

**Scandinavian Sarcoma Group and
Oncologic Center, Lund, Sweden**

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Recommendations for the Diagnosis and Treatment of Intraabdominal, Retroperitoneal, and Uterine Sarcoma



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Cover photograph:

CT of the abdomen in a patient with a retroperitoneal paraganglioma. Though a close relationship of the tumor to especially the inferior vena cava and aorta can be noted, the tumor is fairly well delimited and shows no invasion into surrounding structures.

Preface

Purpose of the current draft

All patients should at suspicion or diagnosis of a sarcoma be referred to a specialised centre for further evaluation and treatment.

The management of intraabdominal, retroperitoneal and pelvic soft tissue tumors is complex and the prognosis of patients with such tumors can be affected from the earliest stages of work-up. All patients should therefore be treated by a multidisciplinary group with interest and experience in sarcoma. That includes all categories involved in the evaluation and treatment as surgeon, oncologist, cytologist, pathologist and radiologist. The only way to achieve this is by gather these patients to only a few units. Furthermore, for a group of patients this rare, is centralisation the only way to be able to collect patients enough to get and maintain skill and experience, to develop and improve treatment, to collect patients and biological material enough for e.g. tissue bank and scientific studies and to be able to report outcome and follow up.

These recommendations are based on proposals made by the Scandinavian Sarcoma Group (SSG) members, mainly from the recently established group responsible for intraabdominal, retroperitoneal, pelvic and uterine soft tissue sarcoma.

The guidelines are aimed to give a general overview for the most important and initial decisions to be made and will provide recommendations that are based on the best available evidence. They will be updated periodically in accordance to the current knowledge of these disease entities.

Soft tissue sarcoma arising in the retroperitoneal space or in the intraabdominal cavity traditionally carries a poor prognosis. Many factors contribute to the fact that both the disease free and overall survival figures are poor among patients with sarcoma within these areas (see chapters 2.0 and 3.0). However, the introduction of tyrosine kinase inhibitors has dramatically changed the treatment and course of Gastrointestinal stromal tumors (GIST). Even in metastatic disease the maximum duration of response to Imatinib and other tyrosine kinase inhibitors is not yet known, and some patients may respond for longer than 5 years.

With the goal to improve the course and increase the survival of this group of sarcoma patients, the subsequent recommendations will focus on:

- Organisation and management
- pathological diagnosis
- anatomical evaluation
- surgical management
- adjuvant and palliative therapy
- clinical trials
- follow-up

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1.0 Introduction

Sarcoma that arise in the retroperitoneum or in the abdominal cavity are relatively rare tumors that constitute approximately 20-25% of all soft tissue sarcomas.

Patients commonly present with a large, non-tender abdominal mass. Often, symptoms of non-specific abdominal discomfort and a feeling of distension are reported, and approximately half of the patients will report pain. Because of their anatomic location and the non-specific symptoms, tumors in the retroperitoneum often grow to a considerable size before they are diagnosed. On the other hand, sarcomas arising in the gastrointestinal tract are more likely to give earlier symptoms and patients often present with bleeding, abdominal pain or obstruction.

Historically, the prognosis for these patients has been poor (Herman et al., 1999). Overall survival in most retrospective series is approximately 55% at five years with a range of 30-75%. Recurrence after 5 years is not uncommon and despite 5 years disease-free survival, 4 % will recur in the subsequent 5 years. On the other hand, the prognosis for GIST is today, after the introduction of tyrosine kinase inhibitors, not yet known. Even some patients with metastatic disease may respond for longer than 5 years (Blanke et al., 2008). GIST as entity, has many specific features and is therefore described separately in chapter 9.

There is general agreement in the literature that complete surgical resection is the most important factor for cure or prolonged survival (Dalton et al., 1999, Lewis et al., 1996, Ferrario et al., 2003, Singer et al., 2003). Furthermore, it has been shown that surgical treatment of retroperitoneal sarcomas at a specialised centre, where a relatively greater number of similar cases are treated, confers the patient a significantly better prognosis (Sæter et al., 1999). Complete resection can also be attained for recurrent disease, but the likelihood of achieving clear margins declines significantly as the number of recurrences increases (Lewis et al. 1998).

Nevertheless, due to anatomical considerations and the often extensive size of the tumors, it is often difficult to obtain adequate margins in the retroperitoneal compartment. Local recurrence is therefore more common than distant metastases which occur predominantly to the liver and lung in about one third of patients. Extensive locoregional tumor growth is commonly the cause of death.

In addition to non-complete surgical resection, also high malignancy grade, tumor size >10 cm, histological subtype (leiomyosarcoma unfavourable, liposarcoma favourable), and age >60 years, have been found to be related to worse survival by many groups.

Although adjuvant radiation reduces the local recurrence rate in extremity and superficial trunk sarcomas, gastrointestinal toxicity often limits the delivery of radiation to the retroperitoneum. Several retrospective studies suggest that adjuvant radiation improves local control after complete macroscopic resection is performed (Cody et al., 1981, Harrison et al., 1986, van Doorn et al., 1993, Catton et al., 1994). Other investigators found no benefit in adjuvant radiation therapy for completely resected retroperitoneal sarcomas (McGrath et al., 1984, Jaques et al., 1990, Heslin et al., 1997).

Intraoperative radiation therapy (IORT) and external beam radiation have been evaluated in two series (Sindelar et al., 1993, Willett et al., 1991). Though local control could be improved in the IORT arm, there was no survival advantage in either of the treatment arms and significant complications were attributed to both (Sindelar et al., 1993). A study from the Massachusetts General Hospital evaluated combined preoperative high-dose external beam radiation and intraoperative electron beam radiation. Although the number of patients in this

preliminary study was small, the results were encouraging in achieving local control (Willett et al., 1991).

