions that require further stimuli to develop into clinically identifiable GISTs, with the hypothesis of a hyperplasia/neoplasia sequence (as already

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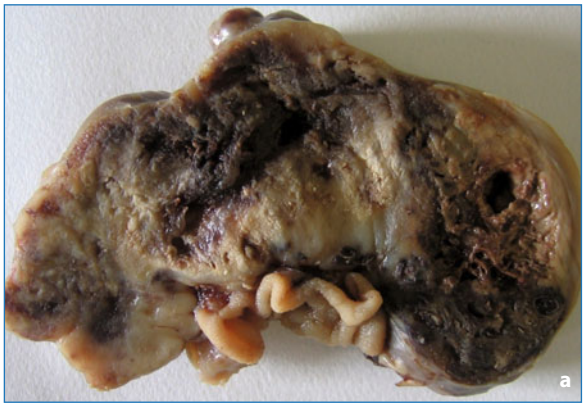

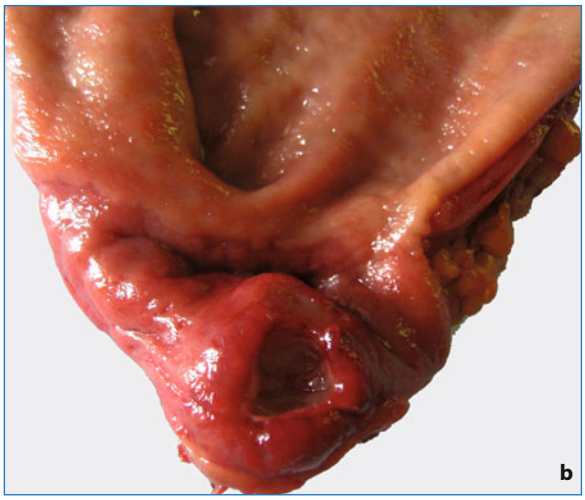

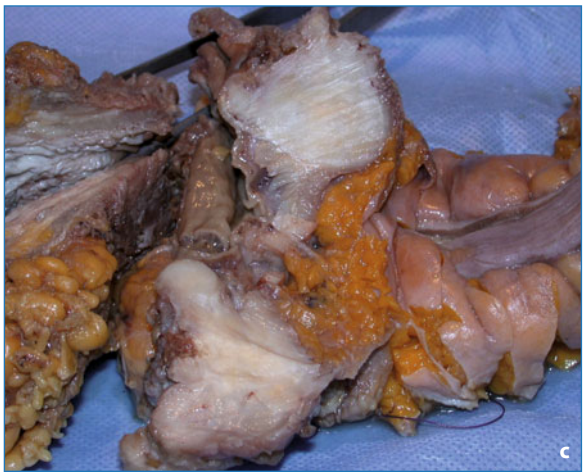

Fig. 1.1 GIST surgical specimens. **a** Stomach, mainly extraluminal (cut section, after formalin fixation). The gastric mucosa covering the neoplasm can be seen below. **b** Duodenum, mainly intraluminal. The neoplasm appears with a central ulceration of the overlying mucosa. **c** Rectum (cut section). Full infiltration of the rectal wall can be seen immediately above the pectinate line

hypothesized for other histotypes) [1, 2, 4].

GISTs most commonly occur in the stomach (60%) (Fig. 1.1a) and in the jejuno-ileum (30%), followed by the duodenum (5%) (Fig. 1.1b) and the colorectum (4%) (Fig. 1.1c) and rarely in the esophagus and the appendix [5-8]. GISTs identified outside the GI tract (without any anatomic relations with the bowel wall) are defined as extra-gastrointestinal stromal tumors (EGISTs) and may be found in the mesentery, omentum and retroperitoneum [9-11], but also in rare sites such as the gallbladder [12, 13], liver [14-18], pancreas [19], vaginal septum [20] and pleura [21].

1.2 Clinical Presentation

The symptoms associated with GISTs are abdominal pain, dysphagia, early satiety and obstruction. More rarely there may be anemia (due to chronic bleeding) or hemorrhage (due to direct erosion of the GI or abdominal mucosa). Approximately 70% of GISTs are symptomatic, 20% are asymptomatic and identified during staging or follow-up for other malignancies, while 10% are discovered during autopsy [22].

1.3 Molecular Genetics

Approximately 85% of GISTs show an activating mutation in the *KIT* gene located on chromosome arm 4q12, which results in a ligand-independent phosphorylation and consequent constitutive activation of the signaling pathway to the nucleus [23]. In 5-8% of GISTs and in 40% of GISTs with no *KIT* mutation (wild-type) there are mutations in the platelet-derived growth factor receptor alpha (*PDGFRA*) gene [24], which is located on the same chromosome region as *KIT* [25]. Both genes encode receptor tyrosine kinases, which are composed of an extracellular (EC) region that binds to the ligand, a transmembrane sequence, a juxtamembrane (JM) domain and two cytoplasmic kinase domains [26]. Under normal circumstances KIT and PDGFRA activation is initiated when the ligands (stem-cell factor and PDGFA, respectively) bind to the EC domain. This leads to the homodimerization of the receptor and the phosphorylation of cytoplasmic tyrosines which in turn initiate a signaling cascade on various substrates, with activation of cellular proliferation, adhesion mechanisms, motility and apoptosis [27]. In GISTs, *KIT* and *PDGFRA* muta-

tions cause a constitutive signal that is independent of the ligands [28], with activation of the target proteins downstream (AKT, MAP kinase, STAT) [29]. The finding that *KIT* mutations are present even in very small GISTs and in patients with germline mutations suggests that the *KIT* mutation is a very early tumorigenic event [2-4]. Subsequent cytogenetic hits are thought to be responsible for tumor progression [30]. The most common are monosomy of chromosome 14 or partial loss of 14q, 22q, 1p, 9p and 11p [30, 31], gain on chromosomes 5p, 20q, 8q and 17q [32], or the duplication of chromosome 4 with the mutated allele for *KIT* [33]. The patterns of chromosomal aberration vary from cases to case, but often highly malignant tumors have three or more [24]. Most mutations (~65%) occur in the JM domain of exon 11, followed by the EC domain in exon 9 (~9%) [35, 36], and much more rarely in exons 13 and 17 (~2%). Mutations in exon 11 are found in the entire GI tract. Mutations in exon 9 are typically found in GISTs of the small bowel and the colon [8, 37], whereas the D842V substitution in exon 18 of *PDGFRA* is for the most part limited to the stomach and omentum and is associated with epithelioid histology [23, 38]. In *PDGFRA*, most of the mutations occur in the tyrosine-kinase 2 domain (TK2) in exon 18, followed by the JM domain in exon 12. There appears to be disagreement in the current literature as to the correlation between mutational status and prognosis of GIST. According to some studies, patients with a mutation in exon 11 involving codons 557 and/or 558 have a worse prognosis [39, 40], although this finding has not been completely confirmed [41]. In addition to the mutation status of *KIT*/*PDGFRA*, secondary chromosomal alterations significantly contribute to the progression of GIST, and the genomic complexity seems to have an independent prognostic value that complements the genotypic and phenotypic information [42].

1.4 Pathology

The size of GISTs varies from 1 to 40 cm (mean ~5 cm). Microscopically GISTs are composed mostly by spindle cells (~70%), but they can have an epithelioid (20%) or mixed morphology (10%). In the spindle cell pattern (Fig. 1.2a) the cells are elongated, arranged in

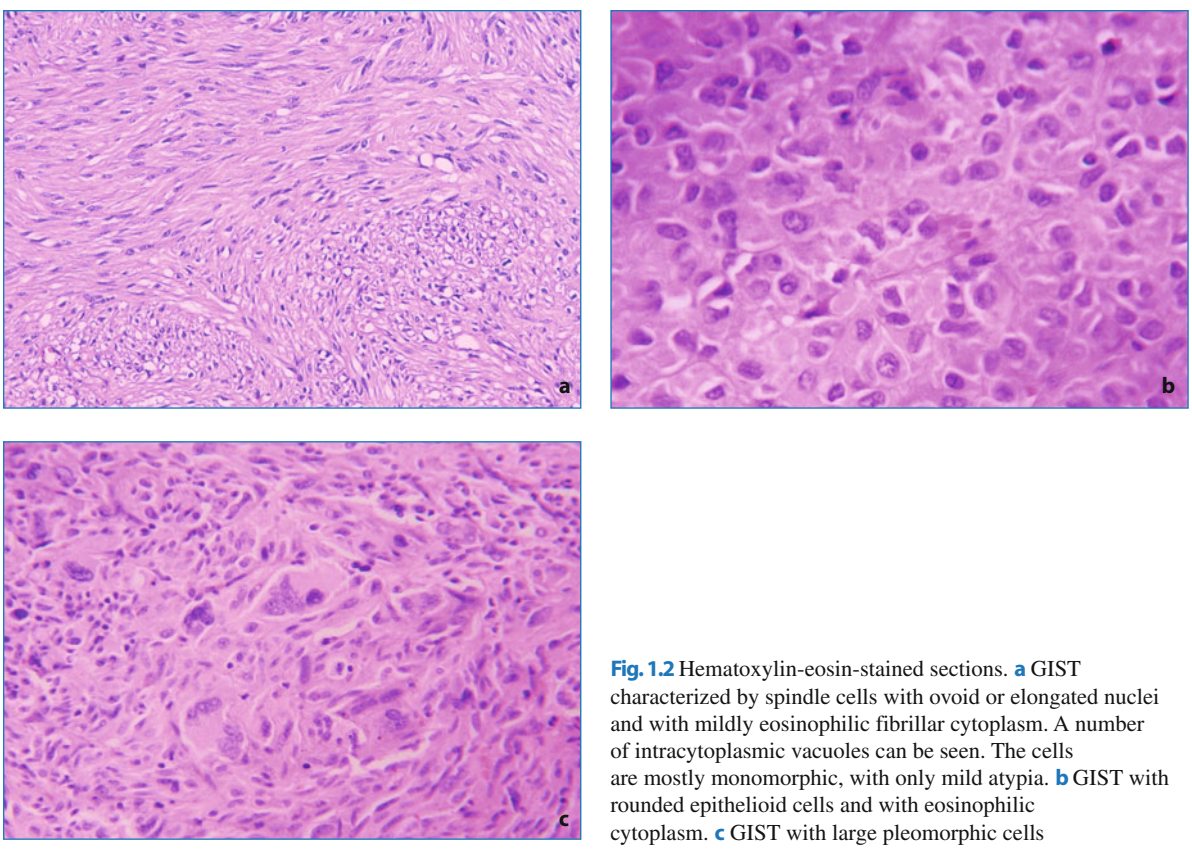

Fig. 1.2 Hematoxylin-eosin-stained sections. **a** GIST characterized by spindle cells with ovoid or elongated nuclei and with mildly eosinophilic fibrillar cytoplasm. A number of intracytoplasmic vacuoles can be seen. The cells are mostly monomorphic, with only mild atypia. **b** GIST with rounded epithelioid cells and with eosinophilic cytoplasm. **c** GIST with large pleomorphic cells

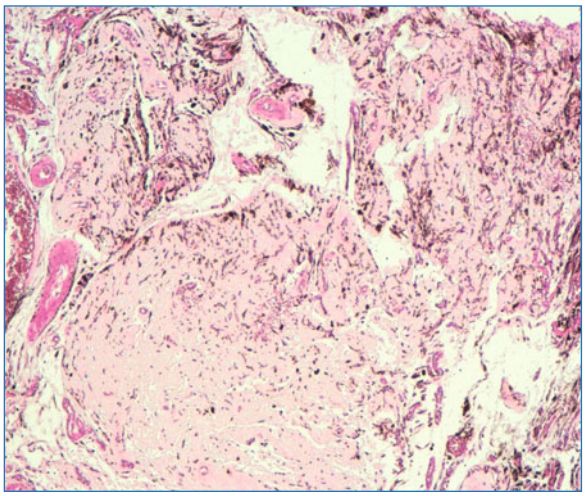

Fig. 1.3 Treatment-induced modifications: myxoid degeneration, fibrosis, hemosiderin deposits. No neoplastic cells are present

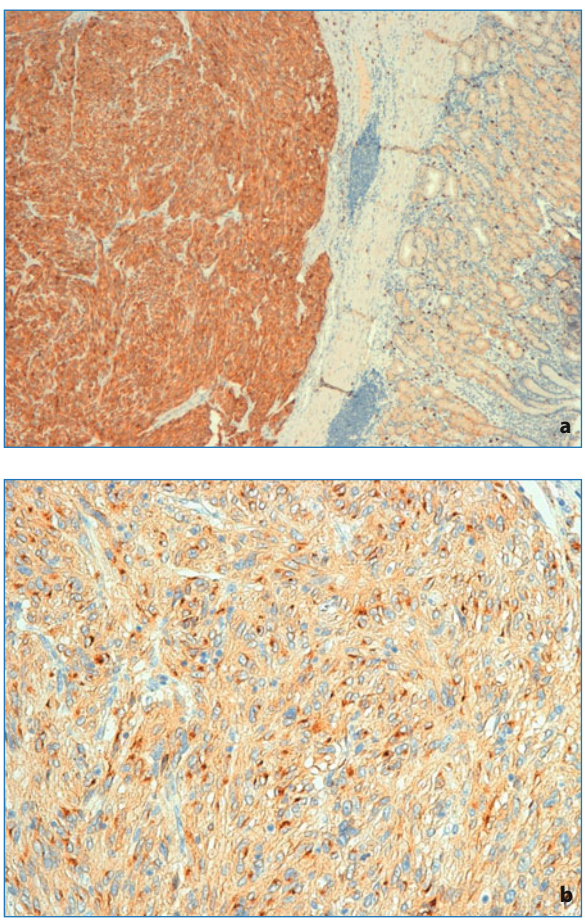

Fig. 1.4 Immunohistochemical staining (peroxidase). **a** Spindle-cell GIST with intense cytoplasmic staining positive for CD117 (*left*). **b** GIST with prevalently dot-like staining positive for CD117

short fascicles and whorls.

In the epitheliod pattern (Fig. 1.2b) the cells are round with eosinophilic cytoplasm. In some cases multinucleated cells may also be present (Fig. 1.2c). In both patterns stromal modifications can be seen, such as perivascular hyalinization, and hyaline material that seem to create a trabecular pattern. Small bowel GISTs may contain skeinoid fibers (eosinophilic aggregates of extracellular collagen) [43].

After treatment with tyrosine-kinase inhibitors (TKI), a marked reduction in cellularity, marked fibrosis and myxohyaline degeneration is usually found (Fig. 1.3).

In general, the cellular morphology remains similar to that of the primary tumor, but cytomorphological differences as well as phenotype modifications such as rhabdomyosarcomatous differentiation may be seen [44].

The diagnosis of GIST is supported by immunohistochemical staining for KIT (CD117) and/or discovered on GIST-1 (DOG1) [45]. In case of negative results for both markers, diagnostic confirmation should be sought by mutational analysis of *KIT* and *PDGFRA* genes.

Approximately 85-95% of GISTs stain for KIT /CD117 [46, 47]. This positive staining is usually intense and diffuse, and can appear with cytoplasmic (Fig. 1.4a), membrane and dot-like paranuclear distribution (Fig. 1.4b).

It should be recalled that other non-GIST malignancies can be positive for KIT/CD117, such as melanomas, angiosarcomas, Ewing/PNET, seminomas and small-cell lung cancers. The immunophenotypic profile should therefore be interpreted in morphological and clinical setting [45]. About 90% of cases of GIST show protein-kinase theta expression (which is involved in T-cell activation, signal translation in smooth muscle cells and neuronal differentiation), although the specificity is lower than KIT [48].

Recently a new antibody, DOG1 clone K9, was introduced, which is a protein of the chloride channel. It appears to be more sensitive than KIT/CD117 in epithelioid gastric GISTs or EGISTs, regardless of the mutation status [49].

In a study carried out on 1168 cases of GIST with different sites and histologic subtypes, the sensitivity of DOG1 and KIT was almost identical: 94.4% and 94.7%, but not equivalent. It was confirmed that

DOG1 is more sensitive in epithelioid gastric GISTs (including those with mutated *PDGFRA*), whereas KIT seems to be more sensitive in intestinal GISTs. Nonetheless, negative results for both antibodies have been observed in 2.6% of cases, so the diagnosis should be supported by mutational analysis [50]. However, used in combination with KIT, it is an excellent biomarker for the identification of GISTs [51].

The differential diagnosis of GIST includes other mesenchymal tumors arising in the GI tract, such as schwannomas (especially in the stomach), intra-abdominal fibromatosis (ileum), leiomyomas (esophagus and rectum) and leiomyosarcomas (colon) [1].

1.5 Evaluation of the Risk of Progression

In the Consensus Conference held at the NIH in 2001, GISTs were stratified by risk category according to mitotic index (cut-off 5/50 and 10/50 HPF) and tumor size (cut-off 2 and 5 cm) [52]. More recently a new classification added the site of the tumor to the two existing parameters, with the result that gastric GISTs are considered to have a better prognosis than intestinal GISTs [53].

Tumor rupture (spontaneous or surgical) is also a highly negative prognostic factor, due to peritoneal contamination, although it is a rather rare event (<5%). Recently a prognostic nomogram was introduced for recurrence-free survival after complete surgical resection of localized primary GIST [54], which could be useful in guiding treatment choices [45].

Metastases are generally to the liver and peritoneum [55], rarely to skin-subcutaneous and soft tissue [56-59] or to bone [60], and very rarely to the lung [61], lymph nodes (with the exception of pediatric GISTs and in Carney-Stratakis syndrome) (Fig. 1.5) and bone marrow [62].

For the correct medical treatment, it is important to discriminate between metastatic GISTs and multiple sporadic GISTs in a single patient. In the latter case, different mutations are evident in the different neoplasms, showing an independent origin for the synchronous lesions [63, 64].

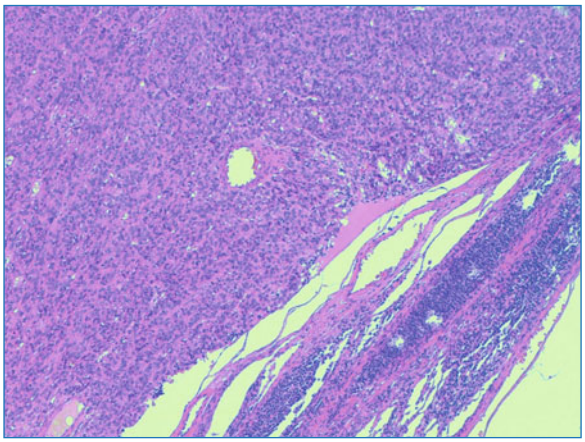

Fig. 1.5 Metastatic lymph node. Residual of lymph node parenchyma is present on the right

1.6 Clinical Utility of Mutational Analysis

Imatinib mesylate, which was originally developed to inhibit Abl tyrosine kinase in chronic myeloid leukemia, is an ATP analog that binds to KIT and, by inhibiting its signal, blocks its activating effect due to mutation. It has been shown that the clinical response to the drug depends on the mutation status, so that a molecular classification of GISTs has been proposed [36].

Patients with a mutation in exon 11 seem to respond better to the drug than patients with a mutation in exon 9 or wild-type [65, 66]. Patients with a mutation in exon 9 of *KIT* also seem to have a better response when treated with a dose of 800 mg instead of the standard dose of 400 mg [67, 68].

In Europe, mutational analysis is recommended for all GISTs, both metastatic and localized.

Recent studies have shown encouraging results on the adjuvant use of imatinib in high-risk localized GISTs [69]. So mutational analysis can be helpful in patient selection.

1.7 Primary and Secondary Resistance

Most inoperable or metastatic GISTs show a clinical response to imatinib which can be verified with the appropriate radiological exams. A portion remain stable while a minority progress in the first six months (primary resistance) (Fig. 1.6a) [67, 70]. Secondary resistance occurs when the disease progresses after an initial response (generally after 12-36 months) (Fig. 1.6b),

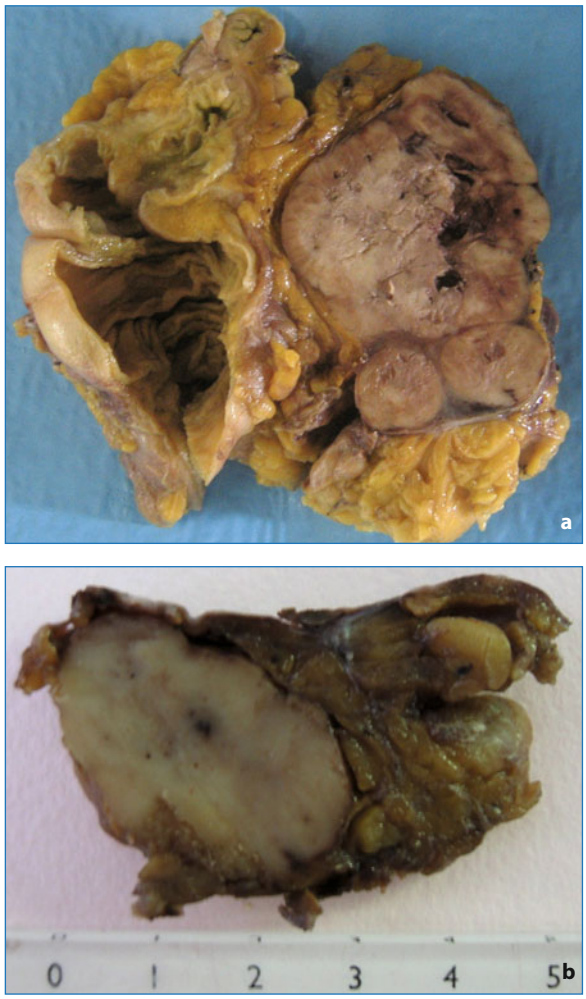

Fig. 1.6 Disease progression after treatment with imatinib. **a** Primary resistance: omental nodule. **b** Secondary resistance: pelvic nodule in a patient treated with imatinib for 7 years

often due to acquired or selected mutations in the kinase domain [71, 72].

These mutations are often located in exons 13, 14 and 17 [65, 73, 74]. The primary mutation in resistant patients is still sensitive to pharmacologic treatment [45].

In the case of disease progression, the pharmacologic option is to increase the dose of imatinib (600-800 mg) [45]. Alternatively, sunitinib may be administered as second-line therapy after the failure of imatinib [45, 75, 76]. In addition to acting as a KIT and PDGFRA inhibitor, sunitinib also acts as antiangiogenic factor, and has demonstrated efficacy against secondary mutations located in exons 13 and 14, but not in 17 and 18 [77]. Sunitinib may also be considered as first-line therapy in cases with mutation in exon 9 or wild-type (including pediatric cases) [75, 77].

Other drugs may be considered in patients resistant to both imatinib and sunitinib [45], including sorafenib [78], nilotinib [79] or dasatinib [80].

1.8 Syndrome-associated GISTs

Familial forms [81, 82] present germline mutations of *KIT* and *PDGFRA* with the substitution of a single nucleotide in exon 11 of *KIT* as the most frequent mutation. These GISTs are often multifocal, most commonly situated in the small bowel and generally have an indolent course [45].

Approximately 7% of patients with type I neurofibromatosis (NF1) may develop one or more GISTs, which usually do not harbour mutations of the *KIT* and *PDGFRA* genes (Fig. 1.7) [83-85].

The autosomal dominant syndrome of Carney-Stratakis, in which gastric GISTs are associated with extra-adrenal paragangliomas [86], is characterized by multifocal lesions in the stomach.

A germline mutation in the genes encoding succinate dehydrogenase subunits (*SDHB, SDHC* or *SDHS*) is found [87]. It should be differentiated from the Carney triad, which is characterized by the occurrence of GISTs, endocrine tumors and pulmonary chondromas [88].

1.9 Pediatric GISTs

About 1-2% of GISTs are found in pediatric patients [89-91]. Females tend to be affected more than males, and the lesions most commonly appear as multiple nodules in the stomach with epithelioid morphology. They tend to metastasize to the lymph nodes and often have late recurrences. They rarely harbour *KIT* or *PDGFRA* mutations [92].

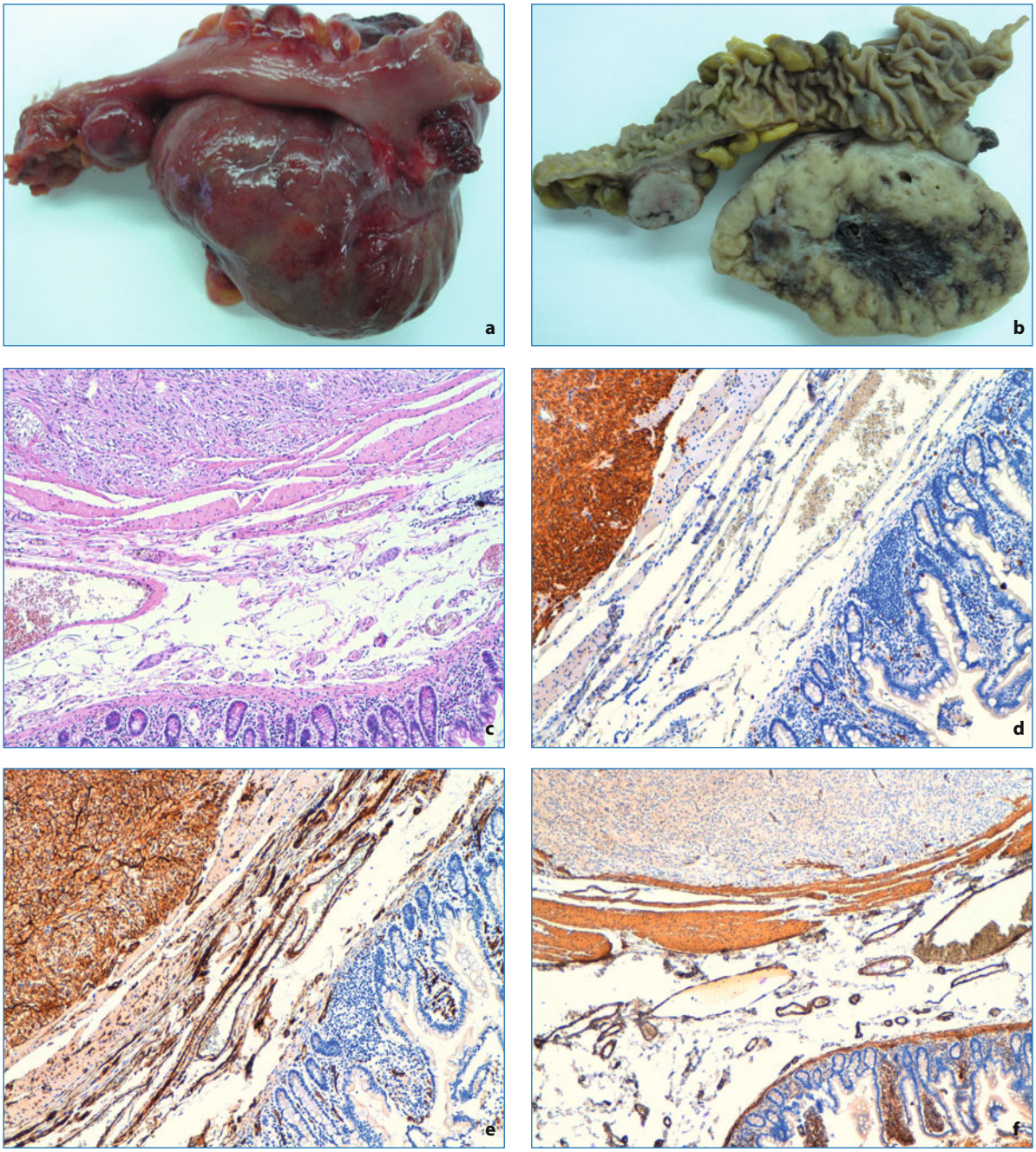

Fig. 1.7 Ileal GIST in neurofibromatosis. **a** Surgical specimen. Two separate nodular lesions are present. **b** Cut section (after formalin fixation) **c** Hematoxylin-eosin-stained section (ileal mucosa *below*). **d** Immunohistochemical staining positive for CD117 (*left*). **e** Immunohistochemical staining positive for CD34 (*left*). **f** Immunohistochemical staining negative for actin (*above*)

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Section II
Imaging

Introduction

2

Elisabetta de Lutio di Castelguidone

Imaging plays an important role in the multidisciplinary study of both primary and metastatic gastrointestinal stromal tumors (GISTs), thanks to the numerous radiologic techniques, such as conventional radiography, ultrasonography with and without color Doppler, contrast-enhanced ultrasound (CEUS), CT, MR and CT/PET, as well as endoscopic techniques such as endoscopy and endoscopic ultrasound (EUS).

Conventional endoscopy and EUS may identify a GIST either incidentally during the course of a study performed for another indication, or in the presence of bleeding caused by ulceration of the lesion. Less frequently a GIST is discovered as a result of obstructive symptoms due to the site or size of the lesion. EUS plays an important role in tumor characterization thanks to the ability to biopsy lesions in the esophagus, stomach and rectum.

Diagnostic imaging is used for the identification, characterization, staging and follow-up of GISTs, and it plays a particularly important role in the evaluation of treatment response. Imaging studies are also indispensable in the guidance of percutaneous biopsy procedures.

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Conventional radiologic studies with single and double contrast techniques can in most cases identify the site of the lesions: indirectly, in the presence of extrinsic dislocation and compression in lesions with extraluminal growth, and directly in the intraluminal lesions.

US, color Doppler and CEUS can provide useful information, not only in the study of primary GISTs but in their follow-up, especially in the vascular study of liver metastases.

CT is the most diffuse technique. It is not only useful in the diagnosis and characterization of the lesion, but also as a reference for staging and especially for follow-up during treatment. Indeed the RECIST criteria are no longer sufficient for evaluating treatment response, as they need to be associated with the Choi criteria based on the vascular pattern and therefore enhancement of the lesion.

Like CT, MR can be useful in the identification, especially in rectal GISTs, and in the characterization of liver metastases and in follow-up during the treatment. Thanks to the new diffusion-weighted imaging techniques, MR is able to provide useful information on the level of activity of the pathologic tissue.

PET-FDG can provide early metabolic information measuring the effect of the drug. The technique is required to confirm a disagreement between CT/MR and

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clinical findings. CT and MR measure real response but not the predictive response as does PET.

Contrast-enhanced PET-CT study has all the advantages of both contrast-enhanced MDCT and PET and could be considered the reference standard tecnique in the study of GIST.

In conclusion, imaging plays a fundamental role in follow-up, can suggest the diagnosis and provides a useful contribution to staging, whereas the major role in lesion characterization is played by anatomic pathology.

Conventional Radiography

3

Francesco La Seta, Teresa Maria Borino, Lorenzo Tesè, Luigi Carlo Cirillo and Filippo Barbiera

Abstract Conventional radiography is nowadays seldom indicated for the diagnosis and follow-up of patients with GISTs. Abdominal plain films, single and double-contrast barium studies of the gastrointestinal tract may, however, be useful (in occasional cases) in demonstrating direct and/or indirect signs of GISTs.

The radiological characteristics of this kind of tumor on conventional barium studies are often non-specific. The tumor's growth pattern may be intra- and/or extraluminal, and the various radiological examinations are generally able to give information only about the presence of a neoplastic alteration with a pattern suggesting a 'non-mucosal' origin of the tumour. The size of the mass is obviously an important factor for the detectability of the lesion. Secondary intestinal obstruction or perforation may be easily detected on abdominal plain films in patients with acute clinical presentations.

GISTs may certainly be detected with conventional radiography, but today barium examinations are no longer indicated as first-line studies in this clinical context. The diagnosis of GIST with conventional radiography may be considered an incidental report in clinical practice, because ultrasound, CT and MR directly delineate the tumor itself, as well as its relationships with other abdominal organs, the peritoneal cavity and retroperitoneum.

Keywords Gastrointestinal stromal tumors • Gastrointestinal tract • Neoplasm • Mesenchymal neoplasm • Abdominal neoplasm

3.1 Introduction

As for other gastro-intestinal diseases, the study of GISTs by conventional radiographic studies consists of abdominal plain films, single and double contrast barium examinations of the esophagus and stomach, small bowel follow-through and enteroclysis and double contrast enema of the colon. In most cases these techniques may only contribute to the detection and localization of the tumors, either indirectly with signs of extrinsic compression, displacement of intestinal loops and distension of the bowel proximal to stenosis, or directly with evidence of an expansive parietal lesion. Direct signs of a "mural mass" are best identified with double contrast examinations, given the greater detail they provide of the mucosal surface. With barium studies alone it is impossible to directly evaluate the peritoneal cavity, the other abdominal organs and

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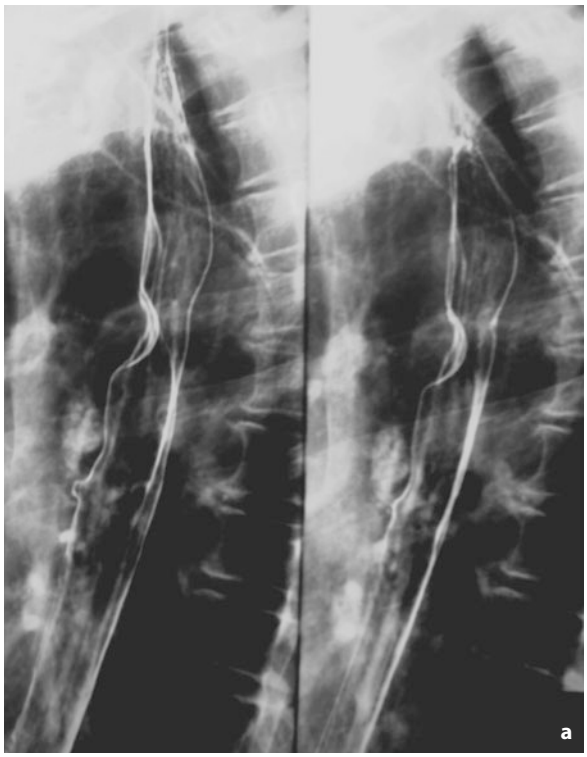


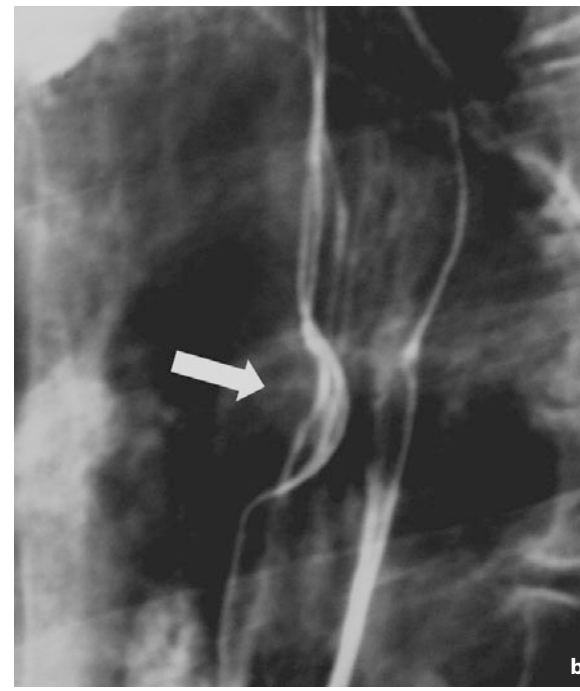


Fig. 3.1 a,b Small esophageal leiomyoma: tangential views show characteristics features of submucosal mass (*arrow*)

the retroperitoneum, so these conventional radiographic studies always need to be integrated with other imaging techniques such as ultrasonography and above all CT and MRI.

3.2 Esophagus

GISTs have seldom been reported in the esophagus; leiomyomas (Fig. 3.1) are generally more common at this level [1, 2].

On plain films of the chest, a mediastinal soft tissue opacity with median retrocardiac location may be seen. On barium studies, small tumors may appear as smooth intramural masses, but in extensive neoplastic disease, large ulcerated masses with prevalent extrinsic growth to the proximal tract of the stomach and adjacent structures may be seen, as in other kind of tumors (Fig. 3.2).

3.3 Stomach

This is the most common site of GISTs.

The abdominal plain films may show a ra-

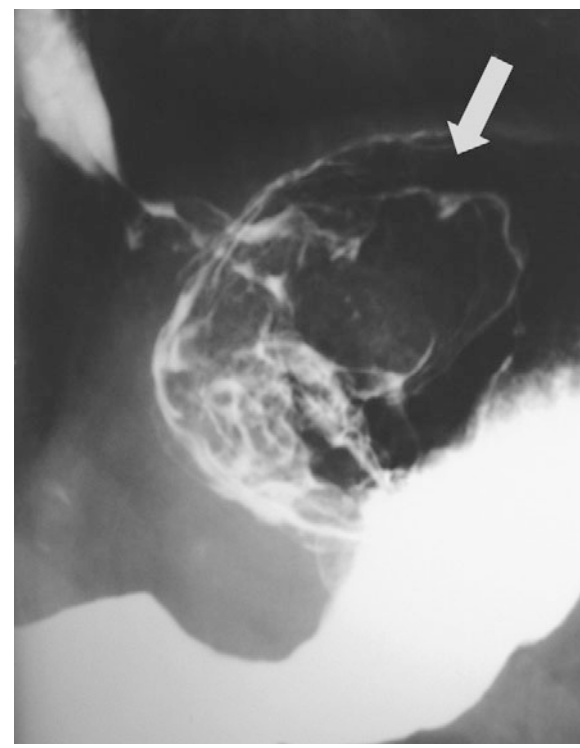


Fig. 3.2 Distal esophageal and gastric lymphoma. Stenosis and irregularity of normal anatomic landmarks at the cardia, with a "mass" extending into the gastric fundus (*arrow*)

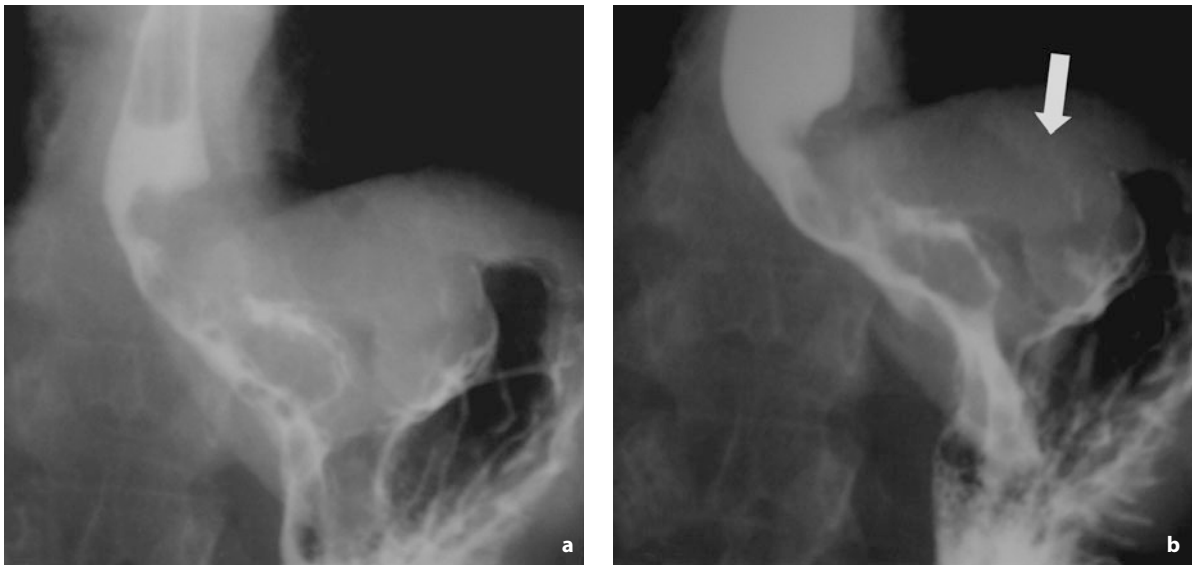


Fig. 3.3 a, b Large infiltrating malignant mass at the gastro-esophageal junction: carcinoma. Note the irregularity of the gastric profile, which may be even appreciated without barium contrast (*arrow*)

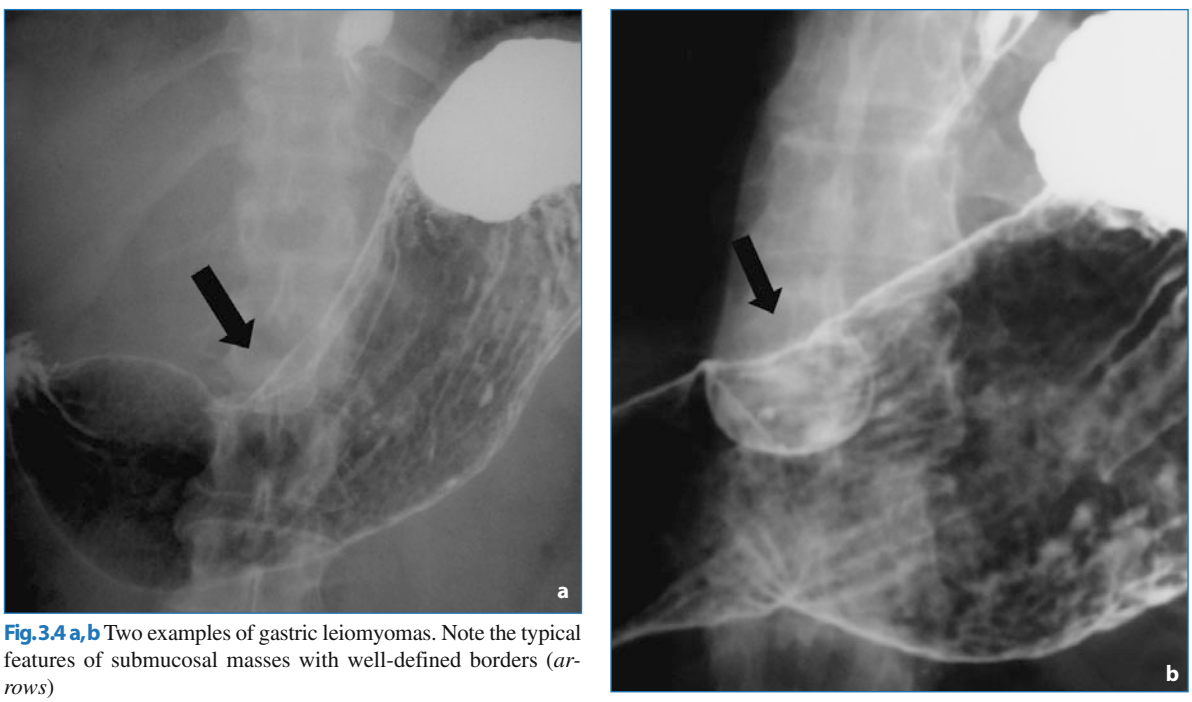


Fig. 3.4 a, b Two examples of gastric leiomyomas. Note the typical features of submucosal masses with well-defined borders (*arrows*)

diopaque 'soft tissue' mass which compresses and/or displaces the gastric profile (Fig. 3.3). Calcifications may also be visible [1, 3].

With barium studies, the most common radiographic signs are those of a submucosal mass (similar to leiomyomas and leiomyosarcomas) (Figs. 3.4, 3.5) with the margins forming obtuse angles with the gastric wall, and a smooth and generally intact surface in the absence of focal areas of ulceration. Occasionally, the appearance may be similar to that of an isolated intraluminal polyp with or without a pedicle. In larger tumors with exophytic growth pattern, areas of hemorrhage and/or necrosis may give rise to deep ulcers (Fig. 3.6) and cavitations which communicate

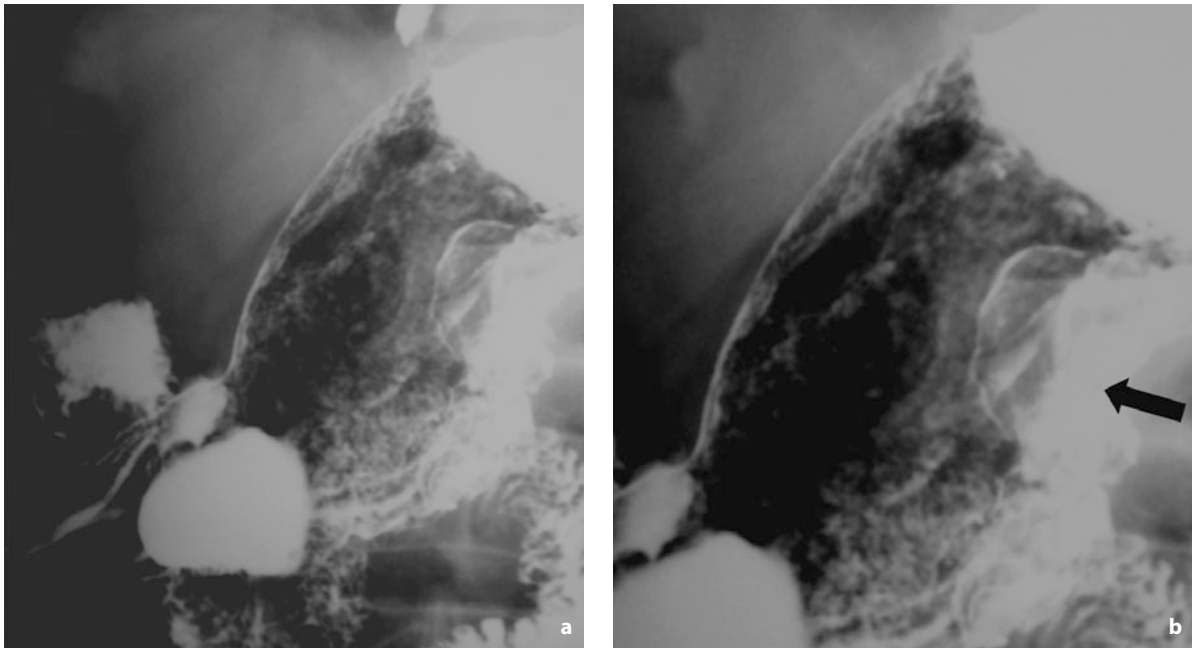


Fig. 3.5 a, b Leiomyoma on the posterior wall of the of the gastric body. Note the typical features of a submucosal mass (*arrow*)

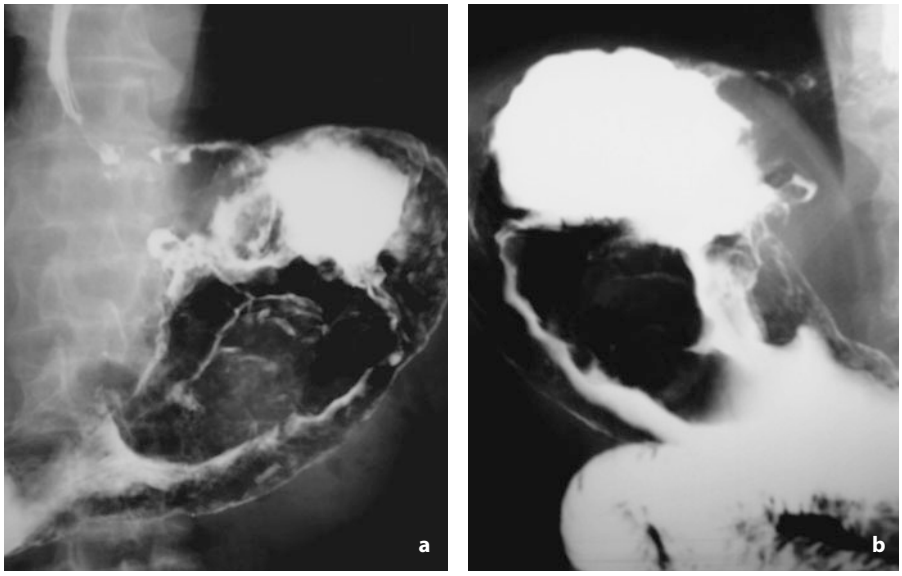


Fig. 3.6 a, b Two different views of a large, ulcerated mass on the anterior wall of the stomach: leiomyosarcoma

with the gastric lumen, containing air or with air-fluid levels, and in which intraluminal contrast material may accumulate [4].

The differential diagnosis of course includes other mesenchymal tumors such as leiomyomas, leiomyosarcomas, schwannomas, neurofibromas and neuroendocrine tumors (such as solitary gastric carcinoids). However, leiomyomas, leiomyosarcomas and schwannomas are relatively rare in the tract considered, whereas the preferential location of carcinoids is the gastric antrum. Gastric lymphomas may present with similar radiological characteristics, although they generally also display lymph-node involvement, which is usually absent in GISTs.

In adenocarcinomas the gastric mucosa should be firstly involved, and on double-contrast studies the mucosal pattern may appear irregular and jagged with distortion of the gastric folds.

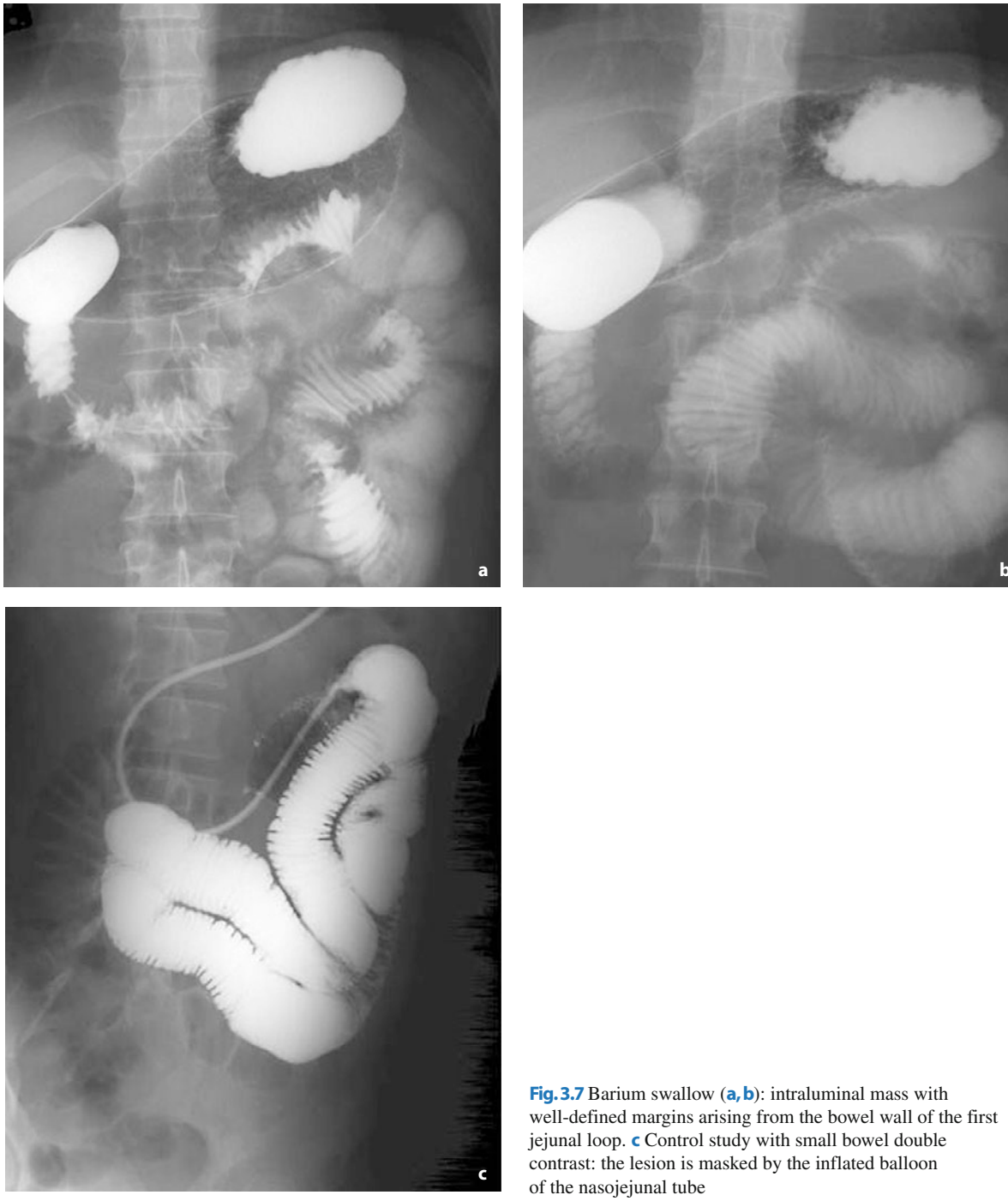
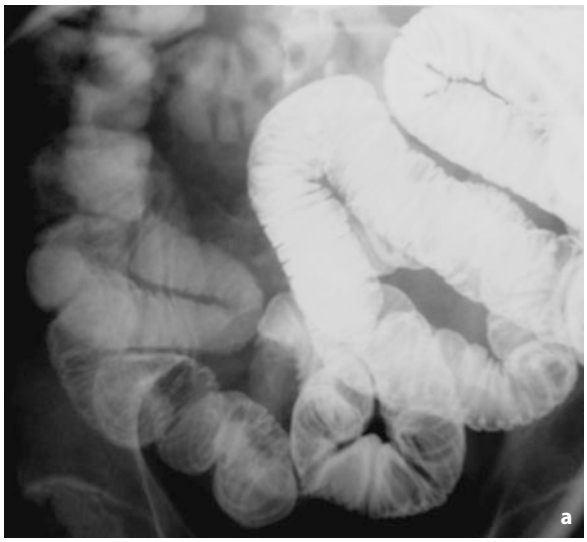


Fig. 3.7 Barium swallow (**a, b**): intraluminal mass with well-defined margins arising from the bowel wall of the first jejunal loop. **c** Control study with small bowel double contrast: the lesion is masked by the inflated balloon of the nasojejunal tube

3.4 Small Bowel

There are no preferential sites for GISTs in the small bowel. Since at this level most GISTs arise within the muscularis propria of the intestinal wall, their growth pattern tends to be extraluminal and the tumor can often reach such a large size as to cause a mass effect on the involved bowel loop and/or the adjacent intestinal segments (Fig. 3.7).