Because of high complication rates of traditional non-conformal radiotherapy in retroperitoneal sarcoma and the lack of a clear demonstrable clinical effect, routine adjuvant radiation therapy is not recommended outside the confines of an investigational clinical trial.

Retrospective studies have not demonstrated any benefit to neoadjuvant (Storm et al., 1981) or adjuvant chemotherapy (Glenn et al., 1985) for retroperitoneal or intraabdominal sarcomas. Some authors even suggest a negative influence of chemotherapeutic regimens on survival, with patients receiving treatment showing an increased risk of death (Singer et al., 1995). As with extremity soft tissue sarcoma, there is no available data to support the routine use of adjuvant chemotherapy in these patients (Lewis et al., 1996).

The largest published series of retroperitoneal sarcomas includes 500 patients treated at the Memorial Sloan-Kettering Cancer Centre. Of the 278 patients (56%) that presented with primary tumors, 168 (60%) had high grade tumors, 198 (71%) had lesions >10 cm, and 136 (49%) were operated with microscopic tumor-free margins. Local recurrence developed in 217 (78%) patients and metastasis in 30 (11%). This group of 278 patients had a median survival of 72 months, while the group of 222 patients (44%) with recurrent or primary metastatic disease, had a median survival of 28 months for those with local recurrence and only 10 months for those with metastasis at presentation. Median follow-up was 28 months for the entire group (40 months for survivors) and this short observation period is an important limitation of the report.

Uterine sarcomas

Uterine sarcomas are usually not grouped with retroperitoneal or intraabdominal sarcomas in the literature. However, these largely preperitoneal lesions occurring in the pelvis share many characteristics with their abdominal and retroperitoneal counterparts and will be included in the present proposal. Even though sarcoma may also occur in the ovaries, vagina or vulva, the discussion here is restricted to the more common uterine sarcomas.

There is now convincing evidence that carcinosarcoma are mostly of monoclonal origin and should be regarded as metaplastic carcinoma, they are therefore excluded in the further description here.

Uterine sarcomas are uncommon accounting for less than 5% of all uterine cancers, yielding an annual incidence of 1,2-1,7/100,000 in the female population (NCCN, 2006, Nordal, 1998). The prognosis has been poor with a 5-year survival rate as low as 30% (Nordal, 1998). As for other sarcomas, surgery is the mainstay of treatment for gynaecological sarcomas and a tumor-free resection margin at primary surgery is the best predictor for survival.

2.0 Experience within the Scandinavian Sarcoma Group

A retrospective review of 36 primary retroperitoneal sarcomas treated at the Norwegian Radium Hospital (NRH) from 1978 to 1982 was published by Wist et al. in 1985. Complete resection with tumor-free margins was attained in only 36% of cases and the prognosis was significantly better in this small group. The other significant prognostic factor found was histological grade. Adjuvant radiotherapy was given to all but one of the patients and adjuvant chemotherapy to 17 patients. Over 15% developed radiation induced intestinal damage. The

relative importance of adjuvant treatment modalities to patient outcome was viewed as inconclusive.

More recently, the experience at the Norwegian Radium Hospital (NRH) of 149 patients with retroperitoneal sarcomas during the period of 1980 to 1997 was reported by Sæter et al. (1999). Of 107 patients with initially localised disease only 32% were referred without prior surgery, 24% after marginal resection and 34% after intralesional interventions including some incisional biopsies at laparotomy. Ten percent were referred only after locoregional relapse or distant metastasis. Microscopic tumor-free margins were obtained in 74% of patients not previously operated on and this figure compares favourably to radical resection rates (51%) obtained in other centres within Norway.

Favourable factors for survival in patients with localised disease using a multivariate analysis were non-contaminated surgery that had a 76% 5 year survival vs. 36% for the contaminated group, low malignancy grade with a 67% 5 year survival vs. 46% for high grade lesions, age <60 years with a 65% 5 year survival vs. 49% for patients >60 years, and female gender with a 63% 5 year survival rate vs. 47 % for the male gender (Sæter et al., 1999).

The conclusions emphasise the need for greater expertise in the handling of these rare tumors. In order to achieve better results, all patients should be referred to a specialised sarcoma centre before surgery. There, a multidisciplinary team, and specifically for these types of tumors, surgeons having a special interest and a relative greater experience in this field, can provide optimal treatment. Due to the rarity of these tumors expertise may be achieved in only a few centres. Furthermore, reporting of patients with intraabdominal, retroperitoneal and pelvic sarcomas to the SSG register is essential to gain further knowledge of these tumor types.

3.0 Pathology

3.1 Histological types

Sarcomas in the abdominal region (retroperitoneal, intraabdominal and pelvic tumors) include a broad spectrum of histological entities with both low-grade, intermediate and high-grade malignant tumors. The morphological classification is based on the WHO-classification system (Hamilton et al., 2000, Fletcher et al., 2002a, Tavassoli et al., 2003).

Retroperitoneal sarcomas

A retroperitoneal tumor is defined as being located posterior to the posterior peritoneum from the diaphragm to the pelvic floor (Heslin et al., 1997). The relative frequency of primary retroperitoneal sarcomas according to histological subtype is listed below (adapted from Lewis et al., 1998):

Sarcomas in retroperitoneum	Relative frequency
Liposarcoma	41%
Leiomyosarcoma	27%
Malignant fibrous histiocytoma	7%
Fibrosarcoma	6%
Hemangiopericytoma/Solitary fibrous tumor	3%
Malignant peripheral nerve sheath tumor	3%
Others	14%

Intra-abdominal sarcomas

The most abundant histological subtypes of sarcomas in the abdominal region are:

- Gastrointestinal stromal tumor (GIST)
- Leiomyosarcoma
- Malignant fibrous histiocytoma
- Rhabdomyosarcoma
- Others

Uterine sarcomas

The most common histological types of uterine sarcomas are (Abeler et al. in manuscript):

Uterine sarcomas	Relative frequency
Leiomyosarcoma	63%
Endometrial stromal sarcoma	21%
Adenosarcoma	6%
Undifferentiated endometrial/uterine sarcoma	5%
Other types	5%

The usual *leiomyosarcoma* (LMS) is a cellular neoplasm with atypical nuclei, high mitotic rate, necrosis and vascular invasion in up to 25% of the cases. The most important factors are mitotic rate, coagulative necrosis and grade of atypia and at least two of these factors should be present before diagnosing a leiomyomatous tumor as malignant. The utility of grading uterine LMS is controversial as there is no universally accepted grading system for these tumors.