As in the stomach, relatively common phenomena in large tumors with marked malignant characteristics include the formation of a cavity within the mass and/or



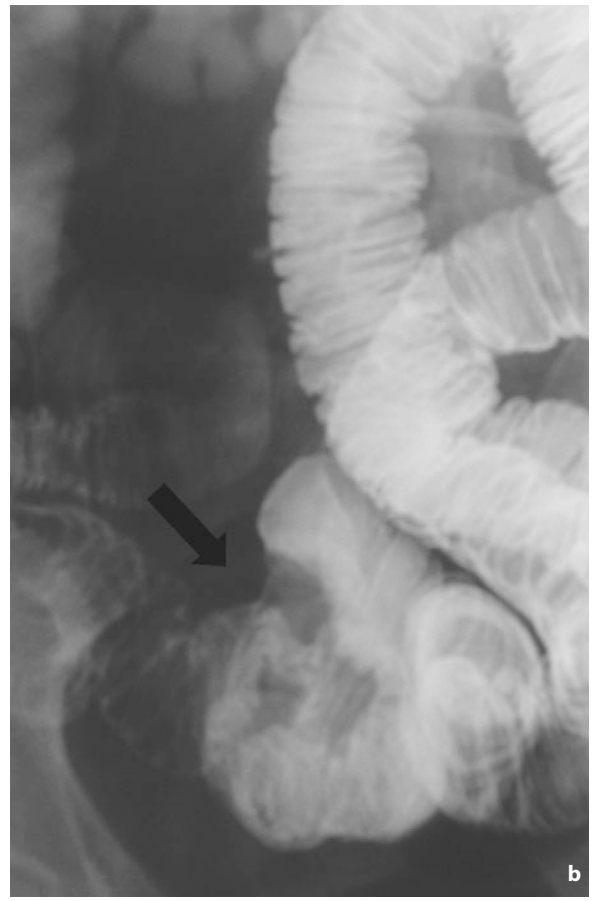


Fig. 3.8 a, b Double-contrast small bowel enteroclysis. Small "non-mucosal" mass (*arrow*) in a pelvic loop: GIST

fistula with the adjacent bowel loops, and possible findings of calcifications. Frequently, there may also be involvement of the mesentery (with signs of rigidity of the small bowel wall or the colon), the urinary bladder and the ureters.

Large GISTs may cause intestinal obstruction; in these cases, radiological signs of bowel distension will be seen on the abdominal plain films. Small GISTs, generally do not give rise to intestinal obstruction. On single-contrast barium studies (small bowel follow-through), intramural and/or intraluminal GISTs may appear as small masses projecting into the lumen with generally well-defined margins and possible ulceration. Double-contrast studies (small bowel enteroclysis) may better define the submucosal origin of the tumor, as the mucosal surface and fold pattern are generally not involved in small masses (Figs. 3.8, 3.9) .

The differential diagnosis includes benign and malignant, primary and secondary tumors.

Benign masses include first of all lipomas and adenomas. Lipomas are preferentially located in the ileum; appear as 'filling defects' oval or round in shape, sharply defined, sessile or pedunculated. They are generally deformable following the physiologic activity of intestinal peristalsis and upon targeted compression during radiological examination. Adenomas may also appear as "filling defects" and display a broad base, with a homogeneous or irregular "cauliflower" appearance and radiolucent bands ('soap bubble' appearance described by Waters in 1930) [1, 3-6]. Masses arising from the neurogenic plexuses, which are also intramural, are more commonly found in the distal tract of the ileum; if subserosal, they are generally located on the antimesenteric border, although they may display growth in both directions.

Similar radiologic characteristics may also be seen in vascular lesions such as hemangiomas.

In cases of small tumors, small bowel enteroclysis is indispensable to obtain a differential diagnosis about the mucosal or submucosal origin of the lesions (Fig. 3.9) .

The differential diagnosis with leiomyomas and leiomyosarcomas is impossible to make on the basis

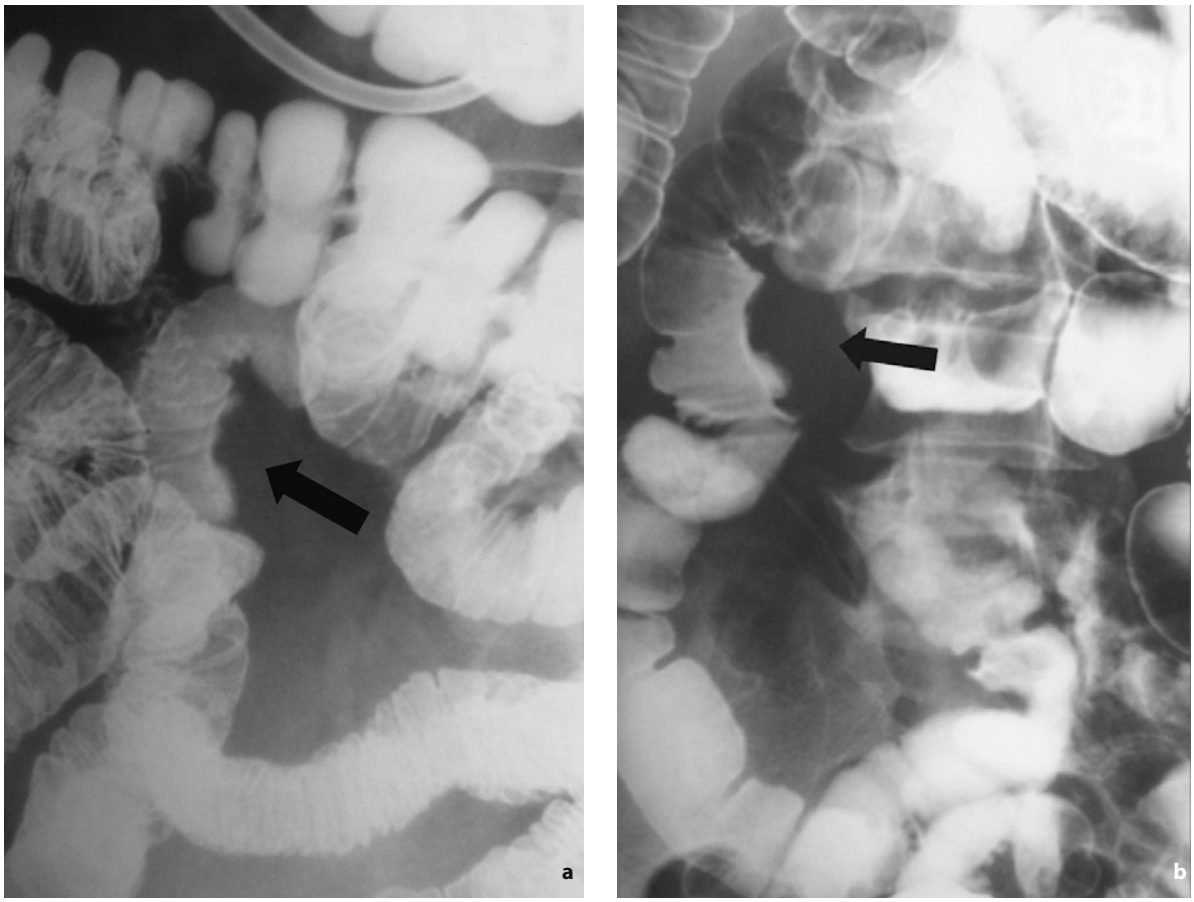


Fig. 3.9 a, b Double-contrast small bowel enteroclysis. Two different views of a small "non-mucosal" mass (*arrow*) in an ileal loop: leiomyoma

of radiographic characteristics alone. Leiomyomas may also appear as circular or crescent-shaped filling defects (Figs. 3.9, 3.10) with invasion of the lumen and mass effect on the adjacent bowel loops. Like GISTs, they tend to have an exophytic growth pattern, with consequent deformation due to compression, distension or traction of the bowel loops. If the tumor develops in a subserosal location, displacement and curvilinear, convex deformities of the intestinal wall may be appreciated together with the typical mass effect ("empty space" appearance) on the opacified bowel loops. Extrinsic compressions are better identified during early filling of the involved intestinal segments, as to avoid "masking" due to the overimposed other adjacent loops. In case of a prevalent intraluminal growth, radiographic signs of intussusceptions may be present (Fig. 3.11). In addition, malignant tumors (leiomyosarcomas) tend to give the bowel loop a "rigid" appearance due to bowel wall infiltration

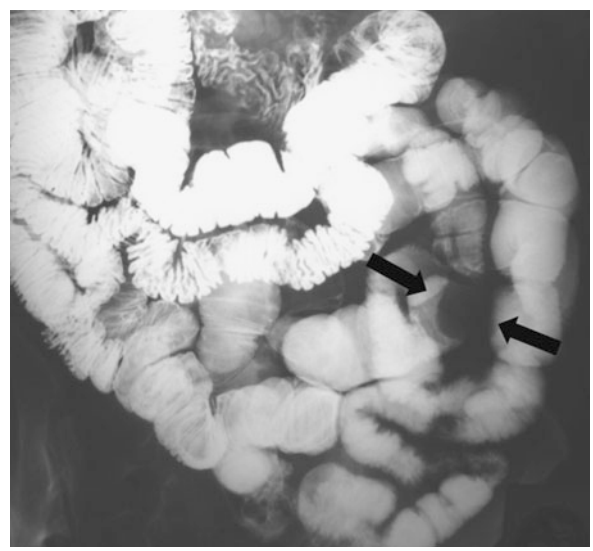
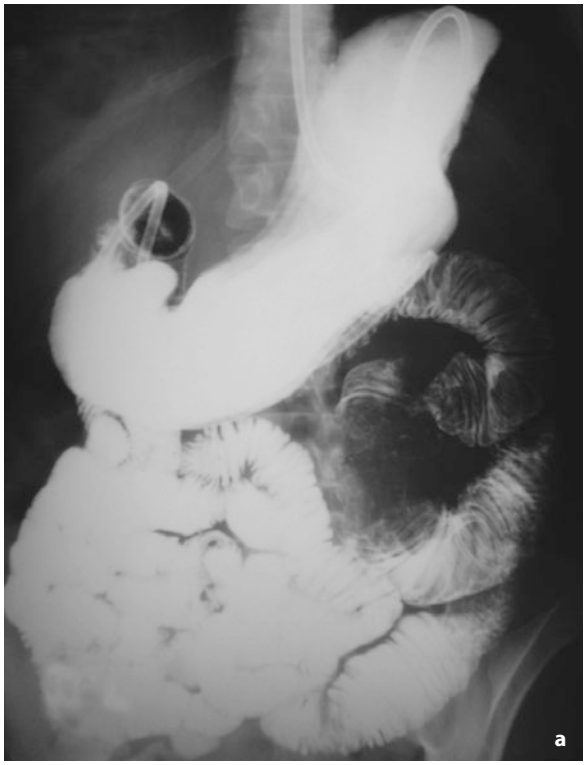


Fig. 3.10 Double-contrast small bowel enteroclysis. Prone overhead view. Typical features of a "non-mucosal" mass (*arrows*) in an ileal loop: leiomyoma



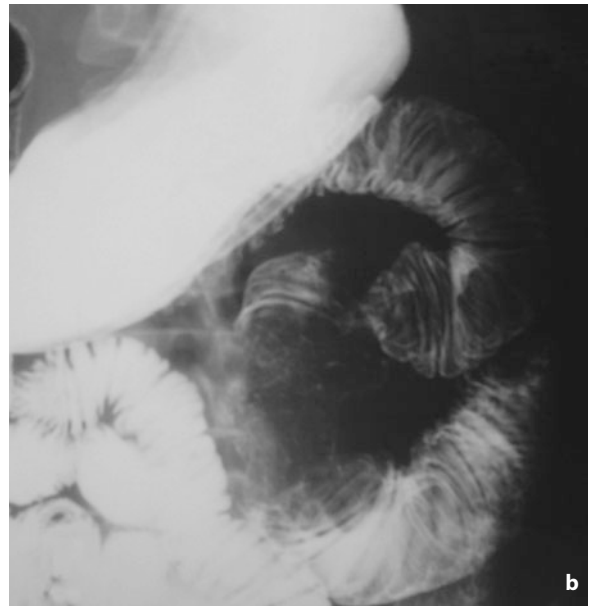
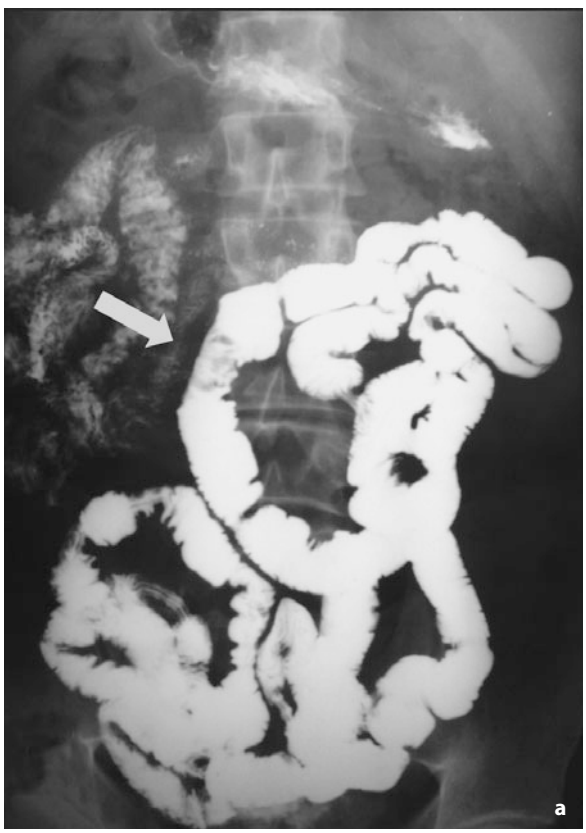


Fig. 3.11 a, b Double-contrast small bowel enteroclysis. A large intraluminal jejunal tumor causing intussusception and intestinal obstruction. Note reflux of barium into the stomach



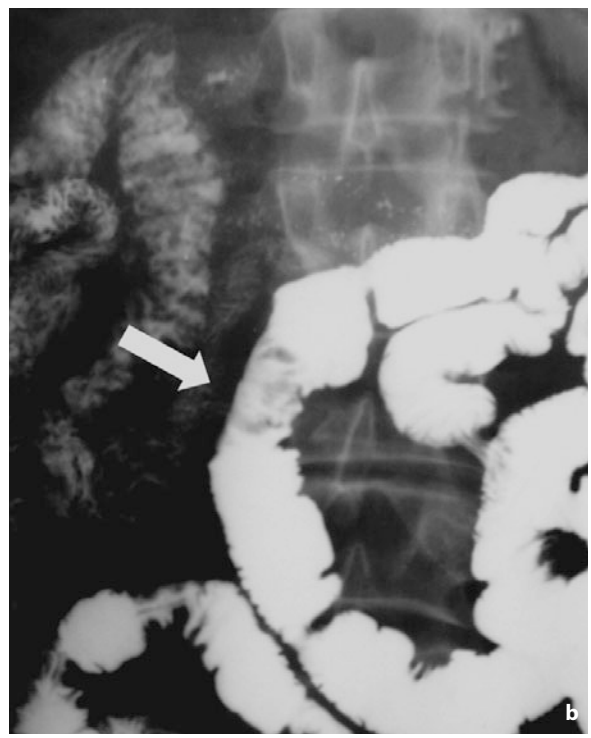


Fig. 3.12 a, b Small bowel follow-through. Prone overhead view. Mostly "parietal" mass (*arrows*) in an ileal loop, with signs of rigidity of the intestinal wall: leiomyosarcoma

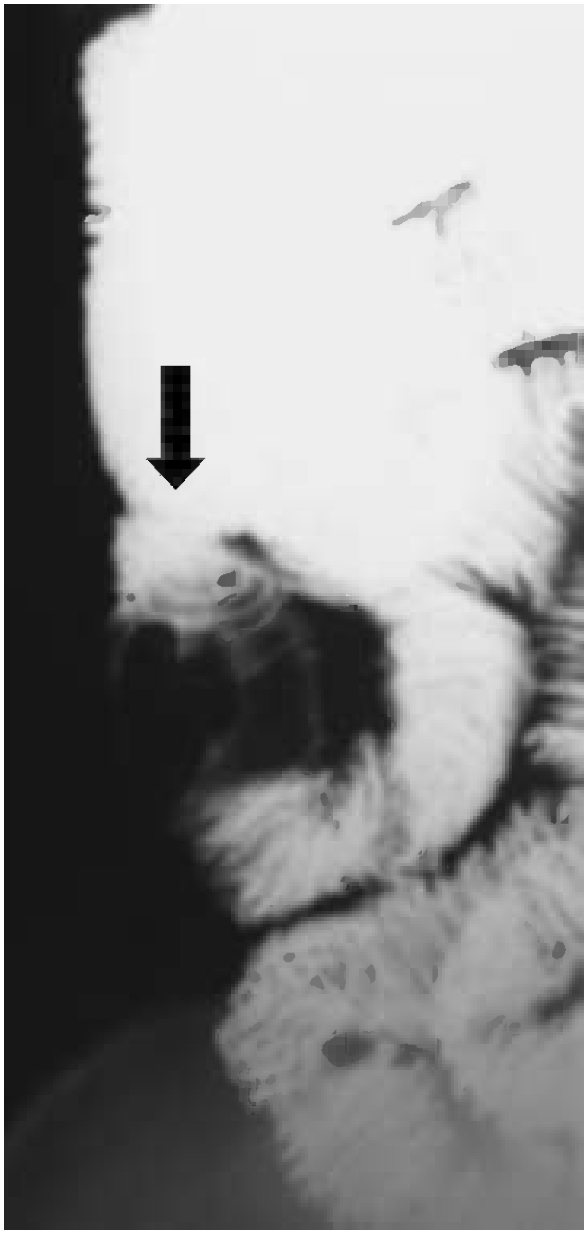


Fig. 3.13 Double-contrast small bowel enteroclysis. Mostly intraluminal jejunal tumor (*arrow*) causing stenosis and partial intestinal obstruction: adenocarcinoma

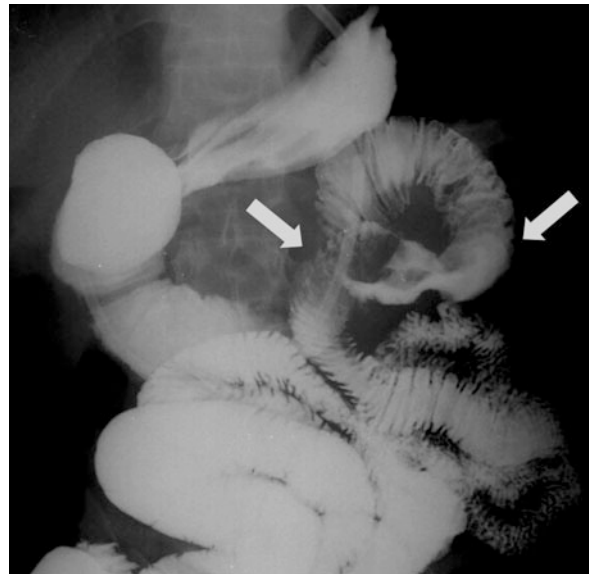


Fig. 3.14 Double-contrast small bowel enteroclysis. Large, infiltrating carcinoma (*arrows*) in the first jejunal loop

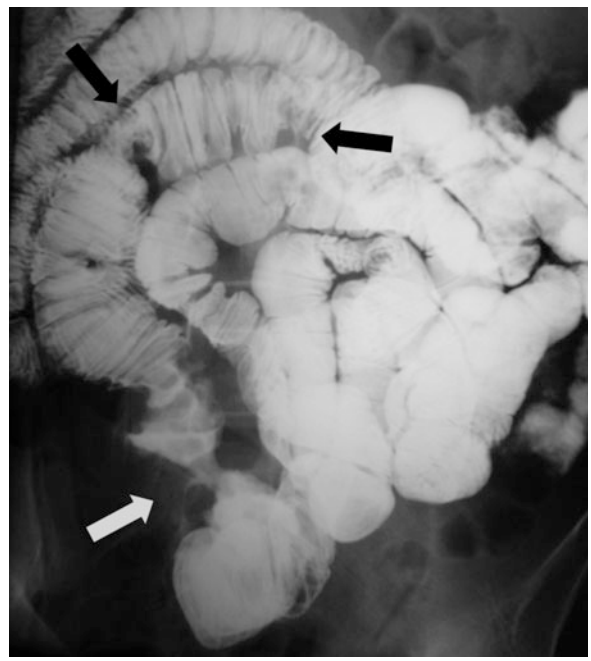


Fig. 3.15 Double-contrast small bowel enteroclysis. Large, infiltrating mass in a distal jejunal loop (*white arrow*): primary non-Hodgkin lymphoma. Note also other small parietal nodules more proximally (*black arrows*)

(Fig. 3.12). Formation of fistula, opacified by the barium may be more frequent [2, 5-9].

Adenocarcinomas generally involve the first 25 cm of the jejunum; due to the circumferential growth of the tumor and consequent ring-like stenosis of the loop, they appear as a rigid and stenotic segment (with the typical "apple core sign") with destruction of the mucosa and dilatation of the prestenotic loops (Figs. 3.13, 3.14). Unlike in benign lesions, the malignant stenosis is difficult to compress with targeted compression.

GISTs are relatively well differentiated from non-Hodgkin lymphomas (Fig. 3.15), which besides the

thickening of the bowel wall often also display a prevalent invasion of the mesentery with major lymph-node and retroperitoneal involvement at CT and MRI.

Carcinoids are preferentially located in the distal ileum. Although in the initial phases small tumors may appear as intramural masses, carcinoids are generally discovered in advanced phase when a prevalent extraintestinal involvement or metastasis are present. On barium studies, a 'mass effect' may be seen, often with a bundled appearance of the bowel fold at the margins of the mass, and kinking of the intestinal loops which appear to be rigid [9].

3.5 Colon and Rectum

Primary colonic GISTs are very rare. They are more frequently encountered in the anorectal area, where commonly they appear as mural masses with possible mucosal ulcerations; in some cases calcifications linked to necrosis or ulceration may be visualized in the central areas [10]. A polypoid appearance is less common. External spread, into the ischiorectal fossa or other adjacent organs is frequent [4].

3.6 Conclusions

Today, the diagnosis of GIST with conventional radiography is only occasionally reported. The radiologic characteristics are nonspecific as they are common to other neoplastic categories. The tumor growth may be intramural and intraluminal, but generally external spread becomes prevalent and a large mass is the most frequent radiologic appearance. Plain films and barium studies are able to supply information only about the presence, site, growth pattern and diagnosis of non-mucosal origin of the tumor, thus orienting the diagnosis and directing the patient towards other imaging techniques such as ultrasonography, CT and/or MR.

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Endoscopy and Endoscopic Ultrasound in the Diagnosis and Staging of GISTs

4

Pietro Marone, Giovanni Battista Rossi, Mario de Bellis and Alfonso Tempesta

Abstract Gastrointestinal stromal tumors (GISTs) are rare tumors, that are usually discovered incidentally during endoscopy. Occasionally, however, they are symptomatic and present mainly with gastrointestinal bleeding.

Since GISTs often present as submucosal lesions, covered by intact and normal mucosa, they cannot be differentiated from other submucosal lesions at traditional endoscopy. This technique has a poor (34%) diagnostic yield, even when it is associated with mucosal biopsy, which should be performed only in the presence of mucosal ulceration.

The second step in the diagnostic process is endoscopic ultrasonography (EUS), which allows both morphological and cytological diagnosis. EUS +/- FNAB allows a differential diagnosis between GIST and other submucosal lesions. A GIST larger than 5 cm, with low echogenicity, internal cysts and irregular margins is highly suspicious for malignancy at EUS. In this case, the patient should undergo surgery without further diagnostic tests. If no signs of malignancy are detected at EUS, then strict follow-up of the lesion can be planned or EUS-FNA should be considered. However, cytological morphology and immunohistochemistry are crucial to the establishment of a final diagnosis. Endoscopic resection of GIST has been attempted in the stomach where small lesions (< 3 cm) have been resected by means of endoscopic submucosal dissection (ESD). Usually, surgical excision is the definitive treatment for all primary GISTs larger than 2 cm, without evidence of peritoneal seeding or metastasis.

Currently, there are no clear indications for endoscopic and/or EUS follow-up of patients operated on for GIST.

Keywords GIST • Endoscopy • Diagnosis • Staging

4.1 Endoscopy

Conventional endoscopy tends to identify a GIST either incidentally during the course of investigations performed for another indication or in the presence of bleeding caused by ulceration of the lesion. Less frequently a GIST is discovered as a result of mechanical symptoms due to the site or size of the lesion. Some 40% of these tumors are nonetheless identified as primary lesions during an endoscopic examination. The appearance of the lesion is of a mass protruding into the gastrointestinal lumen, which may be little mobile

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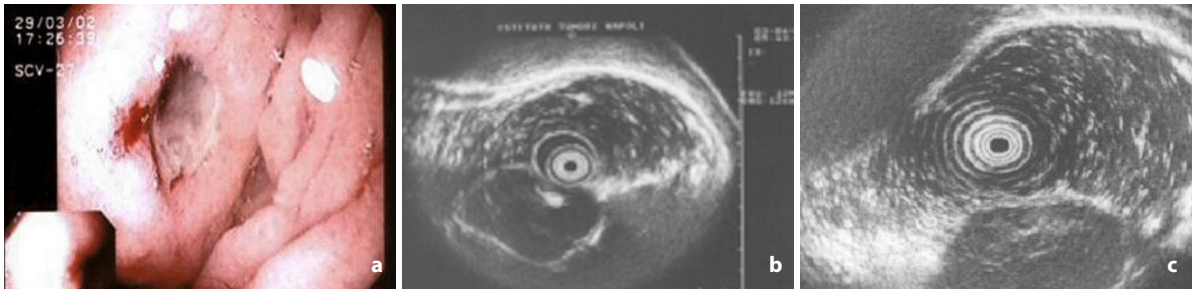


Fig. 4.1 **a** Firm gastric submucosal mass with deep ulceration >2 cm in size in patients with prior episode of hematemesis and melena. **b,c** EUS with radial array transducer, balloon-based technique. Area of the submucosa with inhomogeneous hypoechoic appearance and intense hyperechoic areas due to calcification and broad hyperechoic area of reflection of the ulcer crater. The arrow indicates the transition zone with the origin of the formation from the hypoechoic layer of the muscularis propria (4th echogenic layer of the wall). EUS appearance suggestive of GIST with intermediate characteristics. Histologic diagnosis revealed a large ulcerated leiomyoma with calcifications

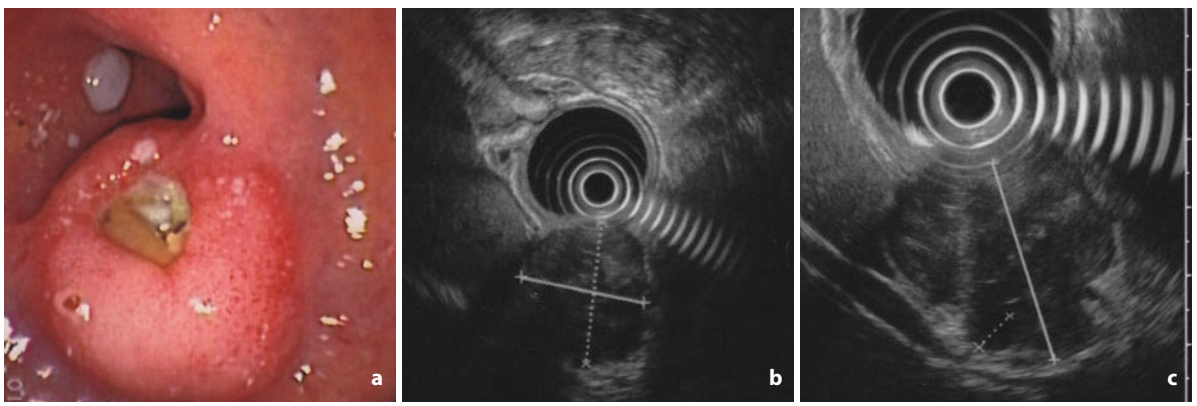


Fig. 4.2 **a** Firm gastric submucosal mass >2 cm in diameter with large and deep ulceration and necrosis. **b** EUS with radial array transducer, balloon-based technique. Area of the submucosa with inhomogeneous hypoechoic appearance and irregular margins and shape, >2 cm in diameter arising from the 4th echogenic layer of the wall (muscularis propria), transition point between normal wall and lesion. GIST with characteristics predictive of malignancy. **c** EUS shows anechoic areas of differing sizes (cystic spaces) within the inhomogeneous hypoechoic area, the presence of which is predictive of malignancy. Mass diagnosed as gastric ulcerated malignant GIST

or have a polypoid appearance. The overlying mucosa is usually normal, although in a minority of cases an umbilication or central ulceration may be present.

The morphologic characteristics of a submucosal lesion such as GIST (Figs. 4.1a, 4.2a, 4.3a, 4.4a, 4.5a) do not allow it to be identified by endoscopic observation alone, nor to differentiate it from other masses: leiomyomas or schwannomas, lipomas, aberrant pancreatic tissue or cysts (Figs. 4.6a, 4.7a, 4.8a, 4.9a, 4.10a). Even the differentiation between lesions of a benign or malignant nature is founded on merely suggestive criteria (Figs. 4.11a, 4.12a, 4.13a, 4.14a).

The biopsy performed on lesions with an intact overlying mucosa is of little help for diagnostic purposes, whereas significant tissue samples can be obtained from ulcerated lesions. The overall contribution of endoscopy with possible biopsy to the formulation of a correct diagnosis is 34% according to a large and recent meta-analysis [4]. This is comparable to radiology but markedly inferior to EUS with or without fine needle aspiration. A flowchart aimed at clarifying the nature of a lesion discovered incidentally during radiologic examinations sees EUS as the next step. Conventional endoscopy is indicated as a first-choice technique in the presence of bleeding.

Findings of a marked increase in size after a limited time period, ulceration or – if recognizable at endoscopy – multiple lobulations are all signs of malignancy.

In recent years endoscopic techniques for the study of the small bowel have become increasingly widespread. One third of small bowel tumors identified by

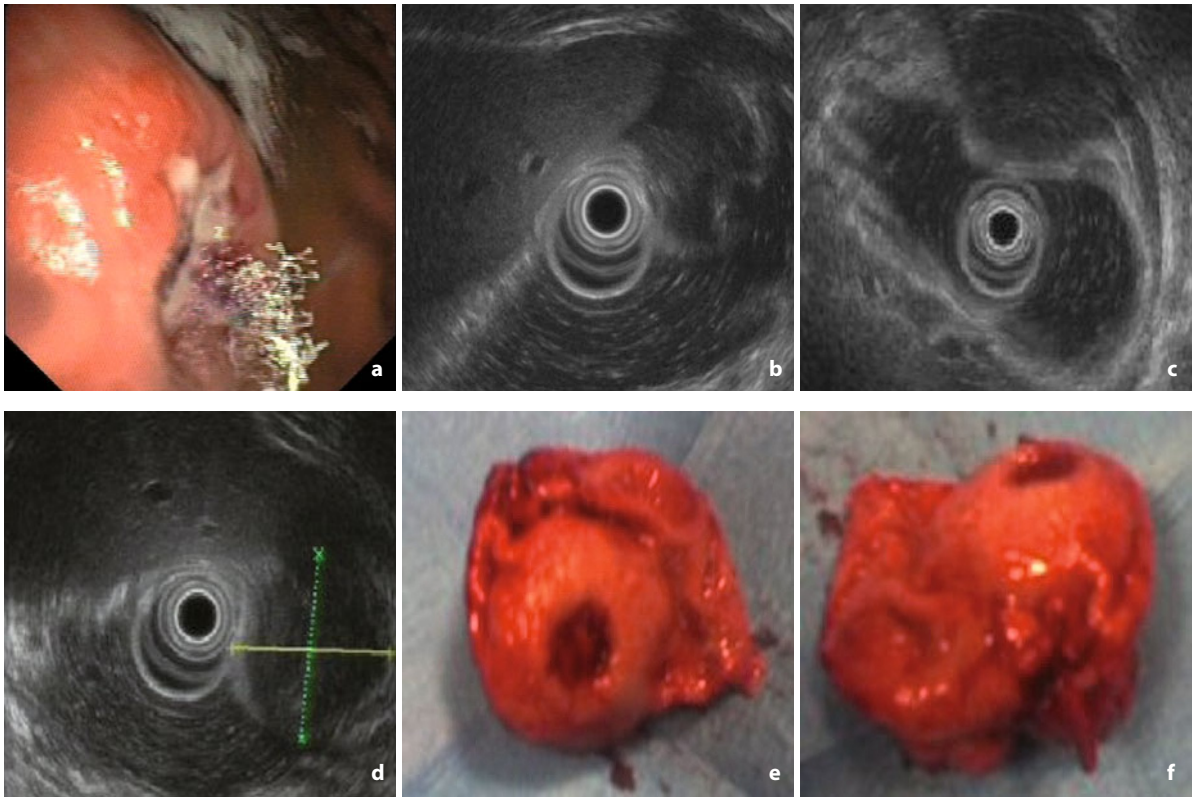


Fig. 4.3 a Ulcerated gastric submucosal mass in a patient with epigastric pain and history of breast cancer. EUS shows a large submucosal mass with irregular and inhomogeneous hypoechoic echostructure, calcifications and internal cystic spaces suggestive of malignant GIST. Anatomic Pathology consistent with malignant GIST with internal metastasis from breast carcinoma. **b, c, d** EUS shows the origin of the submucosal mass arising from the hypoechoic layer of the muscularis propria. **e, f** Surgical specimen of malignant gastric GIST with internal metastasis from breast carcinoma

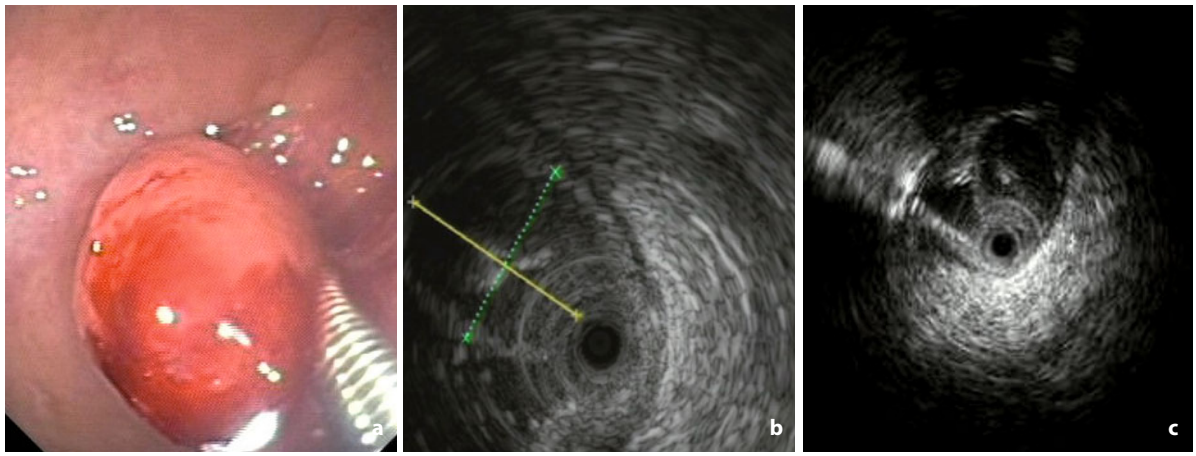


Fig. 4.4 a Submucosal mass with overlying normal mucosa, >1 cm in diameter. Incidental finding during screening. **b, c** EUS with 12 MHz miniature transducer and balloon-based technique shows a submucosal mass arising from the 2nd echogenic layer of the wall (hypoechoic) corresponding to the muscularis mucosa, with regular shape and margins and homogeneous hypoechoic echogenicity with some hyperechoic areas due to calcifications. The integrity of the hypoechoic 4th echogenic layer of the muscularis propria can be seen. The mass was resected with mucosectomy: diagnosis of rectal GIST with no signs of malignancy. Follow-up at one year was normal

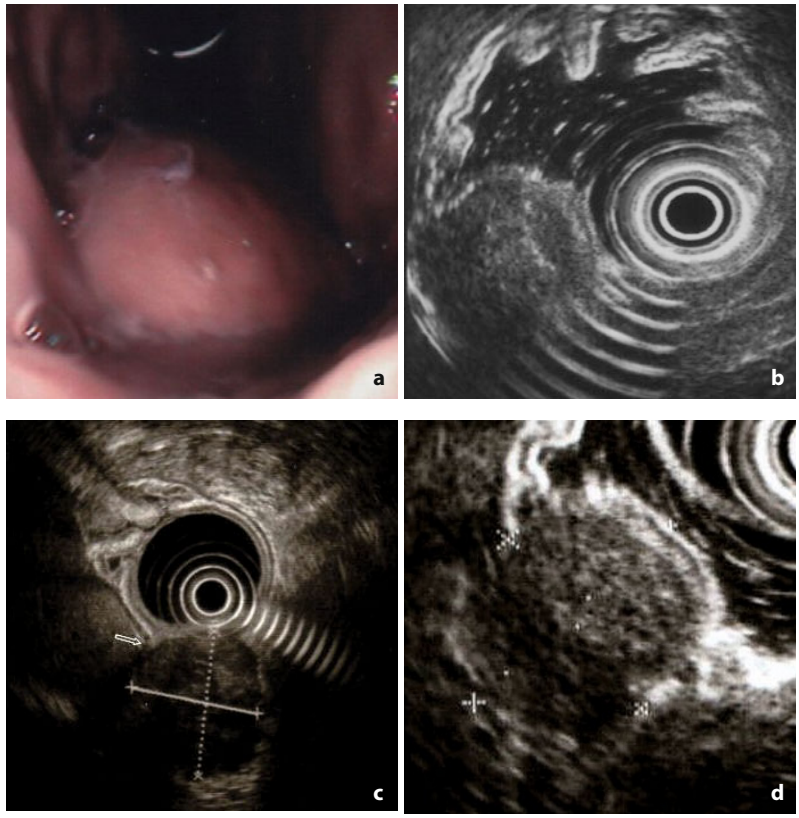


Fig. 4.5 **a** Gastric submucosal mass with normal overlying mucosa. **b-d** EUS appearance of the submucosal mass arising from the hypoechoic layer of the muscularis propria with internal echostructure and size, shape and margins suggestive of a GIST with malignant characteristics

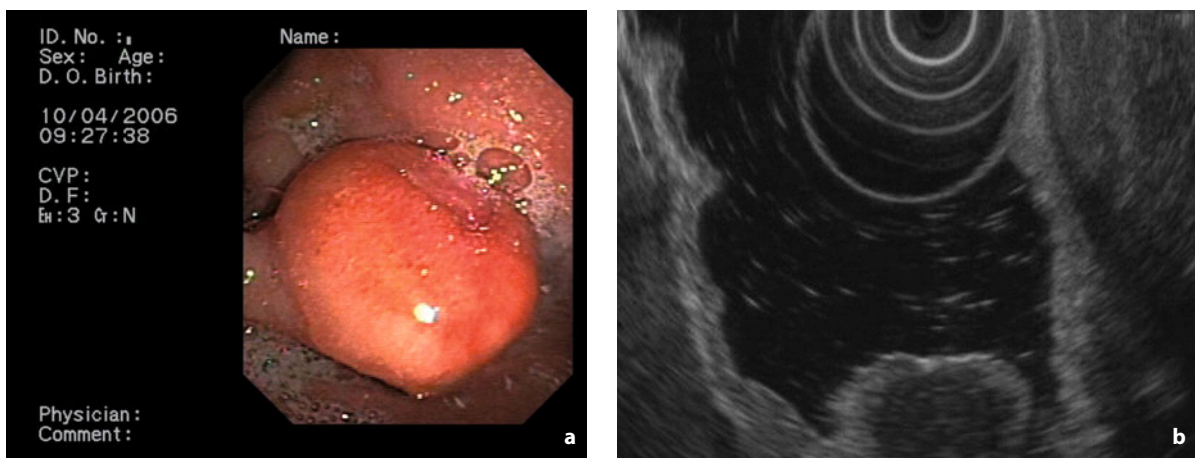


Fig. 4.6 **a** Ulcerated polypoid mass of the gastric submucosa. **b** At EUS with multifrequency radial array transducer (5-20 MHz) and balloon-based technique a polypoid mass of the submucosa can be seen with isoechoic margin and internal hypoechoic area and intact muscularis propria. Endoscopic removal; fibrous polyp of the gastric antrum

capsule endoscopy are GISTs and the absolute frequency is 0.8% of all capsule endoscopies of the small bowel. More than one lesion is identifiable in 10% of cases [4, 5]. However, in a Japanese multicenter trial on the use of double-balloon enteroscopy, GISTs accounted for 18% of small bowel tumors, second only to lymphomas [2]. The selection of the cases is the most likely explanation for these differences.

The endoscopic removal of a GIST has very limited indications and may be considered for gastric submucosal tumors less than 3 cm in diameter, with no EUS signs of malignancy and no apparent adherence to the

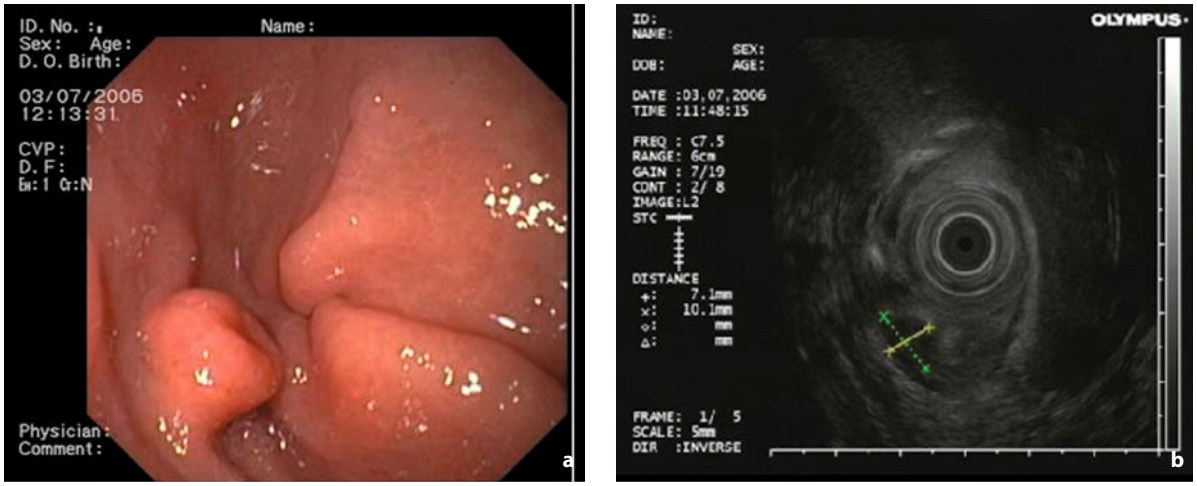


Fig. 4.7 **a** Endoscopic appearance of a submucosal lesion of the gastric antrum with umbilication above. **b** At gastric EUS a small hypoechoic area of the mucosa is visible. Aberrant papilla of the gastric antrum

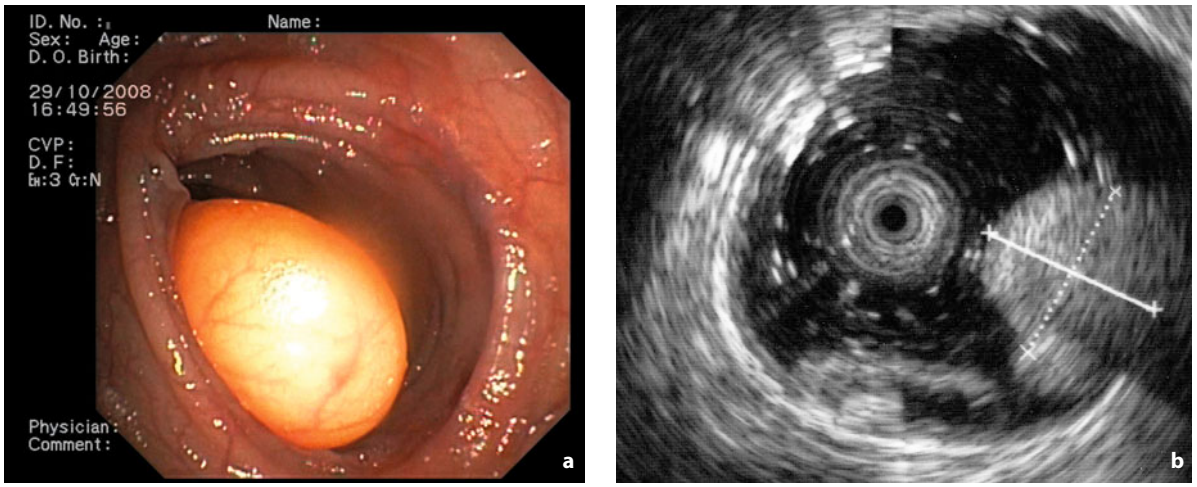


Fig. 4.8 **a** Soft sessile submucosal lesion of the colon with overlying yellowish mucosa. **b** EUS with 12 MHz miniature transducer and balloon-based technique shows intact colon wall with a homogeneous hyperechoic area of sessile submucosa protruding into the lumen arising from the submucosa. Lipoma of the colon

muscularis propria [6, 7]. The most commonly adopted technique involves the injection of a saline or macromolecular solution below the lesion, the subsequent incision of the mucosa and the freeing of the tumor using endoscopic submucosal dissection (ESD). Tumor removal is completed with a diathermic loop when sufficient mobilization is achieved. The risk of perforation is not negligible, but particularly in Asian studies the closure of the wall defect is achieved with endoscopic clips. However, it has been postulated that iatrogenic perforation of the GI wall, especially if associated with incomplete resection of the lesion, can induce subsequent disease recurrence in the peritoneum [8].

4.2 Gastrointestinal Stromal Tumors: The Role of Endoscopic Ultrasound

4.2.1 *Definition, Instrumentation and General Principles of the Technique*

Endoscopic ultrasound (EUS) is an instrumental examination involving the simultaneous use of endoscopy and ultrasonography, thus making possible a detailed intraluminal ultrasound study of the wall of the portions of the gastrointestinal (GI) tract accessible to the endoscope and the organs immediately adjacent to it.

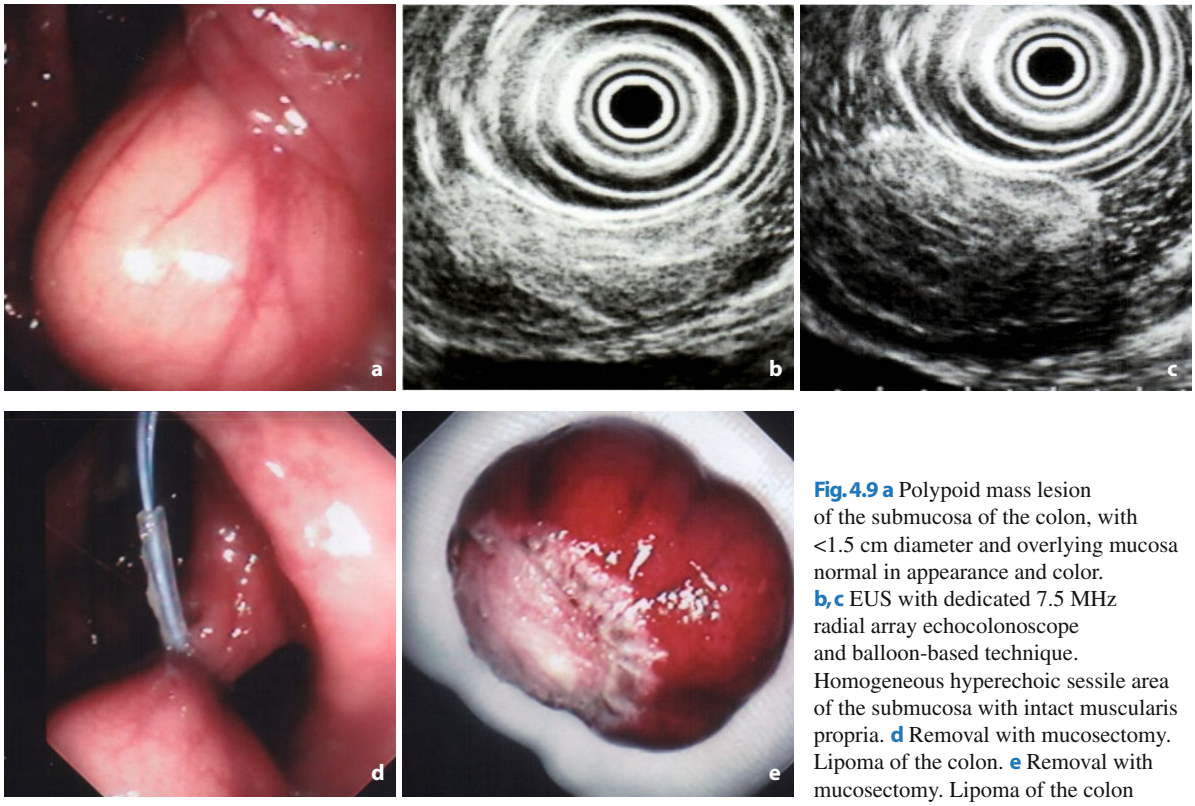


Fig. 4.9 a Polypoid mass lesion of the submucosa of the colon, with <1.5 cm diameter and overlying mucosa normal in appearance and color. **b, c** EUS with dedicated 7.5 MHz radial array echocolonoscope and balloon-based technique. Homogeneous hyperechoic sessile area of the submucosa with intact muscularis propria. **d** Removal with mucosectomy. Lipoma of the colon. **e** Removal with mucosectomy. Lipoma of the colon

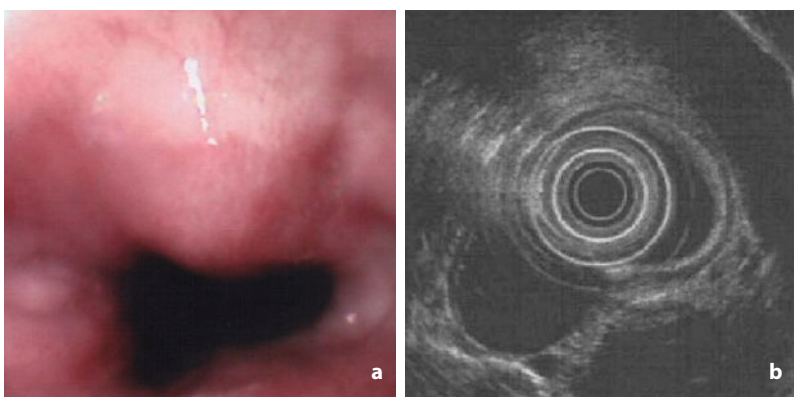


Fig. 4.10 a Mass lesion of the esophageal submucosa with overlying mucosa normal in appearance and color. **b** EUS of the esophageal hypo-anechoic mass arising from the muscularis propria with regular shape and margins. The aorta and the aortic arch can be identified. Esophageal leiomyoma

The miniaturized ultrasound transducers positioned at the distal end of the endoscope may be mechanical or electronic probes with either radial or linear array.

Radial array transducers allow scanning of an image through 360° around the axis of the probe. Linear array transducers instead produce a linear projection with which the trajectory of a fine needle introduced through the echoendoscope channel can be followed, thus allowing echoendoscopy-guided fine needle aspiration (EUS-FNA) of the lesion to be performed in safety.

The electronic instruments also have the possibility of applying color-Doppler to the echoendoscope, with the evident advantage of the study of vascular structures.

Technological development has lead to the creation and enhancement of miniature ultrasonographic probes composed of high-frequency transducers (12-20 MHz) which, thanks to their small diameter, can be introduced into the echoendoscope channel.

EUS uses high frequency transducers with high power resolution, making it possible to obtain highly detailed images of the individual layers of the wall of

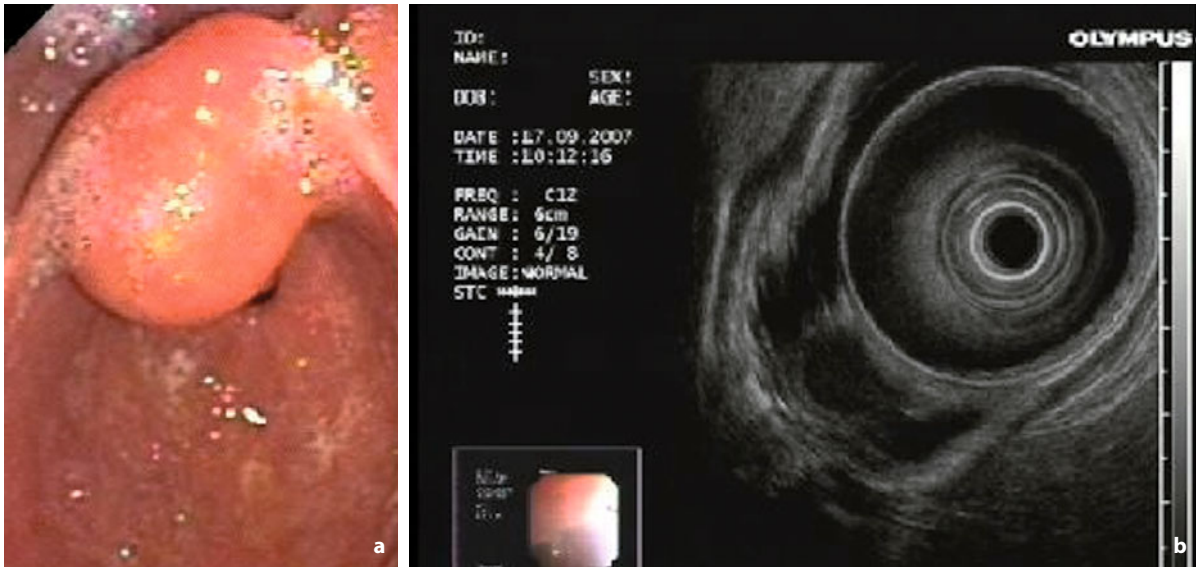


Fig. 4.11 **a** Submucosal mass with <1 cm diameter overlying the mucosa, with normal appearance and color and bridging folds. **b** EUS performed with radial array transducer and balloon-based technique. Area of the submucosa arising from the layer of the muscularis propria, <1 cm in diameter with regular shape and margins and homogeneous echostructure with small hyperechoic area due to calcifications. Absence of cystic spaces. EUS appearance suggestive of benign submucosal mass of the muscularis propria. Follow-up is underway

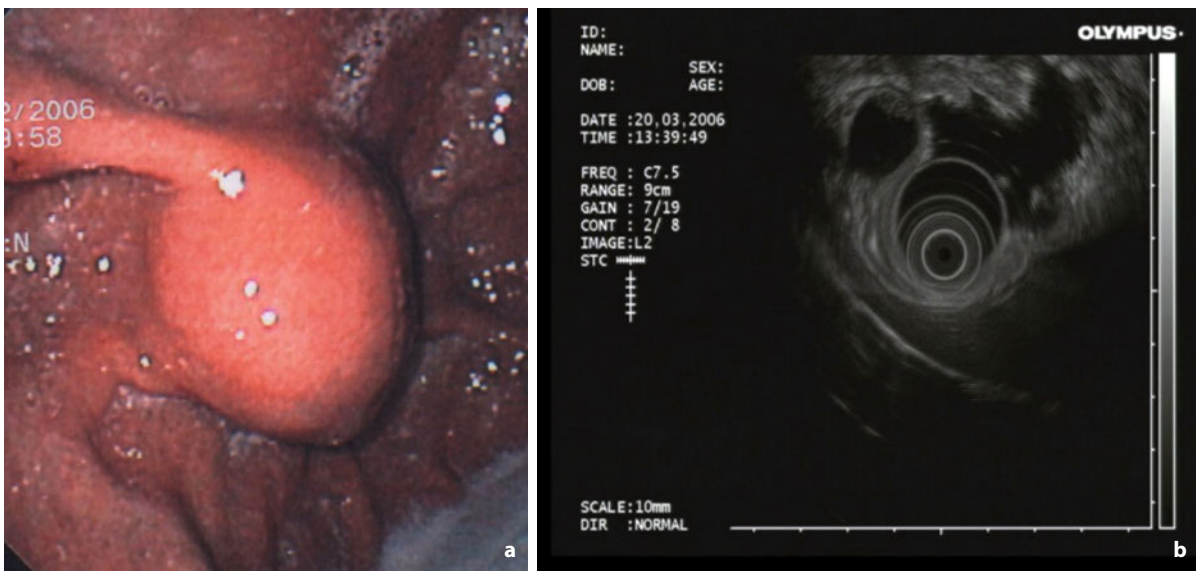
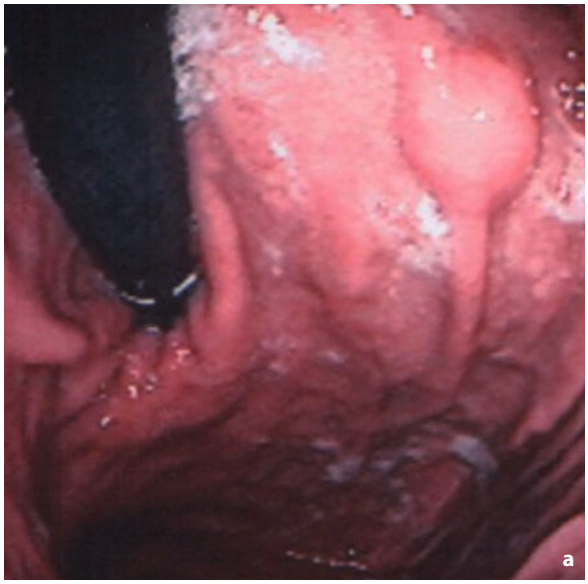


Fig. 4.12 **a** Submucosal mass lesion with <1 cm diameter overlying the mucosa, with normal appearance and color and bridging folds. **b** EUS appearance suggestive of benign submucosal mass of the muscularis propria. Follow-up is underway

the digestive tract. There is a good correlation between EUS images and the anatomy of the wall of the digestive tract (Fig. 4.15).

Although there are some differences in relation to the tract examined, at EUS the intestinal wall appears to be composed of five distinct echogenic layers, characterized by the alternation of images with hyperechoic and hypoechoic appearance, which internally-to-externally are as follows:

– the interface between the mucosa and the organ lumen (hyperechoic layer);
– the deep mucosa (hypoechoic layer);



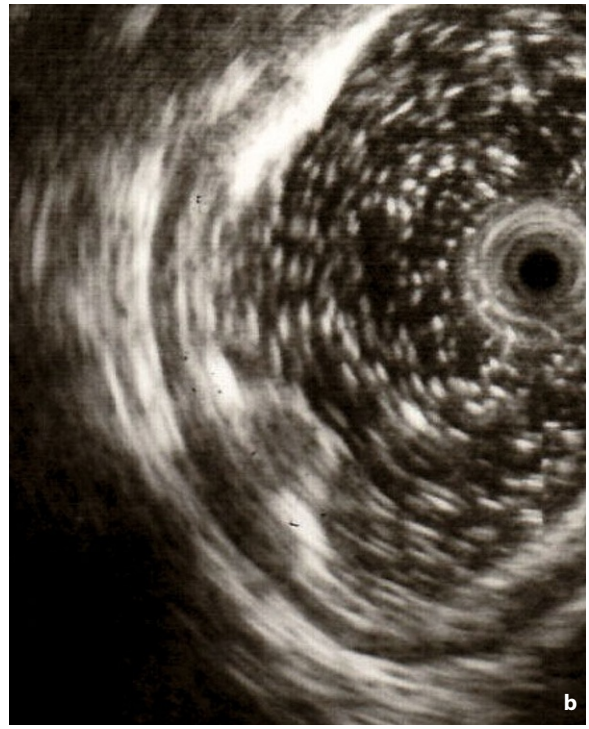
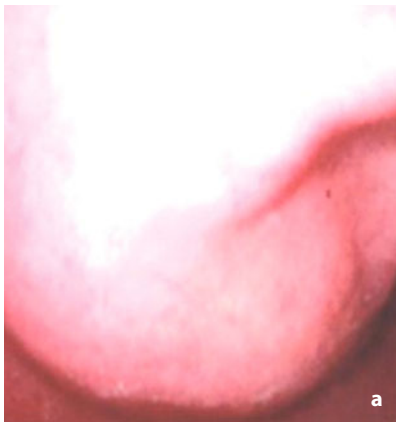
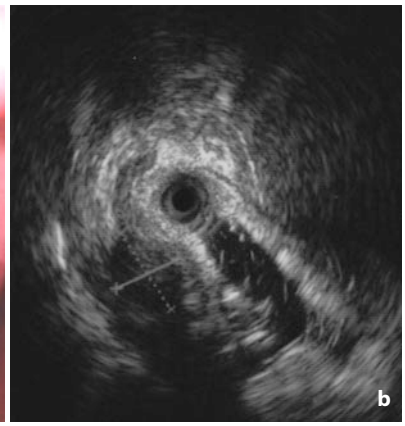
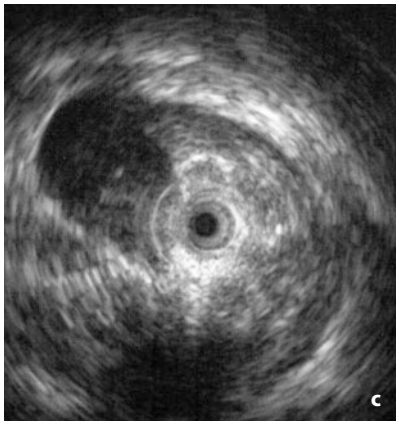


Fig. 4.13 **a** Submucosal mass <1 cm with bridging folds and overlying mucosa normal in appearance and color. **b** EUS with 12 MHz miniature transducer and balloon-based technique shows small hypo-anechoic area of the muscularis propria with benign appearance. Small gastric leiomyoma







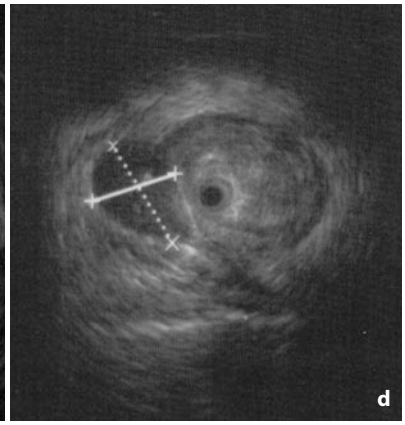


Fig. 4.14 **a** Gastric submucosal mass with overlying mucosa normal in appearance and color. **b, c** EUS with multifrequency radial array transducer (5-20 MHz) and balloon-based technique shows homogeneous hypoechoic area with some hyperechoic areas due to calcifications, approximately 1 cm in diameter with regular shape and margins and no other characteristics predictive of malignancy. **d** Image suggestive of gastric leiomyoma/GIST without malignant characteristics

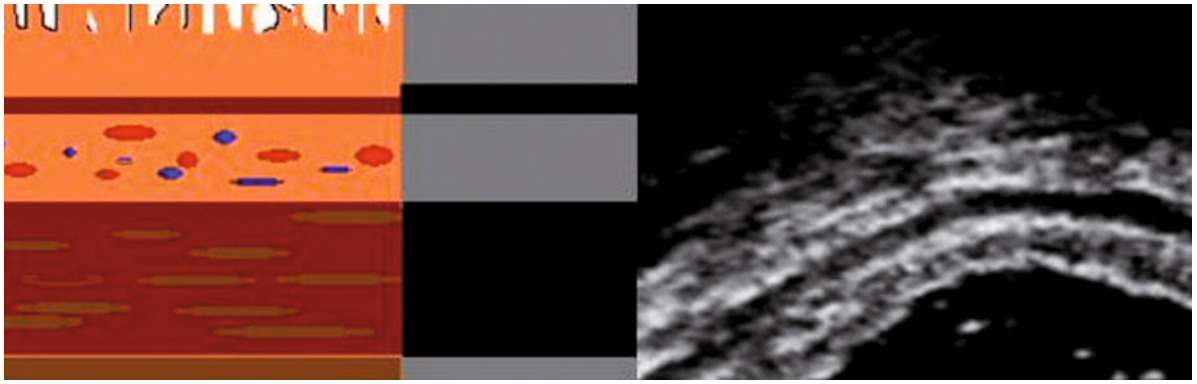


Fig. 4.15 Diagram of the architecture of the wall of the GI tract and its correlation with EUS. At EUS, the GI wall appears as alternating hyperechoic and hypoechoic layers

– the submucosa (hyperechoic layer);
– the muscularis propria (hypoechoic layer);
– the serosa (hyperechoic layer).

The ability to obtain such detailed images of the architecture of the wall has proven to be extremely useful in the locoregional staging of GI tract tumors, both for the definition of the T stage (degree of penetration of the tumor into the wall) and the definition of the N stage (metastatic involvement of the lymph nodes), as well as in the study of submucosal/intraparietal masses.

Currently the main indications of EUS are: locoregional staging of GI tract tumors, the histologic diagnosis and staging of biliopancreatic lesions, non-small-cell lung cancer, mediastinal diseases and the evaluation of submucosal GI lesions [9-12].

4.2.2 Gastrointestinal Stromal Tumors

Submucosal/intraparietal lesions make up a vast and heterogeneous group of lesions that arise within the wall of the GI tract, with possible origin from any of the individual layers composing the wall (muscularis mucosa, submucosa, muscularis propria and serosa). As such they present with a different nature and different potential progression. In the setting of these lesions, GISTs are of particular interest given their potential malignancy.

GISTs are mesenchymal neoplasms that typically arise from the muscularis propria (from the interstitial cells of Cajal).

Given its potential malignacy, the identification of a GIST is important, but in the presence of a submucosal mass, endoscopy is unable to differentiate it from other submucosal masses with a benign progression. The ability of EUS to identify the individual layers making up the wall of the GI tract has therefore made the technique invaluable and highly accurate in the study of submucosal/intraparietal lesions.

EUS is able to identify the mass within the wall and to define its size, margins, the wall layer of origin and the echostructure, and it enables the differential diagnosis between intramural and extramural lesions with a high degree of accuracy. The accuracy in defining the layer of origin is 97%, in the differential diagnosis between intramural and extramural lesion it is 100%, while in distinguishing between benignity and malignancy it is 83% [13-15].

Thanks to its accuracy in the study of the intestinal wall (definition of the individual layers comprising it, definition of its thickness and echostructure), EUS is an irreplaceable technique in the diagnosis of submucosal lesions and in particular GISTs.

With EUS, submucosal masses can be subdivided into three broad categories based on the echostructure of the lesion: anechoic lesions (cystic structure), hyperechoic lesions (adipose tumors such as lipoma or liposarcoma) and hypoechoic lesions of the 4th or less frequently the 2nd echogenic layer (leiomyomas or GISTs).

At EUS, a GIST appears as a hypoechoic area arising from the hypoechoic 4th echogenic layer of the wall corresponding to the muscularis propria, or less frequently from the hypoechoic 2nd echogenic layer of the muscularis mucosa.

The main predictive factors of malignancy at EUS are: the size of the lesion, appearance of the echogenicity,

the presence or lack of cystic spaces (number and size) within the lesion, and the irregularity of the external margins of the lesion.

The identification at EUS of a mass >4-5 cm in size, with irregular external margins and prevalently inhomogeneous hypoechoic echogenicity with hyperechoic foci and presence of internal cystic space, is highly suggestive of a malignant GIST, with an accuracy of 80-90% (Figs. 4.1b-c, 4.2b-c, 4.3b-d, 4.4b-c, 4.5b-d). In contrast, the observation of a mass <2-3 cm in size, with regular external margins and homogeneous hypoechoic-anechoic echogenicity and no internal cystic spaces, is highly suggestive of a GIST with no current characteristics of malignancy (Figs. 4.11b, 4.12b, 4.13b, 4.14b-d). In the definition of the malignant nature of a submucosal lesion EUS has a sensitivity, specificity, positive predictive value and negative predictive value of 89.5, 90.9, 89.5 and 90.9%, respectively [16-18].

GISTs can be differentiated from other masses such as lipomas, cysts, intraparietal vascular structures, aberrant pancreatic tissue, etc. on the basis of the wall layer of origin and echogenicity (Figs.4.6b, 4.7b, 4.8b, 4.9b-c, 4.10b, 4.16).

In GISTs, the additional contribution of EUS-FNA seems limited compared to other neoplasms – the cytologic diagnosis of malignancy is generally not possible because the samples obtained with FNA are small and do not allow an evaluation of the tumor mitotic index (Fig. 4.17).

The addition of EUS-FNA to immunohistochemical staining, however, has shown promising results: CD117 (c-KIT protein) is expressed in 85-95% of GISTs and CD34 is expressed in around 60-70% of GISTs, whereas SMA and desmin are generally expressed in benign leiomyomas and staining for S-100 protein is suggestive of a neuronal origin for the lesion.

The addition of immunohistochemical staining increases accuracy to 91.3% with 100% specificity. EUS-FNA with the addition of immunohistochemical staining (SMA+, desmin+, CD34, CD117, K 67) has a promising role in the preoperative and prognostic evaluation of GISTs [19, 20].

However, follow-up post-treatment for the identification of the recurrence of GISTs is more complex. The accuracy of EUS is limited by postoperative anatomic changes, inflammation and post-treatment fibrosis which negatively effect the accuracy of the technique. To date no studies have been performed on large enough populations to answer several important

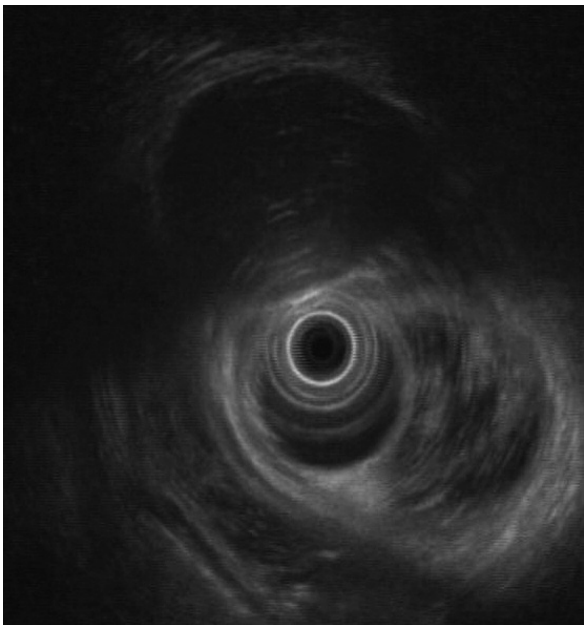


Fig. 4.16 Pelvic teratoma compressing but not invading the rectum. Isoechoic mass with regular shape and margins

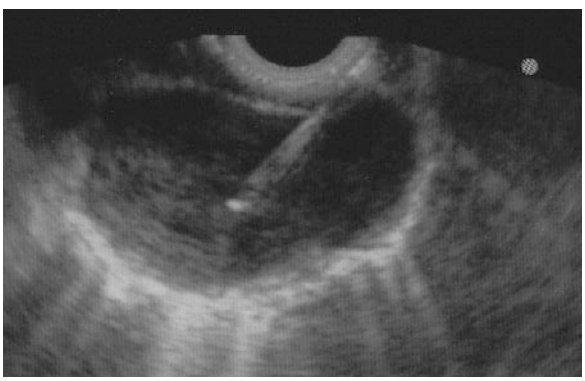


Fig. 4.17 EUS-FNA of paraesophageal hypoechoic mass of the mediastinum in patient with GIST

open questions, such as which patients with prior GIST should undergo EUS +/- FNA, what follow-up interval should be used and what impact the technique has in the treatment planning and prognosis of these patients. In addition there is a need to evaluate how to integrate EUS with other techniques to improve cost-benefit ratios [21].

EUS is a technique that in recent years has undergone rapid development. Its continued development and application in the various sectors of oncology, including the diagnosis and staging of GISTs, will depend on a number of closely inter-related factors, such

as the development and technological comparison of EUS instrumentation with other imaging modalities (CT, MR, US, PET) and the inevitable and rapid development of new therapeutic approaches.

All of these factors taken together will determine the role and future use of EUS, define which of the the currently emerging indications will become standard indications and identify new indications or supersede those currently considered valid, as well as better defining the clinical impact, the cost-benefit ratio, the influence on survival and the quality of the treatment.

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5 Ultrasound, Color-Doppler Ultrasound and Contrast-enhanced Ultrasound of Primary GISTs and Liver Metastases

Orlando Catalano and Vincenza Granata

Abstract Transabdominal ultrasound (US) is employed in the screening, detection, differential diagnosis, staging, and follow-up of gastrointestinal stromal tumors (GISTs). Although there are well-known limitations in the use of ultrasounds to scan the gastrointestinal tract, US can assess the primary site of growth of GISTs as well as their metastasis to the liver. Gray-scale US, color-power-Doppler techniques, and contrast-enhanced US (CEUS) are all useful modalities employed to assess the GIST patient. US can help in detecting GIST masses, particularly as incidental findings or in patients with atypical clinical presentation. Doppler techniques are employed to demonstrate the presence and degree of vascularization in gastrointestinal masses and liver metastases. CEUS is particularly useful in the early assessment of response to treatment of patients with hepatic metastasis.

Keywords GIST • Sonography • Color-Doppler • Contrast-enhanced sonography • Gastrointestinal tract • Liver • Tumor

5.1 Gastrointestinal Tract and Peritoneal GISTs

Transabdominal ultrasound (US) is definitely not the technique to use when a gastrointestinal (GI) tract tumor is suspected, as there are radiographic and endoscopic modalities that are able to study the intestinal mucosa which are more suited to the task (in addition to endoscopic ultrasound, covered in Chapter 4). However, it is not uncommon to identify a GI tract tumor in a patient examined with abdominal US for vague symptoms, weight loss and anemia, as well as in a patient examined for other reasons. Even in patients with a known GI tract tumor and examined with US for other reasons (e.g. search for liver metastases), the opportunity to perform a US evaluation of the primary tumor should not be missed. The study can in fact identify signs of spread into the surrounding peritoneum or into the lymph nodes adjacent to the lesion and can therefore be useful for treatment planning.

The use of US in the identification of GISTs is primarily dependent on tumor size. In symptomatic cases (palpable mass, subocclusive phenomena, etc.) US is often the first choice modality. Indeed most incidental findings of GIST are made by US. In "advanced" forms there are numerous possibilities for applying the technique given the different presentations of the disease.

With the abdominal transducer, the classic US appearance of GI tract tumors consists of the “pseudokidney” sign, with the hypoechoic infiltrated intestinal wall appearing similar to the renal cortex and the echogenic mucosa–lumen complex similar to the fat of the renal sinus [1, 2]. With the use of high-frequency

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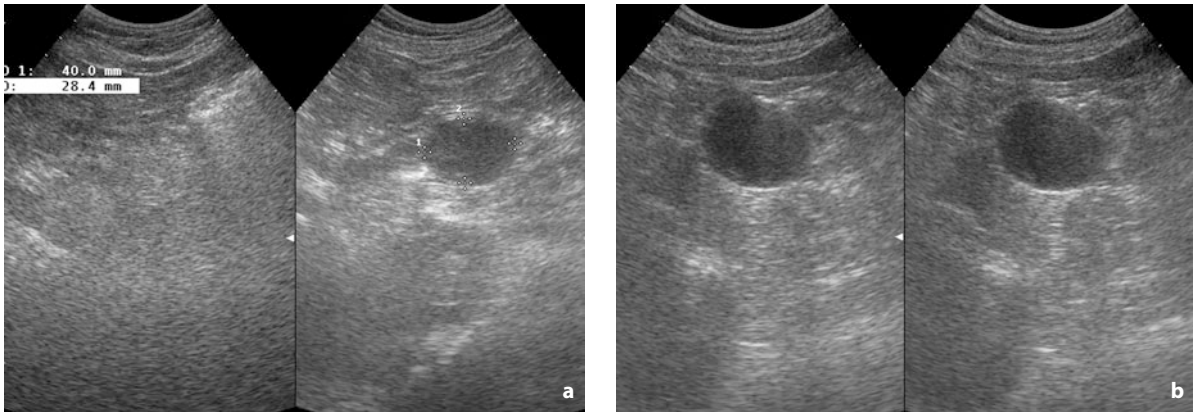

Fig. 5.1 Gastric GIST. Relatively well-circumscribed and homogeneous hypoechoic mass approximately 4 cm in size located in the gastric antrum

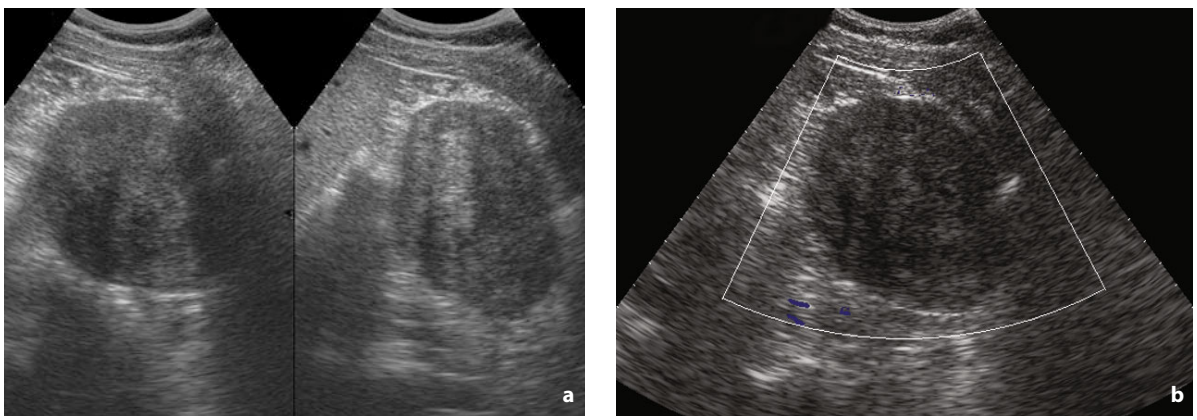

Fig. 5.2 Ileal GIST. Relatively well-circumscribed and hypovascular mass with inhomogeneous hypoechoic appearance

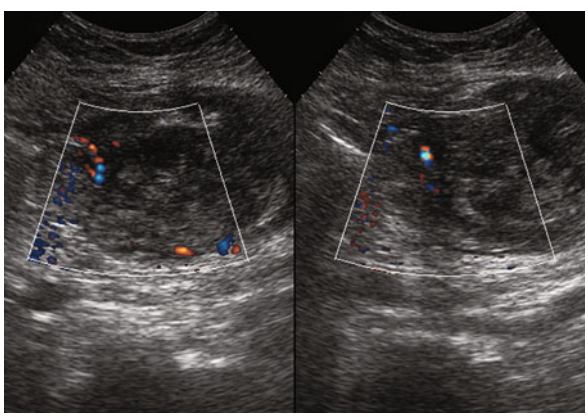

Fig. 5.3 GIST of the sigmoid colon. Relatively well-circumscribed and hypovascular mass with inhomogeneous hypoechoic appearance

transducers and the tissue compression technique the neoplastic lesion can be examined in much more detail. Liquid distension of the GI tract by mouth (for the small bowel) or enteroclysis (for the colon-rectum) may be useful [3-5], although this technique has been little used. The normal stratification of the GI tract wall is disrupted, unlike with benign mural thickening where with the exception of advanced transmural forms of Crohn's disease it appears intact, and may even appear accentuated as a result of the preferential inflammation of a certain layer. The lumen surface appears irregular, with possible ulcerations that appear as an interruption in the integrity of the wall into which the hyperechogenicity of the luminal gas penetrates (Figs. 5.1-5.4) [6].

GISTs appear as hypoechoic, inhomogeneous, moderately sized masses with possible hypo-anechoic cavitation due to necrosis-liquefaction (single central cavitation or multiple cavitations) or with a patently pseudocystic appearance. More specifically they can present as medium-to-large intrabdominal (intraperitoneal) masses in abutment with the GI tract structures (especially stomach and small bowel), although without

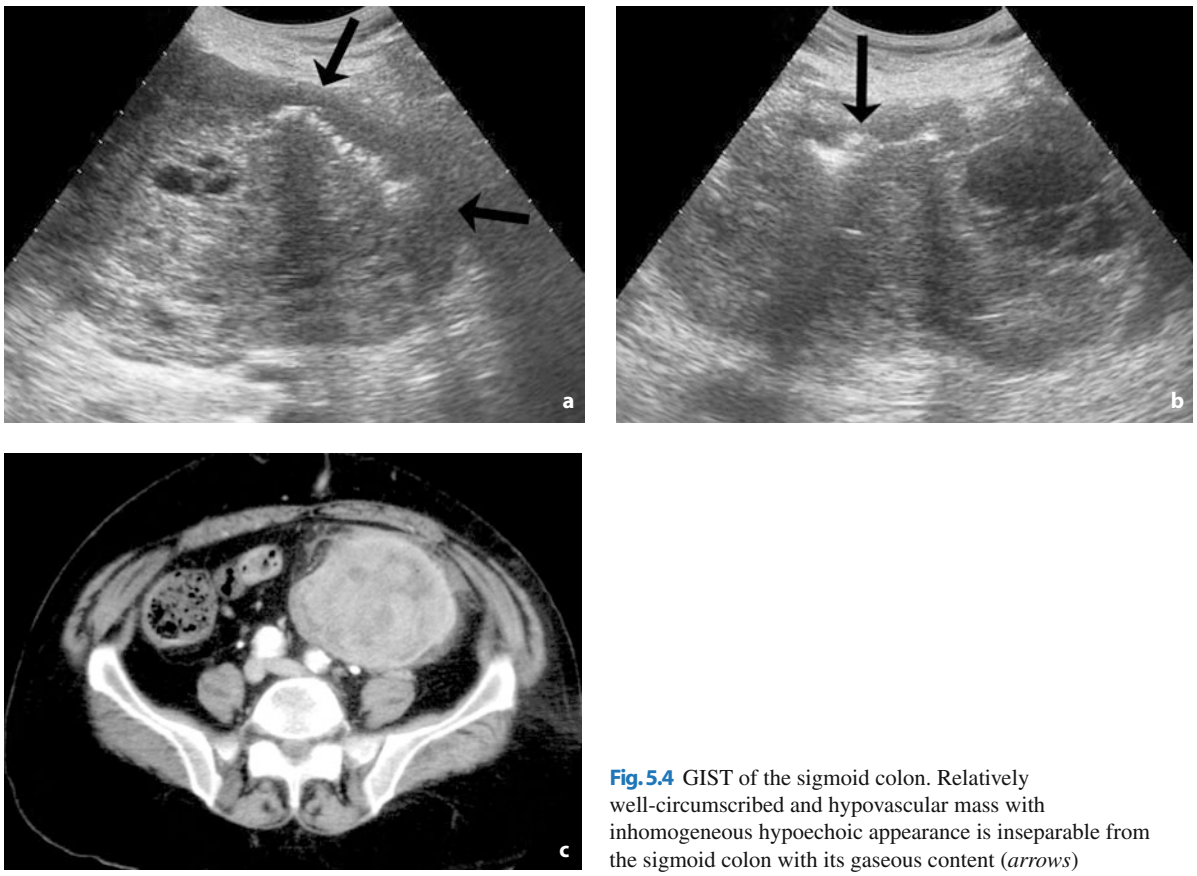

Fig. 5.4 GIST of the sigmoid colon. Relatively well-circumscribed and hypovascular mass with inhomogeneous hypoechoic appearance is inseparable from the sigmoid colon with its gaseous content (*arrows*)

occlusion. The margins appear circumscribed with compression of the adjacent structures, and the echostructure is more or less inhomogeneous or patently complex, with possible cystic-necrotic components; calcifications are rare [2, 6, 7]. At color-Doppler, and even more so at contrast-enhanced US (CEUS), the moderate vascularity of these lesions can be appreciated, with early contrast enhancement given by an arteriole arising from the GI tract wall and a more-or-less slow and inhomogeneous wash-out (Fig. 5.5). In particular, CEUS study with low mechanical index and "second generation" contrast medium is able to display the perfusion of these lesions in real time. In the presence of fistulae with the intestinal lumen the liquefied masses may feature internal gas which appears in the form of hyperechoic bands or foci, with possible posterior acoustic shadowing.

The US appearance depends above all on the size of the tumor and the organ of origin (in addition to the mitotic rate). The benign forms are usually rounded or oval in shape, with an intraluminal growth pattern and relatively homogeneous appearance. The size criterion is the most reliable for gauging the malignancy potential of the lesion and the prognosis. Other features that suggest malignancy include inhomogeneity, central liquefied necrosis, intralesional cystic spaces, irregular margins, prevalently exophytic growth pattern, infiltration of the adjacent structures, peritoneal spread and distant metastasis. The heterogeneity and degree of enhancement (at CEUS), while being predictive elements of high-grade malignancy are not specific parameters in this sense.

Several studies [8] have demonstrated a significant correlation between the degree of contrast enhancement at CEUS and the level of aggressiveness of GISTs, with the demonstration of a "richer" vascularity (greater enhancement including central enhancement) in malignant forms.

The often exophytic growth of GISTs creates difficulties in their differential diagnosis from other abdominal-pelvic masses, so that identifying inseparability from GI tract structures is pivotal. Indeed, GISTs tend to develop towards the external part of

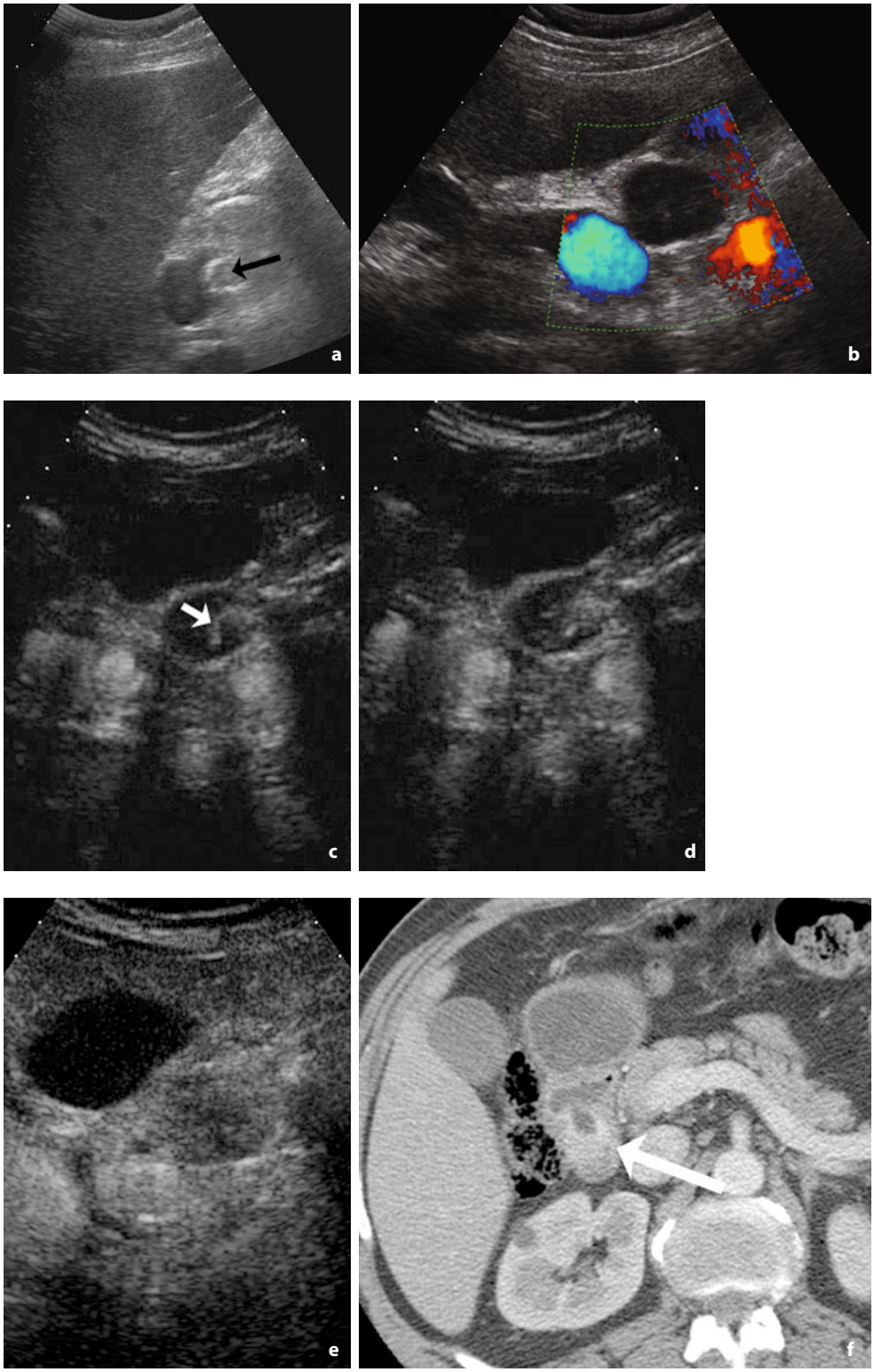

Fig. 5.5 Duodenal GIST. Small hypoechoic mass with central umbilication on the mucosa (*arrow* in **a**). Lack of significant flow signal at directional power-Doppler (**b**). Marked enhancement at CEUS (**c-e**) with vascular pedicle arising from the internal wall (*arrow* in **c**). CT correlation (*arrow* in **f**)

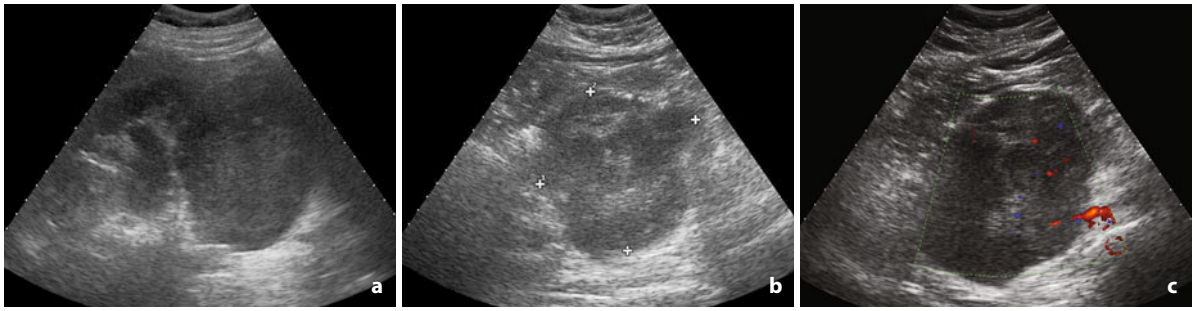

Fig. 5.6 Duodenal GIST. Inhomogeneous hypoechoic mass around 10 cm in size related to the inferior duodenal angle. The exophytic growth has brought the lesion into contact with the right kidney, causing hydronephrosis and mimicking a primary lesion of the retroperitoneum (**a**,**b**). Moderate vascular signals at color-Doppler (**c**)

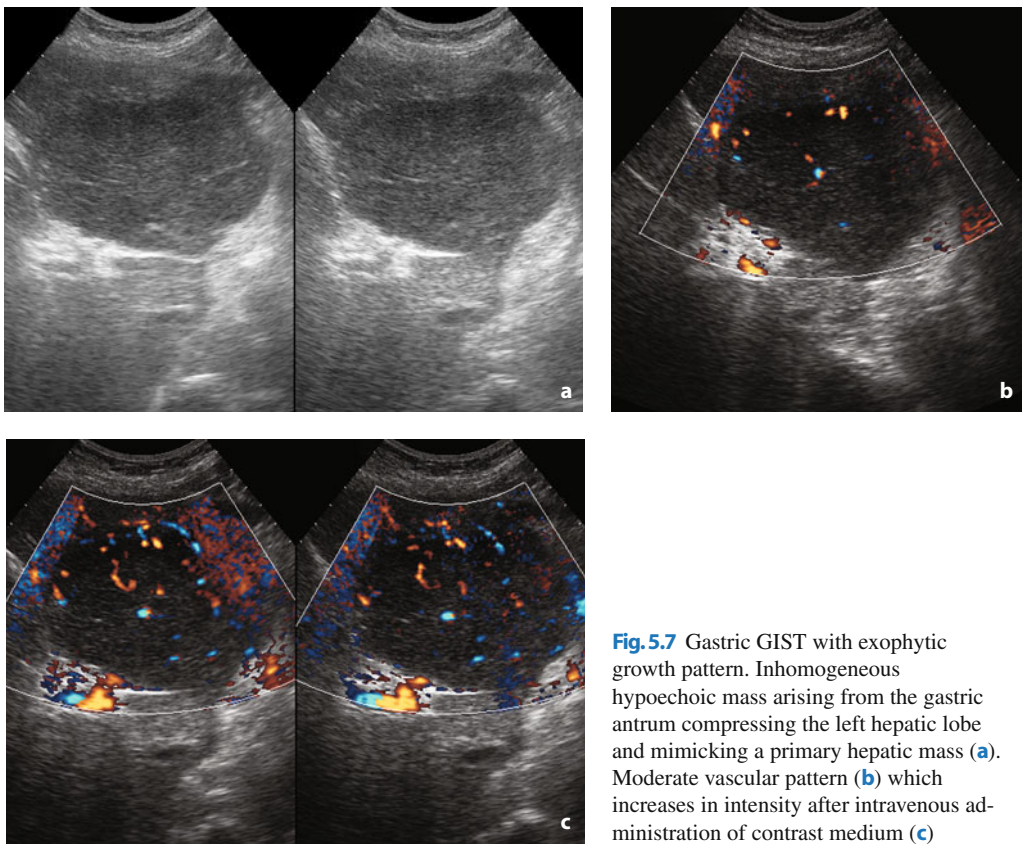

Fig. 5.7 Gastric GIST with exophytic growth pattern. Inhomogeneous hypoechoic mass arising from the gastric antrum compressing the left hepatic lobe and mimicking a primary hepatic mass (**a**). Moderate vascular pattern (**b**) which increases in intensity after intravenous administration of contrast medium (**c**)

the GI tract and can therefore mimic or be mimicked by "masses" of the adjacent organs and structures (Figs. 5.6, 5.7). In the presence of an abdominal-pelvic mass with no clear parenchymal relations a GIST should always be included in the differential diagnosis [2].

The appearance of abdominal-pelvic and peritoneal recurrences is similar to the primary lesions (Fig. 5.8). US can of course be used to guide the biopsy of GISTs and GI tract masses in general.

5.2 Liver Metastases

US, color-Doppler and CEUS also have a role to play in the study of hematogenous metastasis, particularly in the liver. The techniques may be used for lesion detection and characterization, as well as in the evaluation of response to targeted therapy and in long-term follow-up.

Liver metastases from GIST generally have an inhomogeneous hypoechoic appearance in the case of

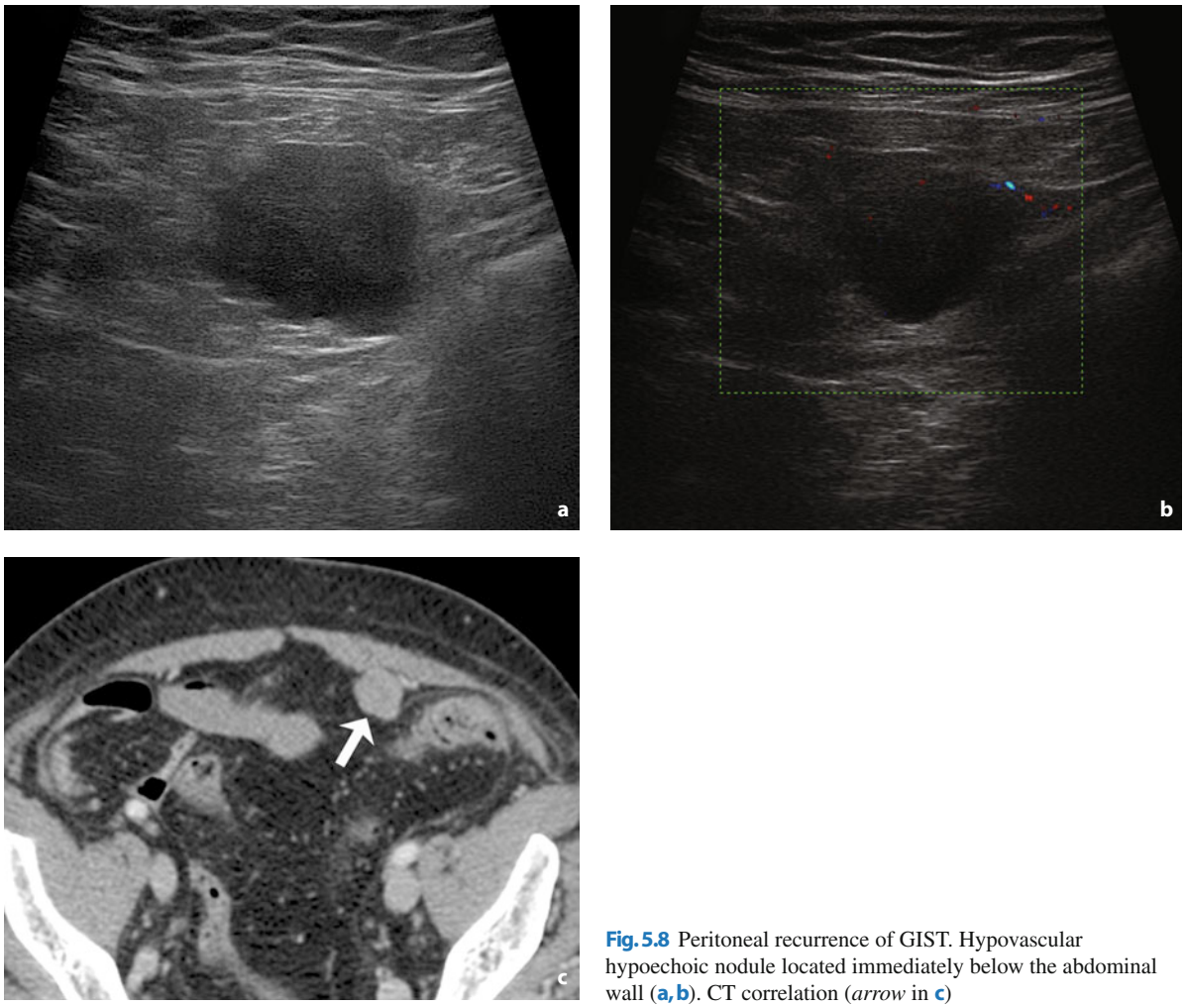

Fig. 5.8 Peritoneal recurrence of GIST. Hypovascular hypoechoic nodule located immediately below the abdominal wall (**a, b**). CT correlation (*arrow* in **c**)

larger lesions, with some vascular signals (particularly peripheral) at color Doppler and more-or-less early and inhomogeneous enhancement in the arterial phase of the CEUS study. Nonetheless a pseudocystic appearance is also possible, even in the absence of treatment [6, 9] (Fig. 5.9).

When they are large, hepatic lesions may be exophytic and therefore mimic cystic or solid masses of adjacent organs, especially gastroduodenal masses. This is especially the case with US, which being less panoramic can have more difficulty than other imaging modalities in defining the organ of origin of the lesion. The opposite may also be true: for example, the case of a complex hepatic cyst incorrectly interpreted as a gastric GIST has been described [10].

It should also be borne in mind that some rare cases of primary hepatic GIST have been described, and clearly in these cases the lesion is in differential diagnosis with all focal hepatic lesions and especially malignant lesions, even though the definitive characterization can only be histologic [6, 11].

Liver metastases from GISTs which respond to treatment tend to take on a pseudocystic appearance (which occasionally may be seen in untreated metastases, arising for example from ovarian cystadenocarcinoma or pancreatic mucinous carcinomas). In this case it is clear that only the patient history can provide the correct interpretation of this presentation and differentiate it from other more-or-less complex cystic hepatic lesions [6, 9]. The lesion size can at first remain stable or even show a slight increase after targeted therapy with imatinib. Therefore the size criterion is unreliable and signs of perfusion need to be identified. Indeed, very early in treatment a sign of necrosis in these lesions that may be visualized with color-Doppler but above all with CEUS is the marked devasculariza-

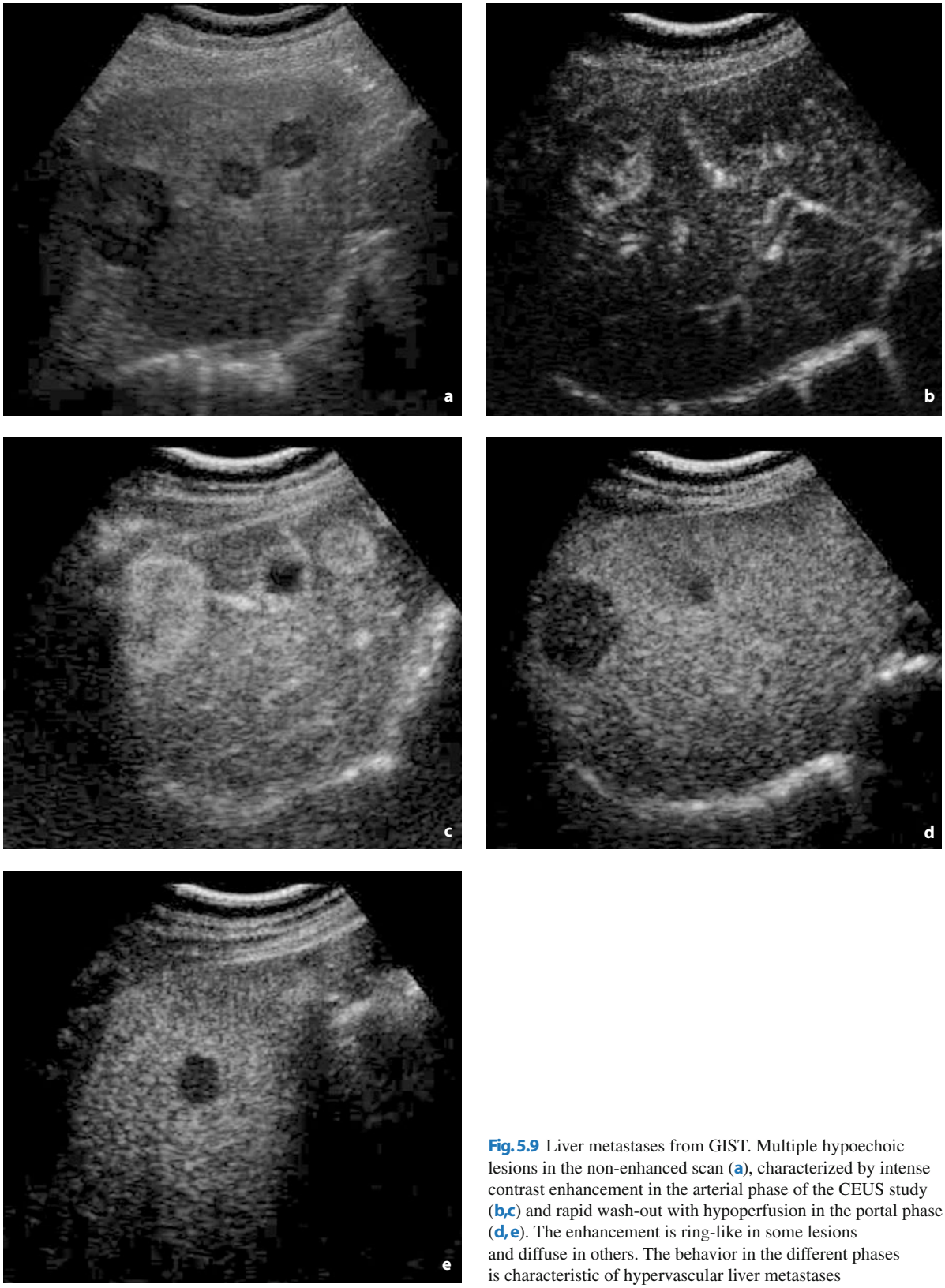

Fig. 5.9 Liver metastases from GIST. Multiple hypoechoic lesions in the non-enhanced scan (**a**), characterized by intense contrast enhancement in the arterial phase of the CEUS study (**b,c**) and rapid wash-out with hypoperfusion in the portal phase (**d, e**). The enhancement is ring-like in some lesions and diffuse in others. The behavior in the different phases is characteristic of hypervascular liver metastases

tion of the metastases. The lesions display loss of contrast enhancement, first at the center and then diffusely, and finish up hypo-aperfused but with a relatively stable size because the reduction in volume is much more slow and partial [12]. In this way the early identification of residual tumor or recurrence is also possible, appearing in the form of one or more solid perfused components located peripherally in the lesion (nodule-within-a-nodule); subsequently there is an increase in the size of the lesion [13].

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Computed Tomography

6

Elisabetta de Lutio di Castelguidone, Sergio Venanzio Setola, Antonella Messina, Carlo Morosi, Maria Cristina Bellucci, Secondo Lastoria and Roberto di Mizio

Abstract CT is considered to be the imaging modality of choice for the detection, staging, surgical planning and follow-up of patients with GIST. We describe CT features of GISTs. They commonly have an exophytic growth pattern and appear as large masses outside the organ of origin. Intramural and intraluminal masses are less common radiologic manifestations. GISTs may contain areas of hemorrhage, necrosis, or myxohyaline degeneration that appear as focal areas of low attenuation. A reduction in tumor size, extensive myxohyaline degeneration, and calcification in primary and metastatic GISTs indicate disease response to therapy. The early detection of focal solid or new solid lesions during imatinib treatment suggests disease progression. Radiologists must recognize CT features of GISTs, so they are able to detect, characterize the lesions and evaluate the tumor response during specific treatment. Modified CT criteria using a combination of tumor density and tumor size are promising in early response evaluation, and have excellent prognostic value.

Keywords GISTs • CT • RECIST criteria • CHOI criteria • Imatinib

Computed Tomography (CT) is the most diffuse imaging technique and most widely used in the suspect of gastrointestinal stromal tumors (GISTs).

It is considered the reference examination for both the local study and evaluation of tumor spread.

A fundamental role is played by CT in follow-up and especially in the evaluation of the response to medical treatment with imatinib [1].

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6.1 Technique

A CT study of the abdominal–pelvic region is performed, possibly integrated with a thoracic study, with and without iodinated intravenous contrast material (flow rate at least 2,5-3 mL/s with dual phase technique) – arterial phase with bolus tracking and venous phase. In the suspect of gastric involvement a targeted study of the stomach is performed. This involves distending the stomach with water and effervescent powders with prior administration of antispastic agents (Fig. 6.1). This method is also used in the suspect of lesions in the esophagus. If there is the suspect of lesions located in the small bowel, a CT enteroclysis should be performed to better define the site of origin, the growth pattern and the relations with the bowel wall (Fig. 6.2).

E. de Lutio di Castelguidone, A. Messina (eds.), *GISTs – Gastrointestinal Stromal Tumors*.

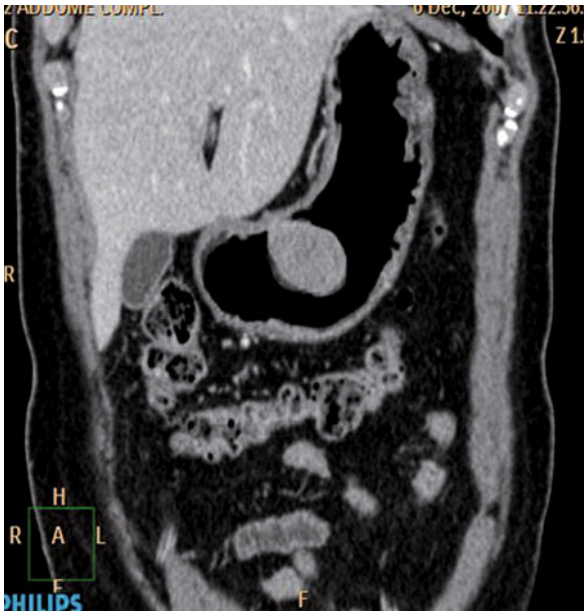


Fig. 6.1 Contrast-enhanced CT. Double-contrast study of the stomach. Primary gastric GIST: coronal multiplanar reconstruction of GIST of the lesser curve with intraluminal growth

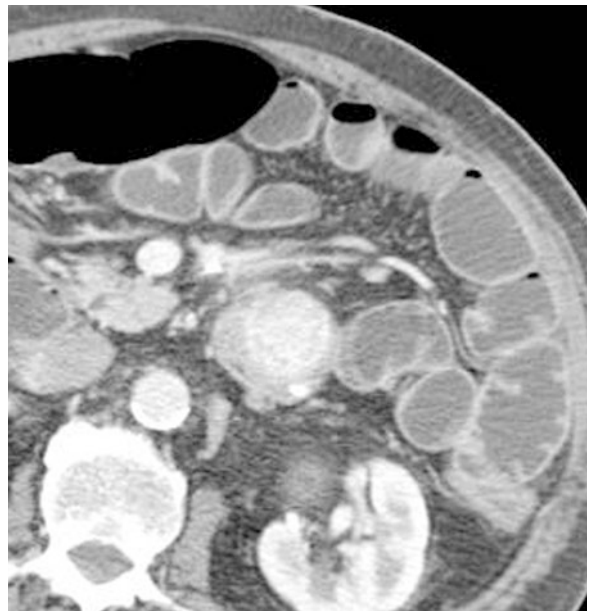


Fig. 6.2 CT enteroclysis. Hypervascular inhomogeneous primary GIST of the proximal jejunal loops with intraluminal growth

In the presence of tumors located at the level of the colon–rectum the distension of this portion of the GI tract with retrograde gas insufflation may prove useful.

Multiplanar reconstructions (MPR) and maximum intensity projection (MIP) reconstructions are useful for evaluating the site, extension and vascular pedicles (Fig. 6.3) [2, 3].

6.2 Primary GIST

The CT characteristics of GISTs are highly variable in relation to the size, site and aggressiveness of the tumor [4]. They are often identified as an incidental finding during a CT examination (Fig. 6.4).

Primary GISTs typically present as solitary masses without a capsule but well circumscribed, with well-defined margins and variable in size [5].

Small tumors may appear as intraluminal or intramural masses, with a generally homogeneous structure and moderate/high contrast enhancement [6]. In cases of very small lesions, especially when intramural, close monitoring is recommended because of the high risk of inadeguate tissue sampling during endoscopic biopsy (Fig. 6.5).