Endometrial stromal sarcoma (ESS) is composed of stromal cells resembling those of the proliferating endometrium. Numerous small and thin walled vessels of the arteriolar type are characteristically present. The tumor cells infiltrate the myometrium diffusely and protrude into the larger vessels in the myometrium and in the parametrium. It is therefore of great importance to take sections from the parametria to detect extrauterine growth. Endometrial stromal sarcoma were previously subdivided into low-grade and high-grade. Today ESS by definition is a low-grade sarcoma and previously high-grade endometrial stromal sarcoma are classified as *undifferentiated endometrial/uterine sarcoma* which are highly aggressive and should be treated as such.

Adenosarcoma is a biphasic neoplasm containing a benign epithelial component and a sarcomatous mesenchymal component. The tumor may contain heterologues elements such as striated muscle cells, cartilage, fat and other components. Adenosarcoma typically grow as in exophytic polypoid masses in the uterine cavity. Most of the tumors do not invade the myometrium.

The current uterine neoplasm classification of the International Society of Gynecologic Pathology and WHO histological classification of tumors of the uterine corpus, renames *malignant mixed Müllerian sarcoma* as *carcinosarcoma* (malignant mixed epithelial and mesenchymal tumors) (Tavassoli et al., 2003). There is however, convincing evidence that carcinosarcoma are of monoclonal origin and should be regarded as metaplastic carcinomas and consequently excluded from the sarcoma group of tumors. Treatment of these neoplasms should probably be similar to that directed to aggressive high grade endometrial carcinomas (McCluggage, 2002). These tumors are excluded in the further description here.

3.2 Preoperative diagnosis

Diagnostic biopsy in abdominal sarcoma:

The method to use depends on the type of tumor and how much information needed, (see chapters 5.0, 6.2). Fine needle aspiration biopsy or a core-needle biopsy can be used. If possible an ultrasound guided fine needle aspiration biopsy is recommended as a first choice. If additional information is needed a core needle biopsy can be performed. When radiological examination shows a lipomatous tumor typical for a well-differentiated liposarcoma no further biopsy is needed.

The close cooperation between surgeon, radiologist and pathologist in the preoperative evaluation of a tumor is of utmost importance. An accurate diagnosis on a small sample from a large abdominal tumor is made more comfortably when information is gathered from all available sources.

Preoperative diagnosis of uterine sarcoma

If sarcoma is suspected is curettage indicated as first choice for evaluation.

Fine needle or core needle biopsy in the case of uterine sarcoma can also be used.

3.3 Handling of the surgical specimens

Fresh specimens:

Fresh (unfixed) surgical specimens should be submitted immediately after removal to the Department of Pathology. If it is not possible to send the tumor fresh, use formalin as a fixative. The specimen should be handled immediately upon arrival for deep-freezing of samples (at least -70°) for tissue banking and optimal fixation for electron microscopy when this analysis is wanted. It is recommended to send samples for cytogenetic analysis. When there is a reason to believe that the sarcoma may have a characteristic cytogenetic abnormality, samples should be processed for genetic analyses (FISH-analysis and/or RT-PCR). Imprints (touch preparations) of samples that are deep-frozen or saved for special analyses are recommended to certify that representative sarcoma tissue has been saved. Frozen sections can also be performed later for the same purpose.

Macroscopic examination:

1. Ideally the surgeon and the pathologist should examine the specimen together or at least communicate about problems that may arise regarding orientation of the specimen and resection margins. The surgeon can help to identify the most critical resection margins by marking with sutures. Radiological studies are useful for orientation. Drawings should be submitted with the specimen whenever possible. Photographic documentation is advised.
2. The specimen and the tumor size are measured in three dimensions on the fixed specimen.
3. The type of surrounding tissues should be described.
4. The margin is assessed on the pathological specimens after fixation in formalin and ink dyeing of the specimen's surface. Acetic acid can fixate the ink better.
5. The specimen is sliced at maximum 1 cm increments and sections are made from areas of closest margin. The closest margin of resection should be measured and its type of tissue recorded. Cut also perpendicular to the first cut for better analysis of the margins.
6. The percentage of macroscopic necrosis (based on tumor volume) should be estimated.
7. The consistency, colour and haemorrhage should be stated.
8. At least as many sections as the largest tumor dimension should be examined, e.g. at least 6 sections of a 6 cm tumor. A block guide is recommended. For very large tumors it is rarely necessary to take more than 10 blocks of the tumor itself.

Recommended sections:

Sections of the tumor interface with surrounding tissues as well as macroscopically divergent areas including necrotic and hemorrhagic areas.

It is recommended to take several sections from the peripheral part of the tumor. Vascular invasion is seen best in the tumor periphery.

Examine vessels at the margins.

Sample skin to include biopsy tract.

Any lymph nodes received should be sampled.

Whole tumor or large and middle sized sections are excellent for the examination of tumor heterogeneity, relationship of the tumor to surrounding tissues (growth pattern with either pushing border or diffuse infiltration) and the presence of vascular invasion.

For gynaecological tumors one should follow guidelines for examining the relevant organs as well.