Larger GISTs have a prevalently exophytic growth

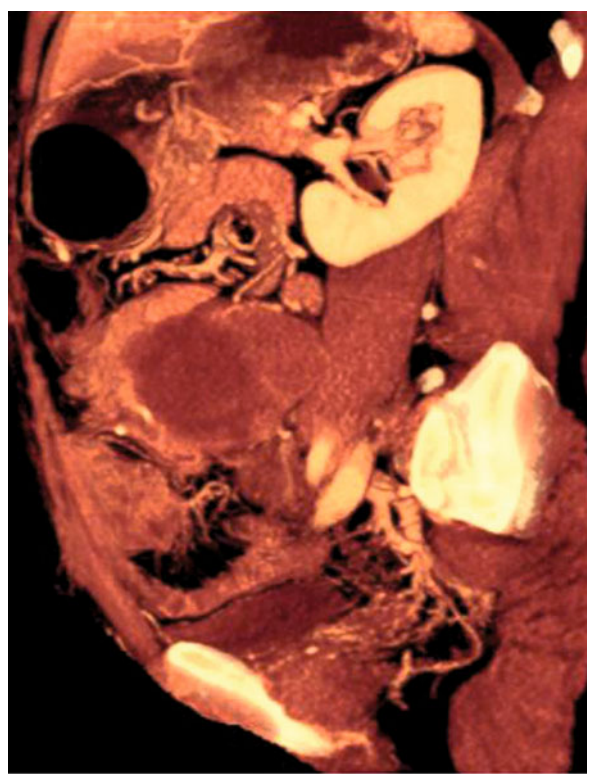


Fig. 6.3 Sagittal/oblique volume rendering reconstruction. Evidence of vascular pedicle and of vascularity of the peripheral portion of a large exophytic GIST of the small bowel

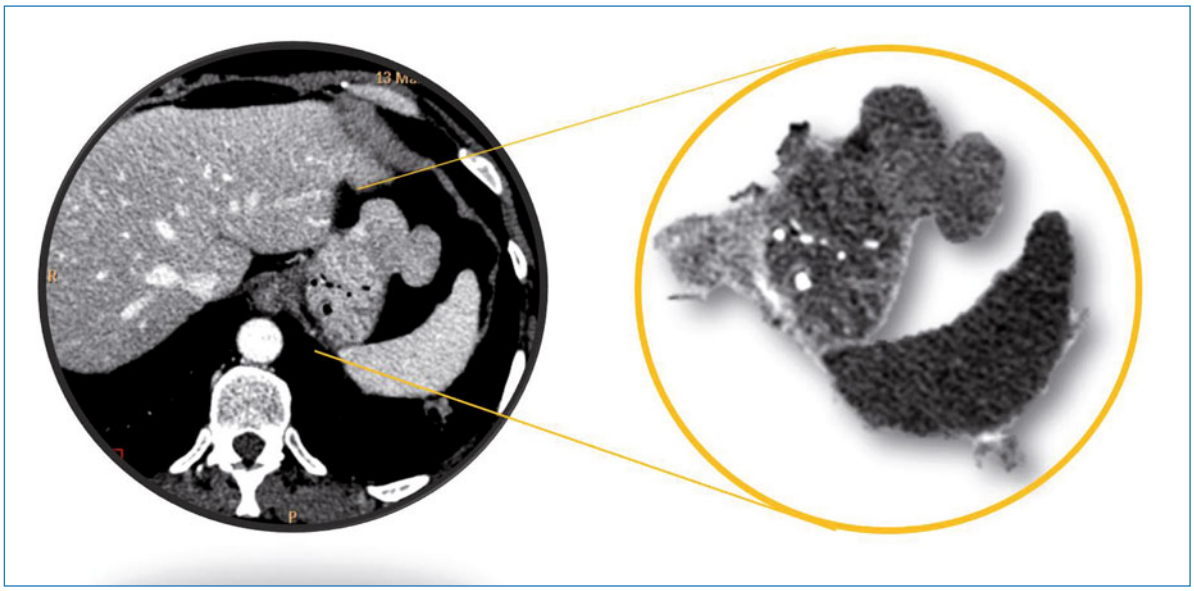


Fig. 6.4 Tumor-in-tumor incidentaloma. Axial scan with detailed section: multilobulated exophytic mass with smooth well-defined margins of the gastric fundus diagnosed at histologic examination as metastasis of breast carcinoma in gastric GIST

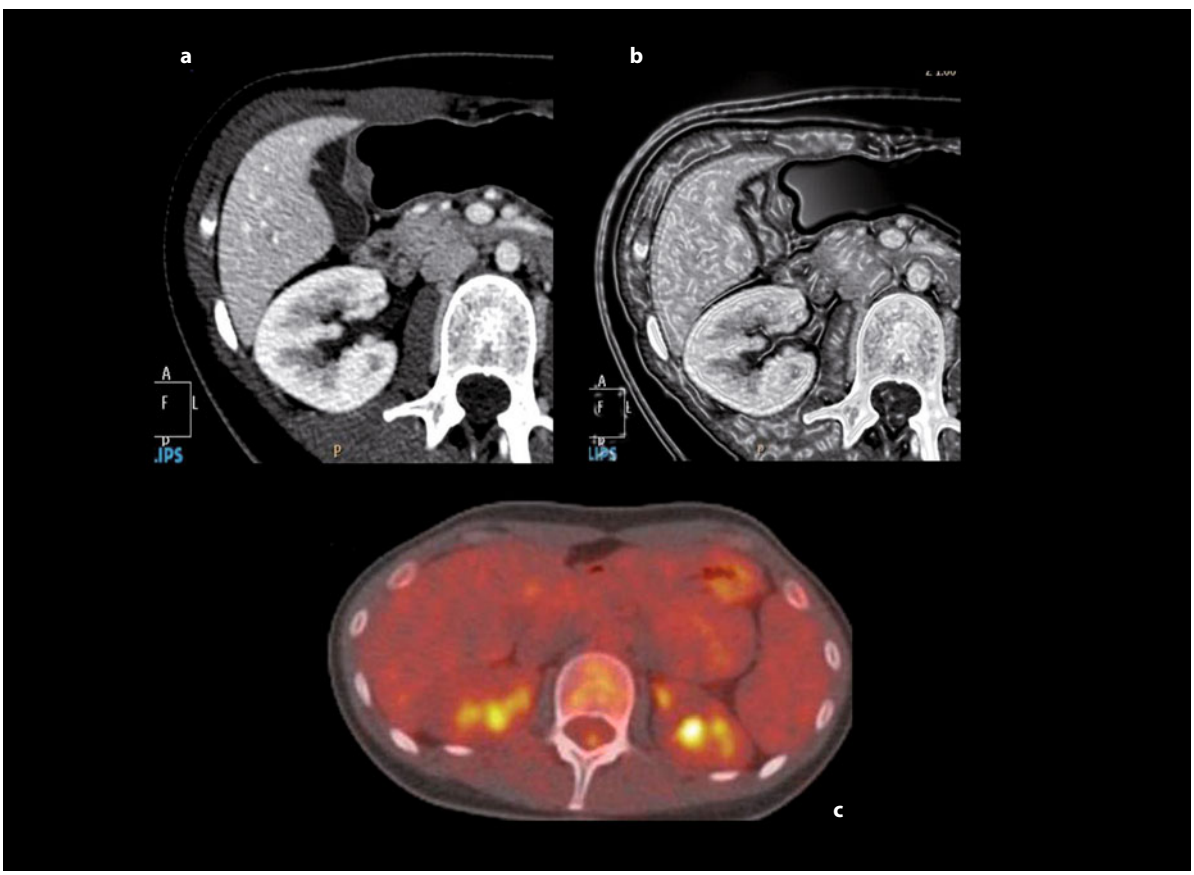


Fig. 6.5 Primary gastric GIST. Double-contrast CT study: small intramural lesion of the gastric antrum (**a**). Corresponding 3D relief (**b**) and CT/PET (**c**)

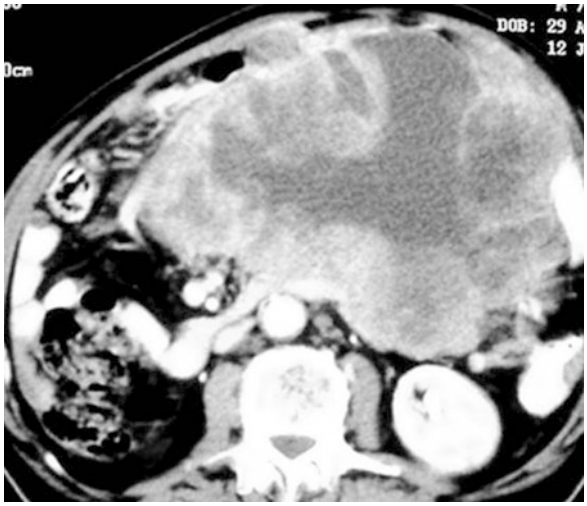


Fig. 6.6 Primary gastric GIST of the greater curve. Large mass with extraluminal growth and sharp but polycyclic margins with markedly inhomogeneous enhancement. Dense peripheral tissue with large colliquative necrotic center and vascular septa

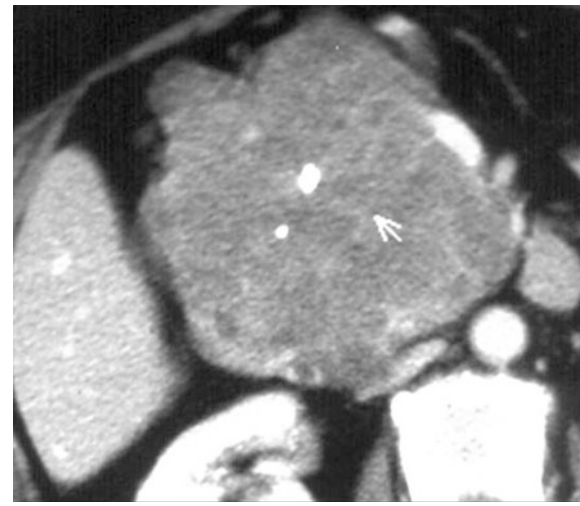


Fig. 6.7 Primary duodenal GIST. Large mass with extraluminal growth such that its site of origin cannot be identified, multilobulated margins, inhomogeneous with thin hyperdense septa, internal necrosis and calcified nuclei

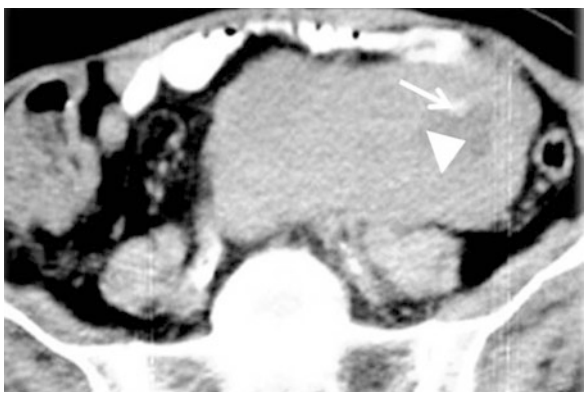


Fig. 6.8 Primary peritoneal GIST. Large pelvic mass with irregular margins and internal areas of active bleeding (*arrow*) in the fluid–fluid level (*arrowhead*)

pattern and present as heterogeneous masses typically with a hypodense central portion, due to the presence of areas of necrosis and/or myxohyaline or cystic degeneration, and a solid peripheral portion with soft-tissue density (Fig. 6.6) [7, 8]. The lesion may occasionally appear multiseptated with tumor vessels within the septa. In some cases hyperdense areas may be seen, indicating areas of hemorrhage. The finding of calcifications is rare before treatment [9].

In the presence of deep ulcerations or massive hemorrhages or necrosis, cavities may form with fistulae communicating with the intestinal lumen. In these cases the CT finding is provided by bubbles of gas or contrast medium in the neoplastic mass or air–fluid levels mimicking abscess collections.

Microcalcifications, intralesional hemorrhage and ulcerations are considered signs of potential malignancy (Figs. 6.7-6.9).

Large masses with extraluminal growth pattern dislocate adjacent organs and the vessels, generally without signs of infiltration, and in some cases, when they become huge, identifying the site of origin can be difficult (Fig. 6.10).

In agreement with Ghanem et al. [10], GISTs less than 5 cm in size are usually homogeneous, with smooth edges and intraluminal development. Larger sized GISTs instead are prevalently exophytic, with irregular margins and inhomogeneous enhancement with a hypodense center and peripheral vascularity. In some cases these masses can infiltrate adjacent peritoneal fat tissue as organs and structures.

6.3 Specific Tumor Sites

The CT characteristics of GISTs are highly variable especially in relation to their site [11].

The most frequent site is the GI tract and the peritoneum, unfrequently they could be found in the retroperitoneal space and the abdominal wall (Fig. 6.11). Primary liver GIST is very rare (Fig. 6.12) [12, 13].

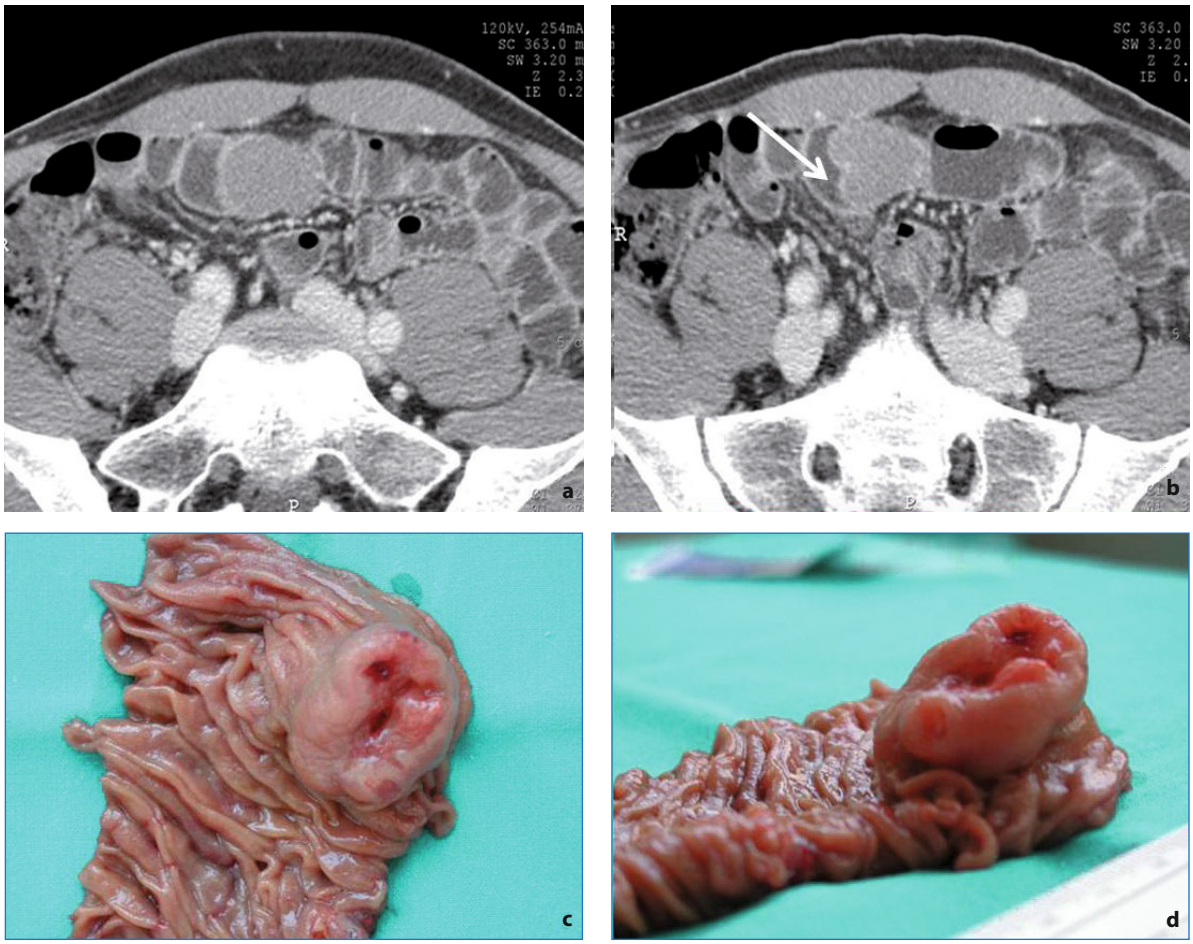


Fig. 6.9 Primary small bowel GIST. CT enteroclysis: Intraluminal lesion with well-defined and regular margins (**a**) but with umbilication (*arrow*) indicative of an ulcerative crater (**b**). Surgical specimen (**c, d**)

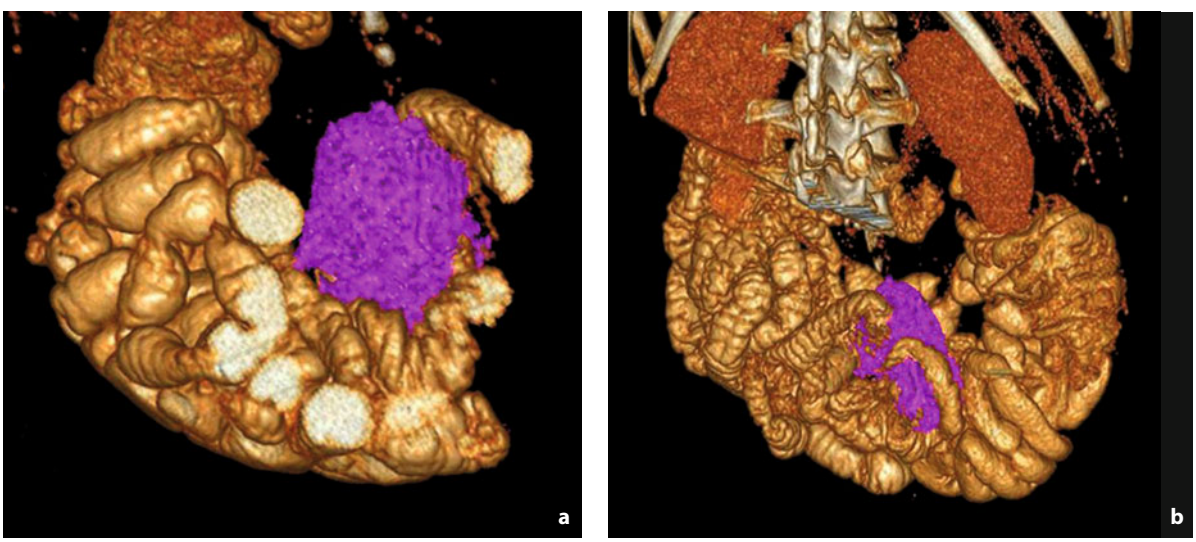


Fig. 6.10 Primary small bowel GIST. 3D reconstruction: Large mass of the jejunal–ileal junction with almost exophytic growth (**a**). The adjacent loops surrounding the mass appear compressed and displaced, with no evident signs of invasion (**b**)

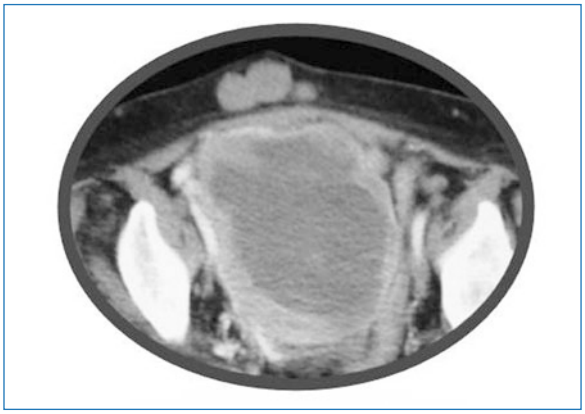


Fig. 6.11 Abdominal wall GISTs. Small nodules, in part confluent and almost homogeneous, with sharp and well-defined margins in the pelvic subcutaneous tissue

Gastric GISTs, which are the most frequent site, show a lower malignant behavior.

They are usually small in size, with well-defined margins, either intraluminal or intramural, with homogeneous or finely inhomogeneous enhancement due to the presence of a small hypodense center (Figs. 6.13, 6.14). Larger lesions generally show exophytic growth with more heterogeneous enhancement (Fig. 6.15).

In the small bowel, the second most common site, GISTs generally arise from the external layer of tunica muscolaris and appear as voluminous and inhomogeneous masses with extraparietal growth (Fig. 6.16). Less frequently they are intraluminal lesions with a polypoid appearance (Fig. 6.17) which can cause

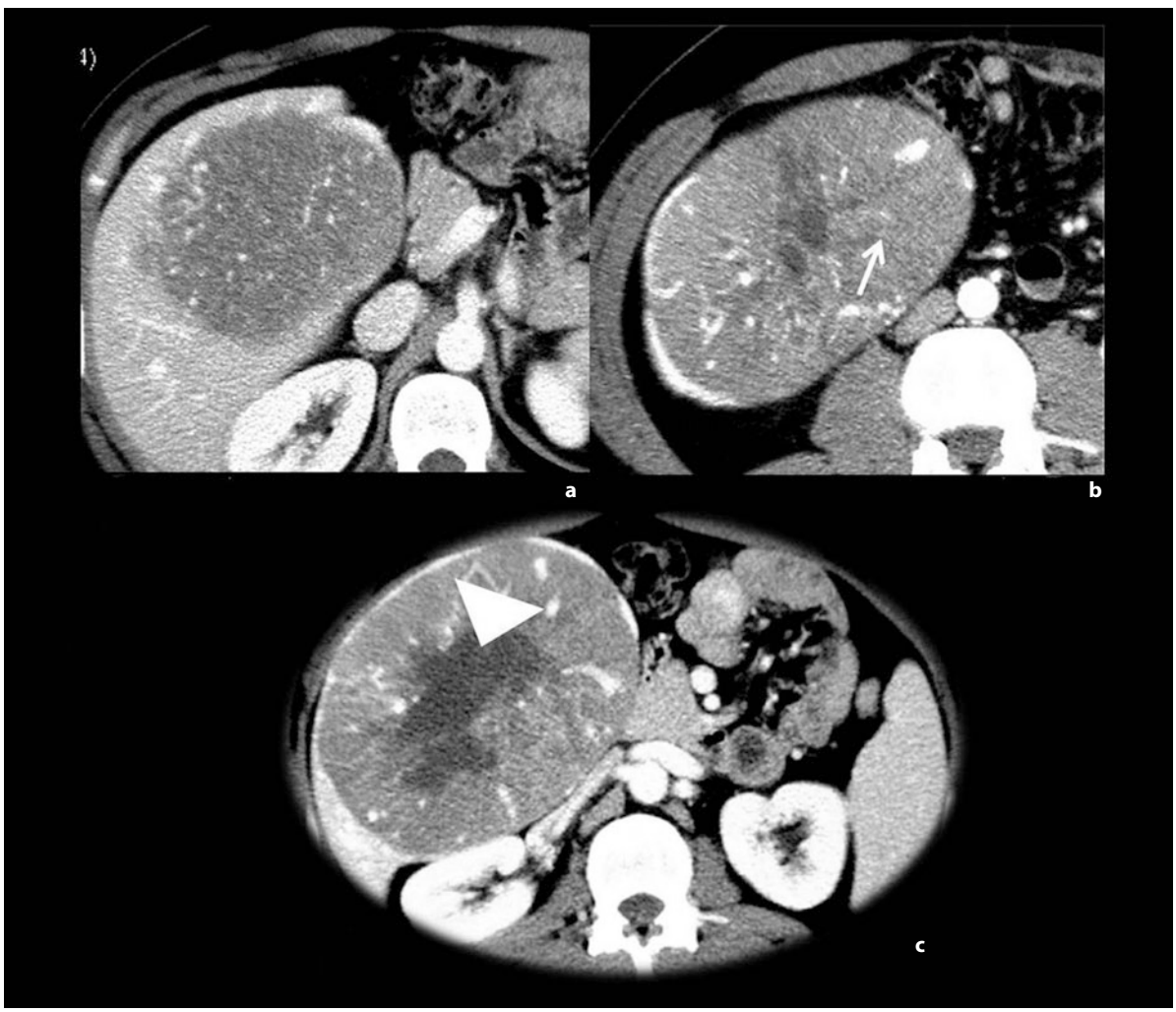


Fig. 6.12 Primary hepatic GIST. Large mass of the right hepatic lobe (**a**) which appears markedly inhomogeneous with thick hypervascular septa (*arrow*) (**b**) and wide and irregular central colliquative necrotic hypoattenuation (*arrowhead*) (**c**)

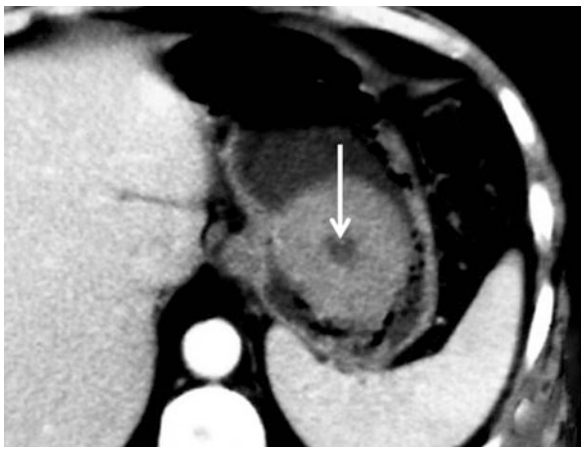


Fig. 6.13 Primary gastric GIST. Macronodular lesion of the gastric body with intraluminal growth pattern, finely inhomogeneous appearance, characteristic small central hypoattenuation (*arrow*) and dense peripheral tissue

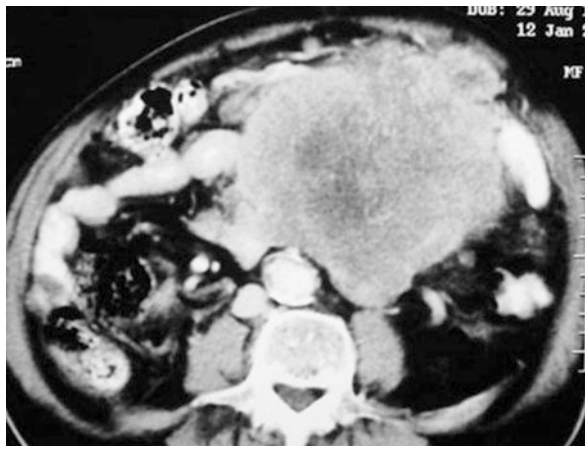
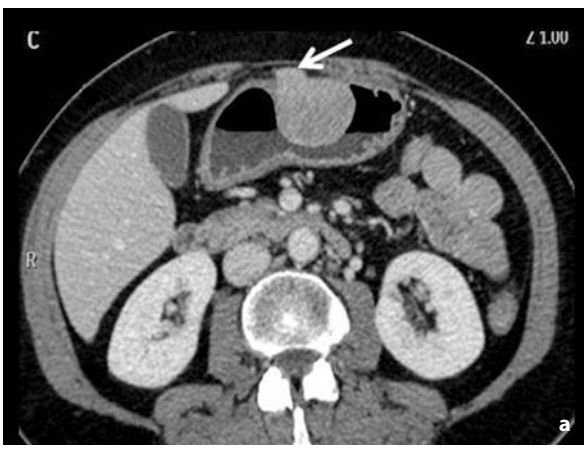


Fig. 6.15 Primary gastric GIST. Large and heterogeneous mass arising from the greater curvature, with irregular edges and an almost entirely exophytic growth pattern such that its origin is unrecognizable



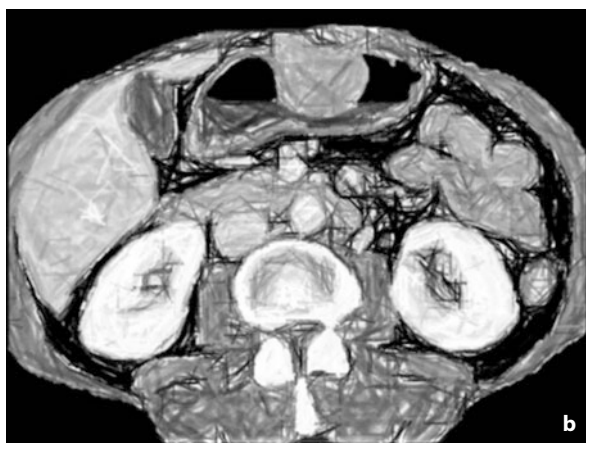
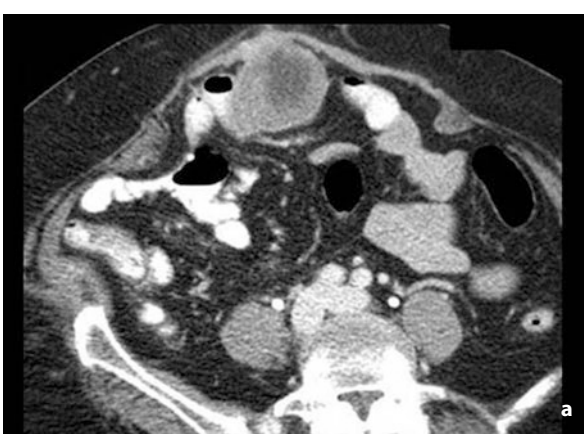


Fig. 6.14 Primary gastric GIST. Intraluminal mass almost homogeneous with evident signs of infiltration of the serosa and adjacent peritoneal tissue (*arrow*) (**a**). Additional post processing (**b**)



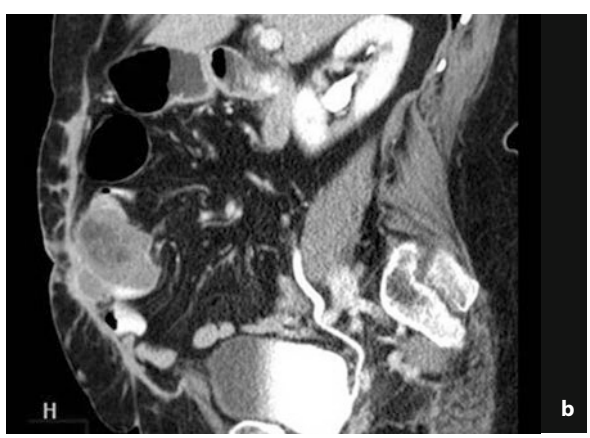


Fig. 6.16 Primary small bowel GIST. Axial (**a**) and sagittal reconstruction (**b**): ileal mass with exophytic growth, colliquative necrotic center and dense peripheral tissue. The adjacent bowel loops are dislocated and compressed. The anterior abdominal wall is infiltrated

invagination and/or occlusion (Fig. 6.18), or more rarely they show intra/extraluminal growth pattern (Figs. 6.19, 6.20).

Duodenal GISTs are less frequent and can present either as hypervascular almost homogeneous intraluminal masses (Figs. 6.21, 6.22) or heterogeneous extraluminal masses. Rectal GISTs are rare and can present as small homogeneous intramural (Fig. 6.23) and/or intraluminal lesions. In this site too, when their growth is mostly exophytic, they can become large (Fig. 6.24) [14].

In the esophagus, frequent site of leiomyomas, a GIST may be suspected in the presence of a large and inhomogeneous mass.

6.4 Staging

From a biologic point of view GISTs are currently considered potentially malignant tumors, and can be classified into very low, low, intermediate and high risk categories [15].

Local aggressive tumor features can be the infiltration of the mesentery or extension into adjacent organs and structures [16].

Metastatic lesions are generally found in the advanced phase of disease or in GISTs with high-risk malignancy.

Metastases can also occur with a latency of 10–15 years after diagnosis.

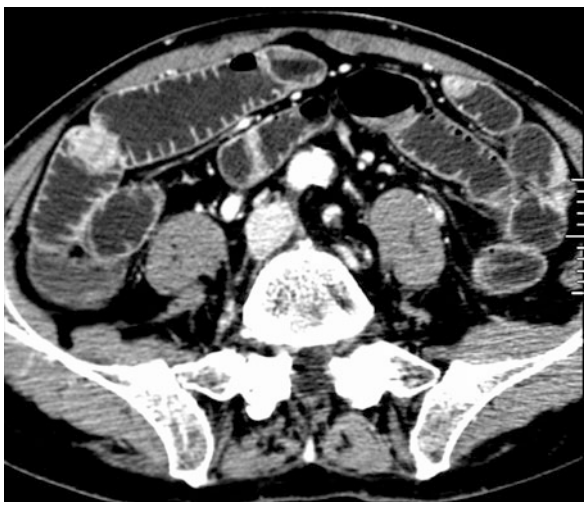


Fig. 6.17 Primary small bowel GIST. CT enteroclysis: polypoid intraluminal mass of the ileum (*right flank*) showing intense enhancement due to hypervascularity

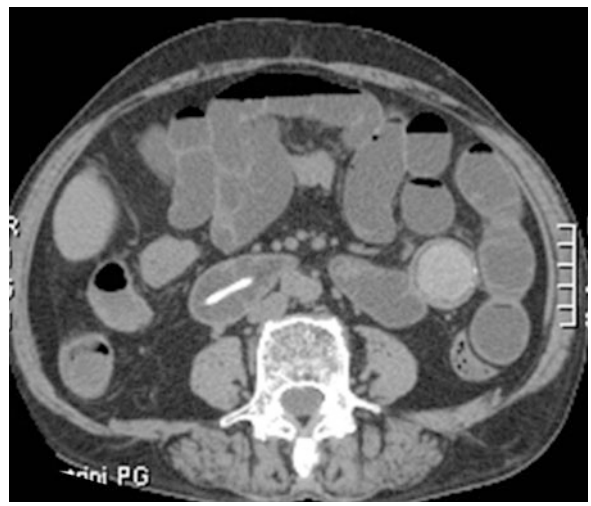
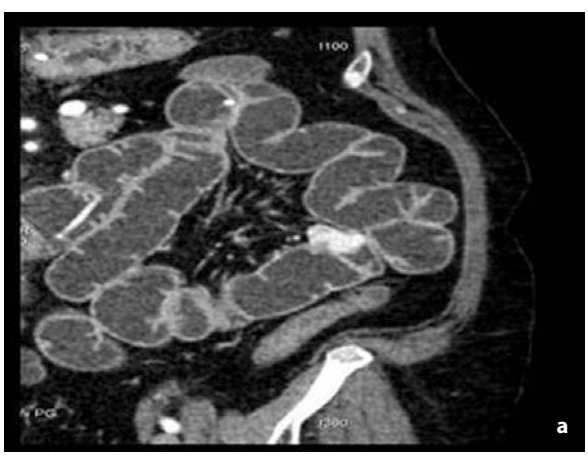


Fig. 6.18 Primary small bowel GIST. CT enteroclysis: Axial scan of homogeneous intraluminal jejunal GIST (*left flank*)



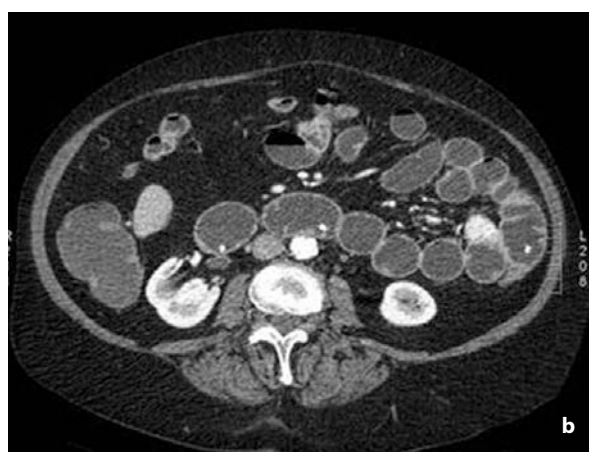


Fig. 6.19 Primary small bowel GIST. CT enteroclysis: Small hypervascular jejunal GIST with intraluminal (**a**, coronal reconstruction) and extraluminal (**b**, axial scan) portions

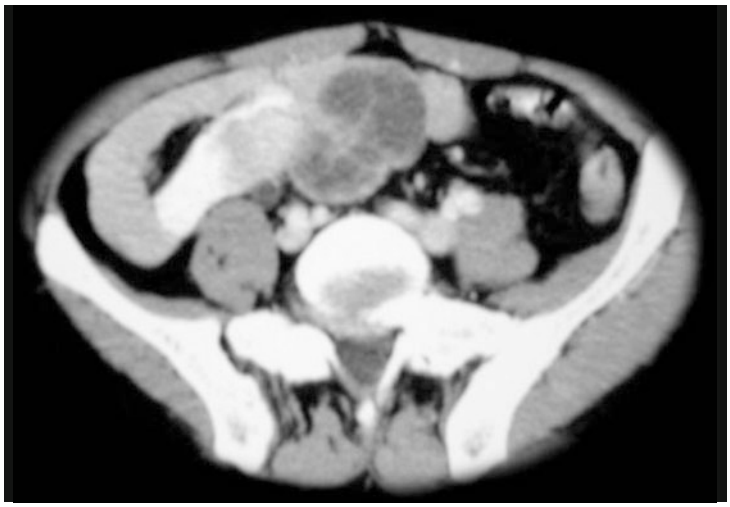
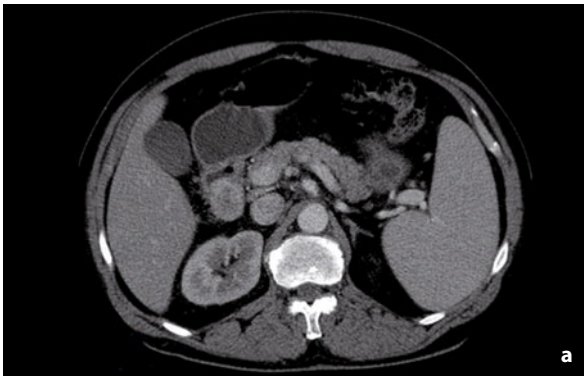
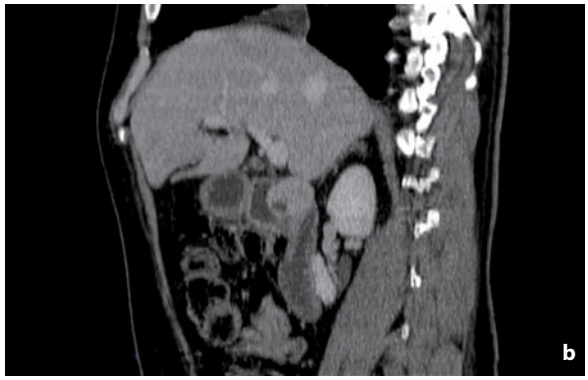
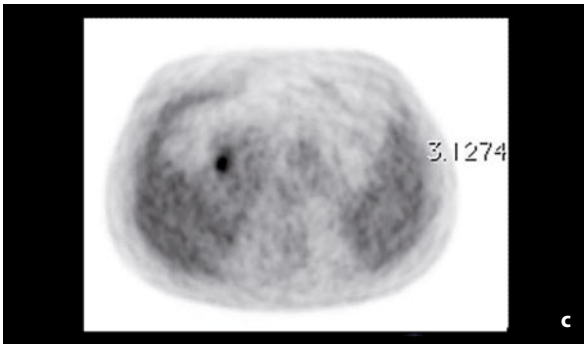
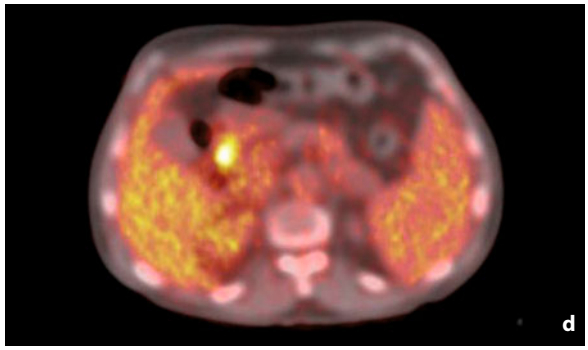


Fig. 6.20 Primary small bowel GIST: large ileal GIST with solid intraluminal portion, larger hypodense exophytic portion with hypervascular septa









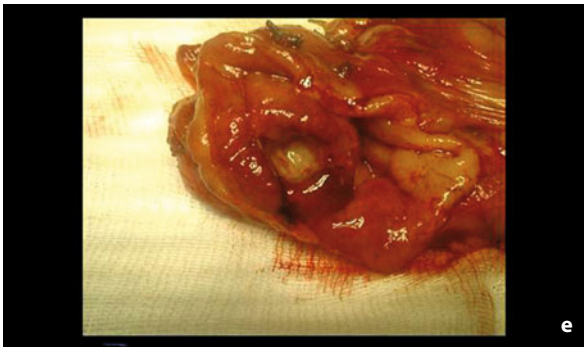


Fig. 6.21 Primary duodenal GIST. Intraluminal mass almost occupying the entire lumen (**a**), inhomogeneous with small eccentric area of hypoattenuation better seen in the oblique view (**b**). CT/PET correlation (**c, d**). Surgical specimen (**e**)

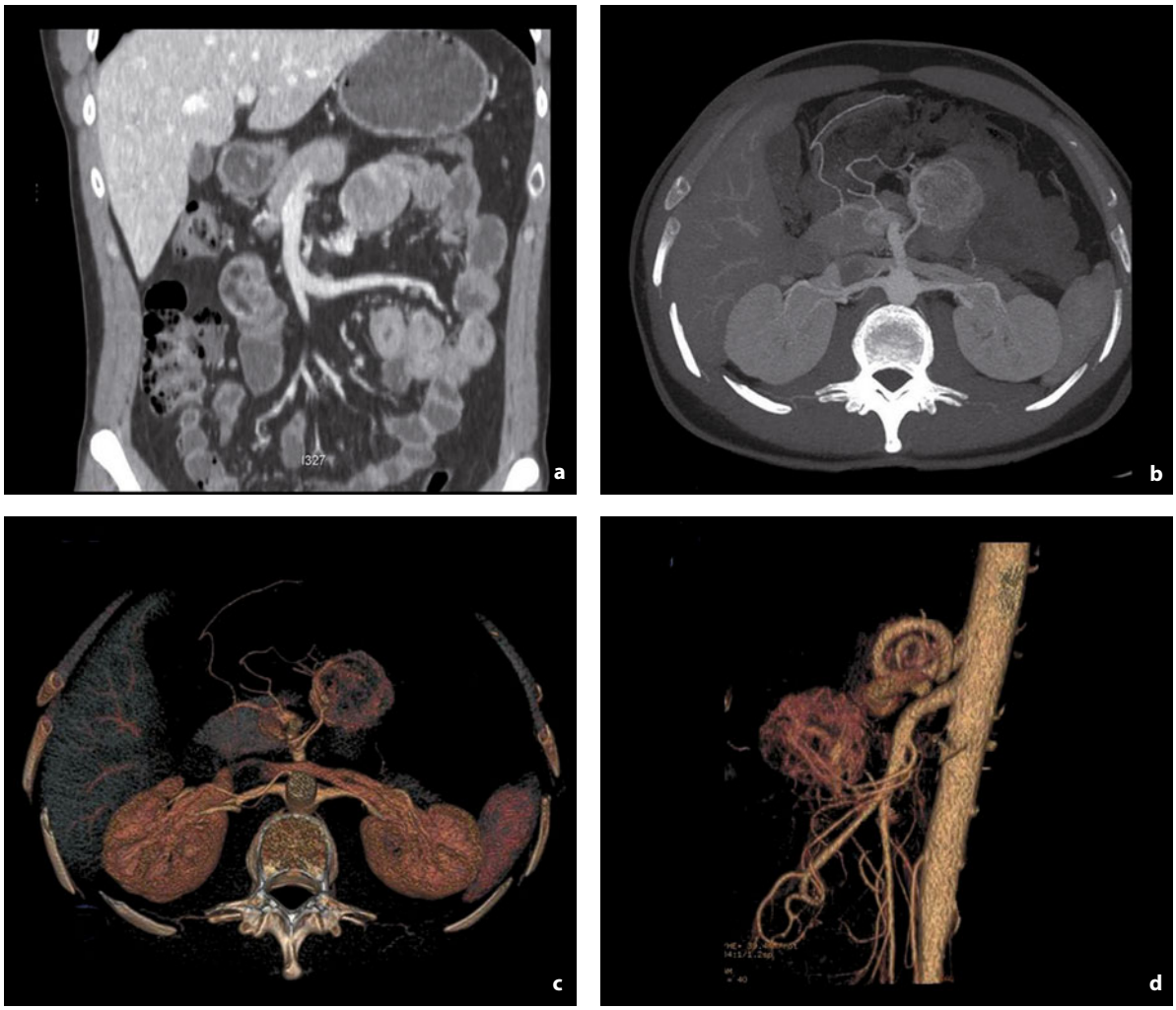


Fig. 6.22 Primary duodeno-jejunal GIST. Inhomogeneous hypervascular intraluminal mass (**a**). Vascular pedicles well visualized in the post-processing reconstructions (**b-d**). Courtesy of Dott. F. La Seta

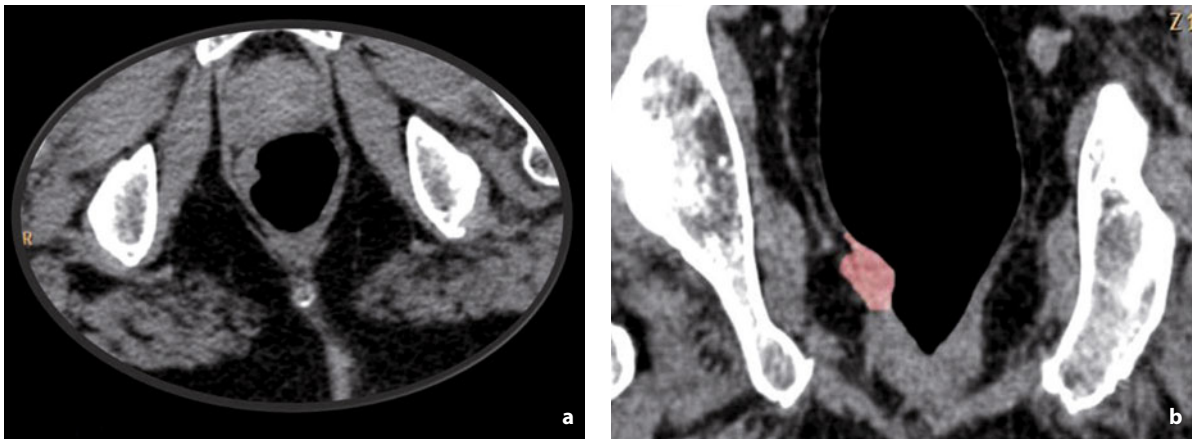


Fig. 6.23 Primary rectal GIST. Small right intramural mass of the rectum (**a**). Coronal reconstruction after rectal gas insufflation (**b**)

The most commonly affected sites are the omentum, peritoneum and mesentery, where the disease initially presents as small, well-defined and homogeneous nodules which can be well identified in the venous–parenchymal phase of the contrast-enhanced CT study (Fig. 6.25). In the liver, in contrast, nodules of different sizes and different degrees of vascularity can develop.

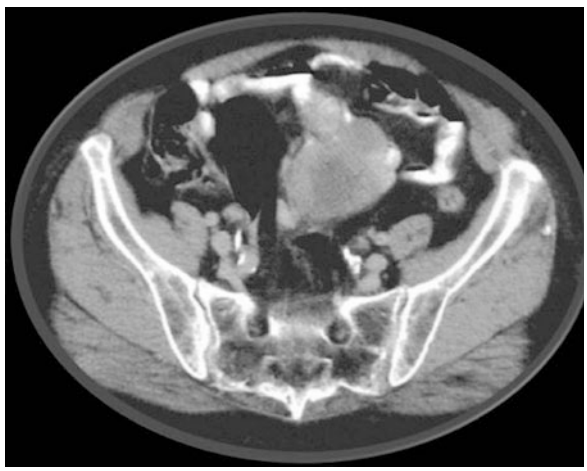


Fig. 6.24 Primary GIST of the sigmoid colon. Inhomogeneous solid mass of the sigmoid colon with large central necrosis and prevalently exophytic growth

Enhancement can in fact be mild/moderate in hypovascular metastases (Fig. 6.26) or less frequently intense/marked in the arterial phase in hypervascular nodules.

Hypervascular nodules can become, in the venous phase, isodense to the adjacent liver parenchyma and therefore be undetectable. That is why arterial phase should be obtained [17].

Macronodular metastases are inhomogeneous (Fig. 6.27) like primary tumor due to necrosis and/or hemorrhage.

Metastases in the lungs, pleura and musculoskeletal system are uncommon, in the lymph nodes are rarer.

6.5 Recurrence

Although surgery is the only available radical treatment of primary tumor, recurrence occurs in many patients even after complete surgical resection with tumor-free margins. The mean time to recurrence after surgery is around two years.

In case of recurrence, GISTs usually have an aggressive behaviour: large masses with irregular edges, invasion of adjacent organs (Fig. 6.28) and distant metastases [18]. That is not always true. Recurrent

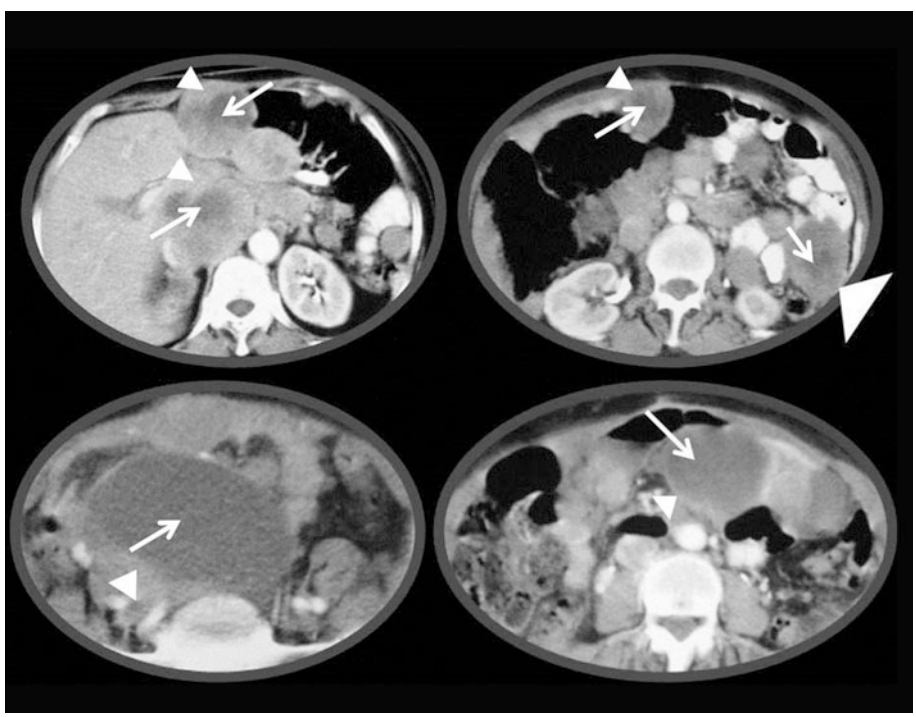


Fig. 6.25 Omental–peritoneal metastatic GIST. Multiple nodules disseminated in the abdominal-pelvic cavity various in size, with heterogeneous attenuation: some with peripheral hypervascular solid tissue (*arrowhead*) and central hypodense colliquative necrosis (*arrows*). Others with complete colliquative necrosis (*arrows*) and thin peripheral hypervascular ring (*arrowhead*)

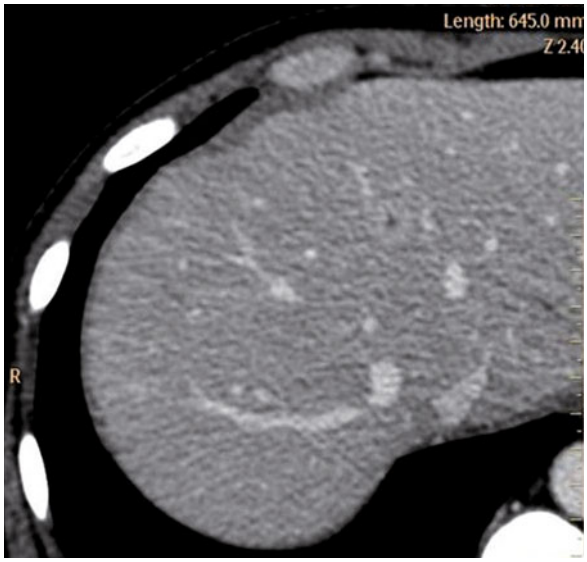


Fig. 6.26 Liver metastasis from GIST. Small secondary hypodense lesions, with hyperdense rim in the right hepatic lobe

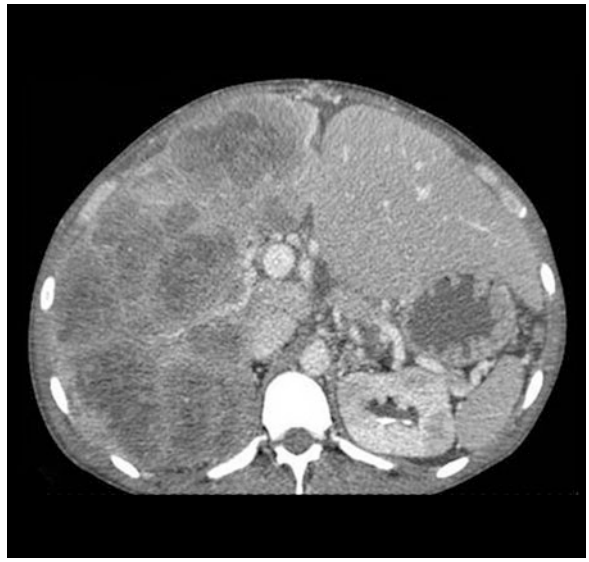


Fig. 6.27 Liver metastasis from GIST. Multiple secondary macronodules, some confluent, with inhomogeneous attenuation and internal areas of colliquative necrosis

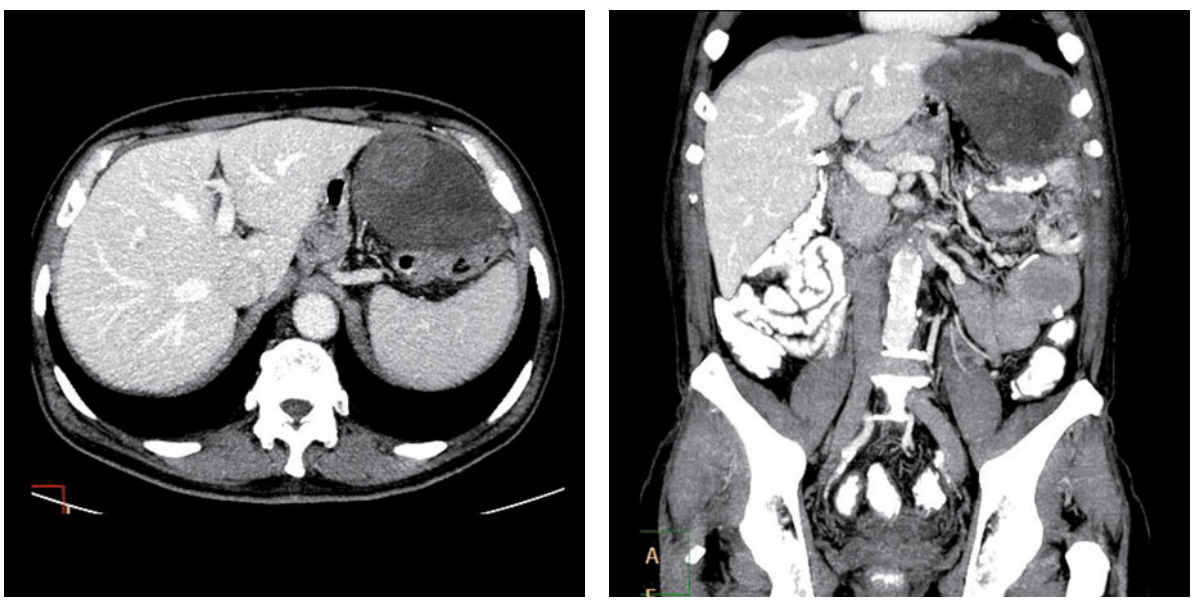


Fig. 6.28 Postsurgical recurrence of GIST. Large and mostly hypodense peritoneal recurrence with eccentric hypervascular nodule

GISTs can also appear as small nodules either at the surgical site or in the peritoneal cavity (Fig. 6.29).