Microscopic examination:

Standardized histological diagnosis according to the WHO blue books should be used. Immunohistochemistry should be performed when needed in the classification. For many tumors, especially the spindle cell tumors, a panel including CD117, CD34, CD10, smooth muscle actin, desmin, protein S-100 and AE1/AE3 is recommended. See also separate section 9 about gastrointestinal stromal tumor (GIST). “Second opinion“ diagnoses are strongly recommended.

It is difficult to apply diagnostic recommendations on sarcoma *pretreated* with radiotherapy and/or chemotherapy. Histological typing, assessment of necrosis and grading of tumor tissue are difficult in such cases.

Tumor depth

In resected specimens the tumor depth of infiltration should be recorded.

Definition of pathological and surgical resection margin

The most important margin is the poorest margin, i.e the part of the specimen where the tissue coverage is poorest (qualitatively and quantitatively). In that area the pathologist should record the type of tissue (e.g. fat, connective tissue) and the thickness (mm) of tissues covering the tumor.

Two positive margins are defined

Gross tumor left

The tumor is transected during the operation and macroscopic tissue is left. This is reported by the surgeon.

Intralesional

Microscopic tumor tissue is seen at the resection border (reported by the pathologist) or leakage of fluid/tissue from the tumor into the wound occurs during surgery (reported by the surgeon).

Negative margins are defined

There are no tumor cells at the resection margin. In case of a negative margin the pathologist reports the shortest distance (mm) between tumor and resection border in fat, muscle or loose areolar tissue.

Mitotic count

Generally one should only grade untreated primary sarcoma using good quality slides and representative tissue. Mitotic activity is counted in 10 high power field (HPF) and a 40 x

objective should be used. For GISTs 50 high power field should be counted (Fletcher et al., 2002b).

Vascular invasion

Vascular invasion can be seen within the tumor or in the adjacent tissues and is defined as the presence of tumor cells within any space having an obvious endothelial lining. Such tumor either has to be adherent to the luminal aspect of the vessel wall or, if free-floating, has to be associated with adherent fibrin, red blood cells, or leucocytes. If an intact layer of endothelium covers the tumor, if the involved space has no discernible endothelial lining or if the tumor invades the vessel wall (but not the lumen), then this is not accepted within the definition of vascular invasion. In other words bulging of tumor cells into a vessel space is not considered as vascular invasion. Immunostaining for CD31 or other vascular marker can be used to confirm the endothelial differentiation.

Tumor size

Tumor size is the maximum tumor diameter as measured on the surgical specimen, ideally before fixation in formalaldehyde, but if this is not possible no account is made for possible tumor shrinkage in the process of fixation.

Growth pattern

The peripheral tumor growth pattern is assessed microscopically. A pushing border has no signs of infiltrative growth. If there is any sign of infiltration into the surrounding tissue independent of amount, the growth pattern is classified as infiltrative. The amount of infiltration is not assessed.

Necrosis

Microscopic tumor necrosis is defined as the presence of amorphous cellular debris, usually associated with a neutrophil polymorphonuclear cell response. Dead cells are generally arranged in sheets, often with ghost nuclear outlines. Individual cell death, apoptotic bodies, areas of hyalinosis or oedema, areas of fibrinous exudate lacking tumor cells, and areas of acellular fibrosis are not accepted within the definition of necrosis. The amount should be stated in percent. Macroscopic necrosis, see above in *Macroscopic examination*.

3.4 Characteristic genetic features

Several sarcomas of the abdominal/retroperitoneal region and the female genital tract have characteristic somatic mutations that may be detected by cytogenetic, fluorescence in situ hybridization (FISH) and/or reverse transcribed polymerase chain reaction (RT-PCR) analysis. Sarcomas not listed in table below, such as adult fibrosarcoma, leiomyosarcoma, MFH, and MPNST, all have more or less complex karyotypic aberrations, without any tumor-specific feature.

Abdominal/retroperitoneal/uterine sarcomas with characteristic genetic features

Tumor type	Cytogenetic features	Molecular genetic features
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	<i>EWSR1/WT1</i> fusion gene
Endometrial stromal cell sarcoma of the uterus	t(7;17)(p15;q11) t(6;7)(p21;p15) t(6;10)(p21;p11)	<i>JAZF1/SUZ12</i> <i>JAZF1/PHF1</i> <i>EPC1/PHF1</i> fusion gene
Gastrointestinal stromal tumor (GIST)	Complex, no specific changes	Activating mutations in <i>KIT</i> or <i>PDGFRA</i>
Inflammatory myofibroblastic tumor	Translocations affecting band 2p23	<i>ALK</i> rearrangements
Liposarcoma, myxoid/round cell	t(12;16)(q13;p11) t(12;22)(q13;q12)	<i>FUS/DDIT3</i> <i>EWSR1/DDIT3</i> fusion gene
Liposarcoma, well-differentiated and dedifferentiated	Ring chromosomes/giant marker chromosomes	Amplification of e.g., <i>SAS</i> , <i>CDK4</i> , <i>MDM2</i>
Rhabdomyosarcoma, alveolar	t(1;13)(p36;q14) t(2;13)(q36;q14)	<i>PAX7/FOXO1A</i> <i>PAX3/FOXO1A</i> fusion gene
Synovial sarcoma	t(X;18)(p11;q11)	SS18/SSX fusion genes

Mitelman Database of Chromosome Aberrations in Cancer 2007. Mitelman F, Johansson B and Mertens F (Eds.)

3.5 Grading

There is no universally accepted grading system for sarcomas (Deyrup and Weiss, 2006). For retroperitoneal and intraabdominal tumors the pathologist should give a grade based on the Scandinavian and the French system. GISTs are not graded, but a risk assessment according to Fletcher et al (2002) should be given. The utility of grading in uterine leiomyosarcoma is controversial, and no accepted grading system exists.

It may be difficult to grade the malignancy on small tissue fragments from large tumors, because of tumor heterogeneity or sampling error. Very often the final grading will have to wait until the operation specimen is available.

If preoperative therapy will be given, one can easily undergrade the tumors in the final diagnosis.

The four-tiered grading system

In the Scandinavian Sarcoma Group the four-tiered grading system is used. Grade 1 and 2 means low grade malignancy and grade 3 and 4, high grade malignancy. This system is primarily based on Broders grading of malignant tumors and considers the amount of necrosis, bleeding, mitotic count, cellularity, cell and nuclear polymorphism, and differentiation without given a score to the different parameters (Broders, 1920 and 1939).

For many soft tissue sarcoma the grade is understood or implicit in the diagnosis. Immunostaining for proliferative activity with Ki-67 (MIB1) is highly recommended.

The French grading system (FNCLCC)

- is based on tumor differentiation, mitotic count and the amount of tumor necrosis (Guillou et al., 1997). The total score of these parameters gives the grade. Grade 2 and grade 3 are considered high-grade malignant tumors. See appendix.

Risk assessment in GIST

Risk assessment by Fletcher et al 2002 should be used in GIST tumors. It is based on tumor size and mitotic count and is divided into 5 risk groups, (see chapter 9.5).

3.6 Final diagnosis

The final diagnosis on the operation specimen should contain the following information (Rubin et al., 2007).

- 1 Histological diagnosis. According to WHO
- 2 Size. Three dimensions, cm
- 3 Presence of vascular invasion
- 4 Presence of necrosis. Yes or no, and $<$ or $\geq 50\%$
- 5 Growth pattern. Pushing or infiltrative
- 6 Specimen type with localisation and statement of which tissue infiltrated
- 7 Statement about resection margins
- 8 Mitotic count including Ki-67 . Per 10 HPF (for GISTs per 50 HPF)
- 9 Grade
- 10 Results of ancillary studies. Immunohistochemistry, genetic analysis, ultrastructural pathology

4.0 Imaging

4.1 Preoperative imaging evaluation

Multidetector spiral computed tomography (CT) and magnetic resonance imaging (MRI) are today the most comprehensive imaging techniques available to evaluate soft tissue tumors of the retroperitoneum, intraabdominal cavity and the lesser pelvis.

CT is preferred as a general screening tool for abdominal and retroperitoneal pathology. It has the main advantages of short scanning times, reproducibility and limited motion artefacts. The introduction of helical CT and especially the multi-detector technique has contributed to improvement in temporal and spatial resolution, allowing multi-planar reconstructions, and has reduced examination time considerably.

CT is superior to MRI in showing calcifications and abnormal gas collections, but has a limited soft tissue contrast resolution compared to MRI. The contrast resolution can be helpful, for example, to distinguish tumors from hematomas and abscesses. In patients with verified retroperitoneal masses, especially neoplastic lesions, MRI is a valuable adjunct to CT and has significant advantages that make it the method of choice for secondary evaluation. Knowledge about the location of the mass prior to the MR-examination is important to be able to obtain adequate information. Beside almost unlimited alternative means of acquiring images with different image contrast, the magnetic field homogeneity limits most detailed MR-applications to use no more than a 50 cm field of view.

The retroperitoneum is well suited for MR imaging because its contents are relatively stationary and localised. Retroperitoneal sarcoma are usually large at diagnosis and reduce movement artefacts by compressing the surrounding structures. Even without the use of contrast agents, MRI allows recognition of major blood vessels and evaluation of blood flow. The intrinsic high soft tissue contrast resolution of MR-imaging facilitates identification of adipose tissues (normal fat versus a well-differentiated liposarcoma), necrosis (most frequent in leiomyosarcoma), fibrous components, and intratumoral haemorrhage. However, high-resolution MR-imaging requires scanning times that are longer than on CT. This frequently leads to motion artefacts that may reduce image quality and also contributes to less reproducibility compared to CT.

As a general rule, contrast-enhanced CT of the chest, abdomen and pelvis should always be performed in patients with abdominal or retroperitoneal tumors. These examinations may be done at local hospitals. A pre-contrast series in the first diagnostic CT may be useful to identify tumor calcification. Intravenous contrast medium should always be used.

MRI for further diagnosis should be performed at, or in close co-operation with the centralised sarcoma centre where the treatment will eventually be instituted. Based on the earlier CT findings, the MR examination can then be tailored for optimal definition of the pathology in each tumor depending on the specific anatomical site.

The optimal examination protocol for MRI depends on the equipment. Minimum field strength should be 1.0 Tesla. Phased array coils must be available. Basic sequences should comprise coronal fast (turbo) T2-weighted respiratory triggered or single shot sequence followed by an axial T2-weighted sequence. T1-weighted images are performed with gradient echo sequences, upper abdomen breath-hold in and opposed phase and lower abdomen preferably a 3D sequence. The tumor area is imaged with axial T1-weighted fat-saturated 3D-gradient-echo images before and after injection of a gadolinium chelate (if not contraindicated). Additional sequences may be added depending on tumor characteristics and anatomical site.

MR angiography may be useful, especially to evaluate venous invasion, mapping of the vessels in proximity of the tumor and the tumor blood supply as well. This is of special importance if there is a risk or need for “en bloc” resection including important adjacent vascular structures. Invasive vascular examinations such as angiography or cavography are rarely indicated today.

MR pyelography can be done in a few seconds with a single shot fast spin echo sequence and should obviate the need for intravenous pyelography. If the kidney of one side may have to be removed with the tumor, renography is the method of choice for calculation of the left/right ratio of kidney function.

CT of the lungs is a necessary adjunct to a plain chest radiograph in order to diagnose or exclude pulmonary metastases and evaluate the mediastinum.

If available, positron emission tomography (PET) or preferably PET-CT using ¹⁸F fluoro-deoxy glucose (FDG) is helpful in dedicated cases for detailed mapping of metastatic deposition in the planning of major surgical procedures. FDG PET-CT, Functional MR-imaging techniques (diffusion weighted imaging and dynamic contrast enhanced techniques) and contrast-enhanced ultrasound (CEUS) are promising for therapy assessment, especially in smaller clinical trials.