The main aim of imaging, therefore, is a long and accurate follow-up to identify as early as possible metastases and/or recurrences with the purpose of performing, when possible, local treatment such as ablation and/or resection.

6.6 Evaluation of Response

Classically, tumor response to medical treatment has been evaluated by size criteria – the RECIST criteria [19].

An evaluation of the change in size of the target lesions provides the following responses to treatment:

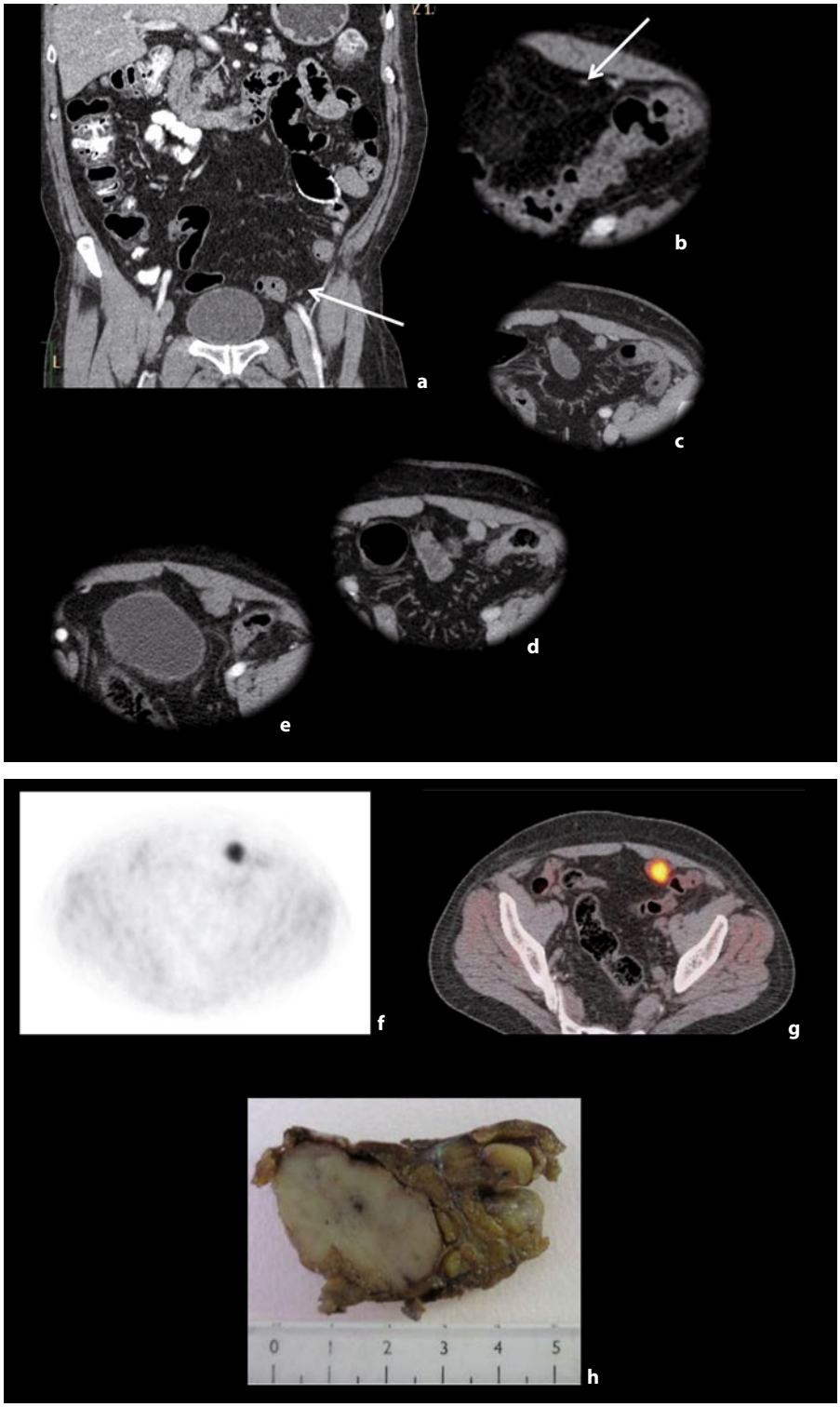


Fig. 6.29 Postsurgical peritoneal recurrence. **a-e** Abdominal–pelvic coronal reconstruction with evidence of small peritoneal recurrence nodule (**a**, *arrow*). Axial scan view (**b**, *arrow*). Follow-up every three months reveals a progressive increase in size of the lesion (**c-e**). **f-h** CT/PET integration (**f, g**) and surgical specimen (**h**)

– complete response (CR): disappearance of all target lesions. Each pathologic lymph node (both target and non-target) must have undergone a reduction of its short axis such that it should get back less than 10 mm;
– partial response (PR): a reduction of at least 30% of the sum of the diameters of the target lesions, using as reference the sum of the diameters at the baseline examination;
– progression of disease (PD): an increase of at least 20% in the sum of the diameters of the target lesions, using as reference the smallest sum of the study. In addition to the relative increase of 20%, the sum must also show an absolute increase of at least 5 mm. (N.B. the appearance of one or more new lesions is also considered progression);
– stable disease (SD): includes all cases where there is no significant decrease in the volume of the target lesions to be able to define them as partial response nor a sufficient increase to consider them as disease progression.

Clinical management of patients with GISTs has dramatically changed with the introduction of new molecular drugs, such as a c-KIT inhibitor imatinib mesylate, making them the first tumor response to molecular target therapy [20].

The histologic response to the drug is given by necrosis, loss of cellularity, myxohyaline degeneration and formation of pseudocysts. These phenomena translate at CT into a progressive transition from a heterogeneous enhancement pattern to one almost homogeneous, with a significant reduction in the enhancement of the lesion and the internal tumor vessels. The density of the entire lesion decreases drastically, alongside the development of areas of colliquative and myxohyaline degeneration, with a progressive reduction in the peripheral vascular soft tissue which may thin to become a pseudocapsule [21] (Fig. 6.30).

In this sense the term cyst or cystic change should be avoided when referring to the appearance of the tumor after treatment. A more correct term is pseudocystic to indicate the myxohyaline transformation.

In some responding tumors, the tumor's density increases as a result of intratumoral hemorrhage. During treatment with imatinib there occurs an increase in tumor size associated with a decrease in density. These changes do not indicate a disease progression, but rather a treatment response; this is the consequence of the intratumoral development – either myxohyaline degeneration or necrosis ("paradoxic" response) (Fig. 6.31). This demonstrates that there is a close correlation between histologic and CT density changes [22]. Therefore size-based response criteria such as the RECIST significantly understimate the response to ima-

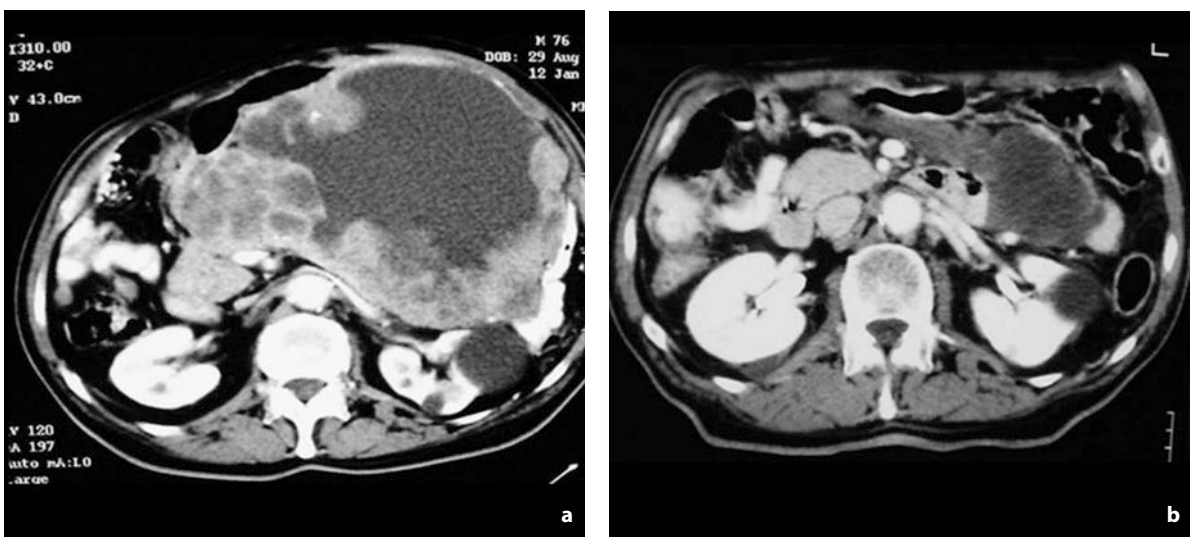


Fig. 6.30 Response to treatment with imatinib. **a** Large gastric GIST deforming the anterior abdominal profile, displacing and compressing adjacent organs. The appearance is heterogeneous due to large central necrosis and peripheral inhomogeneous confluent solid nodules. **b** During treatment with imatinib – follow-up examination at two months: evident reduction in both size and attenuation, with the disappearance of the almost vascular component (response according to both the RECIST and the Choi criteria)

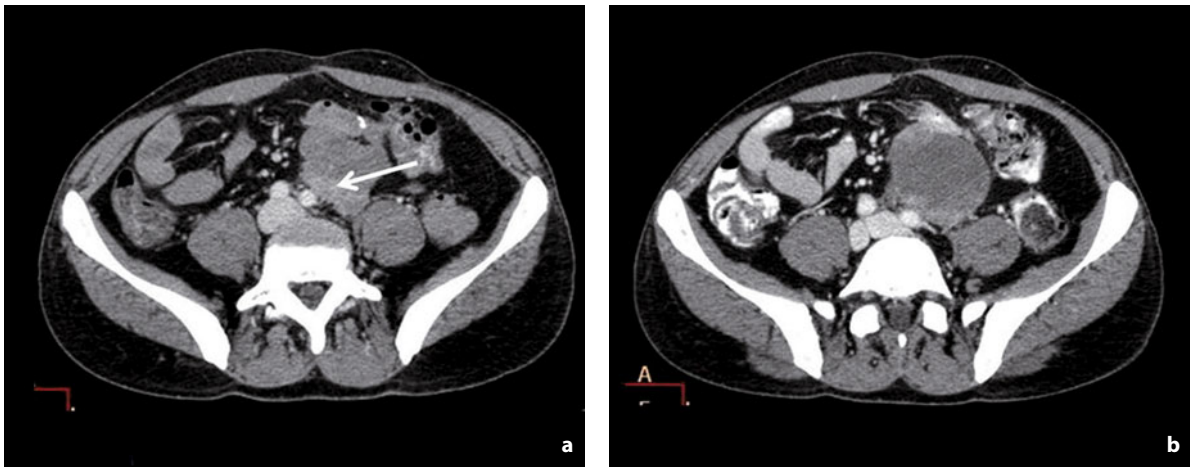


Fig. 6.31 Peritoneal GIST – "Paradoxic Response". **a** Before treatment – Peritoneal GIST with inhomogeneous appearance and dense peripheral tissue (*arrow*). **b** During treatment – increase in size of the lesion associated with a decrease in density (progression of disease according to the RECIST criteria and response according to Choi criteria)

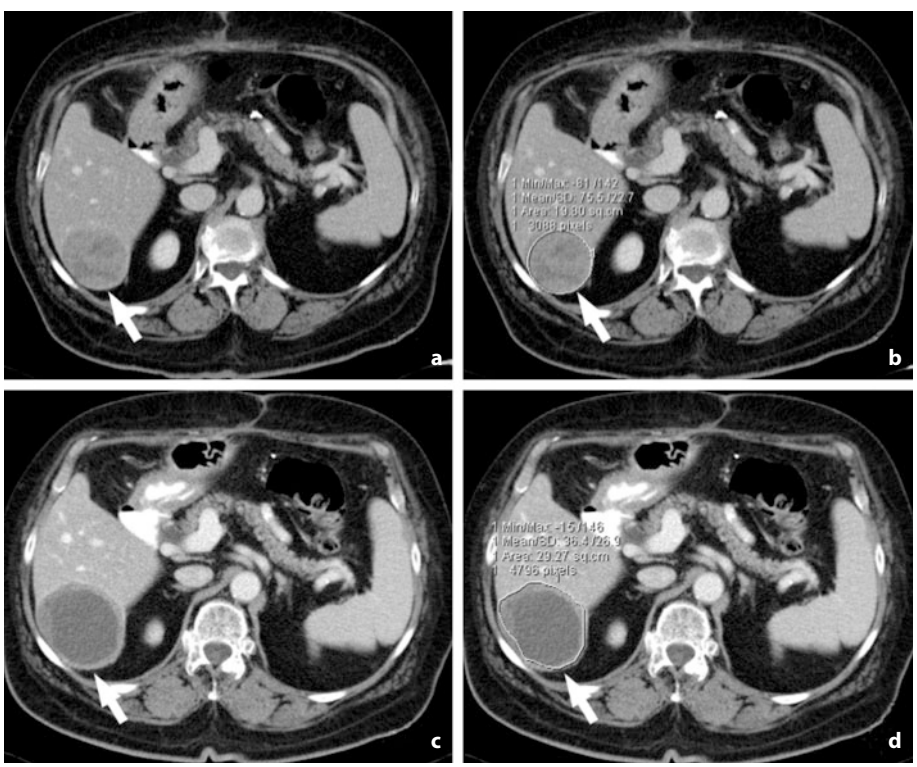


Fig. 6.32 Liver metastatic GIST. Contrast-enhanced CT (**a-d**). Before treatment (**a, b**) the hepatic lesion of the VI segment shows inhomogeneous enhancement. After treatment (**c, d**) an increase in the lesion's size can be appreciated (RECIST progression) associated with a decrease in density of 52% (response according to the Choi criteria)

tinib in GIST. New criteria have been proposed – the Choi criteria – which include an evaluation of the tumor density as well as the size of the tumor vascularization [23].

With the intention of making the evaluation of treatment response as objective as possible, Choi et al. [24] have suggested that a reduction of more than 10% in a one-dimensional measure of the lesions and a post-treatment decrease of more than 15% CT density after the injection of contrast medium are more reliable and complete for the evaluation of treatment response and better correlate with patient survival than the RECIST criteria alone (Fig. 6.32) [25, 26].

The development of new lesions, the increase in

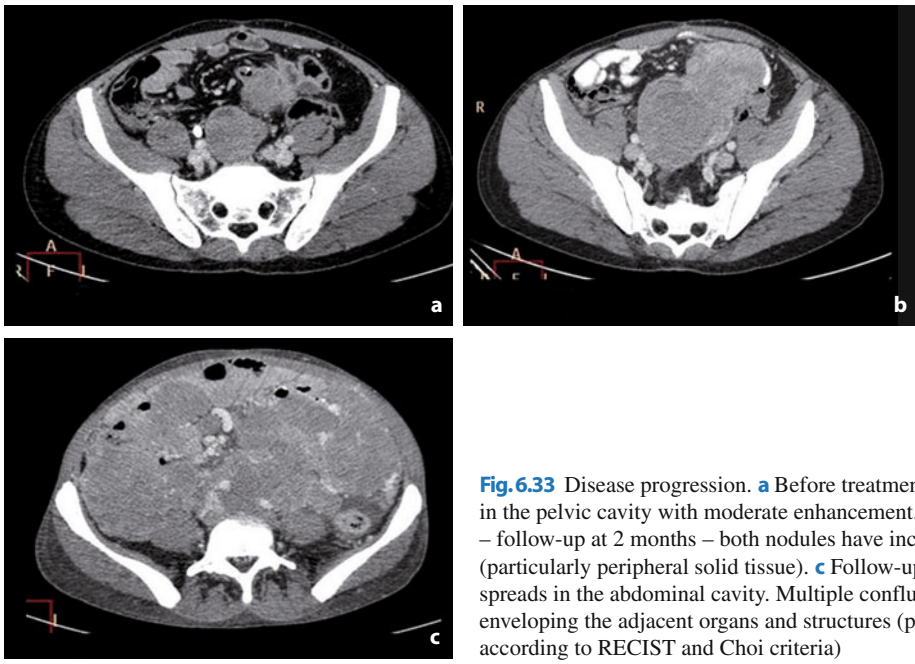


Fig. 6.33 Disease progression. **a** Before treatment – peritoneal nodules in the pelvic cavity with moderate enhancement. **b** During medical treatment – follow-up at 2 months – both nodules have increased in size and in density (particularly peripheral solid tissue). **c** Follow-up at 6 months – the disease spreads in the abdominal cavity. Multiple confluent nodules clumped enveloping the adjacent organs and structures (progression of disease according to RECIST and Choi criteria)

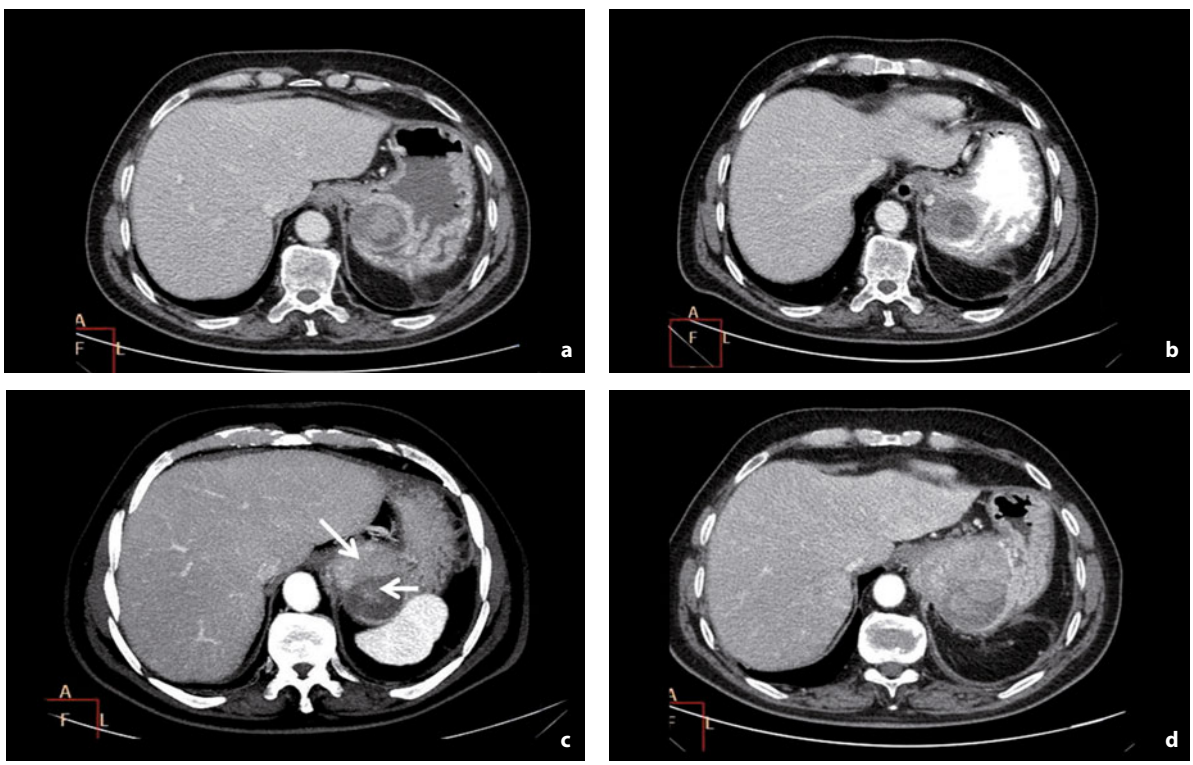


Fig. 6.34 Disease progression – nodule within a nodule. Gastric GIST – before treatment: inhomogeneous cardias nodule at the level of the cardias (**a**). During treatment: stable size with a density reduction due to colliquative necrosis (stable disease according to the RECIST criteria – response according to the Choi criteria) (**b**). Follow-up at 6 months – progression of disease: increase in size with evidence of solid eccentric tissue (*arrow*) and appearance of a nodule within hypodense nodule (*arrow*) (**c**). Follow-up at 8 months: further increase in size either of dense eccentric portion, than the solid nodule within the hypodense treated nodule (**d**)

size and in the peripheral solid portion, with more inhomogeneous enhancement (Fig. 6.33), or the appearance of hypervascular nodules within the treated hypodense tumor without changing the tumor size (nodule within a nodule), are all signs suggesting resistance or inefficacy of imatinib treatment and therefore progression of disease (Figs. 6.34–6.36) [27].

In addition, we should remember that the evaluation of treatment response can be incorrect when a pre-treatment arterial phase study of the liver has not been performed. In fact, some small hypervascular metastases unidentified during the pre-treatment portal phase

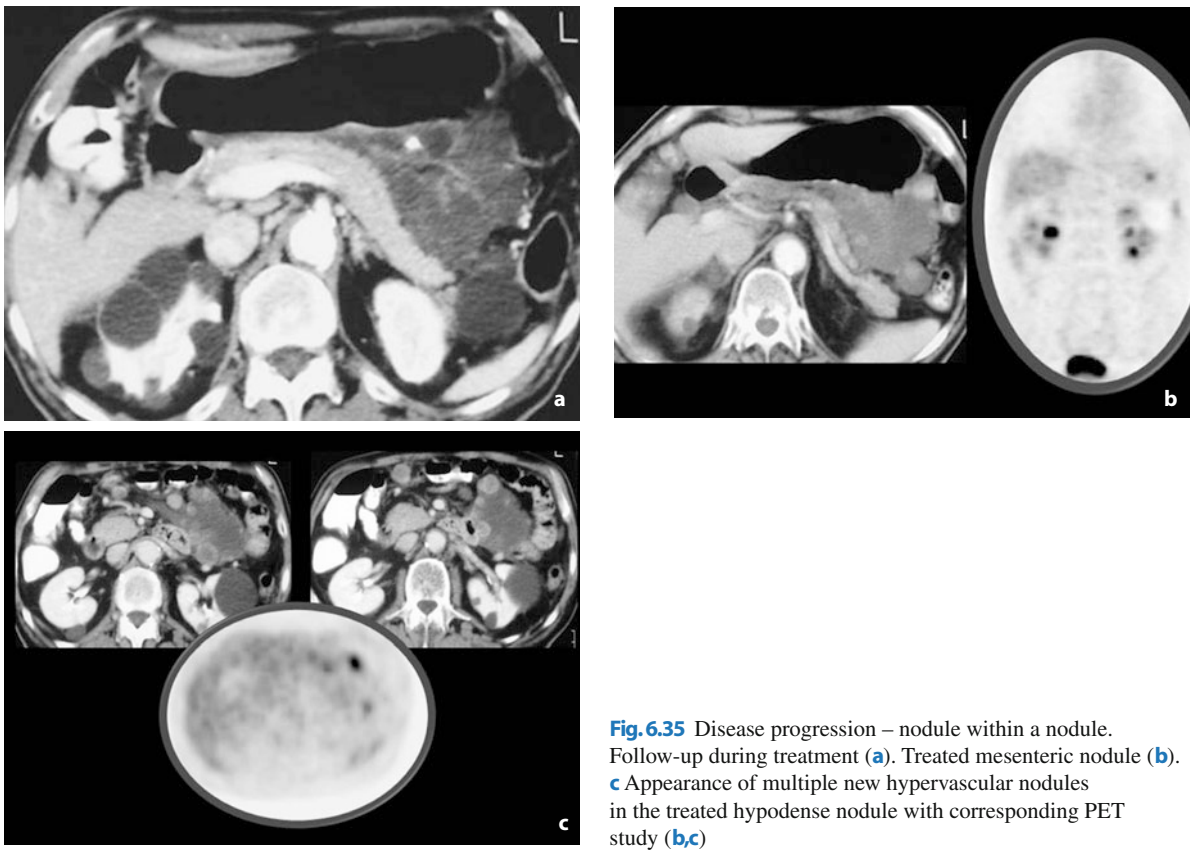


Fig. 6.35 Disease progression – nodule within a nodule. Follow-up during treatment (**a**). Treated mesenteric nodule (**b**). **c** Appearance of multiple new hypervascular nodules in the treated hypodense nodule with corresponding PET study (**b,c**)

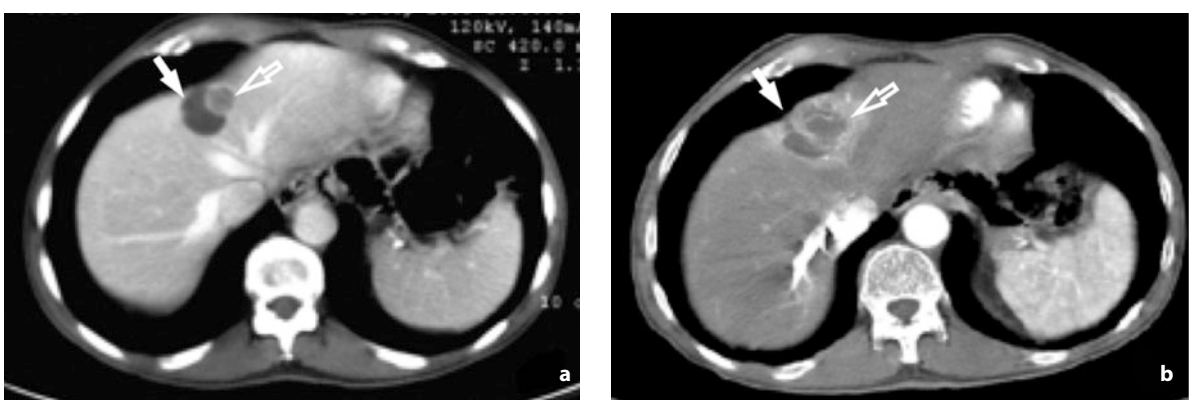


Fig. 6.36 Liver metastatic GIST. Contrast-enhanced CT (**a, b**). In the hepatic lesion (**a**) (*solid arrow*) a well-circumscribed, solid nodule can be seen showing peripheral enhancement (nodule within a nodule) (*empty arrow*) indicative of active tissue. This is confirmed by follow-up at 3 months (**b**) which shows an increase in size and in density (*empty arrow*)

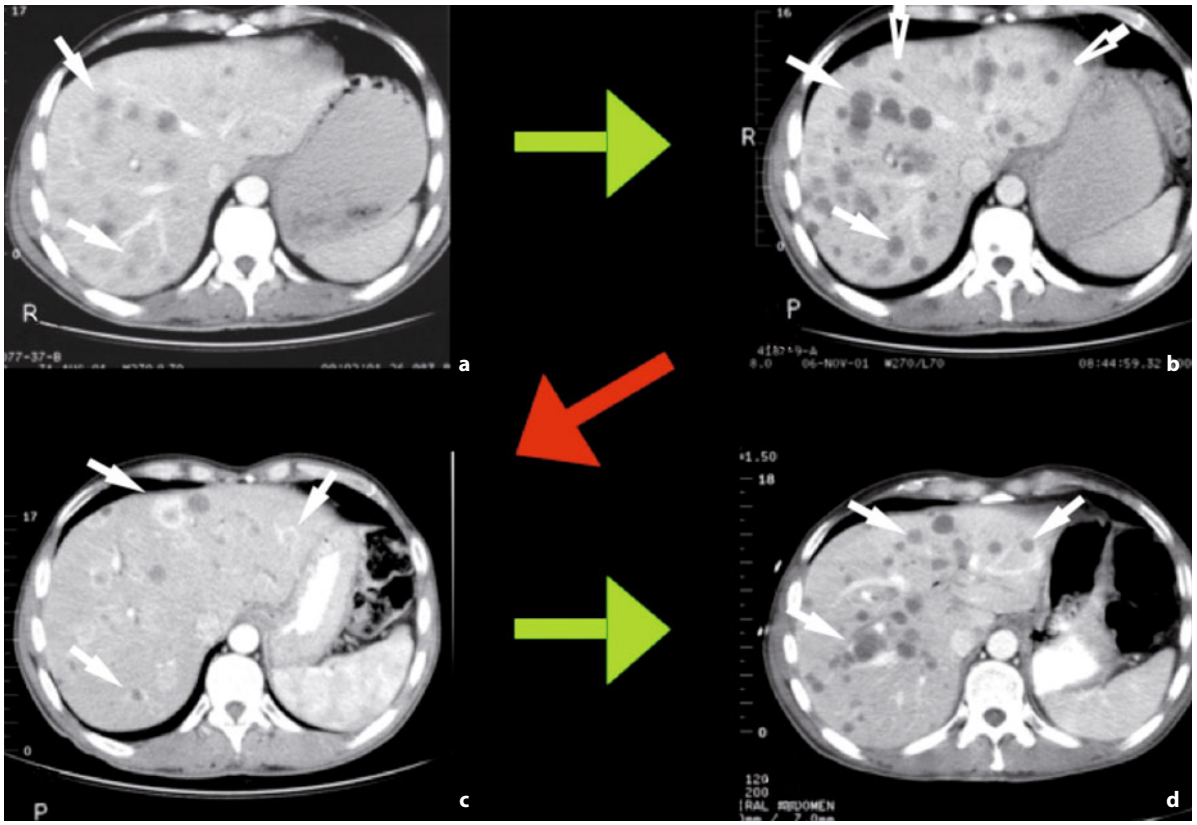


Fig. 6.37 Liver metastatic GIST. Contrast-enhanced CT (**a-d**). At baseline CT the multiple liver metastases show slight and inhomogeneous enhancement (*solid arrows*) (**a**). After treatment: reduction in density of target lesion indicating response according to the Choi criteria (*solid arrows*) (**b**). Evidence of new hypodense nodules (*empty arrows*). This should not be interpreted as a focal progression, but as a response, too, because they were isovascular to the liver parenchyma and therefore non-detectable at the previous examination (*empty arrows*) (**b**). With the interruption of therapy, the recurrence of nodules can be seen indicative of disease progression (*solid arrows*) (**c**). Starting over the therapy, the peripheral vascularization of nodules disappears (response to the Choi criteria) (*solid arrows*) (**d**)

can become hypodense and therefore visible after treatment and be incorrectly considered new lesions (Fig. 6.37).

Another and rare response to treatment may be the calcification of the nodules, particularly in the presence of peritoneal microdissemination. This process of calcification can be complete in the small nodules and incomplete, with hypodense residual central tissue and calcification of the peripheral dense tissue, in the larger nodules (Fig. 6.38) [9].

6.7 Differential Diagnosis

GISTs have radiologic characteristics similar to other tumors that are included in the differential diagnosis.

The differential diagnosis includes epithelial tumors, such as adenomas and adenocarcinomas due to their high frequency in the GI tract. However, these tend to be located in the duodenum–jejunum, they are rarely exophytic, they generally have more irregular and poorly defined margins, they are not well circumscribed like most GISTs, have a greater tendency to perforation (Fig. 6.39) and metastasize more frequently to the lymph nodes [28].

GISTs are difficult to differentiate from other mesenchymal tumors. In particular, if they are small, homogeneous and hypervascular they are indistinguishable from leiomyomas (Fig. 6.40) and neurinomas, and in case of more aggressive tumors from leiomyosarcomas (Fig. 6.41) [29]. Nonetheless, it should be recalled that GISTs are the most common mesenchymal tumors of the GI tract with the exception of the esophagus.

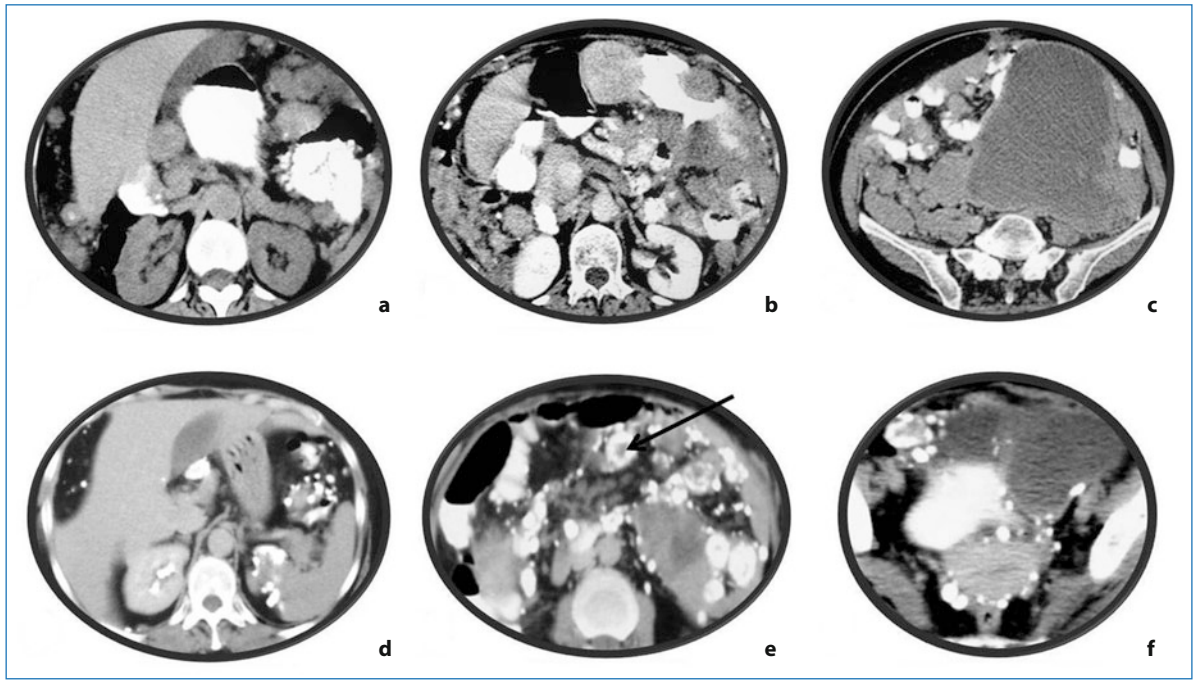


Fig. 6.38 Calcification of peritoneal nodules – rare type of treatment response. **a-c** Before treatment: multiple and diffuse peritoneal nodules various in size and density. **d-f** During treatment. Progressive calcification of most of the peritoneal nodules. Some micronodules show complete calcification, while other show partial calcification only in peripheral soft-tissue portion (*arrow*)

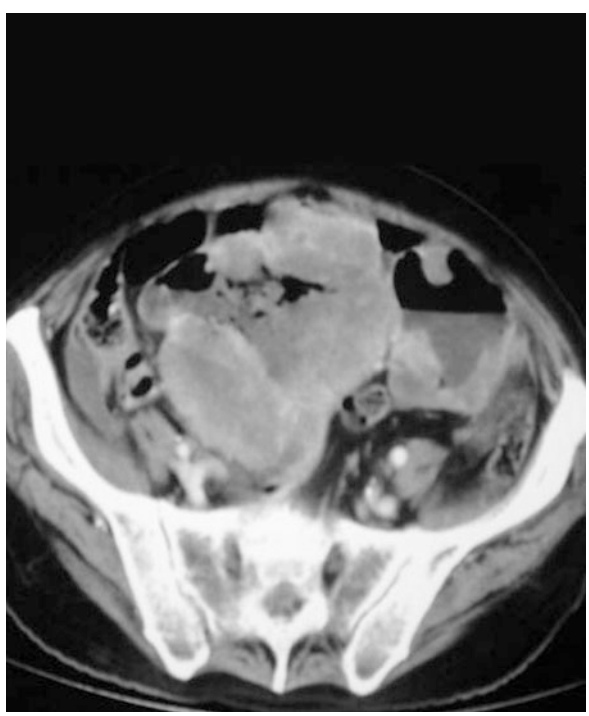


Fig. 6.39 Perforated small bowel adenocarcinoma. Presence of fluid and air in the peritoneal fat tissue indirectly indicative of a covered perforation

Lymphomas can also create problems for the differential diagnosis of GISTs, but unlike the latter, they tend to cause marked mural thickening which is often associated with aneurysmal dilatation of the portion of the GI tract involved (Fig. 6.42). However, in some cases lymphomas appear as polypoid or exophytic mass, although the lymph node involvement is more frequently diffuse and significant [30].

When not associated with a desmoplastic reaction, carcinoid tumors may show characteristics similar to the hypervascular forms of GISTs with intraluminal growth (Fig. 6.43) [31].

In addition to the clinical findings the number (often multiple) and the site (ileum) of the lesions may be useful in their diagnosis.

The differential diagnosis should also be made between paragangliomas and duodenal GISTs. The former are benign tumors of the second part of the duodenum and they appear as prevalently exophytic masses with homogeneous contrast enhancement.

Last of all the differential diagnosis should include intra-abdominal fibromatosis as well as its progression towards the formation of desmoid tumors – tumors of mesenchymal origin which at the level of

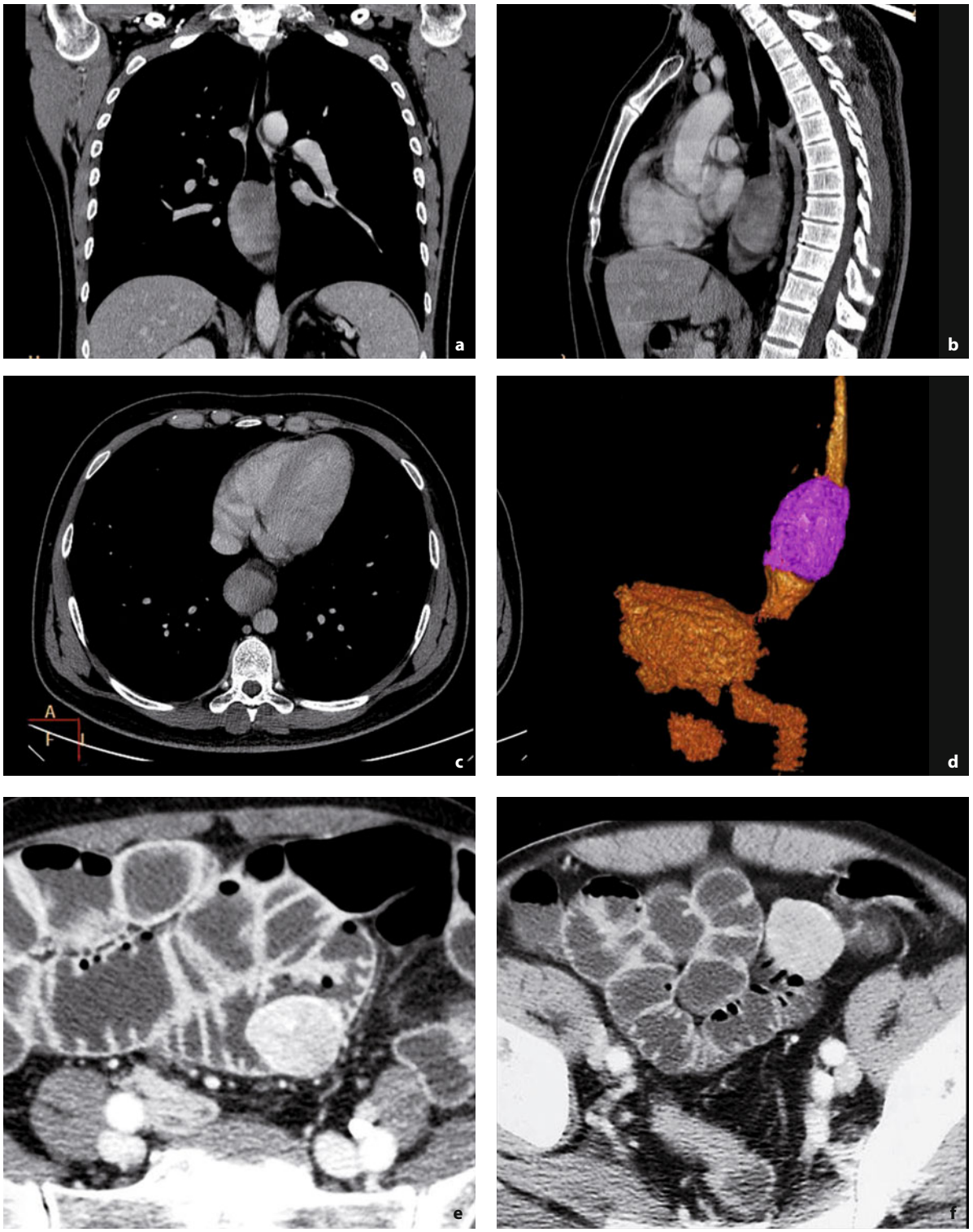


Fig. 6.40 Leiomyomas. **a-d** Esophagus: large mass with intraluminal growth pattern located in the distal esophagus with sharp and well-defined margins and finely inhomogeneous enhancement. Coronal and sagittal reconstruction (**a-c**). 3D reconstruction (**d**). **e, f** CT enteroclysis: Submucosal lesion with intraluminal growth seen lifting the mucosa without damaging it; intense and homogeneous enhancement (**e**). Another extra/intraluminal hypervascular mass with homogeneous enhancement (**f**)

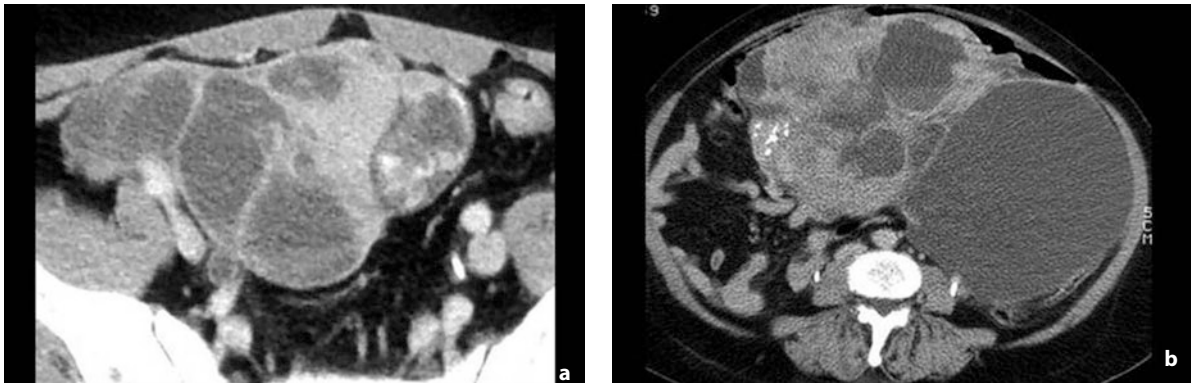


Fig. 6.41 Small bowel leiomyosarcomas. **a** Inhomogeneous mass with necrosis crossed by vascular septa, areas of dense tissue and internal calcifications. **b** Huge heterogeneous mass: moderate dense tissue component with calcified nuclei and large areas of necrosis–degeneration

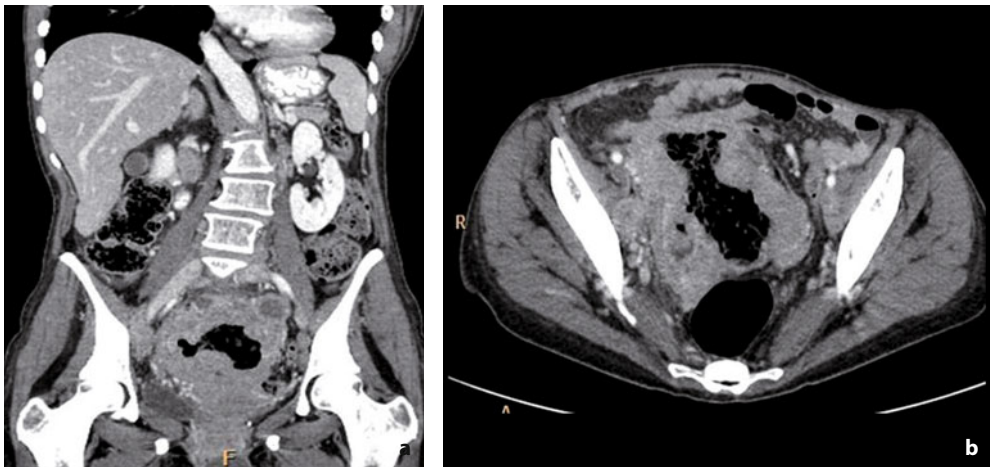


Fig. 6.42 Lymphoma: coronal reconstruction (**a**) and axial scan (**b**) Marked wall thickening with aneurysmal dilatation and lymph node involvement

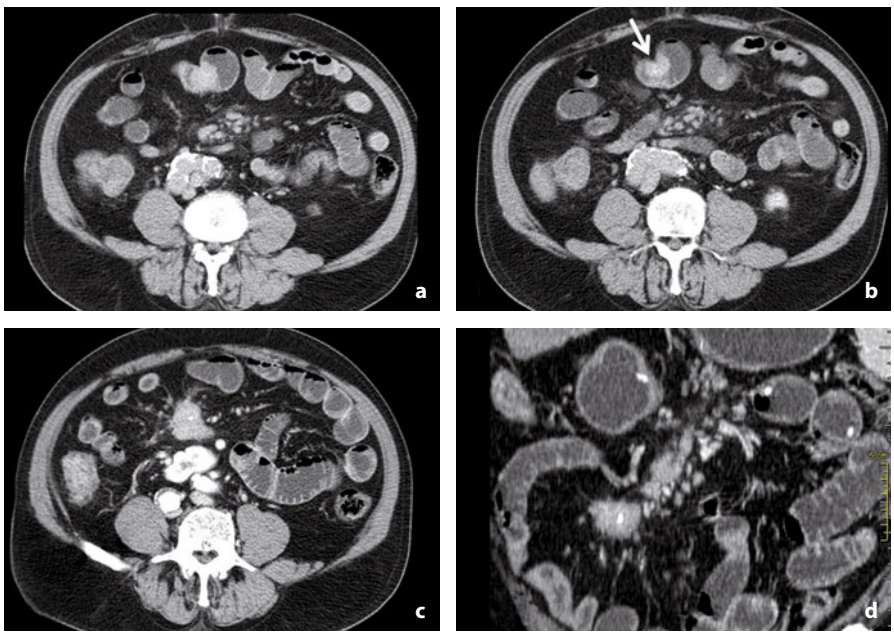


Fig. 6.43 Small bowel carcinoid tumors. CT enteroclysis. **a, b** Solid hypervascular intraluminal lesion. The index sign (*arrow*) suggests the diagnosis of carcinoid. **c, d** Typical mesenteric mass with calcifications and radiating infiltration of the mesentery (desmoplastic reaction) with multiple lymph-nodes

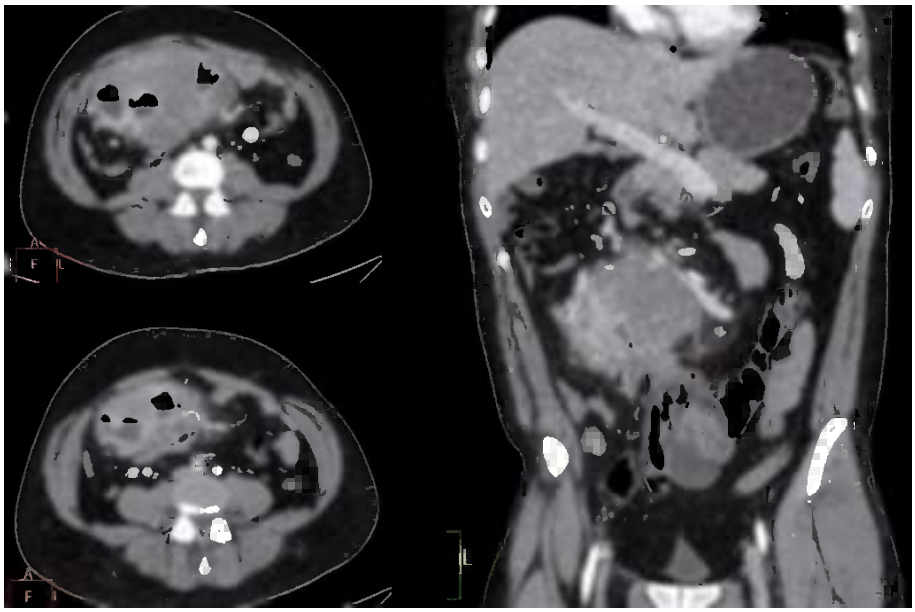


Fig. 6.44 Intra-abdominal fibromatosis. Axial scans and coronal reconstruction: large solid noncapsulated mass with inhomogeneous appearance enveloping the ileal loops and infiltrating the mesentery and adjacent structures

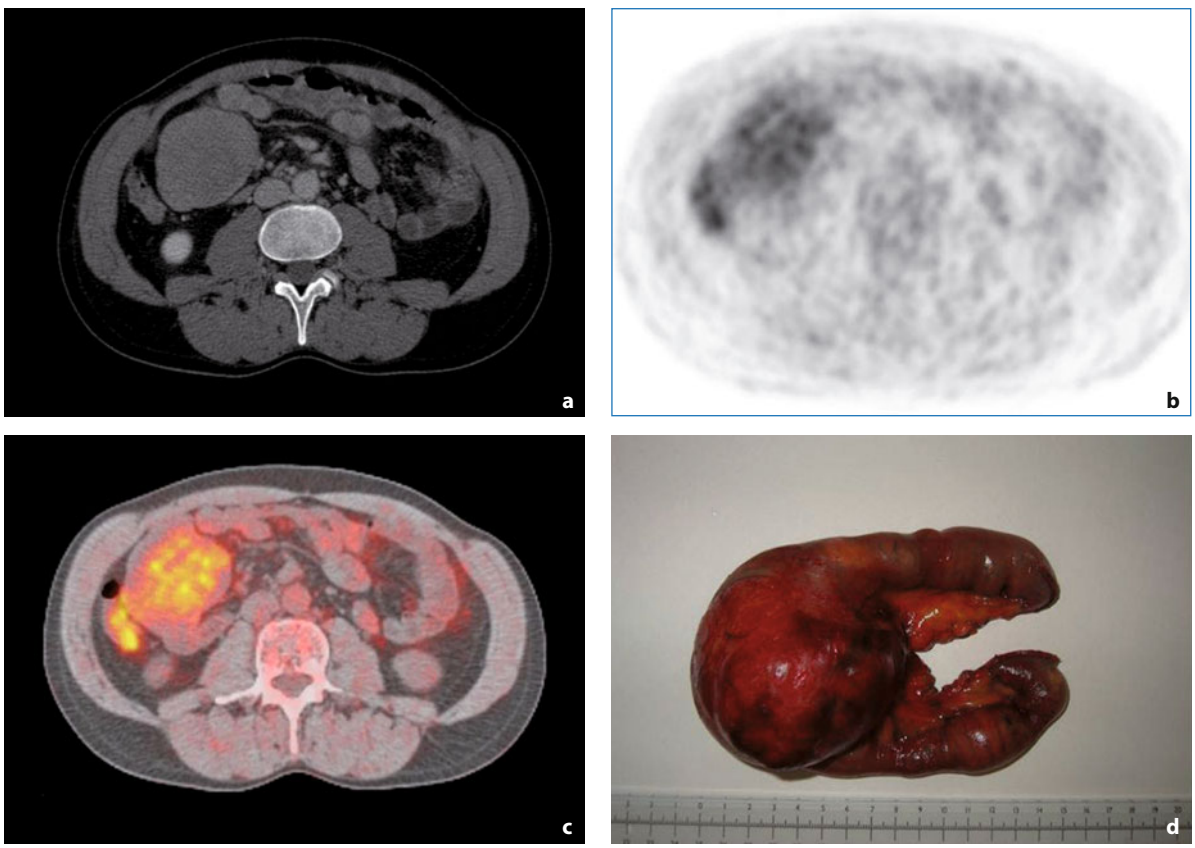


Fig. 6.45 Intra-abdominal fibromatosis. Large solid noncapsulated mass with inhomogeneous appearance in the right flank arising from the mesentery and inseparable from some of the ileal loops. CT (**a**), PET (**b**), CT/PET (**c**) and surgical specimen (**d**)

the mesentery can become very large, appearing at CT as solid noncapsulated and finely inhomogeneous masses, generally without the characteristic hypodense center, with intermediate/low enhancement and which cause compression and invasion of the bowel loops and the adjacent abdominal organs (Figs. 6.44, 6.45).

The association with familial adenomatous polyposis or a history of surgical trauma, laparascopic procedures, hormone therapy, together with the greater tendency to infiltrate the mesenteric fat, bowel loops and/or abdominal organs may suggest the diagnosis [32].

In conclusion, as there are still no well-defined criteria nor pathognomonic signs for differentiating GISTs from other tumors at CT, especially nonepithelial tumors, the definitive diagnosis is confirmed by histology and immunohistochemistry.

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Magnetic Resonance

7

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Antonella Petrillo and Daniele Vergnaghi

Abstract Diagnostic imaging provides a valuable contribution to the study of primary and metastatic gastrointestinal stromal tumors (GISTs) with Magnetic Resonance (MR). MR can be used in the identification, characterization and staging of GISTs, as well as in the evaluation of response to treatment, showing the tissue changes induced in cancer cells by molecular targeted therapies, including myxohyaline changes, fibrosis, hemorrhagic necrosis and cellularity reduction. Tumor response to medical treatment has to date been evaluated by size criteria (RECIST). However, in the case of GISTs, size criteria alone cannot provide an objective evaluation of response: in the early months of treatment a "paradoxic" response in relation to tumor size may occur, with stable or even increased size of the tumor due to hemorrhage-necrosis or myxohyaline degeneration. MR is able to assess the vascular patterns of neoplastic lesions and to quantify the reduction in vascularity and the presence of necrosis induced by the therapy, even in the early phase of treatment.
MR is an effective examination technique in the evaluation of GISTs, with high-contrast resolution and multiplanar capability. The most effective examination techniques are morphologic T1w and T2w sequences, combined with dynamic ce T1w sequences, to evaluate the vascular patterns of the lesions.

Keywords Morphologic study • Dynamic evaluations • Diffusion-weighted Imaging (DWI) • Identification of GIST • Characterization of GIST • Staging of GIST • Response to treatment • Molecular target therapy • RECIST, CHOI criteria adapted to MR

7.1 Introduction

Diagnostic imaging provides a valuable contribution to the study of primary and metastatic Gastro Intestinal Stromal Tumors (GISTs) with Magnetic Resonance (MR).

Progressive advances in technology have enabled MRI to overcome the limitations of the early equipment, increasing the spatial resolution and signal-to-noise ratio (SNR) (with the use of high-field magnets and phased-array surface coils) and reducing the length of the examination (with the introduction of fast sequences). In recent years the MR study of the abdomen has been further enriched by the possibility of performing not only a conventional morphologic study, but also dynamic functional evaluations and diffusion-weighted imaging (DWI) [1].

7.2 MR Study Technique of GISTs

The best results in terms of spatial resolution and SNR in the abdominal examination can be achieved with

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the use of multichannel coils placed on the upper and lower abdomen to obtain a panoramic evaluation of the entire abdomen.

7.3 Preparation

In clinical practice, no specific preparation is required for patients undergoing an MR examination of the abdomen for the study of GISTs. However, in cases of gastric GISTs the distension of the stomach with water may prove useful, whereas in rectal GISTs preparation of the bowel may be indicated.

7.4 Technical Aspects

Routinary MR study of the abdomen in the evaluation of GIST must include both conventional morphologic T1w and T2w sequences and dynamic contrast-enhanced T1w sequences, available on most high-field MR systems, even in the absence of particular software or hardware options. Recently the MR abdominal study has been enriched with Diffusion-Weighted Imaging (DWI) techniques [1].

7.4.1 Morphologic Study

The MR morphologic study performed the use of TSE T1w and HASTE T2w sequences (Fig. 7.1). The use of the correct temporal parameters in the acquisition of T2w images (high TR and TE values) is particularly important to obtain correct differentiation between normal and pathologic tissue. Routine MR study is performed in axial planes, and additional planes can be added.

7.4.2 Dynamic Contrast-enhanced Study

The dynamic MR study of GISTs is based on the evaluation of tumor vascularization [2]. Axial GRE T1w sequences are used, preferably associated with fat-signal suppression, acquired before contrast medium administration and then repeated three times before and 30”, 60” and 120” after contrast media administration (arterial phase, venous phase and late phase). The acquired datasets are post-processed with the digital subtraction technique to increase the identification of the areas of parenchymal enhancement and to minimize the effects on the parenchymal signal induced by intralesional bleeding where present. The images obtained then undergo an initial qualitative evaluation to identify the presence of pathologic areas of marked parenchymal enhancement. The qualitative evaluation is followed by a numerical evaluation, which may be done in semiquantitative and/or quantitative modality. The semiquantitative evaluation is performed with the calculation of the signal intensity–time curves which are drawn by sampling the signal with a region of interest (ROI) at the level of the entire lesion, including any necrotic areas (Fig. 7.2) [3] and the calculation of the area under the gadolinium curve (AUGC). The quantitative evaluation is obtained using dedicated software applications able to calculate various numerical parameters such as ktrans, Ve and Vp. Currently, however, there are

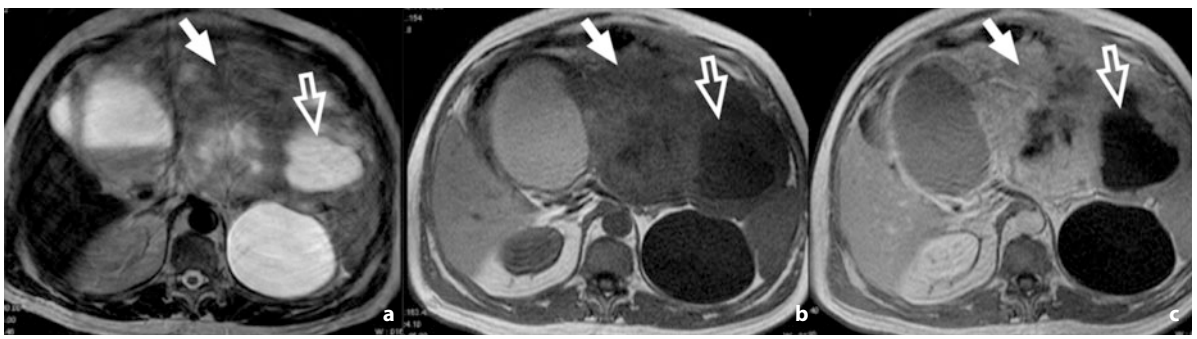

Fig. 7.1 Primary gastric GIST. MR axial HASTE T2w (**a**) and GRE T1w images before (**b**) and after (**c**) intravenous administration of contrast medium of a large primary gastric GIST. The signal intensity is heterogeneous, with solid areas characterized by low signal on the T2w images and moderate contrast enhancement (*solid arrows*) and areas of necrosis characterized by high signal intensity on T2w and lack of contrast enhancement (*empty arrows*)

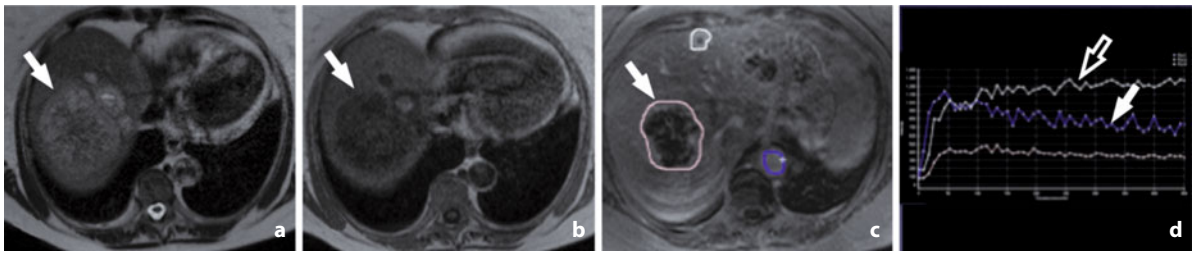

Fig. 7.2 Liver metastases from GIST. MR axial TSE T2w (**a**) and GRE T1w images before (**b**) and after (**c**) administration of paramagnetic contrast medium. Functional study with semiquantitative evaluation of the dynamic contrast-enhanced acquisition with signal intensity–time curves (**c**) drawn by sampling the signal with a ROI placed over the entire hepatic lesion (**d**). The hepatic lesion (*solid arrows*) appears heterogeneously hyperintense on the T2w images (**a**), hypointense on the T1w images (**b**), with heterogeneous contrast enhancement (**c**). In the functional study graph (**d**) the blue curve corresponds to the aorta (*solid arrow*), whereas the yellow curve corresponds to the lesion, with strong wash-in and slow wash-out (*empty arrow*)

limitations to the use of the quantitative evaluation of dynamic functional studies with MR associated with the poor availability and standardization of the software.

7.4.3 Diffusion-weighted Imaging Study

Molecular diffusion is thermally induced random microscopic molecular motion, also known as Brownian motion. The properties of tissue diffusion are correlated with the presence of interstitial fluid and the degree of permeability. This molecular motion can be visualized with MR, since it provides a specific type of contrast. In general, neoplastic tissue tends to be characterized by lower diffusion coefficients than normal tissue due to the high cellular density and the abundance of intracellular and intercellular membranes.

In DWI image contrast is provided by the intensity of the microscopic motion of water molecules. In order to make an MR sequence sensitive to diffusion, two gradients (diffusion gradients) on either side of a 180° radiofrequency pulse are added. In the presence of stationary spins, spin dephasing produced by the first diffusion gradient is followed by perfect rephasing by the second gradient. In the presence of spin in motion, the rephasing will instead be incomplete, with the result of a signal loss within the voxel. The attenuation of the signal in DWI images depends on the diffusion factor b and the tissue apparent diffusion coefficient (ADC). The diffusion factor b represents the weighting factor of the diffusion sequences, and it determines the intensity and the duration of the diffusion gradients. The tissue ADC instead varies according to the tissue (Fig. 7.3) [1].

In GISTs, the normal structural architecture is replaced by spindle cells (around 70%) and to a lesser extent epithelioid cells (20%) or mixed (10%) and extensive stromal modifications such as perivascular hyalinization. These changes inhibit the motion of water molecules, thus producing a reduction in diffusion and ADC values in neoplastic tissue.

In the DWI sequences used in the study of GISTs multiple b-values are used (50, 400, 800 s/mm^2) (Fig. 7.3). In DWI, in a clinically relevant range of b-values (50-800 s/mm2), the following rules are applied: the

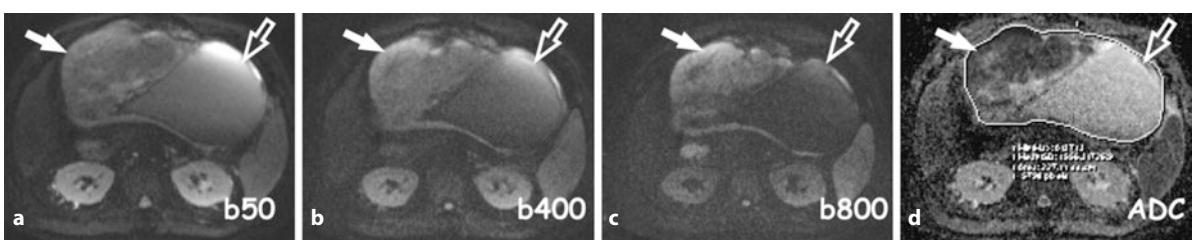

Fig. 7.3 Primary gastric GIST. Diffusion-weighted MR images: b50 (**a**), b400 (**b**), b800 (**c**) and ADC map (**d**). The images obtained with low b-values (50-400) display elevated signal both in the active solid component (*solid arrows*) and the cystic-necrotic component (*empty arrows*). In the images obtained with elevated b-values (800) the solid component maintains its elevated signal (solid arrow), whereas the cystic-necrotic component shows a reduction in signal intensity (*empty arrow*). In the ADC map the active solid tissue appears hypointense (*solid arrow*), whereas the cystic-necrotic tissue is hyperintense (*empty arrow*)

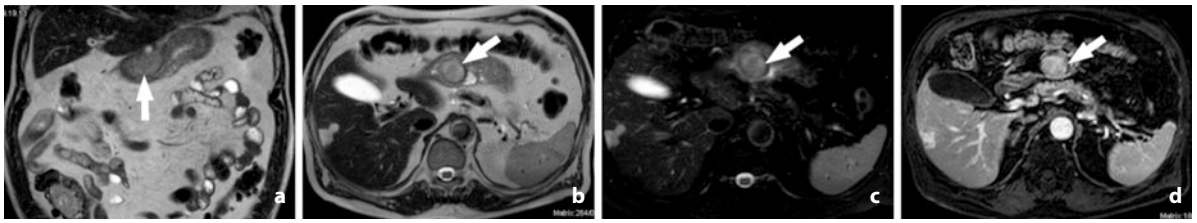

Fig. 7.4 Primary gastric GIST. MR coronal TSE T2w (**a**), axial TSE T2w images without (**b**) and with fat signal suppression (**c**) and contrast-enhanced GRE T1w image (**d**) of a primary gastric GIST. The lesion (*arrows*) is well circumscribed, intraluminal and slightly hyperintense on T2 (**a-c**), with moderate contrast enhancement (**d**)

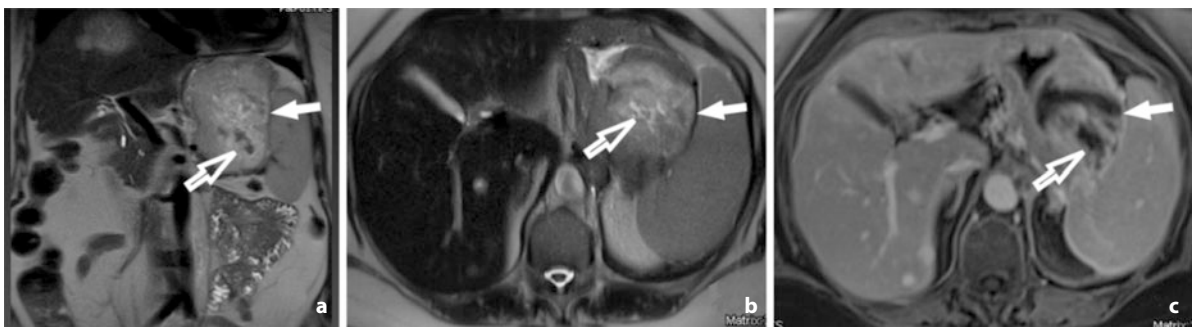

Fig. 7.5 Primary gastric GIST. MR coronal TSE T2w (**a**), axial TSE T2w (**b**) and contrast-enhanced GRE T1w images (**c**) of a primary gastric GIST. The signal intensity is heterogeneous, with solid areas characterized by low signal on the T2w images and moderate contrast enhancement (*solid arrows*) and areas of necrosis characterized by high signal intensity on T2 and without contrast enhancement (*empty arrows*)

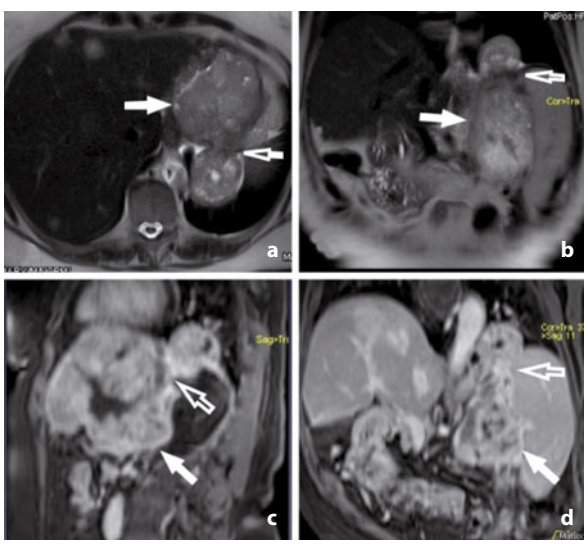

Fig. 7.6 Primary gastric GIST with liver metastases. MR axial (**a**) and coronal (**b**) TSE T2w (**b**) and sagittal contrast-enhanced GRE T1w images (**c**) of a primary gastric GIST (*solid arrows*) herniated into the thoracic cavity. The empty arrows indicate the site of passage

higher the b-value, the higher the diffusion weighting and the greater the contrast in the pathologic region, which presents an elevated signal. DWI images obtained with long echo times nonetheless also contain an amount of T2 contrast, which can mimic a reduction in diffusion (T2 shine through). Therefore it is advisable to calculate ADC maps from diffusion images obtained with at least two different b-values able to highlight pure diffusion coefficients pixel by pixel. Areas of reduced diffusion are given in the ADC maps by low signal (Fig. 7.3) [1].

Although diffusion techniques are currently considered promising in the MR study of the abdomen, the limitations to the technique should be pointed out, including the low spatial resolution and the lack of standardization of the acquisition protocols.

At our center DWI in the study of GIST is performed using axial diffusion-weighted echoplanar sequences with high TR and TE values, a wide field of view (380 mm), 4 mm slice thickness, diffusion direction in the three planes in space and b-values of 50, 400 and 800 s/mm^2.

7.5 MR Imaging in GISTs

MR can be used in the identification, the characterization and the staging of GISTs, as well as in evaluating the response to treatment.

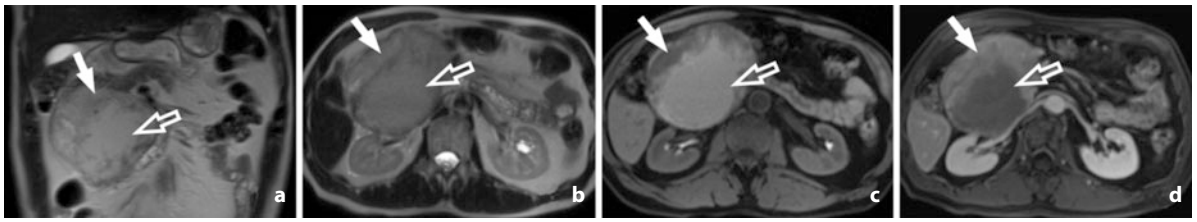

Fig. 7.7 Primary duodenal GIST. MR coronal HASTE T2w (**a**), axial (**b**) and GRE T1w images before (**c**) and after (**d**) intravenous administration of contrast medium of a large primary duodenal GIST. The solid portion (*solid arrows*) appears slightly hyperintense on T2, hypointense on T1 and moderately enhancing after administration of contrast medium, whereas the central necrotic area (*empty arrows*) appear hyperintense both on T1 and on T2, but without contrast enhancement

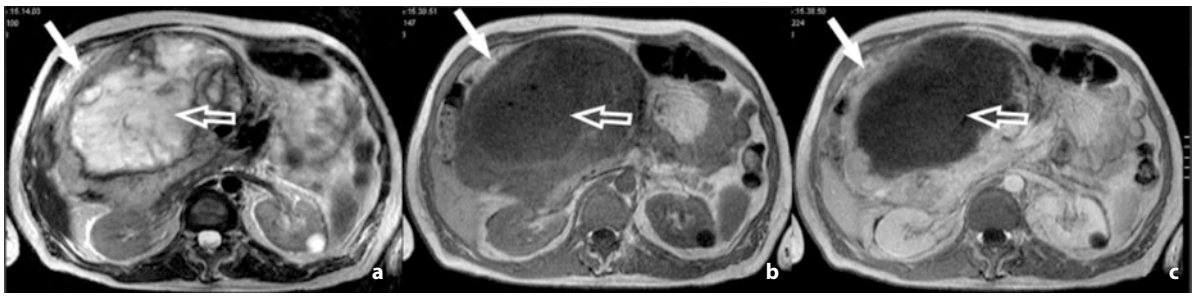

Fig. 7.8 Primary duodenal GIST. MR axial HASTE T2w (**a**) and GRE T1w images before (**b**) and after (**c**) intravenous administration of contrast medium of a large primary duodenal GIST. The solid portion (*solid arrows*) appears slightly hyperintense on T2, hypointense on T1 and moderately enhancing after administration of contrast medium, whereas the central necrotic area (*empty arrows*) appear hyperintense both on T1 and on T2, but without contrast enhancement

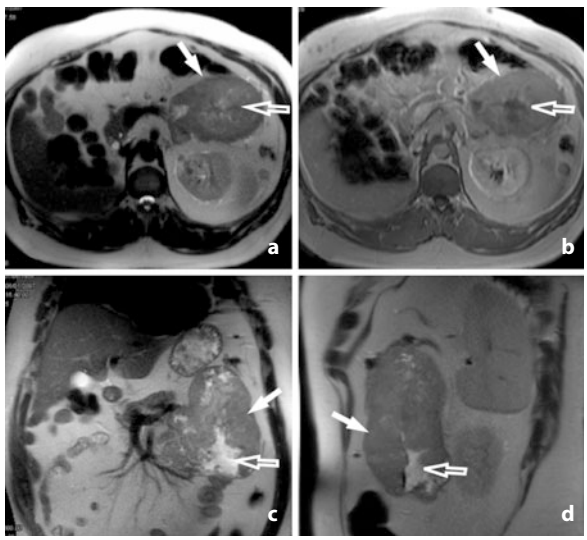

Fig. 7.9 Primary small bowel GIST. MR axial TSE T2w (**a**) and GRE T1w images after contrast medium administration (**b**) and coronal (**c**) and sagittal TSE T2w images (**d**) of a large primary GIST of the small bowel.
The solid portion (*solid arrows*) appears slightly hyperintense on T2, hypointense on T1 and moderately enhancing after administration of contrast medium, whereas the central necrotic area (*empty arrows*) appear hyperintense both on T1 and on T2, but without contrast enhancement

7.5.1 Identification

The identification of GISTs with MR is related to the site and the morphologic appearance of the lesions. The most common sites are represented by the stomach (Figs. 7.4-7.6) and the bowel (Figs. 7.7-7.9) [4]. Primary rectal GISTs are less common (Fig. 7.10). Primary lesions can present at onset as small intramural lesions, but they may have extramural extension and reach considerable dimensions. Small lesions present as small expansive processes of the bowel wall, and are better visualized with radiographic contrast-enhanced techniques, which provide greater detail for the evaluation of bowel wall alterations. Larger primary lesions are visualized as voluminous expansive masses inseparable from the bowel loops and may also be visualized by other

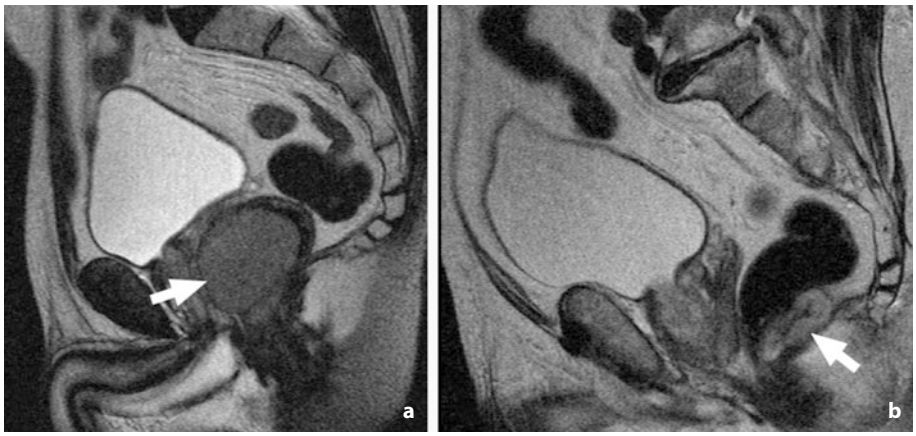

Fig. 7.10 Primary rectal GISTs. MR sagittal TSE T2w images. Primary rectal GISTs (*arrows*) of the anterior wall (**a**) and posterior wall (**b**) appearing mildly hyperintense on T2

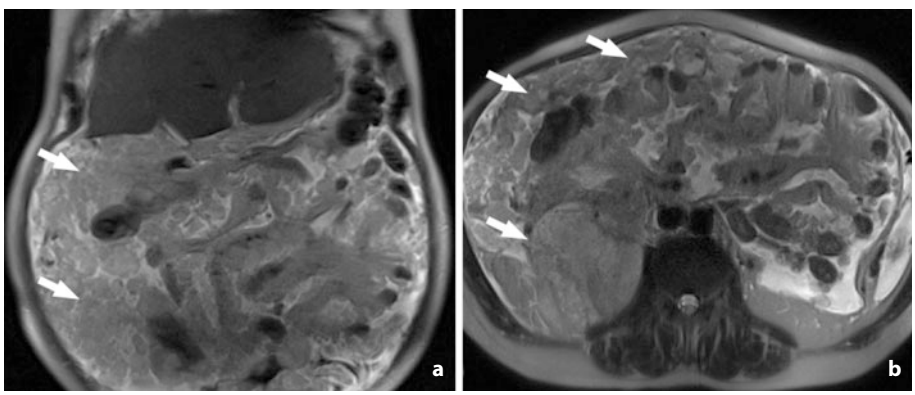

Fig. 7.11 Peritoneal metastases from GIST. MR coronal (**a**) and coronal (**b**) HASTE T2w images show multiple peritoneal lesions of various sizes with mildly hyperintense appearance (*arrows*) A peritoneal fluid is present. The lesions cause a mass effect with initial displacement of the abdominal profile

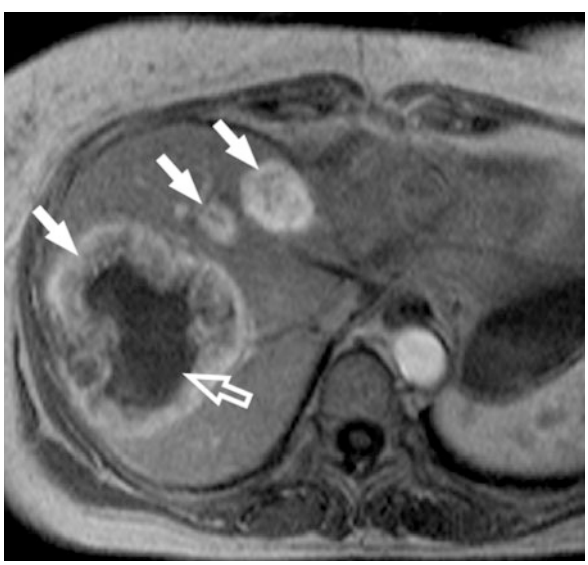

Fig. 7.12 Liver metastases from GIST. MR axial contrast-enhanced GRE T1w images show multiple and heterogeneous liver metastases. The larger lesions display solid peripheral tissue with moderate enhancement (*solid arrow*) and central necrosis (*empty arrow*), whereas the smaller lesions appear hypervascular (*empty arrows*)

diagnostic imaging techniques such as MR. On T2w sequences the signal may be heterogeneous, indicative of the inhomogeneity of the tissue components. Greater signal hyperintensity corresponds to necrotic hypovascular portions, whereas lesser hyperintensity corresponds to solid, active and hypervascular components. On T1w sequences the signal is generally low.

Metastases may be found in the peritoneum (Fig. 7.11), the liver (Figs. 7.12, 7.13) and more rarely bone (Figs. 7.14, 7.15) and lymph nodes (Fig. 7.16). The lesions appear as expansive masses with variable signal and vascular patterns. Small metastases are often homogeneous, slight hyperintense on T2w sequences and hypointense on T1w sequences. Contrast enhancement is predominantly late, although hypervascular liver metastases may be identified in the arterial phase. The use of contrast-enhanced, multiphasic study is therefore crucial.

Larger lesions are often composed of a mildly hyperintense active solid portion on T2w sequences, appearing hypointense on T1w sequences with moderate vascularization, whereas the central pseudo-necrotic portion appears hyperintense on T2 and hypovascular.

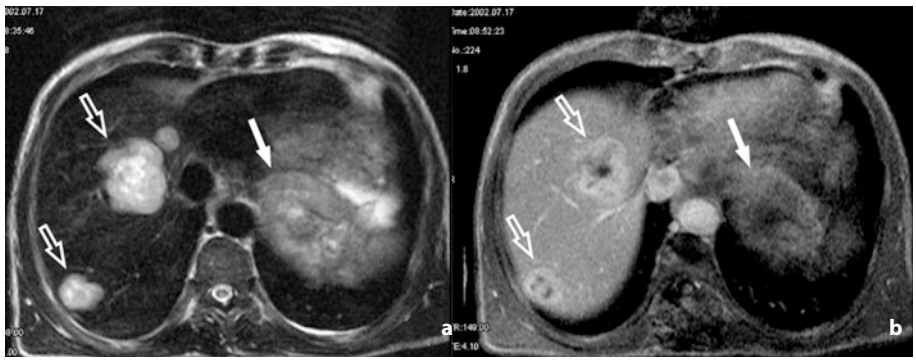

Fig. 7.13 Primary gastric GIST with liver metastases. MR axial TSE T2w (**a**) and axial contrast-enhanced GRE T1w (**b**) images show the presence of a primary gastric GIST (*solid arrow*) and multiple heterogeneous liver metastases (*empty arrows*)

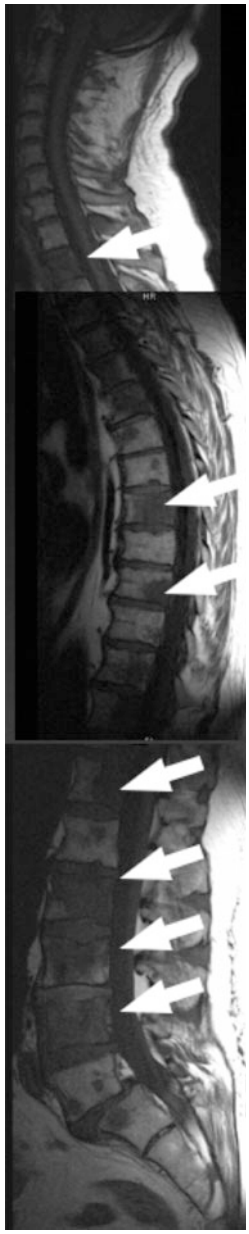

Fig. 7.14 Metastases of GIST to the vertebral column. MR sagittal TSE T1w image of the vertebral column shows multiple hypointense bone metastases (*arrows*)

A limitation of MR in the evaluation of metastases is the technique's low sensitivity in the identification of small peritoneal lesions.

7.5.2 Characterization

The main role in the characterization of GISTs is played by pathologic patterns, even though diagnostic imaging can raise suspicion of a GIST given the site and characteristics of the lesion. When a primary lesion is small it often presents mostly solid characteristics with a variable vascular pattern, whereas when it becomes large and it appears as a mass with well-defined margins, a peripheral hypervascular solid area and a central hypovascular necrotic component (Figs. 7.7, 7.8). Metastatic lesions, and particularly liver metastases, appear as expansive lesions with variable vascular patterns (hypervascular, hypovascular or with areas of central necrosis) (Figs. 7.12, 7.13).

7.5.3 Staging

The possibility of diffuse metastasis makes correct staging of the disease within the abdomen extremely important, giving an advantage to more panoramic diagnostic imaging modalities such as CT and MR. The choice of technique is often related to the geographical diffusion of the imaging systems and the confidence in their use by clinicians, surgeons and radiologists.

7.5.4 Response to Treatment

Diagnostic imaging plays a crucial role in the evaluation of response to treatment [2, 5]. The MR appear-

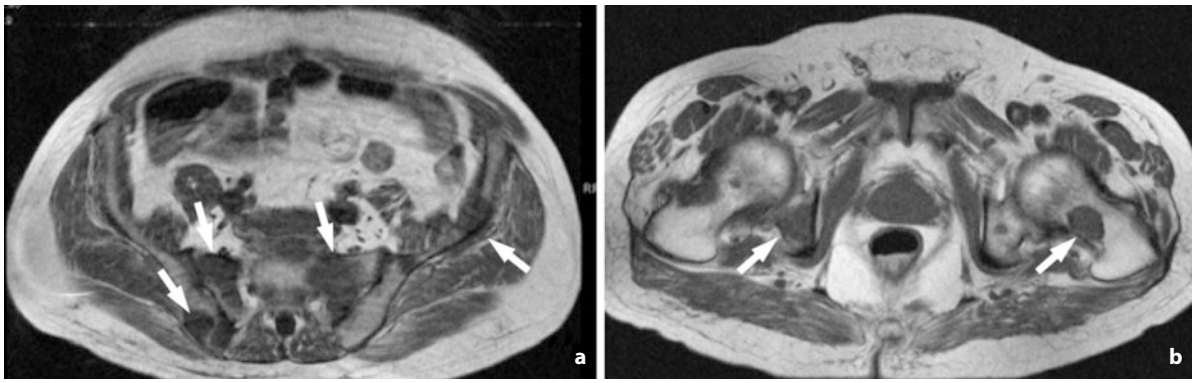

Fig. 7.15 Metastases of GIST to the pelvis and femurs. MR axial TSE T1w images of the pelvis and femurs show multiple hypointense bone metastases (*arrows*)

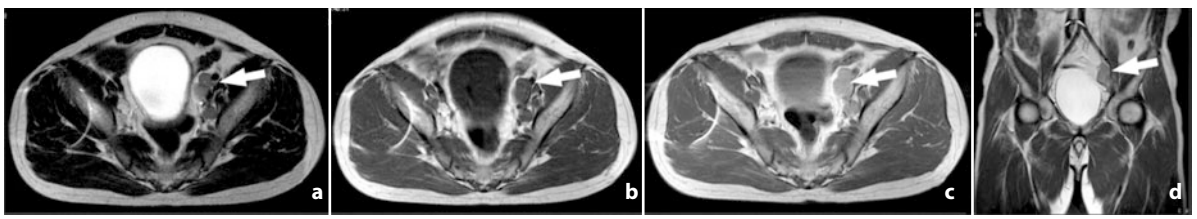

Fig. 7.16 Metastasis of GIST to the lymph nodes. MR axial TSE T2w (**a**) and axial TSE T1w images before (**b**) and after (**c**) administration of contrast medium and coronal contrast-enhanced GRE T1w images (**d**) of some pathologic lymph nodes of the left iliac chain (*arrows*) appearing hyperintense on T2, hypointense on T1 and with moderate contrast enhancement

ance reproduces the tissue changes that molecular target therapy brings about in the neoplastic cells, i.e. the transformation of active tissue into myxohyaline tissue, fibrosis and reduced cellularity or hemorrhagic necrosis.

On T2w sequences the myxohyaline degeneration appears hyperintense, as does any intralesional bleeding.

On T1w and T2w sequences the myxohyaline degeneration produces a low signal, whereas bleeding appears hyperintense due to the effect of products of hemoglobin degradation.

Tissue transformation, i.e the tumor response to medical treatment, is given by a reduction in signal intensity after contrast medium administration.

Classically the tumor response to medical treatment has been evaluated by size criteria, e.g. the response evaluation criteria in solid tumors (RECIST) (Figs. 17, 18) [6].

However, as in other cases it has been seen in GISTs that the size criterion alone cannot provide an objective evaluation of response: in the early months of treatment a "paradoxic" response in terms of tumor size may occur, with stable or even increased size of the tumor due to hemorrhage-necrosis or myxohyaline degeneration (Figs. 7.19-7.21).

Therefore, if the response assessment of GISTs to molecular treatment were limited to the RECIST criteria alone, there would be the risk of underevaluating the response of a significant number of cases, particularly in the early months of treatment.

On the other hand, in subsequent phases most of the tissue responses translate into size responses (Figs. 7.19, 7.20) [2, 3, 5].

Therefore new and more complex parameters for the response to treatment of GISTs with diagnostic imaging were recently proposed, which take into account an evaluation of the reduction of vascularization and the presence of areas of myxohyaline degeneration as well as the simple size criteria (Figs. 7.19-7.21).

A correct interpretation of these parameters with diagnostic imaging requires the use of techniques that enable the evaluation of vascular patterns using intravenous contrast media, such as CT and MR.

In fact new response criteria were recently proposed for CT known as the "Choi criteria" [2, 5]. These define "response" as a reduction in the density

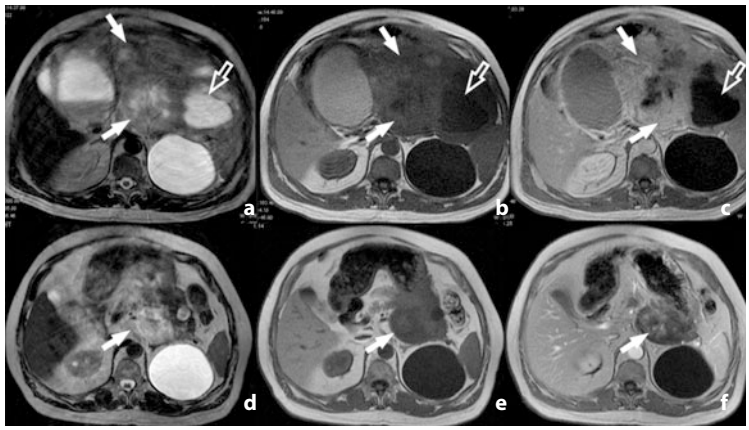

Fig. 7.17 Primary gastric GIST before (**a-c**) and after (**d-f**) treatment with molecular target therapy. MR axial HASTE T2w (**a, d**) and GRE T1w images before (**b, e**) and after (**c, f**) intravenous administration of contrast medium of a large primary gastric GIST. Before treatment (**a-c**) the lesion shows solid vascular areas (*solid arrows*) with medium-low signal on T2 and necrotic areas (*empty arrows*) with high signal on T2s and poor vascularization. After six months of molecular target therapy (**d-f**) a marked reduction in size can be appreciated (RECIST response) associated with a reduction in the active vascular component (myxohyaline degeneration) (*empty arrows*)

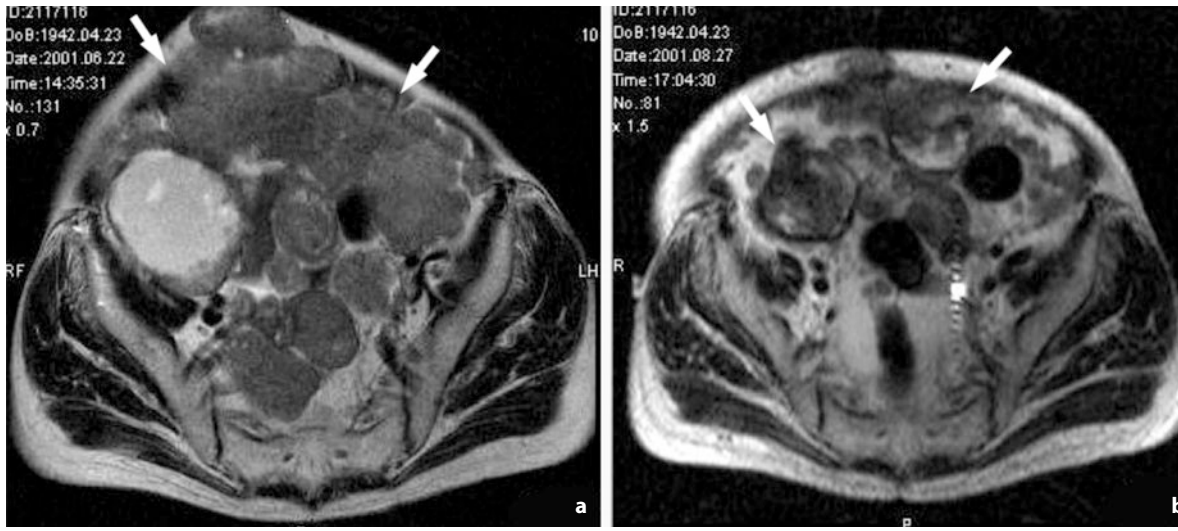

Fig. 7.18 Peritoneal metastasis of GIST before and after treatment with molecular target therapy. MR axial TSE T2w images (**a, b**). Before treatment (**a**) multiple solid peritoneal lesions can be seen (*arrows*) with medium-low signal on T2. After two months of targeted molecular therapy (**b**) a marked reduction in size can be seen (RECIST response)

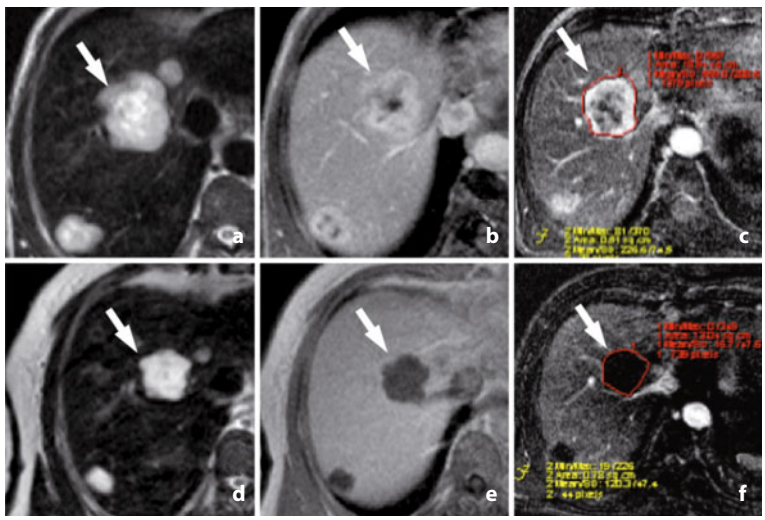

Fig. 7.19 Liver metastasis of GIST before (**a-c**) and after (**d-f**) treatment with molecular target therapy. MR axial TSE T2w (**a, d**), contrast-enhanced GRE T1w images (**b, e**) and images obtained with subtraction technique (**c, f**). Before treatment (**a-c**) multiple liver metastases can be seen with hyperintense appearance on T2, hypointense on T1 and with moderate vascular pattern after contrast medium administration (*arrows*). After three months of molecular target therapy (**d-f**) a reduction in the size of the lesions can be appreciated (RECIST partial response) with evident reduction in vascularization (95%) (**f**) (partial response according to the Choi criteria adapted to MR)

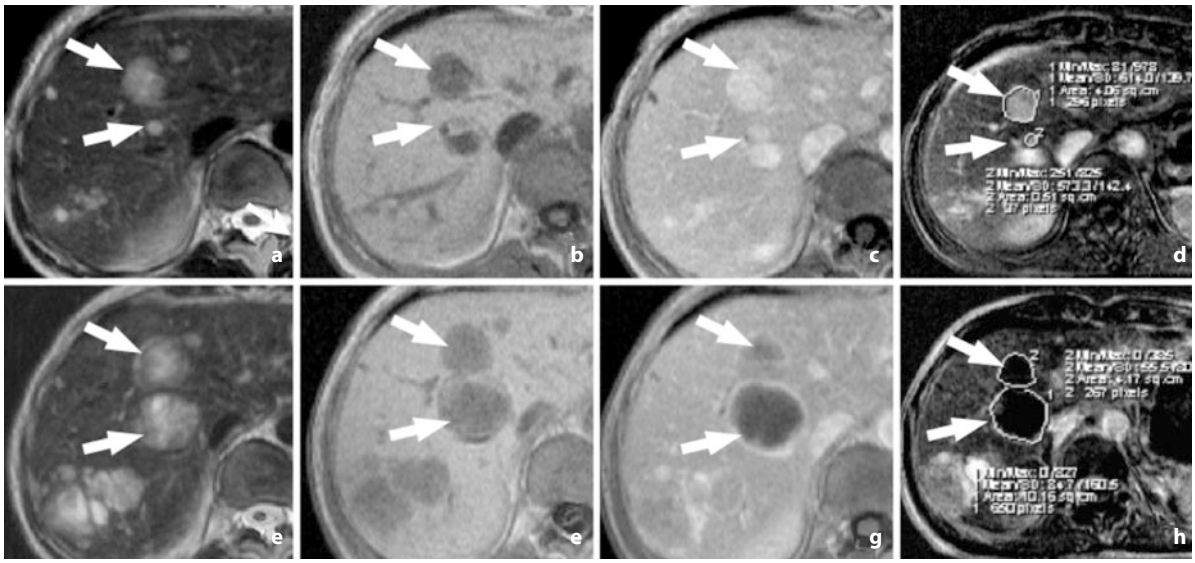

Fig. 7.20 Liver metastasis of GIST before (**a-d**) and after (**e-h**) treatment with molecular target therapy. MR axial TSE T2w (**a, e**) and GRE T1w images before (**b, f**) and after (**c, g**) intravenous administration of contrast medium and images obtained with subtraction technique (**d, h**). Before treatment (**a-d**) multiple liver metastases can be appreciated with hyperintense appearance on T2, hypointense on T1 and with moderate vascularization after contrast medium administration (*arrows*). After four months of molecular target therapy (**e-h**) an increase in the size of the lesions can be seen (RECIST progression) with evident reduction of vascularization (87% and 86%) likely due to myxohyaline degeneration (**h**) (partial response according to the Choi criteria adapted to MR)

of a lesion by at least 15% regardless of whether the size is stable or increased and provide a correct assessment even in cases of "paradoxic response". The new response to treatment criteria defined by Choi for CT can however also be applied to MR. Like CT, MR is able to assess vascular patterns of neoplastic lesions and quantify the reduction in vascularity and the presence of myxohyaline degeneration or hemorrhagic necrosis due to its high contrast resolution and the use of contrast media with both qualitative-semiquantitative (Figs. 7.19-7.21) and quantitative (Fig. 7.22) evaluations [3].

Additional techniques for the MR study in the evaluation of the degree of activity of pathologic tissue have also been recently proposed, such as tissue diffusion techniques (Fig. 7.23).

7.5.5 Complications During Treatment

Complications may occur during the treatment of GISTs with molecular target therapy drugs linked to massive tissue necrosis in cases of response to treatment.

In these cases intratumoral hemorrhage (Figs. 7.24, 7.25), necrosis with overlying infection and consequent abscess formation and perforation (Figs. 7.26, 7.27) can occur. Bleeding is rare and best assessed with MR, which is more sensitive in the identification of intratumoral blood.

In cases of perforation and abscess formation the technique of choice is CT due to its greater spatial resolution and accuracy in identifying gaseous components.

Treatment can also give rise to side effects such as the appearance of peritoneal fluid caused by the retention of liquid produced by imatinib mesylate, which should not be interpreted as a negative prognostic sign (Fig. 7.28).

7.5.6 Secondary Resistance

In cases of secondary resistance diagnostic imaging is able to provide early identification of the presence of active solid tissue into the lesions with the development of a hypervascular nodule within a hypovascular lesion (nodule-in-nodule sign) or the appearance of active perilesional hypervascular tissue (Figs. 7.29, 7.30) [5, 7].

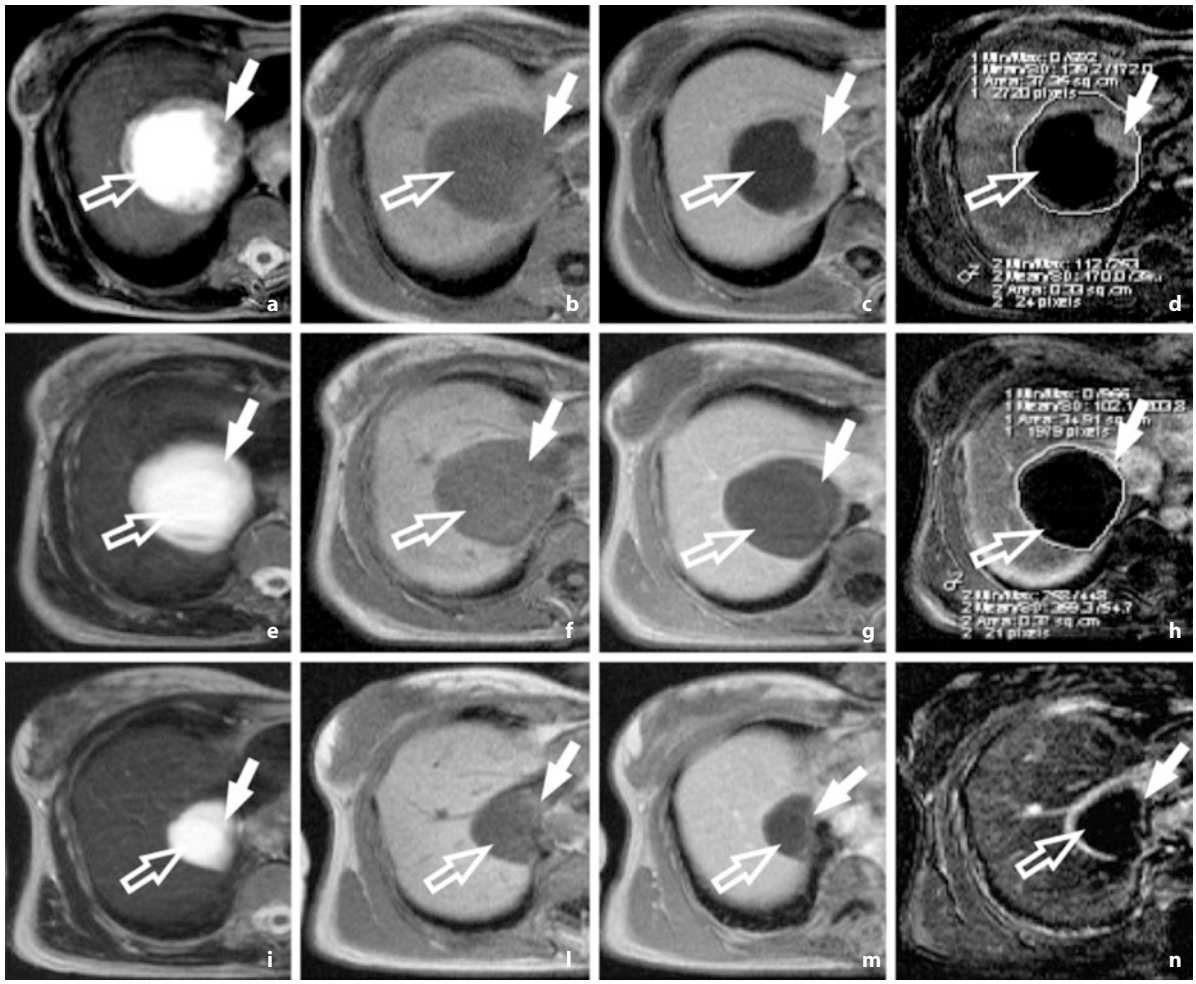

Fig. 7.21 Liver metastasis of GIST before (**a-d**) and after (**e-l**) treatment with molecular target therapy. MR axial TSE T2w (**a, e, f**) and GRE T1w images before (**b, f, j**) and after (**c, g, k**) intravenous administration of contrast medium and images obtained with subtraction technique (**d, h, l**). The images obtained before treatment (**a-d**) show a metastatic hepatic lesion with a peripheral solid portion (*solid arrows*) appearing slightly hyperintense on T2, hypointense on T1 and moderately enhancing after administration of contrast medium, whereas the central necrotic area (*empty arrows*) appears hyperintense on T2, hypointense on T1 without enhancement after contrast medium. After two months of molecular target therapy (**e-h**) the size of the lesion appears relatively stable (stability according to the RECIST criteria) but an evident reduction in vascularization (27%) can be appreciated likely due to myxohyaline degeneration with diffuse signal hyperintensity on T2 (partial response according to the Choi criteria adapted to MR). These data were confirmed at 12 months follow-up (**i-n**), with a moderate reduction in tumor size and in the active tissue

7.6 Conclusions

In conclusion, diagnostic imaging (and particularly CT) is routinely used in the identification and staging of GISTs. During treatment of these lesions with molecular target therapies, MR, together with CT and PET, can be used in the evaluation of response to treatment even in the initial phases, taking care to use not only the size criterion but also to evaluate other signs of activity in the neoplastic tissue such as vascularization and the presence of myxohyaline degeneration or hemorrhagic necrosis. It is therefore important that the radiologist has experience and confidence with the new patterns of response to molecular target therapy in order to be able to recognize the "paradoxic" responses that may occur in the initial phases of treatment.