Endoscopy can be used to evaluate the extension of tumors in the oesophagus, stomach, duodenum and rectum/colon. It allows biopsies and needle cytology to be performed at the same time.

Endoscopic ultrasound (EUS) is a very useful method for the investigation of subepithelial tumors in the gastrointestinal wall in the oesophagus, stomach, duodenum and rectum/colon. With EUS, the layer of origin of the tumor in the gastrointestinal wall, the depth of tumor infiltration and infiltration into adjacent organs can usually be determined. EUS guided fine-needle aspiration biopsies (FNAB) and core biopsies can be performed. On-site cytology is preferably.

Contrast Enhanced Ultrasound (CEUS) with the second generation of ultrasound contrast medium, SonoVue, Sulphur Hexafluoride (SF₆), (Bracco, Milan, Italy) is a well established method for visualisation of macro- and micro-vascularisation and perfusion of different tissues and organs. This contrast agent is a true blood pool agent and the technique has overcome the limitations of conventional and colour and power Doppler US. One of the main indications is detection and characterisation of focal liver lesions and CEUS is very sensitive diagnosing even very small metastases in the liver. (EFSUMB et al.)

Realtime evaluation of tumors with CEUS can show an increase in vascularity in tumor angiogenesis or reduced vascularity in necrotic/ablated tissue. Dynamic contrast-enhanced ultrasound with quantification of tumor perfusion is a new diagnostic tool to evaluate early response to antiangiogenic treatment (Lassau et al.).

Uterine sarcoma

As for other visceral and pelvic sarcoma are CT of thorax, abdomen and pelvis preferred as a general screening tool for basic preoperative evaluation and to exclude lung metastases and intraabdominal spread. A vaginal ultrasound scan can be a helpful method, although, if extrauterine spread is suspected, MRI is to be preferred. In recurrent disease, the extent of disease should be evaluated by CT thorax, abdomen and pelvis. PET-CT may be useful in differentiation between leiomyosarcoma and leiomyoma, in follow up and when planning for extensive surgery of recurrent disease, but the clinical value of PET remains to be proven. (Umesaki, 2001, Chander, 2003).

5.0 Symptoms and diagnostic considerations

5.1 Retroperitoneal and intraabdominal sarcoma

Patients commonly present with a large, non-tender abdominal mass. Often, the patient will experience symptoms of non-specific abdominal discomfort and a feeling of distension, and approximately half of the patients will report pain. Because of their anatomic location and the non-specific symptoms, tumors in the retroperitoneum often grow to a considerable size before they are diagnosed. However, sarcoma arising in the gastrointestinal tract is more likely to give earlier symptoms and patients often present with bleeding, abdominal pain or obstruction.

A close cooperation between surgeon, radiologist and pathologist in the preoperative evaluation of a tumor is of outmost importance. An accurate diagnosis on a small sample from a large abdominal tumor is made more comfortably when information is gathered from all available sources.

The method to use depends on the suspected type of tumor and how much information is needed prior to treatment. In cases where preoperative treatment is a possibility, (e.g. small round cell tumors or primarily inoperable tumors) or the diagnosis will influence the surgical procedure, (e.g. schwannoma) the diagnosis must be more accurate. In other cases an

unspecific diagnosis can be sufficient if just to distinguish between sarcoma and non sarcoma tumors and between malignant or benign tumor.

Cytology by fine needle aspiration biopsy, guided by ultrasound or CT scan is the method of choice for obtaining tissue. This method should in most cases give enough information for diagnosis and malignancy. When additional information is needed a core needle biopsy can be performed, example is if fine needle biopsy has not provided enough information or if preoperative treatment of GIST is planed as mutation analyses has to be discussed. When radiological examination shows a lipomatous tumor typical for a well-differentiated liposarcoma no further biopsy is generally needed.

The diagnostic biopsy should be planned by the surgeon who will be responsible for the definitive surgery. A retroperitoneal puncture route for retroperitoneal lesions may decrease the conceivable risk for dissemination of tumor cells into the abdominal cavity. A transperitoneal approach is usually indicated for intraabdominal lesions. In tumors of the stomach or oesophagus needle cytology can frequently be taken through the gastroscope or with endoscopic ultrasound. Unlike the needle biopsy, a forceps biopsy through the gastroscope is in most cases unreliable as the tumors are frequently covered with normal mucous membranes and the samples may therefore be non-representative.

Open biopsy should always be avoided, since this most certainly leads to dissemination of malignant cells into the abdominal cavity or within the retroperitoneum.

5.2 Uterine sarcoma

The diagnostic problem with uterine leiomyosarcoma is the occurrence of a benign counterpart, namely leiomyomas, which are prevalent in premenopausal women. Less than 1% of uterine myomas are in fact leiomyosarcoma and there is no non invasive procedure to safely differentiate between the two entities. Thus leiomyosarcoma is quite often diagnosed postoperatively by histopathology.

Symptoms arousing suspicion of sarcoma are irregular vaginal bleedings, pain, anemia and a pelvic mass. Growing myomas in a postmenopausal woman without hormone replacement therapy should be highly suspected for sarcoma.

If sarcoma is suspected, curettage is indicated. In leiomyosarcoma less then 50% are diagnosed by curettage as many of the tumors have no connection with the uterine cavity. On the contrary most of the ESS can be diagnosed by this method. Fine needle biopsy in the case of uterine sarcomas can be misinterpreted but can be used if a diagnosis of malignancy will change the surgical procedure.

6.0 Surgical aspects

6.1 Surgical goal

Surgery is today the mainstay treatment for patients with visceral, pelvic and retroperitoneal sarcoma. It is the only potential curative treatment and the goal is complete surgical resection with microscopic tumor-free margins. This still applies to GISTs despite the development of tyrosine kinase inhibitors that have changed the course of this disease entity dramatically (see chapter 9).