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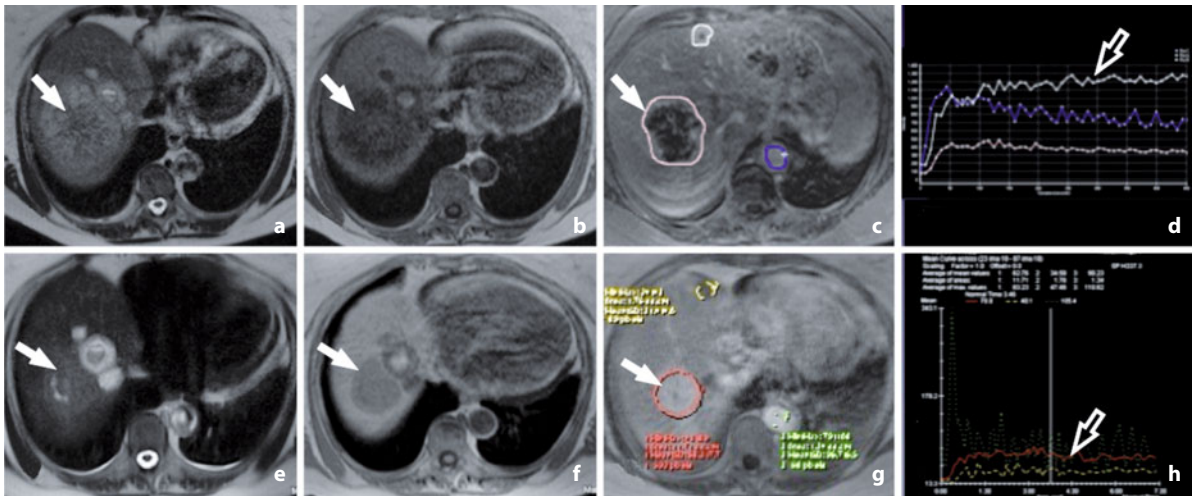

Fig. 7.22 Liver metastasis of GIST before (**a-d**) and after (**e-h**) treatment with molecular target therapy. MR axial TSE T2w (**a,e**) and GRE T1w images before (**b,f**) and after (**c,g**) administration of contrast medium. Functional MR study with contrast intensity–time curves in one of the multiple liver metastases (**d,h**). In the images obtained before treatment (**a-d**) the hepatic lesion appears heterogeneously hyperintense on T2, hypointense on T1 and with heterogeneous enhancement after administration of contrast medium (*arrows*). In the dynamic study the curve of the lesion (*empty arrow*) shows significant wash-in and poor wash-out, indicative of a moderate vascular pattern. After three months of molecular target therapy (**e-h**) a reduction in the size of the lesion and the vascularization can be seen (*arrows*), with a consequent reduction in the slope of the contrast intensity–time curve (*empty arrow*) in the functional evaluation (**h**)

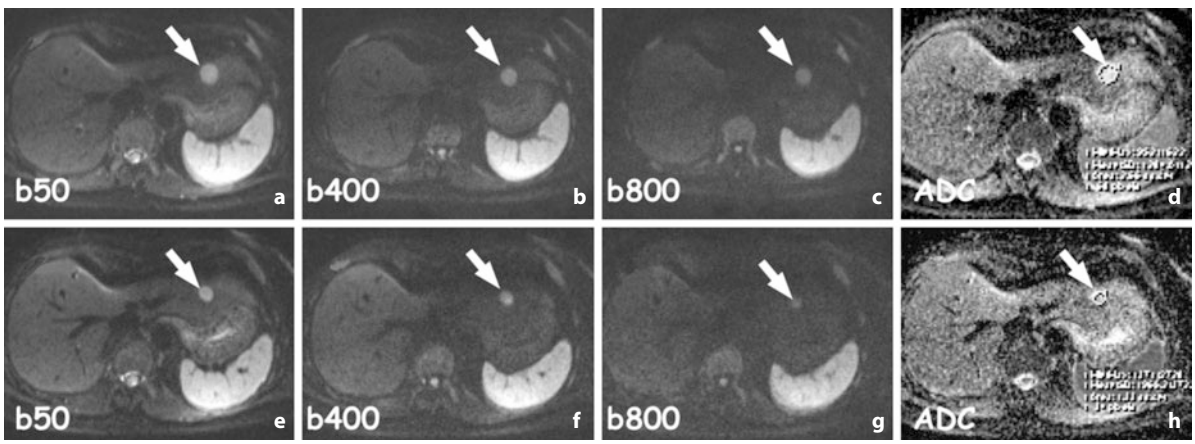

Fig. 7.23 Liver metastasis of GIST with DWI tecnique before (**a-d**) and after molecular target therapy (**e-h**). The axial DWI images before treatment (**a-c**) show high signal of the lesion located in the II liver segment (*arrows*). After treatment the DWI images show a reduction in size of the lesion (response according to RECIST criteria) associated with a reduction in the signal hyperintensity of the images obtained with high b-value (**g**). The ADC maps shows an increase in the values going from 1.3x10-3 before treatment (**d**) to 2.1x10-3 (**h**) indicating a reduction in cellularity and therefore a response to treatment

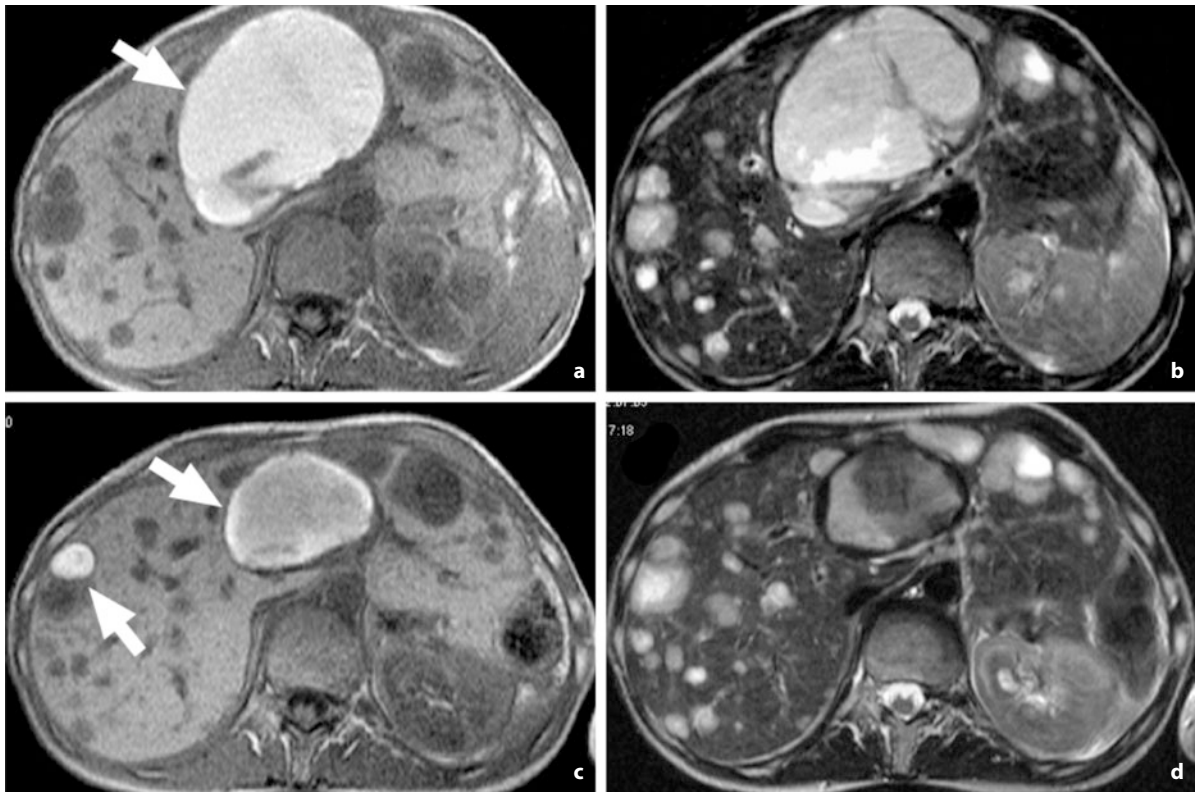

Fig. 7.24 Liver metastasis of GIST (intratumoral bleeding after treatment with molecular target therapy). Multiple liver metastases from GIST in MR axial nonenhanced GRE T1w (**a, c**) and TSE T2w images (**b, d**) after treatment with molecular target therapy. The high signal intensity of the lesions on the T1w images shows the presence of blood components due to recurrent bleeding (*arrows*)

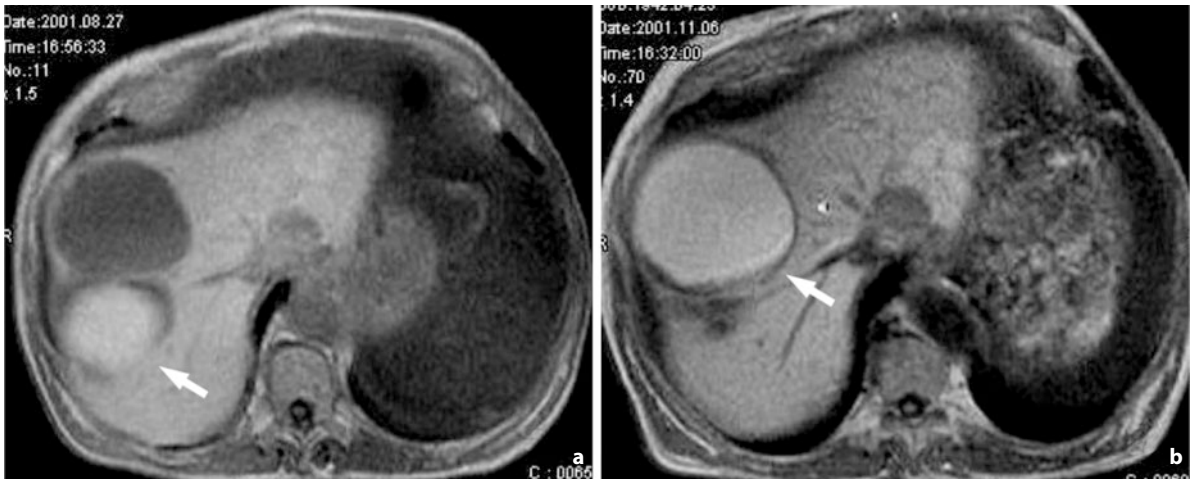

Fig. 7.25 Liver metastasis of GIST (intratumoral bleeding during treatment with molecular target therapy). Multiple liver metastases from GIST in baseline MR axial GRE T1w (**a, b**) images during treatment with molecular target therapy. The high signal intensity of the lesions on the T1w images shows the presence of blood components due to recurrent bleeding (*arrows*)

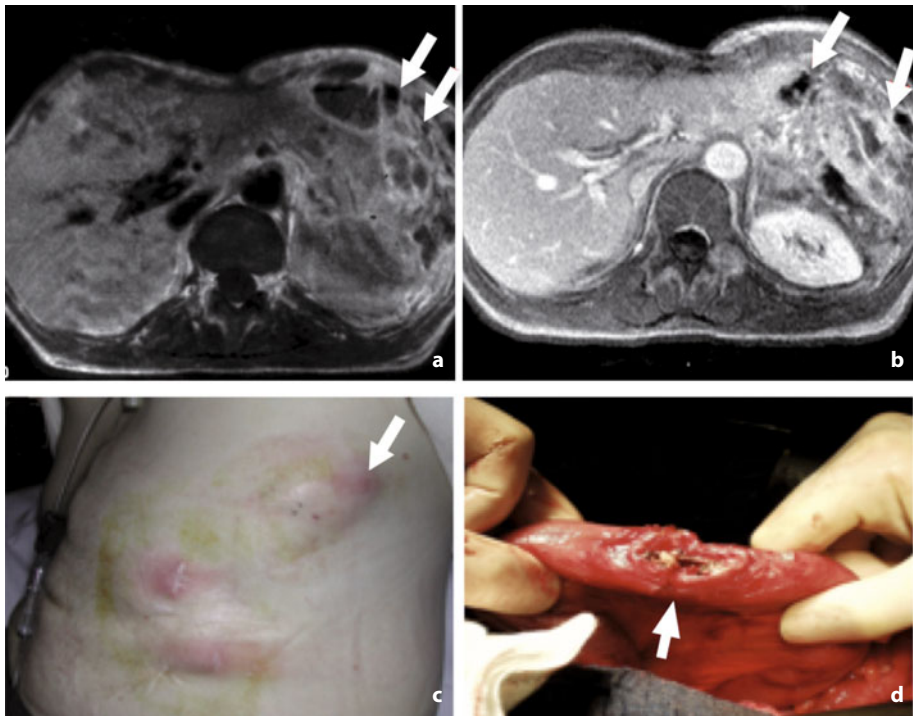

Fig. 7.26 Peritoneal metastasis from GIST treated with molecular target therapy. The MR axial GRE T1w images before (**a**) and after (**b**) intravenous administration of contrast medium show areas of no signal (*arrows*) indicating gas bubbles due to perforation of the bowel loops. Distension of the abdominal wall (**c**) and surgical specimen (**d**)

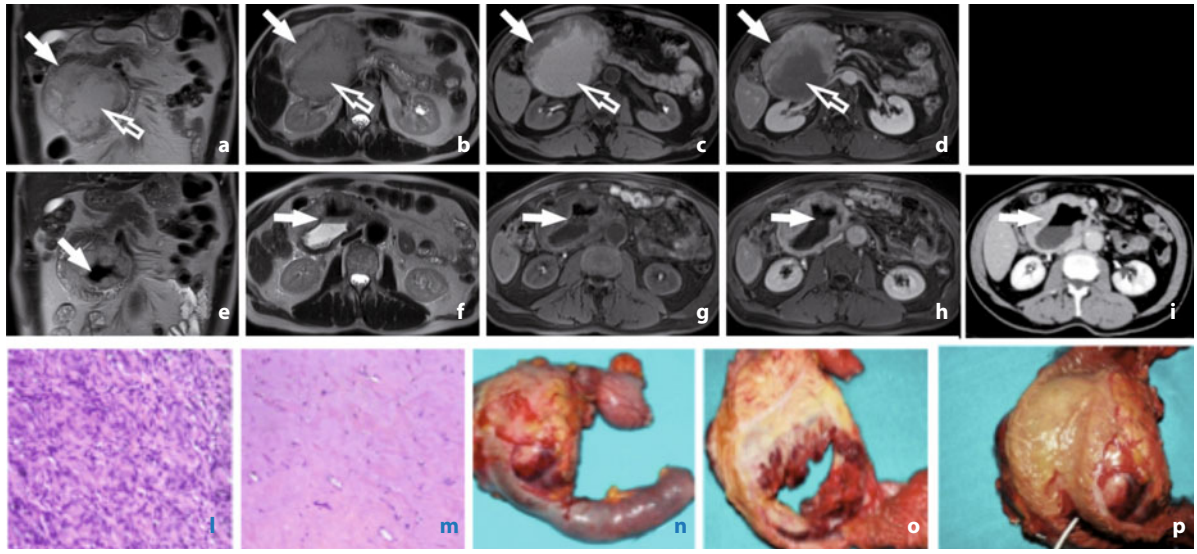

Fig. 7.27 Primary duodenal GIST after treatment with molecular target therapy. MR coronal TSE T2w (**a, e**) and axial TSE T2w images (**b,f**) and GRE T1w images before (**c, g**) and after (**d,h**) intravenous administration of contrast medium before and during treatment with molecular target therapy. The images obtained before treatment (**a-d**) show a solid peripheral portion appearing slightly hyperintense on T2, hypointense on T1 and moderately enhancing after administration of contrast medium (*solid arrows*), whereas the central necrotic area appears moderately hyperintense on T1 and on T2 without enhancement (*empty arrows*). The MR (**e-h**) and CT images (**i**) obtained after treatment show necrosis of the lesion, with perforation and later overlying infection confirmed by surgery (**n-p**). The pathology images show a marked reduction in the cellularity between the biopsy, performed before treatment (**l**) and the postoperative pathology findings after treatment (**m**), indicating response to treatment

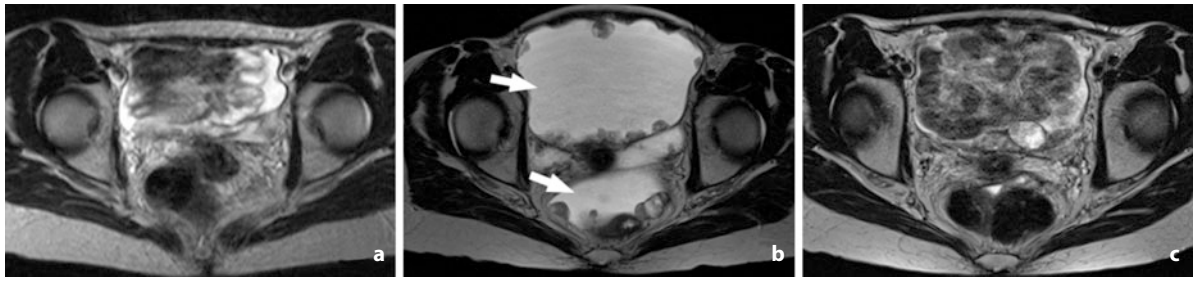

Fig. 7.28 Peritoneal metastases from GIST (development of peritoneal fluid during treatment). The MR axial TSE T2w image obtained after four months of treatment (**b**) shows the presence of peritoneal fluid in the pelvis (*arrows*) due to liquid retention, which had been reabsorbed in the subsequent examination after six months (**c**), and therefore should not be considered a negative prognostic sign

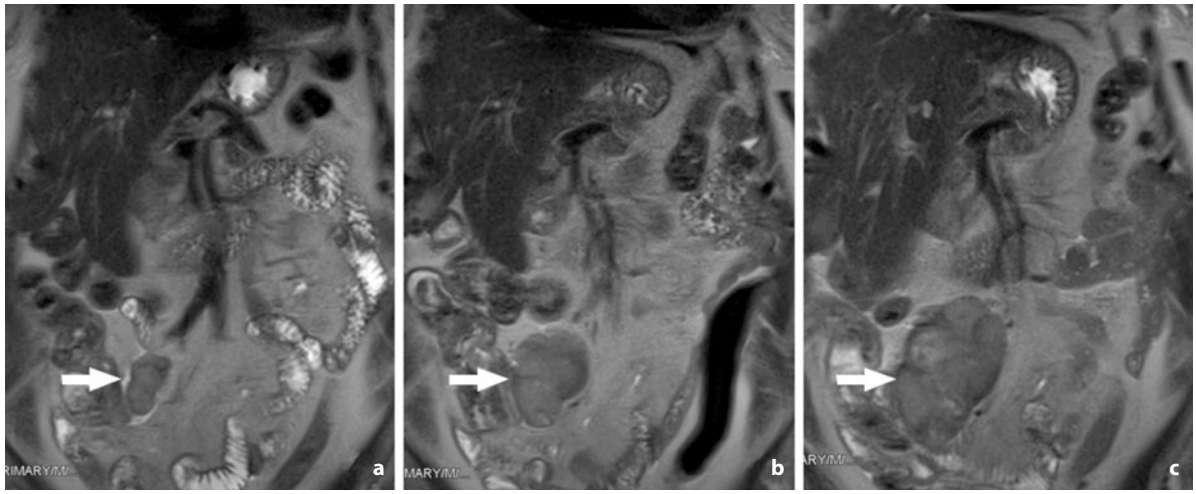

Fig. 7.29 Local recurrence of primary GIST of the small bowel. MR coronal TSE T2w images (**a-c**). The MR images show local recurrence in the mesenteric intestine (**a**) which has increased in size in the following controls performed at three months (**b**) and six months later (**c**) (*arrow*)

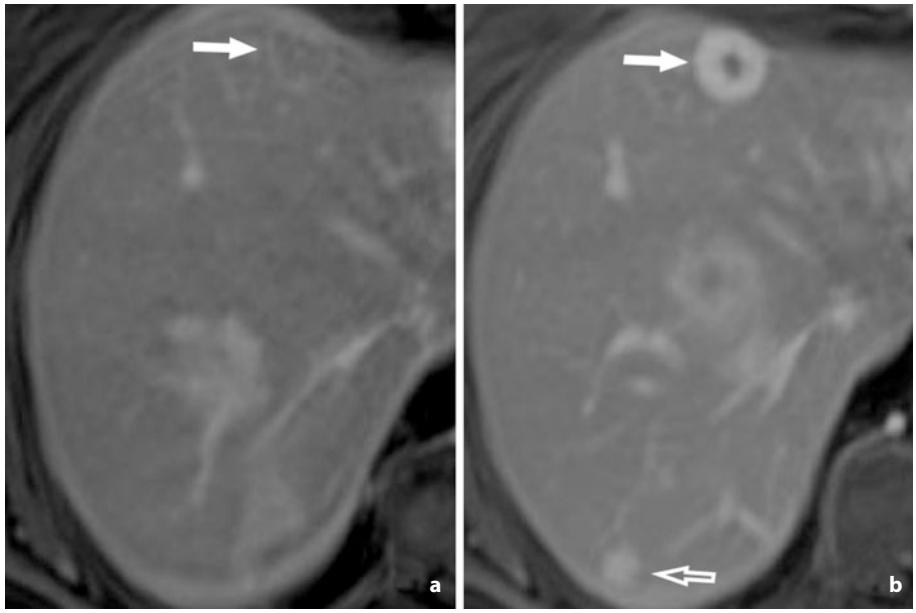

Fig. 7.30 Secondary resistance during treatment of liver metastases from GIST with molecular target therapy. MR contrast-enhanced axial fat suppressed GRE T1w images obtained in the early phase (**a**) and 12 months (**b**) after treatment. MR imaging control at 12 months showed an increase in size and vascularization of the lesion located at the IV segment (*solid arrow*) and the appearance of a new hypervascular lesion at the VII segment (*empty arrow*), due to development of secondary resistance to the treatment with molecular target therapy

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Contrast-enhanced PET/CT in the Follow-up of GISTs

8

Ennio Biscaldi, Arnoldo Piccardo and Gian Andrea Rollandi

Abstract Today, PET/CT is an essential diagnostic tool in the clinical assessment of GIST, mainly during follow-up. PET/CT is sensitive in the early detection of the pharmacological response to Imatinib Mesylate and it is specific in the follow-up of metastatic disease.

In 2004, Choi demonstrated that the information deriving from Multidetector CT (MDCT) and PET are complementary in the evaluation of GIST's response to medical treatment. He showed a correlation between the enhancement intensity of the lesions after iodinated contrast medium (c.m.) injection, estimated in Hounsfield Units (HU), and the 2-[fluorine-18]fluoro-2deoxy-D-glucose(^{18}F-FDG) uptake, measured with the SUV (Standardized Uptake Value).

These concepts, joined with Van den Abbeele's concerns, determined a new version of the criteria used to demonstrate a 'good response' of GIST to the therapy. In 2007, Choi's criteria for the evaluation of GIST were recognized as being more predictive (in terms of TTP, time-to-progression) than the RECIST criteria.

Recently an increased number of publications in the literature revealed the improved clinical use of injected PET/CT. The evaluation of tomodensitometric parameters in residual disease (detection of density or vascularisation modifications, dimensional variations), combined with metabolic parameters (increased/decreased metabolic activity), allows an affordable diagnostic assessment of GIST.

In this chapter our goal is to describe the technique and clinical indications for the use of injected PET/CT in restaging after surgery and/or therapy.

The PET/CT technique does not cause a significant increase in examination costs if related to the clinical advantages.

The combined examination may reduce imaging costs if implemented with other diagnostic resources for GIST assessment (MDCT and MRI) and it requires a synergy between radiology and nuclear medicine in diagnostic performance.

Keywords PET/CT • Iodinated contrast medium • GIST

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E. de Lutio di Castelguidone, A. Messina (eds.), *GISTs – Gastrointestinal Stromal Tumors*.

Multidetector computed tomography (MDCT) is the most widely available and used imaging modality in the follow-up of sarcomas and in particular in the re-evaluation of gastrointestinal stromal tumors (GISTs). The international response evaluation criteria in solid tumors (RECIST) have identified in MDCT and magnetic resonance (MR) the most appropriate diagnostic examinations in oncology for the evaluation and monitoring of "target" lesions during treatment [1].

In addition, in the follow-up of GISTs, after surgery or in the case of medical treatment, positron emission tomography (PET) has joined these imaging modalities as an essential diagnostic tool. PET is sensitive in the early evaluation of the response to imatinib, and in follow-up can identify patients with metastatic disease [2]. Recent and important technological developments have seen PET/CT replace PET and its use is becoming more widespread thanks to the increasing availability of these hybrid systems.

8.1 Response Assessment after Medical Treatment

Contrast-enhanced MDCT is an effective and reliable diagnostic tool in the follow-up of GISTs [3]. After medical therapy the responding tumor changes size becoming smaller [4], although in some cases it can become larger (as a result of intratumoral hemorrhage, necrosis or myxoid degeneration), which is why the RECIST criteria are not applicable to GISTs [5-7]. The histologic changes of the tumor produce an overall reduction in density and the part of the tumor characterized by iodinated contrast enhancement tends to disappear. Therefore, changes occur in the responding tumor with respect to density, enhancement and size. The morphologic characteristics of these alterations do not always respect the convention, i.e. disease recurrence does not always involve an increase in the size of the lesions, the response does not always involve a reduction in the maximum diameters of the tumor. This is why MDCT is not very specific in identifying the most important pathologic modification to be detected: the disease recurrence, if only the RECIST criteria are used.

The first real identifiable sign with MDCT which reliably indicates disease recurrence was described in an interesting study published in Radiology in 2005. The nodule-within-a-mass sign indicates the presence of enhancement in a liquefied or markedly hypoattenuating lesion, and is indicative of focal reactivation of disease [8].

These observations indicate that the MDCT signs of response to treatment and disease recurrence include several exceptions. This is why the MDCT study, associated with the metabolic and functional evaluation, is the most complete and reliable technique in the diagnosis of GIST.

In 2007 Benjamin demonstrated that the criteria used by Choi, which take into consideration changes both in size and density of the lesions, correlate with a good PET response [9]. In addition, they are much more predictive in relation to TTP than the simple RECIST diagnostic criteria. Indeed the Choi criteria consider parameters fundamental to the evaluation of GISTs during treatment with imatinib, thus confirming the need to "desist from using RECIST" [9, 10].

A less recent study [6] showed that PET is sensitive in the identification of early response to treatment with imatinib and in identifying the long-term response in patients being treated for metastatic GIST. The intratumoral changes during treatment with Gleevec can be seen in the first 24 h after a single dose of the drug [11].

In the case of an evaluation done with MDCT alone, the changes induced by disease recurrence may require several weeks to be adequately appreciated [11]. This is why PET and even more so PET/CT are ideal in the follow-up of treated GISTs.

In a study published in 2004, Choi demonstrated the complementary nature of MDCT and PET information, consisting respectively of the degree of lesion enhancement (measured in Hounsfield Units [HU]) and the uptake of ^{18}FDG (measured by the Standardized Uptake Value [SUV]) [4]. The conclusions of the study demonstrated the presence of a correlation, in terms of response to treatment, between enhancement measured in HU and maximum SUV (SUVmax) measured in PET. This type of observation, together with those of Van den Abbeele, Badawi [6] and Antoch [7] suggest a reformulation of the criteria for "good response" to treatment of GISTs: there needs to be a 70% decrease in absolute SUV measured in the lesion with respect to baseline or an absolute fall in SUVmax below 2.5.

Over the past five years, the exponential increase in the clinical applications of PET/CT has seen a flurry of scientific papers whereby diagnostic imaging has been implemented with PET/CT combined with the

injection of iodinated contrast medium during the MDCT phase of the examination.

The studies by Antoch have been indispensable as they have shown that the use of iodinated contrast medium together with the PET examination does not cause anomalies in the metabolic registration, nor does it influence their diagnostic validity [10].

8.2 Rationale for the Use of Contrast-enhanced PET/CT

The studies published in the literature up until 2008 demonstrate that MDCT and PET have the ability to identify and monitor a variety of parameters which effectively indicate the response to treatment with imatinib or the progression of disease despite the use of imatinib or second-line drugs (sunitinib). The combination of CT parameters for the evaluation of residual disease (changes in density, vascularity and size), associated with metabolic parameters (decrease/increase in glucose metabolism), enable a reliable diagnostic assessment.

The guidelines suggested by the European Society for Medical Oncology and the American National Comprehensive Cancer Network justify the use of PET/CT as a "problem-solving" diagnostic technique [12, 13], whenever other imaging modalities fail to be conclusive. In the following sections we describe the use of contrast-enhanced PET/CT as a follow-up study for GISTs, based on the experience developed in five years of follow-up in a group of patients studied repeatedly with this technique.

8.3 Study Technique

The contrast-enhanced PET/CT study is not radically different from the conventional PET/CT protocol. The study begins with the standard MDCT acquisition which has the purpose of mapping the attenuation for subsequent PET registration.

The second part of the examination, with the patient in the same position, consists of the registration of the full-body PET map.

At the end of this phase the contrast-enhanced MDCT acquisition is performed. The study requires that the MDCT examination has the same extension as the PET map to allow the images to perfectly overlap the metabolic map, thus allowing image reconstructions and postprocessing at workstations.

The injection of contrast medium is done with a mechanical injector. The availability of a dual-head injector to allow the ideal combination of contrast and physiologic solution (saline flush) is a considerable advantage in the management of the flow of iodinated contrast. However, in its absence the need to combine the contrast medium and saline solution in a single syringe does not compromise the success of the examination.

The quantity of iodinated contrast medium to be injected should be calculated as for a standard MDCT examination [14].

The injection phases are established in accordance with the clinical query and the characteristics of the MDCT examination are defined regardless of the metabolic information. The need to perform a dual-phase study of the liver parenchyma will require an early CT acquisition (arterial phase) with regard to the injection of iodinated contrast medium and a subsequent acquisition in the portal phase. The portal-phase acquisition will have a craniocaudal extension comparable to that of the PET map.

The dual-phase study of the liver parenchyma may be indicated in the evaluation of metastatic GISTs, a situation that requires the most complete study technique possible. The early study phase is late arterial and is followed by the portal-venous evaluation.

In order to correctly manage the injection times the use of a method for monitoring the increase in the concentration of contrast medium in the aorta is indispensable. This will not only guarantee the precision of the late arterial phase but also the technical success of a particularly extensive study which goes from the head to the distal third of the femoral shafts.

The flow intensity of the contrast medium and the saline solution when present is the same as that used in a standard MDCT examination, and strictly depends on the type of venous access available. An ideal mean flow rate is between 3 and 4 cc/s in the case that this type of measure is still used, otherwise a flow rate of 1.0-1.2 grams of iodine per second needs to be calculated. The use of grams of iodine per second to measure the quantity of contrast medium injected is helpful to select the type of contrast medium with freedom in relation to the concentration of iodine, wich tends to vary between products. The choice of the type of contrast medium to use follows the same principles as

those for establishing which iodinated contrast medium to use in a traditional MDCT examination for oncologic evaluation. High concentrations are mainly used in studies that give preference to vascular evaluation, whereas the study of GISTs with PET/CT has no special clinical requirements dedicated only to the vessels and can therefore benefit from a contrast medium with concentrations between 350 and 370 mg I/mL. Products with lower iodine concentrations require greater flow rates, expressed in grams of iodine per second.

The technical parameters expressed in kV and mA are the same as those used in a conventional MDCT examination of the neck, thorax and abdomen. The presence of the radiopharmaceutical does not modify tissue attenuation and the MDCT study is similar to all other examinations not coupled with PET and done with a normal MDCT system.

The choice of fundamental parameters for the management of the examination, such as acquisition slice thickness and reconstruction interval, are closely correlated with the number of MDCT scanner detectors used in the hybrid system. Currently the MDCT scanners available in nuclear medicine systems have at least sixteen detector-rows, even though 64-row MDCT scanners used in these systems are becoming progressively more widespread, thus modifying the choice of technical parameters that were available when these high performance devices first became available in radiology.

The images are normally postprocessed at the workstation and the widespread diffusion of filmless radiology has made it possible to process images directly from the picture archiving communication system (PACS).

8.4 Indications for the Use of Contrast-enhanced PET/CT

8.4.1 Perioperative Staging

The combination of PET and contrast-enhanced MDCT in the study of GISTs, as with the evaluation of other diseases where the technique is currently used [15, 16], brings together the advantages of the two imaging modalities, multiplies their benefits and demonstrates how the two techniques are highly complementary.

The association of the two modalities improves the

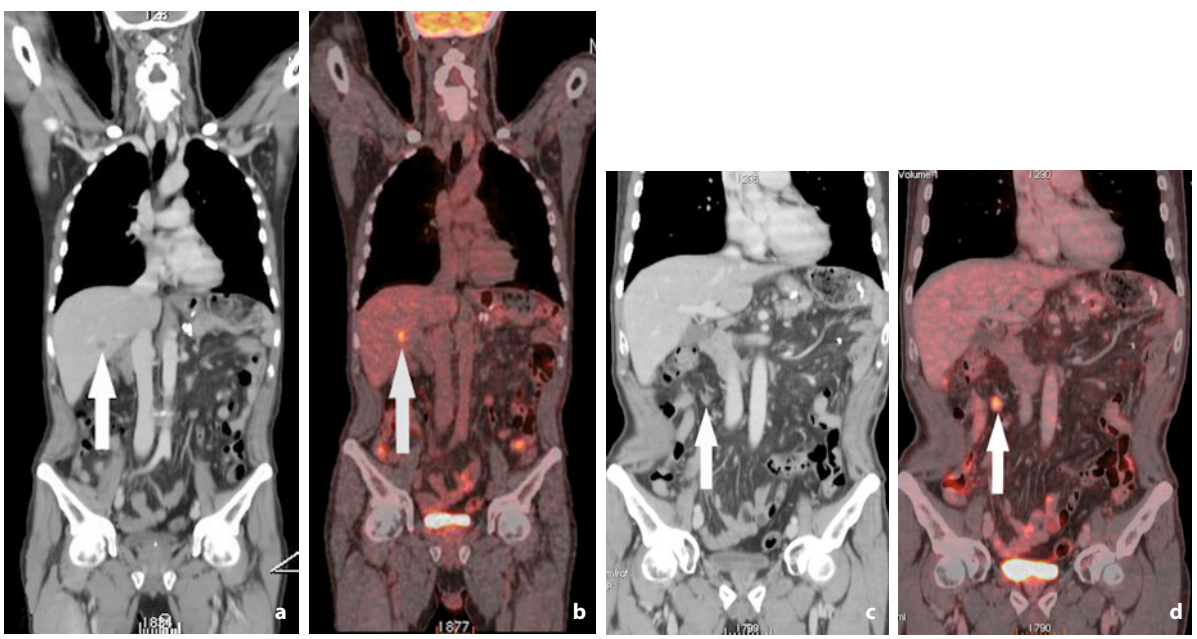


Fig. 8.1 **a-d** Coronal reconstruction of contrast-enhanced PET/CT examination. **a, c** Coronal MDCT images. **b, d** Hybrid images of PET/CT fusion in a patient operated upon for small bowel GIST. **a, b** PET/CT study performed postoperatively identifies a small metabolically active hepatic hypodensity interpreted as a metastatic lesion from GIST in the right hepatic lobe (*arrow*). **c, d** In the coronal image (**c**) the arrow indicates a small peritoneal nodule which is indistinguishable except for the finding visible on the hybrid image (**d**). In **d** the arrow indicates the small nodule, site of hypermetabolism (SUV>5), consisting of a peritoneal metastasis, unrecognized at the recent surgical procedure

sensitivity and specificity of the hybrid technique over the two techniques considered separately, and improves the overall accuracy of the study of GISTs in the different phases of the disease (preoperatively, after treatment and in the subsequent phases of follow-up of metastatic disease) [11].

Contrast-enhanced PET/CT is able to identify more lesions even at the first examination [7]. It is therefore possible to visualize more lesions from the beginning of staging with an increase in sensitivity and specificity of the study that continues into each phase of follow-up. The fusion of the metabolic and anatomic images enables the surgeon even to visualize lesions that may have been underevaluated intraoperatively (Fig. 8.1).

In Italy the few guidelines available that suggest the clinical indications for the use of PET/CT do not contemplate the use of iodinated contrast medium, rather they establish general clinical indications for the use of the technique. PET/CT is still today considered a "suggested" technique in staging of a metastatic GIST or in case of therapy with imatinib mesylate. Contrast-enhanced PET/CT has all the advantages of both contrast-enhanced MDCT and PET and has a greater diagnostic power than MDCT alone. It already has a role in the preoperative staging of disease, even though in this particular phase a delicate clinical problem emerges: GISTs characterized by very low metabolic activity may be encountered, precisely at the initial diagnosis. The result is that their PET map shows no pathologic uptake of the ^{18}FDG. This creates an important difference between the diagnostic outcome of the metabolic map which shows no sign of active disease and the contrast-enhanced MDCT study which can identify well-defined lesions. An example of this situation is given in Figure 8.2. The gastric lesion is easily identified in the contrast-enhanced MDCT images, but the metabolic map fails to identify significant pathologic activity in the well visualized lesion. This can create difficulties in interpretation.

The literature describes low-metabolism GISTs which render the indication of PET in evaluation of the lesion extremely relative, precisely because it is unable to provide sufficient information with regard to low-metabolism lesions.

In initial staging, therefore, PET/CT can provide important information in cases of disease characterized by intense metabolism, but it may also provide misleading information in cases where the lesion has no intense uptake of the radiopharmaceutical and can only be identified by MDCT.

This of course should not detract from the fact that the metabolic map can provide fundamental clinical information even at the initial diagnosis of disease. Contrast-enhanced CT in turn is able to identify the

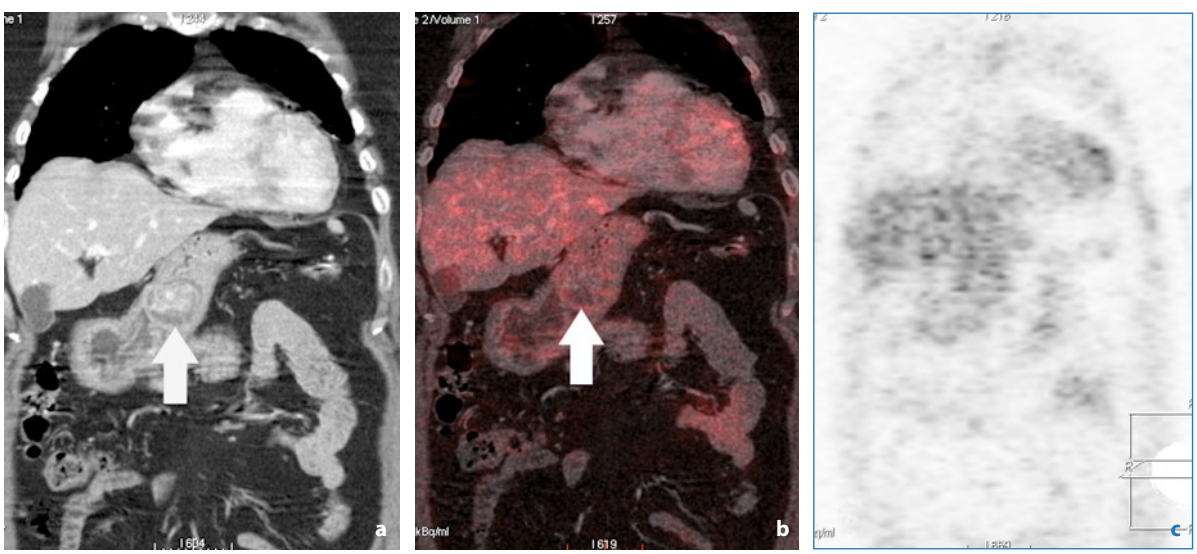


Fig. 8.2 a-c Coronal reconstructions of contrast-enhanced PET/CT acquisition. In **a** the arrow indicates an expansive gastric lesion identified at gastroscopy. The submucosal site of the lesion can be appreciated in the image. In **b** the lesion has no metabolism of its own and is visible only thanks to the contrast-enhanced CT. The metabolic map confirms the absence of demonstrable pathologic metabolism in the stomach (**c**)

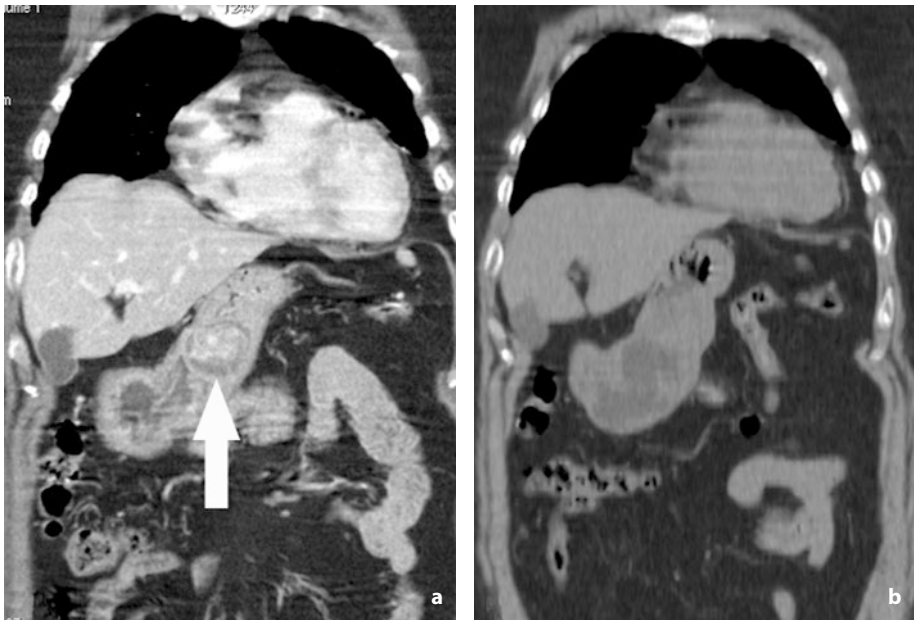


Fig. 8.3 a, b Coronal reconstructions of PET/CT acquisition. The same patient as Figure 8.2. **a** The coronal reconstruction of the contrast-enhanced acquisition shows the gastric lesion. **b** In the non-enhanced image, performed only for the attenuation map, the lesion is not visible. At surgery the diagnosis was of gastric GIST

lesion providing information which the non-enhanced MDCT study would nonetheless be able to provide (Fig. 8.3). At the same time the limited metabolic activity documented by PET provides useful information for the entire follow-up of the patient.

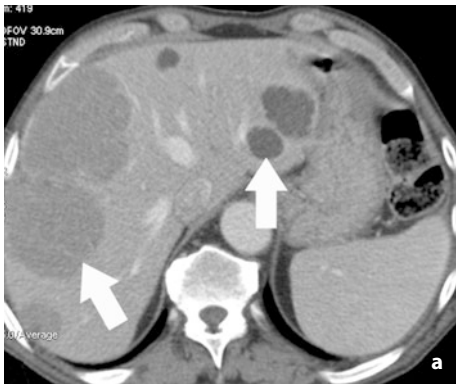
8.4.2 Staging During Treatment with Imatinib Mesylate

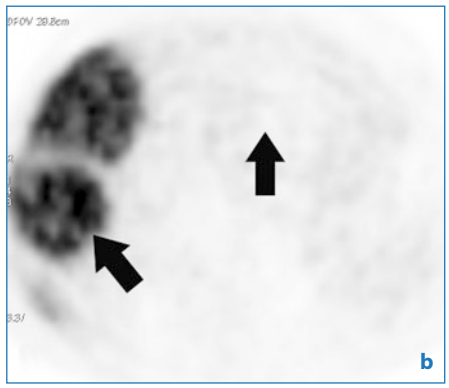
Each time PET/CT is re-used in follow-up it's important to remember the metabolic characteristics of the original lesion. Before any treatment should be recalled if a prior PET/CT examination is available. The possibility of comparing examinations, in case of disease progression, strengthens the diagnostic role of this technique.

Lesions that constitute residual disease are readily identifiable and their enhancement or degree of residual metabolic activity, if present, can be evaluated (Fig. 8.4). The functional map constantly monitors residual metabolism. In the case of recurrence, metabolic reactivation is an early finding with respect to an increase in size or an increase in enhancement even if the lesion remains hypoattenuating after the intravenous injection of iodinated contrast medium. The variation in size of the lesion is in fact often ambiguous. MDCT is a diagnostic technique with low sensitivity or low specificity in the case of large residual lesions where it is difficult to understand which are the significantly changed diameters for recognizing the presence of recurrence, while in the case of numerous abdominal lesions it is difficult to understand which is the site of disease recurrence. Nonetheless situations can arise where the change in size is much slower than the metabolic change (Fig. 8.5). Therefore, in cases of clinical suspicion of disease recurrence or where there are indirect signs of recurrence, performing a contrast-enhanced PET/CT study can provide early metabolic information which the contrast-enhanced MDCT examination alone is unable to produce.

8.4.3 Evaluation of the Liver

According to the literature, metastases from GISTs to the liver have a tendency towards hypervascular behavior [17]. Therefore, in order to provide a complete picture of the disease, a dual-phase study of the liver should be performed with extension of the MDCT acquisition to the neck, thorax and abdomen in the portal phase, retracing the PET map as described above. Treatment with imatinib produces two important consequences which are observable in the liver. This first occurs during treatment, when some patients apparently develop new hepatic lesions. The lesions have a cystic or at any rate hypoattenuating appearance and can vary in size, sometimes being small in diameter or much larger. If the conventional criteria for the evaluation of





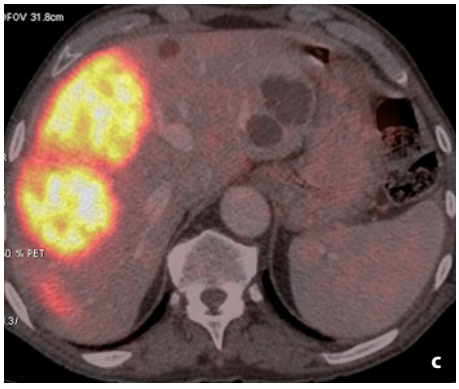
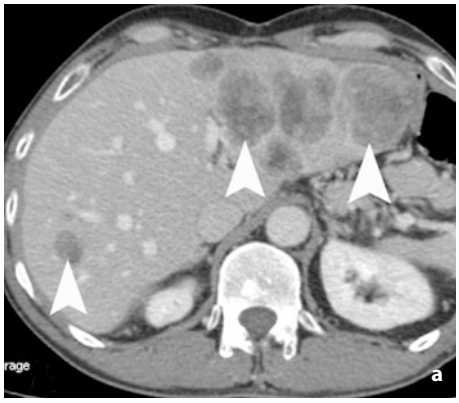
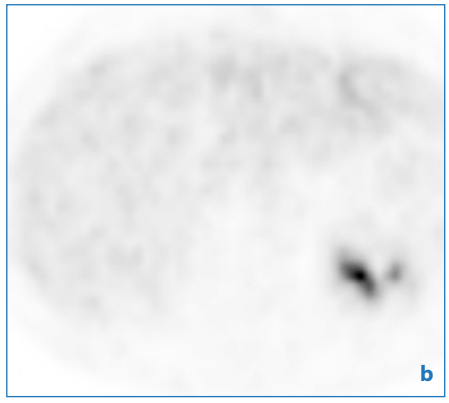


Fig. 8.4 a-c Axial scans, contrast-enhanced PET/CT study. Patient with ileal GIST being treated with imatinib mesylate. In **a** the *arrows* indicate liver metastases from GIST. The lesions in the left lobe appear hypoattenuating and to be responding to treatment, whereas the isoattenuating lesions in the right lobe are not responding to the drug. **b** The corresponding PET acquisition. The larger lesions in the right lobe confirm active metabolism (SUV>6), whereas the *black arrow* in the left lobe indicates the absence of metabolism in the responding metastatic lesions. The fusion of the previous two images (**c**) identifies the metabolically active lesions in the right lobe, whereas the hypoattenuating lesion in the left lobe are not the site of active disease





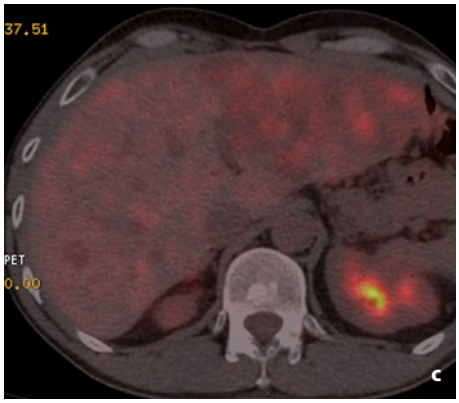
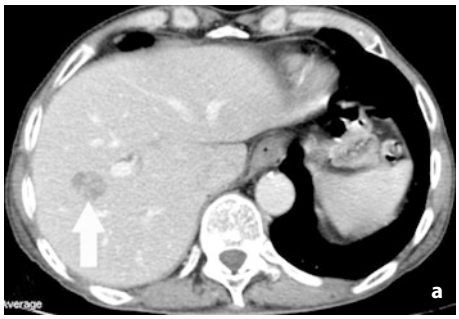


Fig. 8.5 a-c Axial scans, contrast-enhanced PET/CT study. Patient with ileal GIST being treated with imatinib mesylate. In **a** the *arrowheads* indicate liver metastases which appear iso-hypoattenuating to the liver parenchyma. The treatment with imatinib is extremely recent and the response to the drug is confirmed by the corresponding PET map (**b**), and in the hybrid fusion image (**c**) the uptake of the radiotracer is not significant (SUV<1.5)



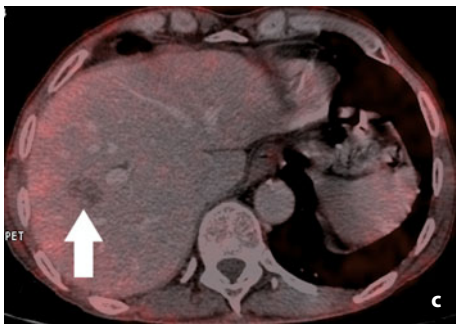
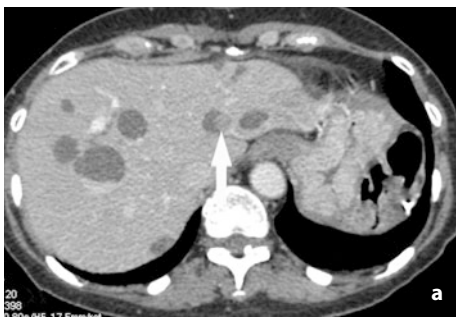
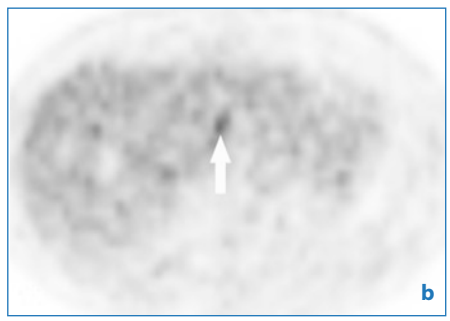


Fig. 8.6 a-c Axial scans from contrast-enhanced PET/CT study in patient with resected gastric GIST. Single phase contrast-enhanced study: MDCT acquisition in the portal phase. Follow-up at six months, patient being treated with imatinib mesylate. In the CT image (**a**) an inhomogeneously enhancing nodular lesion can be seen in the right lobe. The lesion cannot be visualized in the PET map (**b**) and has no positive metabolism (**c**). The lesion appears unchanged in the subsequent examination, repeated three months later (not shown). The lesion is a small capillary hemangioma with atypical contrast enhancement





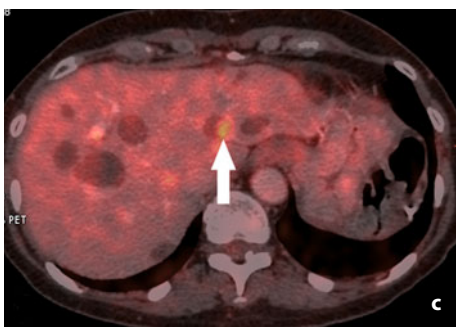


Fig. 8.7 a-c Contrast-enhanced PET/CT in a female patient operated on two years earlier for ileal GIST. She has known metastases. Currently there is suspicion of disease progression. The numerous hepatic nodules are inhomogeneous and moderately hypoattenuating as a result of imatinib mesylate treatment at the time of the examination. The white arrow indicates a nodule which appears to have the nodule-within-a-mass CT sign (**a**). The metabolic map (**b**) and the image derived from the fusion of **a+b** (**c**) confirm the hyperactivity at the level of the indicated nodule, site of disease progression

oncologic response are used (RECIST / WHO), these patients should be considered to have disease recurrence, but in contrast to this initial impression, these patients, at least with regard to the liver, are responding to treatment. Joensuu et al. [18] were the first to observe the initial transformation of these lesions after imatinib mesylate: they became completely hypodense. However the important observation was also made with MDCT [4] when small cystic-like hypoattenuating areas were described that were only visible after the beginning of treatment. The explanation is that occasionally these small lesions appear isoattenuating to the rest of the liver and as such cannot be visualized. Their transformation renders their density so different to the rest of

the liver parenchyma that they become visible in the MDCT scans. Over time, however, it is also possible that these lesions gradually disappear between two follow-up studies and for this reason are not indicative of disease recurrence but simply an additional change in response to imatinib.

Occasionally benign lesions tending to hypervascularity can create ambiguity in the diagnosis of presence or absence of hepatic lesions during staging. If the first examination with contrast-enhanced PET/CT is performed after the beginning of imatinib treatment, the correct interpretation of any pre-existing benign hepatic lesions is all the more difficult and leaves no room for diagnostic certainty (Fig. 8.6).

In the case of recurrence during follow-up of lesions responding to imatinib, the sign of the nodule-within-a-mass in MDCT is the only pathognomonic sign, whether in hepatic lesions or not (Fig. 8.7).

8.4.4 Second-line Treatment: PET/CT During Therapy with Sunitinib

It has been described that after the response to imatinib mesylate potentially half the patients in remission may undergo progression of disease subsequent to the first two years of treatment, often due to the development of further genetic mutations [19].

The recurrence of disease after imatinib is generally associated with a poor prognosis and patients often die within several months [20]. Sunitinib malate (Sutent®) can lengthen survival after the failure of imatinib. The drug produces modifications in tumor glucose metabolism immediately after the beginning of treatment [21] such that PET/CT can provide crucial information on the state of response to second-line treatment.

In these patients the lesions which no longer respond to Gleevec may be difficult to evaluate with MDCT. Their increase in size, the broad areas of necrosis, the histologic transformation induced by imatinib and then modified by disease recurrence and the overlying metabolic and histologic involution caused by sunitinib create a particularly inhomogeneous CT appearance lacking pathognomonic elements. They are therefore no longer easily evaluated on the sole basis of their enhancement, in fact the vascularization often undergoes important changes due to the anti-angiogenetic action of the drug and additional intratumoral necrosis. The changes in size of the lesions are no longer a reliable assessment criterion. Therefore, in the absence of a certain evaluation of the changes in enhancement or size, only the metabolic information is able to monitor the lesions during sunitinib treatment (Fig. 8.8).

This is probably the phase of the disease with the least favorable prognosis and requires an imaging technique with particularly low levels of invasiveness due to the fragility of the patients in this phase of treatment and in this phase of their disease [22]. Imaging with contrast-enhanced PET/CT enables a complete evaluation of all body regions, but the repeated use of the technique is not possible, above all due to the needs of renal and hepatic excretion of the contrast medium.

This is why at times the most frequently used examination is PET/CT with conventional technique.

The contrast-enhanced examination may be indicated for a more precise diagnosis in cases where complications are thought to be overlying the base disease. In addition to the metabolic study to evaluate the response to treatment, the complications also require the overall re-evaluation of the patient in order to identify the presence of any anomalies resulting from the treatment or secondary outcomes of the base disease (perforation of peritoneal lesions, enteroenteric fistulae, peritoneal or extra-peritoneal bleeding).

8.5 Conclusions

Diagnostic imaging of GISTs in the past ten years has brought about a change in many of the conventionally used parameters for classifying tumor response assessment. In addition it has required the introduction of new and different criteria based not solely on the size of the lesions but also on their changes in enhancement and density.

The simple morphologic and geometric criterion used in the follow-up of GISTs being treated with targeted therapy is no longer sufficient for assessing the status of the disease and understanding whether it is in remission, progression or stable.

Where MDCT has demonstrated its greatest interpretation limitations, PET seems to provide more convincing answers due to its ability to observe the "functional" aspect of the lesions, thereby overcoming the known limitation most evident in this tumor of the morphologic evaluation alone.

As stated in a recent radiology study, "size is not

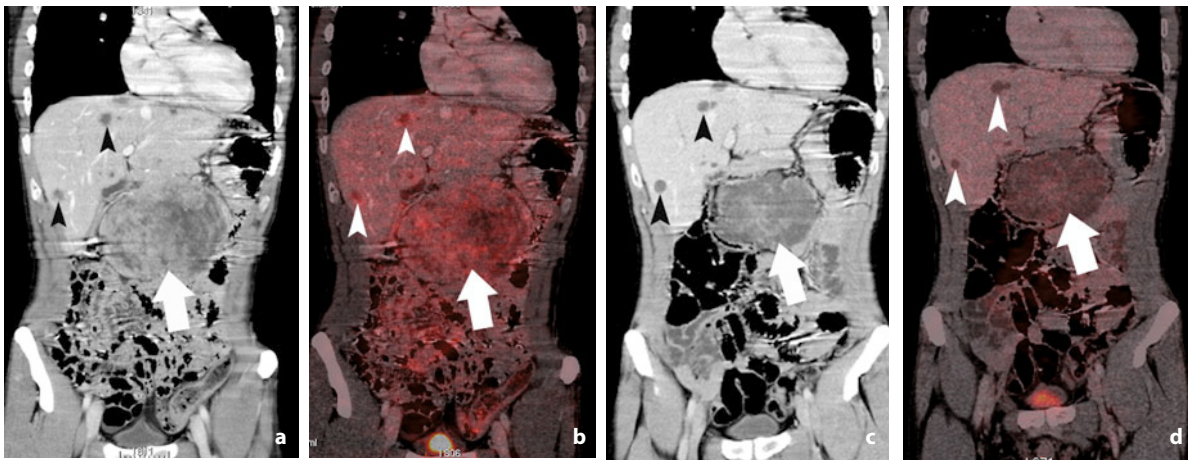


Fig. 8.8 **a-d** Coronal reconstructions from contrast-enhanced PET/CT study in a male patient with recurrent ileal GIST after surgery and 16 months after treatment with imatinib mesylate. In the images the recurrent central abdominal lesion prior to treatment can be appreciated (**a, b**). In the CT image the lesion appears inhomogeneous with liquefied areas, hypodense and inhomogeneously enhancing (*white arrow*). Metastatic lesions are identifiable in the liver: the largest are indicated by the black arrowheads. The PET image shows the inhomogeneous uptake of radiotracer in the central abdominal lesion. The small hepatic lesions have positive metabolism with SUV>4. **c, d** Images from the study performed after two weeks of treatment with sunitinib. In **c** a reduction in the size of the large recurrent lesion can be appreciated, which has a markedly hypodense CT appearance. The hepatic nodules have become hypodense (arrowheads). In **d** the PET image shows the important decrease in metabolic activity of the large lesion (SUVmax<1.5). Even the hepatic lesions appear almost entirely without uptake (SUV<1)

everything!!!" [23].

The development of the contrast-enhanced PET/CT examination technique stands out due to its ability to provide superior detail in the diagnostic evaluation of GIST versus MDCT study alone: it plays a crucial role in diagnosis. It provides information of great value when used in the preoperative evaluation of lesions and becomes irreplaceable and central in the evaluation of tumors during first-line or second-line medical treatment.