Complete resection with adequate margins during the first operation is the single most important determinant for the outcome of these patients (Karakousis et al., 1996, Sæter et al., 1999, Ferrario et al., 2002, Singer et al., 2003). Resectability rates for primary tumors range from 50 to 75% when all patients evaluated for treatment are considered, and up to 95% when based on patients referred to surgery alone (Bautista et al., 2000, Lewis et al., 1998, Karakousis et al., 1996).

6.2 Surgical considerations

6.2.1 Retroperitoneal and intraabdominal tumors

The usually large size attained by retroperitoneal and intraabdominal tumors before diagnosis, the biologic growth characteristics, and the close relationship to vital organs and structures in the retroperitoneum and in the abdominal cavity makes, in most cases, surgical resection of these lesions a complex operative procedure. Specific knowledge of the pattern of growth and spread of sarcomas in these compartments is required by any surgeon attempting to operate on patients with these lesions if adequate results are to be obtained.

Before planning of surgery all patients should be discussed in a multidisciplinary team regarding treatment, surgery, neoadjuvant or adjuvant treatment and inclusion in study protocols.

Preoperative surgical planning is essential. Defining the location, the extent, and the relationship of the tumor to adjoining structures and organs is imperative for adequate surgery. Compression of normal tissues around the lesion versus direct invasion of the tumor into defined structures is one detail that cannot always be foreseen by radiological studies. Nevertheless, all radiological examinations need to be carefully studied in order to plan the extent of the resection. Since a complete resection is the goal, adequate tissue margins around the tumor need to be defined and when necessary, organs adjoining the tumor need to be considered for en bloc resection. It is of utmost importance to be well prepared before any incision is made.

Despite proper preoperative planning, many decisions need to be postponed and taken during the course of the operation. The surgeon has to have an open mind and be prepared to change strategies during the operation. As in all oncological surgery, a balanced decision has to be taken between the benefit of long time survival compared with the risk of immediate morbidity, long term disablement or even mortality that the surgery might cause. From a general point of view one can accept higher surgical risk and degree of mutilation in younger patients with low-grade tumors if this is to achieve complete resection of the lesion and a potential cure.

6.2.2 Uterine sarcoma

In uterine sarcoma total hysterectomy fulfils the claim on radicality if the disease is confined to the uterus. The standard treatment is total abdominal hysterectomy and bilateral salpingoophorectomy (TAH/BSO) by a midline incision.

In early stage of leiomyosarcoma the ovaries can be left behind in premenopausal women as the incidence of metastases to the ovaries is very low. (Leitao et al., 2003, Giuntoli, 2003). Bilateral SOE has usually been performed in ESS due to the risk of ovarian metastases and estrogen dependency of the tumor. There are however reports justifying to preserve the ovaries in premenopausal women with endometrial stromal sarcoma (Amant, 2007, Li, 2005, Chu, 2003). In advanced disease en bloc surgery should be applied to avoid tumor spill, following the principle for other abdominal sarcomas.

As most cases of leiomyosarcoma will remain undiagnosed preoperatively, it is highly recommended to avoid surgical techniques with intraabdominal transection of the uterine corpus in surgery for a presumed leiomyoma, as this will cause intraabdominal seeding in case of a sarcoma. (In case of supravaginal hysterectomy, the transaction of the cervix should be placed well below the isthmus).

For medically inoperable patients with uterine sarcoma, is the options pelvic RT (with or without brachytherapy), chemotherapy or hormone therapy.

6.3 Technical aspects

The preferred surgical incision for resection of visceral, pelvic or retroperitoneal tumors is a generous midline incision that achieves wide exposure. This approach may be extended by a transverse abdominal incision, by an incision into the groin or even into the thorax as dictated by the extension of the lesion. Examination of all organs and structures for determination of the extent of disease is mandatory. The accurate anatomic relationship of the lesion to surrounding structures and organs is evaluated so that a tumor-free resection plane can be determined.

Contiguous organs that are tightly adherent or infiltrated by the tumor must be resected en-bloc with the tumor. Common to retroperitoneal sarcoma resection is the removal of a kidney and adrenal gland. Other organs, like the spleen and the tail of the pancreas for left sided tumors are also frequently considered for resection. With tumors originating in the gastrointestinal tract, gastric or intestinal resections become mandatory. In many others, including gynaecological sarcomas, resection of a segment of small intestine is common due to tight adherences. Vascular structures, like the vena cava and aorta are seldom infiltrated by tumor and dissection can usually be carried out safely under the adventitia. Rarely do these vital structures need to be removed. When collateral veins have formed following chronic compression of the vena cava, then this structure can be ligated and the involved segment resected. Other times, when essential vessels as aorta or vena cava are involved, resection has to be done and repair with autologous or synthetic grafts must be used for as replacement.

The expansive growth of sarcoma in the retroperitoneum and abdominal cavity often cause compression of surrounding structures without direct invasion, and an anatomical tumor-free plane can be found. Utmost care in surgical technique is needed for resection along these planes as they usually are extremely thin. Dissection must always proceed well outside the tumor pseudocapsule and with as much covering of normal tissue as possible. Even the smallest of openings into the pseudocapsule may lead to tumor cell spillage and affect the prognosis negatively.

Resection of sarcoma is usually carried out in a circumferential manner. The tumor and its envelope of normal tissue which may include adjacent organs, is approached from all sides. The easier part of the specimen is usually dissected first, leaving the most difficult part to the end.

Resection of the draining lymph nodes is not necessary in sarcoma surgery unless these are clinically suspicious for the presence of tumor.