Examination with contrast medium does not require particular instrumentation other than that already available to the operator of a PET/CT system and is not particularly burdensome in terms of examination costs. The difference between the conventional and contrast-enhanced PET/CT examination lies in the cost of the dose of iodinated contrast medium used. In this setting it should be noted that in the presence of diagnostic doubt after a conventional PET/CT examination the contrast-enhanced MDCT examination may occasionally need to be performed in addition. Performing the combined examination may therefore prevent or avoid this situation, thus reducing the costs of the examination in terms of discomfort and "emotional" expense for the patient who otherwise would have to undergo two different examinations on two separate occasions.

The real cost of the contrast-enhanced PET/CT examination lies in the need to have two different specialists to interpret the findings: a radiologist and a nuclear medicine physician. Each must "read" the examination based on the their own specialization, with the aim of integrating their respective diagnostic impressions in a single final evaluation.

The diagnostic query that is still open to date is at what point in the history of the disease should contrast-enhanced PET/CT be used as a first choice diagnostic modality. There is no doubt that the initial diagnosis often occurs by chance and cannot always be performed with this technique.

In the event that other instrumental examinations have suggested the presence of a GIST, or if a first-level radiological examination (e.g. ultrasonography) raises suspicion of this disease, the combined technique may be considered in the diagnostic protocol.

PET/CT is first and foremost a functional imaging modality. In diagnostic work-up, therefore, having a previous examination available is particularly valuable in order to compare the evolution of disease during treatment. In each oncologic disease PET underlines the need for a baseline examination, i.e. the examination performed prior to the beginning of treatment where the "original" metabolic state of the lesion being studied is evaluated and which can be used for later

comparison. Each metabolic finding is compared after the changes induced by treatment.

In the re-evaluation of GISTs, knowing the baseline SUV value of primary and metastatic lesions becomes crucial for measuring the corresponding variations observable in the diagnostic and follow-up phases.

In our experience, contrast-enhanced PET/CT is a fundamental examination for orienting the therapeutic choices when a diagnostic "crossroads" is reached: when a global re-evaluation of the extension and degree of activity of the disease is needed to determine the most important medical or surgical treatment choices. The combined examination is the most complete diagnostic tool available. It can be associated with MR in a targeted study of the liver, for example, but it remains a reference diagnostic modality.

During follow-up PET/CT can be alternated with the simpler conventional contrast-enhanced MDCT study. In particular this diagnostic choice can be made when the clinical history of the patient presents no particular modifications, when on the basis of recent controls the disease seems stable and there is no clinical evidence of suspicion requiring a more complete diagnostic study.

In the current literature there are indications for time interval between follow-up examinations with MDCT, which depends on the therapeutic phase in which the patient is (only surgical treatment, treatment with imatinib mesylate, treatment with other drugs), but no reference has been codified for establishing when to use conventional PET/CT.

Undoubtedly the development of our understanding of the molecular mechanisms of the disease and the different genetic patterns that characterize it will help to more accurately codify the time intervals for performing follow-up radiological examinations, but above all will in the future allow contrast-enhanced PET/CT and other new forms of molecular imaging (thanks to new radiotracer molecules) to be inserted in the diagnostic protocol for GISTs.

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Section III
Treatment

Medical Treatment

9

Elena Fumagalli, Gaetano Apice and Paolo Giovanni Casali

Abstract GISTs have become a model for the use of novel target therapies in solid tumors. Thanks to the constitutive activation of KIT or PDGFRA receptor, due to oncogene mutations, they can be targeted effectively by anti-tyrosine kinase agents. Currently, in the first-line therapy of advanced GISTs, imatinib has brought median survival from around one to 5 years. Tumor response rate is high and predictable through the mutational status of the disease. Indeed, different drugs may exert a different antitumor effect against different muations. Patterns of tumor response are representative of the antitumor effect of target therapy in solid tumors and in GISTs reflect a myxoid tissue degeneration. Imatinib is administered indefinitely, until progression (or toxicity, which however is usually limited). Secondary resistance is the limiting factor of target therapy. In GISTs, it emerges after a median of 2 years from starting imatinib, even though a proportion of advanced patients become long-term progression-free survivors. Sunitinib is the standard second-line therapy, and new agents are under study. It is unknown whether adjuvant complete surgery of responding residual metastases may impact the risk of secondary resistance. On the contrary, there is evidence that imatinib following surgery of localized disease delays recurrences in significant-risk GIST patients, although it is still unknown if the relapse rate will decrease. The optimal duration of adjuvant therapy is unknown as well.

Keywords Gastrointestinal stromal tumor (GIST) • Imatinib • Sunitinib • Target therapy

9.1 Introduction

Medical treatment of GIST was revolutionized when the first patient ever was treated with molecular targeted therapy in 2000 [1]. Being one of the first solid tumors benefiting from targeted therapies, GIST have thus become a model for the use of these novel medical agents in medical oncology.

Medical treatment of GIST with targeted therapies has first addressed advanced disease. In GIST, advanced disease is marked by hepatic and/or peritoneal spread. One half of metastatic patients have liver and peritoneal metastases, while others have either peritoneal lesions or, less frequently, only liver metastases [2]. Extra-abdominal spread is possible, but is much less frequent. Interestingly, lung metastases, which are so typical of sarcomas, are exceedingly rare. On the contrary, bone lesions may go underestimated, especially in the context of an already advanced disease, perhaps all the more as long as life expectancy of advanced GIST patients is markedly prolonged thanks to available therapies. In the pre-imatinib era, median

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survival of metastatic GIST patients was in the range of 1-2 years. Today, it is at least 5 years [3]. Thereafter, attention was brought to the localized disease, testing the efficacy of imatinib given as an adjuvant to surgery, or with a neoadjuvant/cytoreductive aim.

The main molecular characteristic of GIST is the constitutive activation of KIT or Platelet-Derived Growth Factor alpha (PDGFRA) receptor [4]. Normally, they are stimulated by their natural ligands, i.e., respectively, the stem cell factor (SCF) and PDGFRA. Stimulation causes the homodimerization of the receptor and autophosphorylation of intracellular tyrosine kinase residues, with subsequent downstream signaling. Most GIST present this kind of constitutive KIT of PDGFRA activation, determined by mutations in either the KIT or PDGFRA genes. The activation leads to cell proliferation and reversal of apoptosis, this being the pathogenesis of the disease. Activating mutations of KIT were first described in 1998 [5]. Currently, activating mutations have been described for exon 11 of KIT (60% of cases), which encodes for the juxtamembrane region of the receptor, exon 9 (<10% of cases), which encodes for the extracellular domain, and (rarely) exons 13 and 17, which encode for intracellular regions of the receptor. PDGFRA mutations account for around 10% of activating mutations. They are found in exons 12, 14 and 18. In GIST, therefore, two alternative oncogenic mechanisms can be identified, leading to similar downstream signalling. However, in 10% of GIST there are no mutations of the KIT and PDGFRA genes. They are thus defined "wild-type" (WT). A WT genotype is typical of syndromic GIST, such as pediatric GIST occurring in the context of the Carney syndrome or GIST arising in patients with type 1 neurofibromatosis [6, 7].

9.2 Advanced Disease

Chemotherapy, as used in soft-tissue sarcomas, is completely inactive on GISTs, with response rates which were <5% in the pre-imatinib era [8]. This contrasts with the high response rates achievable with imatinib.

Imatinib is a competitive inhibitor of several tyrosine kinase activity proteins, such as Abl, PDGFR and KIT. It acts by binding to the ATP ligand site and consequently blocks phosphorylation of substrates. This interrupts the downstream signal cascade, leading to cell apoptosis and other mechanisms underlying the clinical effect.

If the conventional, dimensional tumor response rate to imatinib is in the 50-60% range, the proportion of patients actually responding is in the 80-90% range, i.e. as many as are GIST harboring sensitive mutations [3, 9, 10]. As from the first series of advanced GIST treated with imatinib, median survival was brought from the 1-2 year range to 5 years, thus marking one of the most obvious achievements of molecular targeted therapies in solid cancers. By the way, the first series were made up of highly advanced patients, and it is likely that most recent series will provide better outcomes. This should be allowed also by clinicians' learning curves as well as by the availability of new drugs for salvage therapies. In addition, the tails of survival curves of the first studies are still compatible with a proportion of metastatic GIST patients having a long-term benefit, and indeed attempts are ongoing to understand more of this patient population.

As from the first series of patients treated with imatinib, a correlation was demonstrated between tumor response and mutational status [11]. In fact, mutations of KIT exon 11 were shown to be highly responsive to imatinib 400 mg daily. In randomized trials comparing 400 to 800 mg of imatinib daily, patients with an exon 9 mutation were retrospectively shown to respond better to the higher dose level [12]. The European Society for Medical Oncology (ESMO) Guidelines thus recommend a daily dose of 800 mg of imatinib for these patients [13]. Other rare mutations of KIT and PDGFRA are responsive, with the remarkable exception of the D842V mutation of PDGFRA (i.e., the most frequent mutation of PDFGRA) [14]. This mutation is insensitive to imatinib and sunitinib in vitro and in vivo. Other agents, or combinations, are currently under evaluation for this patient subgroup. WT patients are less sensitive to imatinib, although they are more sensitive to sunitinib and probably other new agents.

Thus, the primary resistance to imatinib, which can be found in 10–15% of advanced GIST patients, is almost entirely predictable through the mutational analysis of the tumor. This is important in clinical practice, so that mutational analysis is currently strongly recommended within the pathologic diagnosis of GIST. Furthermore, mutational status has also prognostic implications, since PDGFRA and WT GIST tend to show a more indolent course of disease, aside from the clinical peculiarities shown by syndromic WT GIST (e.g, multicentric presentation, etc.).

Currently, imatinib is administered indefinitely in

patients with advanced GIST. There is evidence that the interruption of treatment, even after complete surgical resection of residual disease, is followed by early progression [15]. Pathologic assessment of residual disease following tumor response to imatinib typically shows clusters of vital tumor cells, especially at the periphery of lesions. This is seen in the context of a myxoid degeneration of tumor tissue, which is the pathologic hallmark of tumor response of GIST to targeted therapies. In other words, targeted therapy seems to be currently unable to cure a patient with metastatic GIST, although progression-free survival curves have tails which are compatible with a proportion of patients (possibly in the 10-20% range) having a long-term benefit. At the moment, it is impossible to predict their future behavior and it is difficult to identify predictive factors for long-term progression-free survival.

Secondary resistance is the limiting factor of imatinib therapy. The median time to secondary resistance to imatinib in the advanced disease setting is around two years [9, 10]. Clinically, it manifests as a tumor progression following tumor response. In a proportion of patients, it is a kind of "focal" progression, e.g. a solid nodule within a hypodense responding lesion. In most cases, tumor progression is related to the acquisition of new KIT or PDGFRA mutations [16]. These may well cause conformational modifications of the receptors, as to make bonding with imatinib impossible. Sunitinib is standard treatment for advanced GIST failing (or intolerant to) imatinib, following a randomized, placebo-controlled, Phase 3 trial which showed a 6-month benefit in terms of progression-free survival [17]. Sunitinib is an anti-tyrosine kinase agent, with activity against KIT and PDGFR, but also against VEGFR, thus having an antiangiogenic effect as well. The drug is administered at a dose of 50 mg per day for four consecutive weeks followed by two weeks of interruption. The administration of a lower (37.5 mg daily) but continued dose was shown to be active in a Phase 2 setting, and is the preferred option by many institutions [18]. KIT exon 9 mutants and WT GIST were shown to be responsive to sunitinib in vitro, as well as secondary mutations related to the receptor binding pocket of the receptor [19]. Unfortunately, there is convincing evidence that secondary mutations give often rise to an heterogeneous pattern, such that different mutations can be found in the same patient [20]. Of course, this makes any prediction of antitumor activity much more difficult in the second-line than in the first-line setting. More importantly, it is clear that any drug similar to imatinib will face a major limiting factor. This is the reason why current research into new therapies for resistant patients explores agents with a different mechanism of action (such as inhibitors of heat shock proteins or of signaling downstream to the receptor), or combinations. Fortunately, several clinical studies are undergoing on such new strategies.

Indeed, tumor progression following response to imatinib is not necessarily due to a secondary resistance. In fact, one should always rule out patient's lack of compliance with therapy or changes in pharmacokinetics. Indeed, it is possible that plasma levels may change spontaneously over time, or depending on interactions with other concomitant medications [21]. Many agents interact with imatinib, inducing enzymes which increase or decrease imatinib elimination or influencing its absorption. There is also individual variability in plasma levels, which may be related to factors as previous gastrointestinal surgery or polymorphisms in genes encoding for transport proteins or enzymes involved in drug metabolism. This has led to speculate that imatinib plasma levels may play a role in determining patient outcome. At the moment, retrospective evidence has been provided that patients with imatinib plasma levels above a threshold have a better outcome [22]. Of course, this may be a selection bias, so that prospective studies are required to demonstrate whether a policy of active dose tailoring to target optimal plasma levels is superior to a fixed daily dose, as is current standard practice. Nonetheless, assessing plasma levels may be important in the presence of an excess of toxicity, concomitant medications, or progression to imatinib 400 mg. Pragmatically, indeed, increasing the dose to 800 mg is generally the first clinical choice in case of progression, since this may be effective in one quarter of cases, or so [23]. Understandably, progressing patients with decreased plasma levels, in addition to those with an exon 9 mutation who have been treated with 400 mg, will be most likely to respond to increase in dosage.

Tumor response to imatinib is described elsewhere in this book. By and large, it is marked by changes in tumor density on CT scan, which clearly are the radiological counterpart of the myxoid degeneration one can observe pathologically. In addition to these changes, one should always pay attention to signs of possible complications of therapy. An example may be bleeding within lesions (e.g., liver metastases), as

well as direct or indirect signs of perforation of lesions to the gastrointestinal tract. These complications have been shown to be rare (<5% of cases), but they should be promptly recognized in the occasional patient.

Side effects of imatinib are limited and effectively manageable [24]. Some of them are more typical of the early phase of treatment, while others are seen on longer intervals. Early side effects include lower limb and periorbital edema, but occasionally pleural, peritoneal, or pericardial effusion, or worsening thereof, are observed. Mild diarrhea is a frequent complaint. Fatigue is another complaint. Skin rash is relatively rare, as well as muscle cramps and musculoskeletal pain. At a later stage, liver alterations may occur, and patients with HBV or HCV infection may experience a flare-up of viral replication. Bone marrow toxicity tends to be limited in GIST, even though treatment may need to be transiently interrupted, or, in the case of persistent anemia, erythropoietin may be required. Cardiac pump toxicity was shown to be possible, although it has not been a clinically relevant problem in available series [25-27]. Alterations in bone and mineral metabolism have been described [28].

Sunitinib has a different toxicity profile, as is the case with targeted agents, whose side effects tend to be much more drug-specific than those of cytotoxic chemotherapy [24]. One can encounter fatigue, nausea/vomiting and diarrhea, myelodepression, yellow skin discoloration and depigmentation of the hair, lower limb edema and other side effects (joint and muscle pain, headache). Cardiac toxicity can be found, with a reversible decrease in ventricular ejection fraction, as well as lengthening of the QT interval (with a consequent arrhythmic risk) [29]. Hypertension is a possible side effect, as for several antiangiogenic agents. There is the possibility of hypothyroidism, which may require therapy [30].

New agents are currently under study in the first-line setting, aiming at improving the median time to secondary resistance and/or improving antitumor activity for primary resistant GIST. A large randomized trial comparing nilotinib to imatinib is currently underway [31].

9.3 Localized Disease

Complete surgical excision of the lesion is standard treatment of localized GIST [32]. If, overall, roughly half patients are cured thereby, prognostic factors can effectively stratify prognosis. Currently, the mitotic index, tumor size and tumor site make it possible to assign to the individual patient a risk ranging virtually from nil to certainty of relapse [33]. Apparently, the main difficulty is the reproducibility of mitotic index, which in GIST should be carefully assessed out of 50 high-power fields. The mutational status has also prognostic implications. In particular, syndromic GIST have a natural history which is different from typical GIST. All this is obviously important for treatment decisions about adjuvant therapy, which by definition should be reserved to those patients with a significant risk of relapse.

Given its efficacy in metastatic disease, imatinib was an obvious candidate for adjuvant therapy. A clear-cut effect in delaying relapse (of patients due to relapse) was shown by a randomized trial comparing one year of imatinib adjuvant therapy versus placebo [34]. The follow-up is too short as to allow any conclusion about the ability of this adjuvant therapy to improve the cure rate. Likewise, results on a longer follow-up will show the antitumor activity of imatinib when rechallenged after being used as an adjuvant. For this reason, another Phase 3 randomized trial on adjuvant imatinib for 2 years versus no-treatment after surgery, still due to be reported, has selected “time to secondary resistance” as its primary end point, implying that this might be a better surrogate for survival. Another trial, due to be reported, randomized one versus 3 years of adjuvant imatinib, and will allow to understand if a longer adjuvant period is more effective.

Thus, the choice on adjuvant therapy is currently the product of a patient-physician shared decision-making. The decision needs to be tailored on patient’s risk and mutational status, since unresponsive mutations tend to be excluded for obvious reasons, and preliminary evidence has been recently provided that the mutational status impacts on adjuvant therapy’s outcome [35].

Imatinib is also used preoperatively, generally with a cytoreductive aim [36]. Cytoreduction may be a reasonable goal especially when subsequent surgery could be more conservative in the case of response. This can be the case with rectal GIST, with the obvious possibility to spare anal function. Sometimes, gastric surgery may be converted to a more conservative one, or major duodenal surgery may be spared. In addition, preoperative treatment may be useful when the sur-

geon feels that the risk of tumor rupture is high, due to the tumor size. Tumor rupture, in fact, is a major risk factor for subsequent peritoneal (i.e. metastatic) spread [37]. Thus, reducing this risk may be a major result. Of course, in these cases mutational status is exceedingly useful, to select those patients who are most likely to respond. Likewise, early tumor response assessment, possibly incorporating PET scanning, is of particular value.

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Surgical Treatment

10

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Abstract Standard treatment of localized, resectable GIST is surgery. In principle, a preoperative diagnosis should always be considered, i.e. through core-needle biopsies, taken by endoscopic ultrasound or percutaneously. Once the diagnosis of GIST has been established, the goal of surgery is complete resection of visible disease, i.e. with negative margins. Tumor rupture should be avoided, because it is associated with an exceedingly high risk of peritoneal seeding and subsequent metastatic extent. Preoperative treatments should be considered when the surgeon perceives that there is a high risk of tumor rupture, along with those cases in which cytoreduction may lead to more conservative procedures. Surgery does not cure metastatic GIST. All the more today, in the era of targeted therapies for GIST, standard treatment of the advanced disease is medical treatment. In the case of limited progression after response to imatinib, surgery may be an option. At the moment it is uncertain whether surgery of residual metastatic lesions responding to imatinib may help, although by no means it could allow stopping the medical therapy.

Keywords GIST • Surgery

10.1 Biopsy

In principle, a pathologic diagnosis should always be sought in case of abdominal masses entailing GIST in their differential diagnosis [1]. Of course, there are exceptions to this rule, depending on the specific tumor presentation and the difficulties and risks which it could imply.

Moreover, GISTs have a variegated clinical onset, which can reasonably be summarized into four main categories, as follows. In some of them, a preoperative diagnosis is clearly unfeasible.

1. Small nodules incidentally found during endoscopic examination for dyspepsia (Fig. 10.1). Only a proportion of these nodules turn out to be GIST, and indeed their number is still unknown. In principle, it is impossible to predict the clinical behavior even of small GIST, so that ideally they should be always assessed pathologically. However, many of them will be very low-risk lesions and many will not be malignant lesions. Clearly, it is very difficult to obtain a reliable transmucosal histologic diagnosis for small lesions, so that, considering the low risk of many of these lesions, one can reasonably select a policy of clinical follow-up as an alternative to an immediate surgical (e.g., laparoscopic) approach [1]. Exceptions to this general rule include rectal nodules, which in

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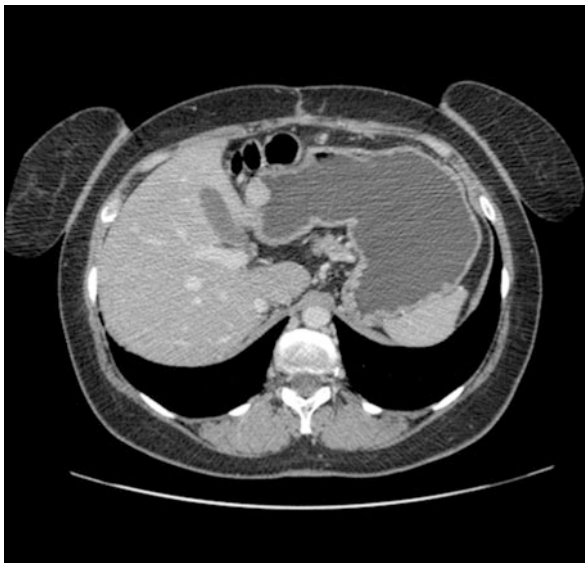

Fig. 10.1 A small nodule incidentally found during endoscopic workup for dyspepsia

principle should be excised due their greater risk overall;

2. Small nodules identified incidentally during abdominal surgery for another reason (Fig. 10.2). Intraoperative frozen section diagnosis can be very difficult. On the other hand, one should be aware that all extramucosal nodules arising from the GI tract wall can be GIST, and they should be treated accordingly. An intraoperative pathologic examination can be requested only if it has an impact on the surgical approach, bearing in mind that the examination may be inconclusive;
3. Abdominal nodules/masses causing acute surgical complications requiring immediate surgery (intestinal perforation, GI tract hemorrhage or hemoperitoneum due to tumor rupture, intestinal obstruction) (Fig. 10.3). In this presentation, one needs to solve the acute problem, possibly by properly excising the nodule/mass liable to be a GIST. With regard

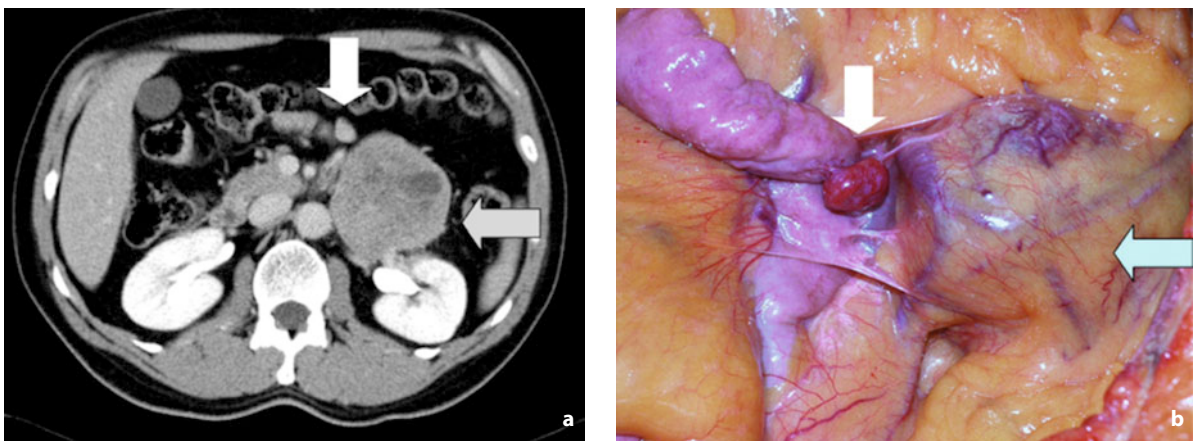

Fig. 10.2 A small nodule (*white arrow*) incidentally identified during abdominal surgery for another reason (left retroperitoneal paraganglioma, *grey arrow* on left panel and *light blue* on right one)

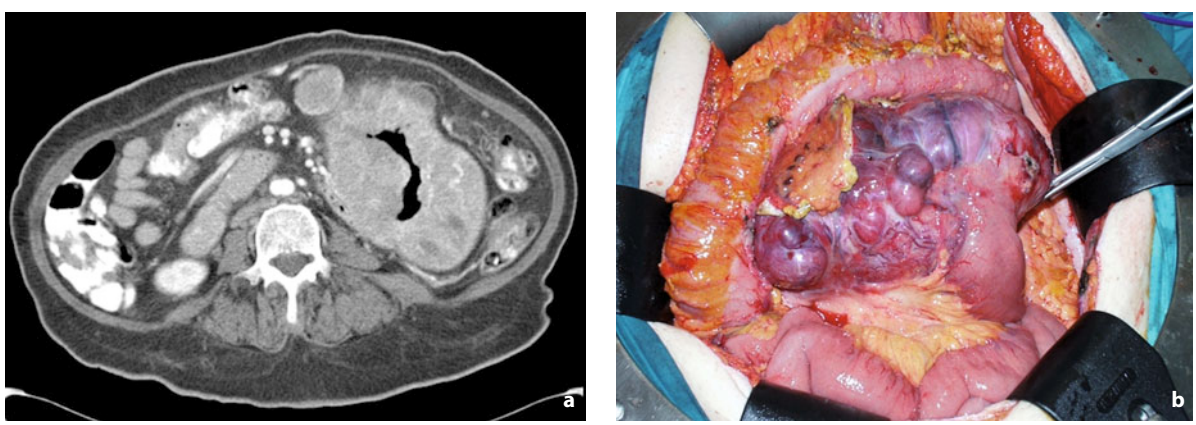

Fig. 10.3 An abdominal nodule/mass requiring immediate surgery

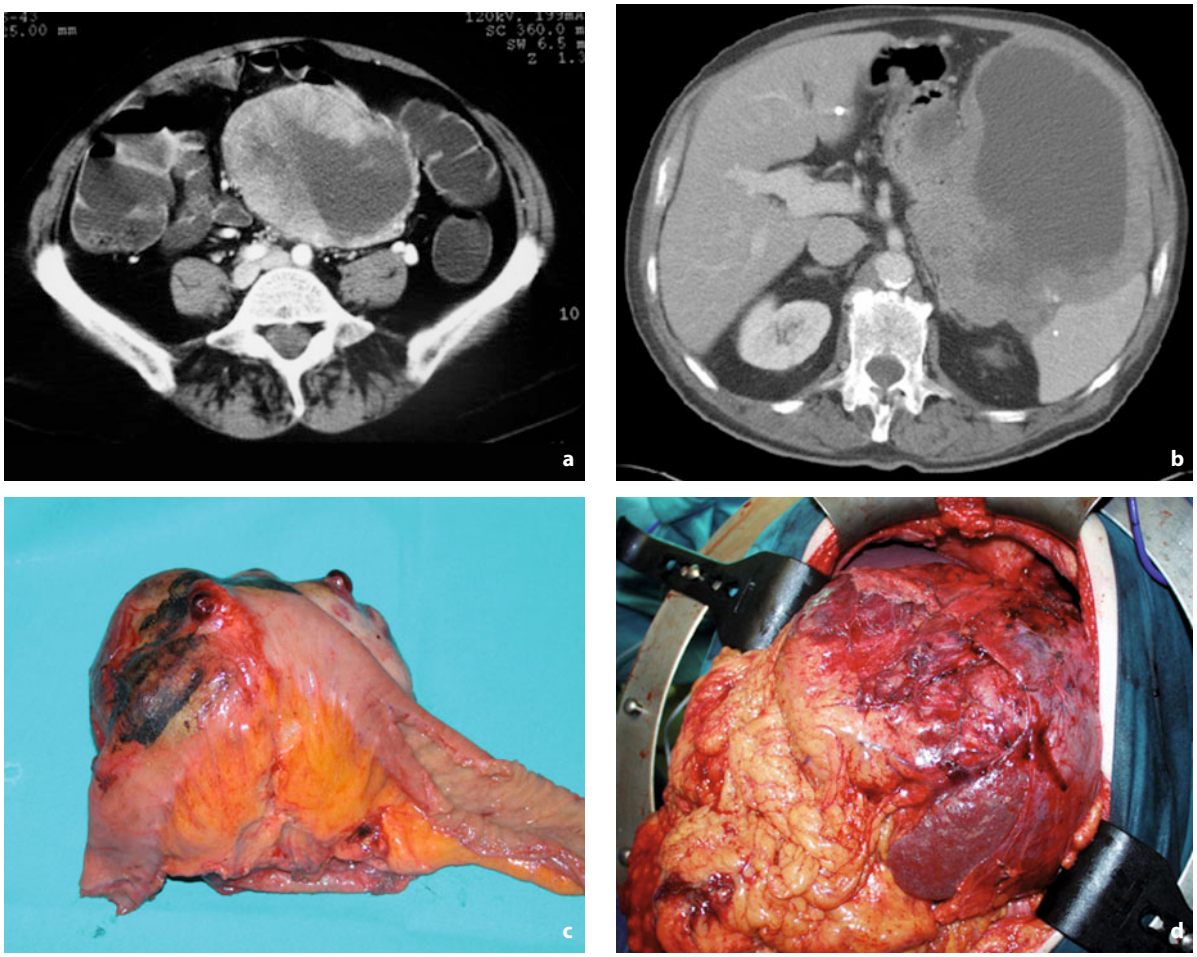

Fig. 10.4 An abdominal nodule (**a, c**) and an abdominal mass (**b, d**) which are both relatively asymptomatic or causes manageable symptoms

to the intraoperative pathologic examination, what said above applies as well;

4. Abdominal nodules/masses which are relatively asymptomatic or cause symptoms which on the whole are manageable (Fig. 10.4 a-d). Obtaining a preoperative pathologic diagnosis is particularly important when the excision of the nodule/mass, regardless of its size, would require major surgery. It should be borne in mind that some diagnostic possibilities (e.g., lymphoma, germinal tumor, mesenteric fibromatosis) would not entail a surgical indication and that major surgical procedures for GIST can be preceded today by preoperative effective treatments, which could be safer and/or more conservative.
   The preoperative pathologic diagnosis can be obtained through a percutaneous core needle biopsy, with needle gauge varying according to the site and the radiologic characteristics of the disease (proper attention should be paid to masses with significant cystic components, due to the actual risk of rupture).

10.2 Treatment of Primary Disease

Complete surgical resection is today the treatment of choice for localized primary GIST, i.e. the only potentially curative treatment available [1].

Typically, for limited tumors (say, less than 10 cm in size), resection can be achieved with minimal morbidity in most gastric and intestinal GIST. Indeed, a wedge resection of the gastric wall or a segmental resection of the intestine guarantee complete removal of lesions. Attention should be paid to obtaining negative resection margins on the organ of origin. It is

true that we lack a formal proof that R0 resections are superior to R1, but several limitations affect available series, so that R0 surgery is clearly recommended [1, 2]. Indeed, particularly for lesions confined to the GI wall and with good prognostic factors, complete surgical resection results in very high cure rates, which the presence of a microscopically positive margin could well compromise. It should also be borne in mind that a locoregional recurrence can develop from the most aggressive component of the disease and could therefore be associated with a poorer prognostic risk.

In the lack of formal evidence of the prognostic impact of the quality of surgical margins, it is always difficult to decide whether a "re-excision" should be carried out in patients who have already undergone microscopically intra-lesional procedures. Planning surgical procedures a priori is therefore very important [1]. There may be exceptions, e.g. for rectal tumors requiring extensive surgery, such as combined abdominoperineal (Miles) resections, or in critical tracts where the morbidity associated with a complete resection is not proportional to the real risk of the disease (small nodules to the esophagus/gastroesophageal junction, or to the second part of the duodenum). At any rate, it should be emphasized that there are no data at all at the moment suggesting that any medical therapy can substitute optimal surgery.

On the contrary, it is not necessary to excise the whole organ of origin as well as locoregional lymph nodes, since the probability of lymph node metastases is very low. Exceptions include the more rare esophageal, duodenal or rectal presentation. In these cases, a segmental resection is often not possible, and en bloc resections is required.

Of course, larger tumors (say, in excess of 10 cm in size, or so) may require multi-organ resections. In addition, the presence of an adherence to an adjacent structure, regardless of tumor size, should be approached with the en bloc resections. Lastly, extreme attention needs to be paid to limiting the risk of intraoperative rupture, given its exceedingly negative prognostic impact [2].

A mini-invasive approach (i.e., through laparoscopy) may be indicated in all cases where the lesion is small. There is no absolute cut-off, provided that the procedure turns out to be similar in principle to what an open surgical procedure would look like. On the contrary, laparoscopic surgery is contraindicated, even in the presence of small tumors, whenever multiorgan resections are required.

In addition, medical therapy with imatinib can be used in the preoperative phase in at least three conditions [3-5]:

- tumors of borderline resectability or patently inoperable;
- tumor which requires multi-organ resections, to minimize surgical morbidity;
- risk of tumor rupture, based on preoperative imaging (Fig. 10.5).

Once surgery is performed, the indication to medical adjuvant therapy with imatinib is based on the prognostic risk, which to date is estimated on the basis of size, tumor mitotic rate and site of origin [1, 6-7].

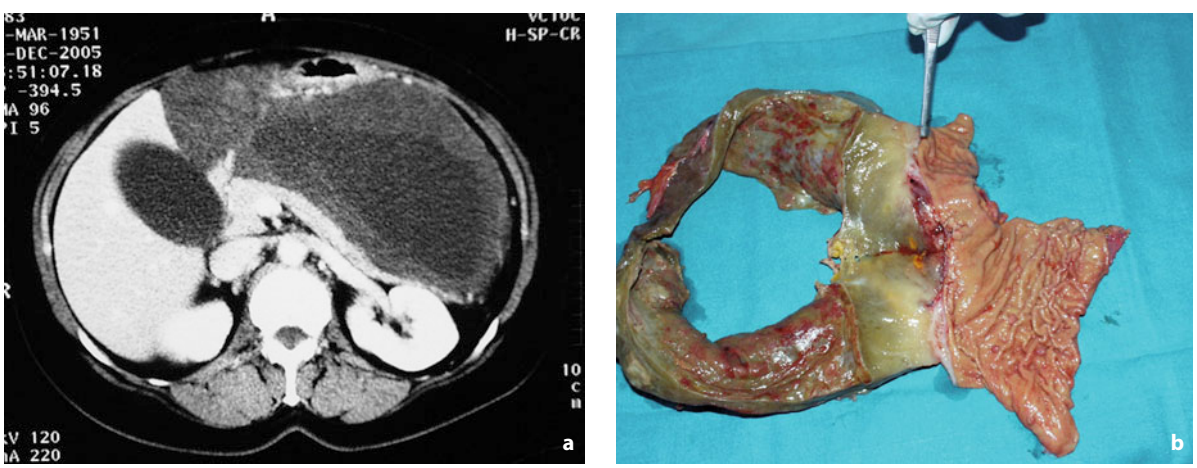

Fig. 10.5 In the preoperative setting, imatinib-based medical therapy can be used for tumors with a borderline resectability or patently inoperable or those which require multi-organ resections, and to minimize surgical morbidity and the risk of tumor rupture

10.3 Treatment of Metastatic Disease

Overall, around 50% of patients with localized GIST do relapse. The median time to recurrence averages around two years, with variations which of course depend on the biology of the tumor [2, 7]. Recurrences typically affect the abdomen (extra-abdominal metastases, such as bone lesions, tend to be rare and/or late events). Even when radiologic findings suggest a single lesion, the treatment of choice is currently medical therapy with imatinib [1, 5].

Indeed surgery alone – as reported in the pre-imatinib era in the few series – failed in almost all patients [8]. In addition, complete resection was achieved in no more than half of patients.

On the contrary, surgery may play an important role in combination with medical therapy, although its indications outside emergencies are still unsettled [9-13].

Surgery could be considered in a number of cases.

1. Acute complications of medical therapy. These may be the result of hemorrhages (inside the tumor, to the gastrointestinal tract, in the peritoneum). Indeed, they proved to be much more rare than feared and can often be treated conservatively. One may encounter septic complications, with abscesses or perforation (whether plugged or open to the peritoneum). The latter is in fact the only absolute indication for surgical repair.

2. Surgery of residual tumor with limited progression. The surgical ablation of a lesion focally progressing on medical therapy, i.e. becoming resistant to it after responding, might be considered. The more limited the progression and the longer the period prior to progression, the greater will be the benefit. This is nonetheless a palliative procedure, which only delays a more generalized progression by a median of 6-12 months, which will then require a medical approach. In fact, surgery of progressing diseases has been proven to be useless in available series, with the possible exception of focal progression. In practice, it is a situation in which the disease is still responding to the medical therapy, which therefore is continued, save for one lesion, or a "nodule with a nodule", which starts to progress. It is therefore an option which may be considered at the onset of secondary resistance to medical therapy, when this is not generalized d'emblée. Since it is a palliative procedure, its morbidity and sequelae should be considered carefully. In any case, surgery should not be performed whenever disease progression is generalized. In these cases, medical therapy should be switched to alternative drugs (sunitinib after imatinib, or new agents thereafter).

3. Surgery of residual lesions responding to medical treatment. In theory, the removal of residual disease responding to medical therapy might be able to lengthen the disease control, delaying secondary resistance, which is the limiting factor of targeted therapy. Currently, however, there are no data to confirm that this is the case, such that it is the subject of a prospective trial which is ongoing in Europe at the moment. The idea that medical therapy may benefit from a complete cytoreductive surgery is reasonable [14, 15] provided selection criteria are followed (30–40% of patients overall will be candidates for this kind of surgery, as long as the probability of performing macroscopically complete surgery is kept high, around 90%).

4. Surgery of the primary tumor responding to treatment in patients with inoperable concomitant metastases. The aim may well be avoiding possible complications which could arise from the primary lesion once the first-line (and most effective) medical therapy is no longer active. A case-by-case decision-making is clearly needed in these cases.

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Section IV
Management

GIST Unit Network

11

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Abstract The continuous introduction of new technologies requires appropriate research and implementation of innovative planning and management models, oriented towards activity and outcomes, such as clinical governance, that can integrate management perspectives with practices and values coming directly from the clinical area.

Clinical governance is a system through which GIST Units are accountable for continuously improving the quality and safeguarding high standards of care.

High standards are achieved by the technological progress in the field of bioimaging. GIST Units take advantage of clinical e-health because bioimages are fundamental to the diagnosis of GIST and/or therapeutic purposes.

The main clinical applications of e-health are the transfer of medical information via database, off-line or on-line sharing of a database's clinical data to allow exchange of opinions, second medical opinions or test interpretation to support or guide care for specific patients and their follow-up, the use of a database for research (clinical trials), for epidemiological purposes, as well as editorial and continuous medical education activities.

Keywords GIST Unit • Network • Telemedicine • Accreditation of Healthcare • Quality Management

11.1 Introduction

The term telemedicine was coined 40 years ago to describe the use of electronic information and communication technologies to provide and support healthcare when distance separates the participants. In the past, most telemedicine projects failed to survive due to technical problems, unreliability and high communication costs. These costs have progressively decreased and network services, using both fast integrated digital terrestrial networks and satellite links, have developed another wave of interest in telemedicine, which has prompted a range of new activities [1].

Following initial telemedicine experience, the term "e-health" was coined around 10 years ago, indicating how the Internet, computers and medicine form a network to ameliorate healthcare. However, good organization and valid business plans are necessary for the functioning and management of clinical e-health projects.

Medicine has made notable technological progress in recent years in the field of bioimaging. Bioimages are today easily translated into electronic signals, and often the source of a bioimage is in electronic format.

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Consequently, the medical specialties that take advantage of clinical e-health are those where bioimages are fundamental for diagnosis and/or therapeutic purposes.

The main clinical e-health applications are (i) the transfer of medical information in a database, (ii) off-line or on-line sharing of a database's clinical data to allow exchange of opinions, second medical opinions or test interpretation to support or guide care for specific patients and their follow-up, (iii) the use of a database for research (clinical trials), (iv) for epidemiological purposes, (v) editorial and continuous medical education activities.

In recent years electronic support has been developed in many areas of society and this technology is one of the fastest changing components of the rapidly evolving healthcare information environment. However, until now, electronic technology has been poorly utilized in healthcare. Electronic support can help healthcare workers in different ways: on-line search of scientific information, digitalization of patient's clinical data, telehealth. The scientific on-line search is an easy modality to keep physicians up-to-date. Clinical data digitalization is an important aspect for improving healthcare quality. Lastly, telemedicine is the use of medical information exchanged from one site to another via electronic communications for the health and education of patients and healthcare providers.

11.2 Comparison Between GIST Units

The clinical trials and studies conducted in recent years in the search for more appropriate and effective diagnostic modalities and therapies for gastrointestinal stromal tumors has been oriented towards a multidisciplinary approach and the integration of organizational models between professionals: GIST Units.

There is increasingly less variability between different regional settings and different services in terms of speed of access, operational efficiency, treatment plans and manner of health care, both in terms of technical-professional quality and the results obtained in the overall care of patients.

There is, however, still the need for a continuous comparison between the different oncology teams to allow different organizational systems to increase their own performance and have the possibility of making comparisons based on uniform standards. These should explore the different areas of care for patients suffering from GISTs and be able to objectively identify strengths and weaknesses and propose interventions for improving the quality of care of the multidisciplinary teams.

The comparison between the levels of results reached by the teams in caring for patients with GISTs underlines the need to have flexible instruments for comparing and evaluating the quality of diagnosis and care, and to constantly improve organizational and professional practice. This can then enhance timely access to treatment, clinical efficacy, the appropriateness and timing of treatment, and the adoption of behavior that meets the real needs of overall patient care.

In addition, the rarity itself of the individual forms of GIST causes problems for the quality of care and clinical research. As a result, clinical studies are much more complex due to the limited patient population, and clinical decision making is more difficult due to the lack of evidence and familiarity with the disease. These difficulties can be insurmountable with the conventional methods of disseminating knowledge. The comparison of experience developed in the field and the comparison of the clinical cases handled by GIST Units can be useful, but it must be set within a broader and more complex framework essentially based on participation in an on-line network consisting of increasingly structured and routine cooperation.

It is clear, however, that only a small part of the biomedical information available on-line to support clinical decision making or as a source of ongoing professional training is used. Very few are aware of what has been defined the "anatomy of databases" [2]. Even more rare is awareness of the criteria of qualitative accreditation of a biomedical website, in practice the Health on Net Foundation criteria [3]. Government agency websites are poorly known, as are websites containing guidelines, systematic reviews, secondary publications or technology assessments. The very few who move freely within this fantastic web of information are able to do so thanks either to their own initiative (self-taught or spontaneous attendance at computer literacy courses) or to some rare initiative of particularly enterprising and far-sighted health care institutions [4].

11.3 Sharing Clinical Cases

The aim of the network is the assimilation of information on the diagnosis and treatment through the remote

sharing of clinical cases that have been through the various stages of their diagnostic-therapeutic protocols in the various cancer centers distributed throughout the country.

The network provides for the network interconnection of the participating centers using IT solutions of varying complexity. It will employ the single service center of the Pascale Foundation which is equipped with the technological infrastructure needed to provide a service to the participating centers.

All of the clinical activities will be centralized with the use of IT services delivered by the service center. The service center will be responsible for the reconstruction of a shared space in which to archive not only diagnostic images but also information on patient histories required to evaluate the therapeutic pathways undertaken.

It will be possible to extract useful information for research on GISTs in real time from this single archive. Communication between the centers and the network will take place through the GARR network, or alternatively through the Internet.

The service center, established by Nexera, will offer dedicated procedures of telepathology and teleradiology based on state-of-the-art technologies which allow not only the sharing of clinical information but also the creation of audio/video sessions aimed at the direct comparison of special clinical cases. Information sharing will take place with the reporting of the case and its registration on-line. There is also an on-line moderator who promotes the sharing of the case among the various centers involved provided they possess the expertise for the teleconsultation of the case in order to enter into the patient's therapeutic program. The services are delivered exclusively via the use of a web browser and do not require the installation of special hardware or software components.

The aim for the future is to integrate the network into a regular operation unit of the National Health Service, so as to improve the quality of the service and reduce health care migration and as a result the social costs, and to provide incentives for clinical research.

The framework is a sort of on-line clinical dossier that can be accessed in complete privacy via a web portal. The portal offers a sophisticated system of teleradiology offering the possibility of synchronous teleconsultation (with the use of an audio/video conference system) or asynchronous teleconsultation (with the exchange of messages). The message, which is exchanged within the site, is absolutely identical to a normal email and is linked to the patient's clinical record and guarantees the protection of sensitive data and offers the possibility of storing (in a database linked to the patient's clinical record) all the messages exchanged regarding the patient. The record also allows images for mostly descriptive purposes to be added. A password is needed to access the site and in order to upload patient data written informed consent from the patient is required.

Histology consultation may be requested within the clinical record. In the same way a clinical teleconsultation may be requested. Steps have been taken to allow the ongoing sharing of information related to the case so that the centers sharing the case can maintain contact with each other for the entire diagnostic and therapeutic pathway (Fig. 11.1).

The case is discussed on a multidisciplinary basis, and, based on the clinical and instrumental findings, the diagnosis, locoregional and general staging and the therapeutic approach to adopt are defined. The need for a multidisciplinary decision makes treatment at highly specialized centers indispensable. The opportunity of treating patients in specialized centers is also a consequence of the greater propensity to operate in compliance with the guidelines issued by multidisciplinary specialist groups. The presence of multidisciplinary groups, the treatment of patients and specialized centers and the organization of oncologic services in networks are in fact considered predictive of good compliance with guidelines [4].

11.4 Towards a National GIST Network

The network aims to be, at the same time:

- a network of subjects;
- a network of services;
- a technological infrastructure;
- an organizational model based on the sharing of knowledge, able to produce and sustain processes of rapid diagnostic and therapeutic innovation in the field of GIST management.

The network is a tool for the integration and optimal utilization of the widespread experiences and abilities of specialists which aims at making them available for the scientific governance of research projects and practical management of clinical cases.

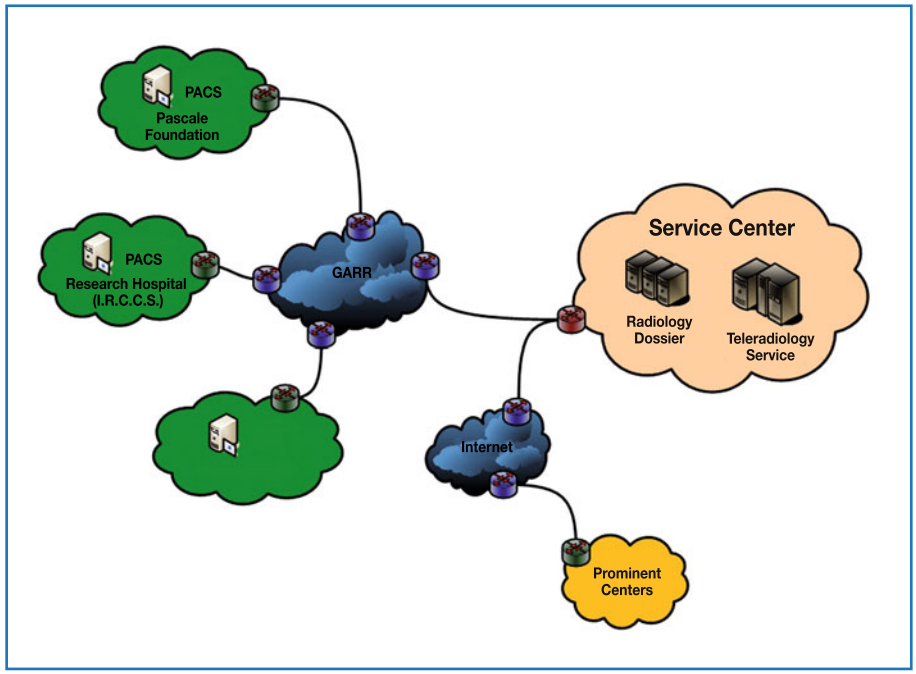

Fig. 11.1 Structure of the GIST network

Table 11.1 Objectives of the national GIST network

1.	Call for a survey of the activities performed by the various GIST Units throughout the country
2.	Organize a system of periodic data updating
3.	Provide a stable infrastructure for the creation and management of large clinical databases with a structure that is unified and shared among the centers and in strict compliance with security and privacy regulations
4.	Promote the formation of groups of competence, dialogue and immediate sharing of the results
5.	Provide visibility to the research and scientific potential of the participating centers, and function as a catalyst for the inflow of new resources
6.	Offer ongoing training with traveling and remote refresher courses
7.	Evaluate, compare and try out solutions and technologies in support of disease management
8.	Develop shared organizational models and act as a benchmark
9.	Make available network services, technological know-how and support applications to the participating centers

The reference management model is based on progressively increasing levels of integration of services and information flows between different level centers. The aim is to structure the network so that quality and excellence emerge. The fundamental concepts governing the network are participation, responsibility and transparency; the level of authority and leadership emerging from the positive contribution to the content of the network made by each participant is recognized.

The ethos dominating the network is of the collaborative type. The contribution of all parties is encouraged in order to develop a network of the highest quality. This includes promoting the desire to know each other and compare each other's experience so as to improve and review one's own (Table 11.1).

The network provides a management model centered on three types of governance and leadership integrated at various levels:

- clinical governance: this is much more specific than the general principles outlined above;
- scientific governance: this is characterized by robust coordination at the inter-regional and national level;

- technical-organizational management; this is characterized by solid technological competence, but able to effectively relate with the responsible parties of clinical and scientific governance [6].

11.5 Accreditation of the GIST Units

An integral part of the quality of care includes the adoption of evaluation instruments. These make possible and explicit the comparison of timely access to care, the maximum clinical efficacy obtainable for each individual patient, the appropriateness and timeliness of interventions, and the adoption of relational and communication behavior which meet the real complete-care needs of the patient and their family.

It is in this setting that terms which once were unknown and unfathomable such as audit, peer review, accreditation, ISO, VRQ, constant quality improvement, performance, risk management and so on have become so familiar that they run the risk that "as soon a word becomes popular it loses its clarity" [7].

This is a danger that is accentuated in the specific case by the fact that this specialized terminology can induce professionals to think that these phenomena are separate and independent of the care and treatment that is given daily to patients. In reality, however, there is a common approach to all of these initiatives and it would be wrong to consider them distant and different from one another. In fact, if they are not seen as different aspects of a common methodological approach, then there is the risk of them being treated as passing trends and being poorly framed by laws and institutions.

This chapter lays down an initial list of minimum standards for good operations and aims to be an incentive for defining the organizational and professional modality of GIST Units in Italy. To achieve this aim an effort has been made to define the standards for management of the common activities of the multidisciplinary team while intentionally leaving out those standards for each specific activity associated with the individual professions (oncology, surgery, radiotherapy, radiology, anatomic pathology) and made explicit in the documents of the reference scientific associations.

The fields to analyze were identified with reference to the management areas, and where possible the selection included those in line with the common criteria and standards of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and the European Foundation for Quality Management (EFQM) [8].

The approach for the management areas allowed the interdisciplinary team to be described regardless of the level of complexity of the services offered and from different points of view, with the results achieved in the organizational and management field being highlighted.

The standards of the management areas can be applied both to teams performing only several activities considered minimum for the definition of a team (evaluation and treatment of the patient decided on a multidisciplinary basis) and to teams with a more diversified range of activities.

The following management areas will be examined:

a) Organization
b) Training
c) Communication management
d) Clinical risk management

11.5.1 Organization

1. The organization guarantees the presence of a stable reference group for the care of GIST patients consisting of at least a surgeon, an oncologist, a radiotherapist, a radiologist and an anatomic pathologist.
2. The multidisciplinary team has defined a procedure/regulation of internal functioning that establishes at least:
   a) the functions, areas and levels of specific competence carried out by each team member;
   b) the organizational pathways of the patient among the different stages of treatment and care, with indications of access times and modalities;
   c) the modalities of communication between team members;
   d) the modality and frequency of meetings;
   e) the modality and frequency of multidisciplinary visits:
      - the multidisciplinary visit of the team should take place once staging is complete;
      - the minimum time of the multidisciplinary visit for in-patients and out-patients should be defined;
      - the reporting of targeted radiologic examinations should not exceed a wait of 1–2 days;
      - the CT report should be available within 1 day of the examination being performed;
      - the GIST patient requiring surgery should not be placed on a waiting list.

11.5.2 Training

1. All of the professionals in the multidisciplinary team possess the specific competence, in addition to the certification required by national law and consistent with the activities performed.
2. The multidisciplinary team members promote the activity of clinical trials, publish articles in medical journals and participate at conferences as speakers.
3. The multidisciplinary team cooperates or has cooperated over the past three years with scientific journals, publishing articles inherent to the specific activities carried out.
4. The multidisciplinary team is open to participating in tutoring programms and welcomes specialist or trainee physicians.
5. Newly appointed personnel operating within the multidisciplinary team are assigned a tutor.
6. Newly appointed personnel are periodically assessed on the degree of autonomy acquired after the opinion expressed by the tutor.
7. There is an annual internal training plan in line with national and regional training objectives, which correspond with the internal planning of the multidisciplinary team.
8. Internal meetings are scheduled for updating information in accordance with the established program and recordings of the meetings are made and archived.
9. Internal training is in place regarding the laws and procedures regulating the care of GIST patients, including prescriptive laws, privacy laws and right-to-information laws.

11.5.3 Communication Management

1. The multidisciplinary team has defined and recorded the phases of interdisciplinary clinical audit.
2. The multidisciplinary team has its own Service Charter which contains the necessary information for safeguarding patient privacy.
3. The Service Charter establishes the patient's right to obtain an appropriate report from the multidisciplinary team in the event of transfer to another specialist facility.
4. The Service Charter establishes the patient's right to obtain a copy of her/his own patient chart, healthcare records or complete report of her/his general clinical presentation.
5. The multidisciplinary team has informed consent forms available for the main types of treatment.
6. The multidisciplinary team has an archiving system for informed consent forms that it has gathered.
7. The multidisciplinary team has a procedure for handling complaints.
8. All of the operators have participated in at least one training course regarding the ethical problems most frequently encountered in the multidisciplinary team.

11.5.4 Clinical Risk Management

1. The multidisciplinary team guarantees the management of clinical and organizational audits as well as audit of the main risks associated with multidisciplinary care.
2. The multidisciplinary team guarantees a control system for verifying the accuracy of the diagnosis upon entrance.
3. The multidisciplinary team has defined a list of specific sentinel events and a procedure for their management.
4. A process has been set up for:
   - identifying all the pharmacologic therapies being undertaken by the patient;
   - noting in the clinical chart all the interactions regarding interferences with the administered therapy;
   - monitoring the side effects and adverse reactions of the prescribed therapy.
5. The multidisciplinary team identifies a reference person for drug surveillance from within the team.
6. The team member responsible for drug surveillance provides prompt and exhaustive information regarding the above mentioned variations to all the multidisciplinary team members, and also evaluates their real understanding and appropriateness of the undertaken treatment.
7. The team member responsible for drug surveillance organizes a pharmacologic audit at least every three months.
8. The multidisciplinary team has a procedure for handling patient complaints with regard to:
   - errors or delays in the diagnostic protocol;

- side effects or inconveniences of the therapy prescribed and carried out;
- inadequate treatment.

9. The multidisciplinary team has adopted an internal process for the voluntary reporting of incidents, errors or organizational and management malfunctions that may pose a clinical risk for patients.

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