Reconstruction of anatomical structures resected during complex sarcoma surgery may involve grafts for abdominal wall defects or diaphragm resections.. As mentioned previously, graft replacement for vascular structures is rare and it is more common that patch reconstruction of vessels is performed to avoid stricture following partial vessel wall resection.

6.4 Surgical treatment report

In order to be able to evaluate the results of surgical treatment of sarcoma of the retroperitoneal and abdominal cavity, it is necessary that resections are evaluated according to clinical and pathological criteria. For the surgeon it is imperative to describe the radicality of the operation (all gross tumor removed “en bloc” or not) and any event that may have led to tumor cell spillage. For the pathologist, it is important to describe the resection margins and report them as other sarcomas (see chapter 3).

Intralesional surgery, defined as dissection into tumor tissue or within the tumor pseudocapsule, does not lead to removal of all tumor tissue and should always be avoided when operating with the intent of cure. Even a small incision into the tumor in the face of complete resection must always be reported, for it carries a high likelihood of tumor cell spillage. Accordingly, an open biopsy must be regarded as intralesional, as this will lead to spillage and seeding of malignant cells into the surrounding tissues. Shelling out a tumor, as described in many gynaecological procedures for leiomyomas, is regarded as intralesional surgery and leads to incomplete removal of the tumor.

After surgical description and complete pathological assessment of the specimen, the following categories of radicality can be established: macroscopic (gross “en bloc” resection) and microscopic tumor-free margins, macroscopic free but microscopic tumor-positive margins, macroscopic and microscopic tumor-positive margins. In addition, intraoperative tumor spillage events should be mentioned under each category.

6.5 Recurrence and metastasis

A significant number of first failures occur at the local resection site only. Many other recurrences are limited to a single or few well-circumscribed lesions within the retroperitoneum or abdominal cavity (Heslin et al., 1997). The standard of care for patients with recurrent sarcoma is repeat surgical resection following the principles of treatment for primary tumors (Wang et al., 1994). Whenever feasible, the intention should still be curative and complete resection with tumor-free margins should be the goal. The indication to operate is based not only on the presence of a clinically or radiologically diagnosed recurrence, but also on symptoms that the patient refers.

Complete resection of all macroscopic tumor tissue is still a significant variable predicting outcome in patients with recurrent disease. Median survival after local recurrence is 60 months in resected patients versus 20 months in unresected patients (Lewis et al., 1998). The rate of success for complete resection decreases after each subsequent recurrence and was 57% after the first, 33% after the second, and 14% after the third recurrence in the analysis of 500 patients treated at The Memorial Sloan-Kettering Cancer Centre (Lewis et al., 1998).

In the face of ineffective adjuvant therapy, patients with locally advanced or disseminated disease, and perhaps even patients with second or third recurrences, should by all purposes be considered incurable. But even when curative surgery with complete microscopic tumor-free resection is no longer possible, palliative surgical resection should still be considered for symptom relief. Many patients with locally advanced or disseminated disease can still have a prolonged survival. Palliative operative treatment with the aim of macroscopic tumor resection can often improve the quality of life.

All patients with recurrent disease should be evaluated and discussed for combination therapy of surgery, radiotherapy, chemotherapy and other agents as for GISTs were, treatment with imatinib (STI571, GLIVEC[®]) is always to be considered if curative intended surgery is not possible (see chapter 9).

Uterine sarcoma

Failure rates in leiomyosarcoma confined to the uterus may be as high as 70 % and distant metastases are more prevalent than local recurrences. Survival for patients with recurrent disease is poor. In a study from the Mayo Clinic comprising 128 patients with recurrent uterine LMS, secondary cytoreductive surgery prolonged survival in a select group of patients (Giuntoli, 2007). Neither chemotherapy nor radiation therapy was associated with improvement in outcome.

Several other studies have evaluated the feasibility of resection of recurrent leiomyosarcoma (Anraku, 2004, Levenback, 1992, Leitao, 2002) In agreement with the Mayo study they found that a survival benefit was seen in patient with a more than 6-month disease-free interval, either local or distant recurrence and optimal resection. These factors should be considered when deciding on secondary cytoreductive surgery. Preoperative evaluation of the extent of disease is vital in determining the possibility of complete resection. CT of the chest, abdomen and pelvis should be performed and in addition MRI if pelvis is included.

ESS is a less aggressive disease than LMS having a more indolent course. Recurrences can appear after long time and are often localized in the pelvis, even if lung metastases occur. Repeated surgery may be indicated. ESS tumors often express oestrogen and progesterone receptors and treatment with progestin has shown effect on recurrent and metastatic disease. This treatment should be considered as adjuvant treatment as well as for recurrent disease (Chu, 2003).

7.0 Radiotherapy

Radiotherapy as an adjunct to surgery in the treatment of intraabdominal and retroperitoneal sarcomas has been used by several groups in an attempt to improve local control. Data regarding the use of radiotherapy has been extrapolated from studies examining the effectiveness of this treatment modality in extremity sarcomas and only very few randomised prospective studies have evaluated the specific use and effectiveness of radiation treatment in retroperitoneal or intraabdominal sarcomas (Herman et al., 1999, McGinn, 2000).

The theoretical advantages of giving preoperative radiation to improve the rate of resection with tumor-free margins and reduce the risk of peritoneal or systemic seeding secondary to operative manipulation are not validated in clinical series. Preoperative therapy involves delivery of radiation to the entire tumor volume, yet this may not be necessary. In addition, appropriate doses of >35 Gy are often associated with delayed wound healing.

The value of intraoperative radiotherapy (IORT) has been investigated in one of the few randomised trials in retroperitoneal sarcoma by Sindelar et al., 1993. Patients that received IORT (20 Gy) followed by postoperative external beam radiation (35-40 Gy) experienced a significant reduction in local failure compared to a control group that received external beam radiation (50-55 Gy) only. However, IORT-treated patients developed a high rate of radiation-related peripheral neuropathy and the control group patients had a higher rate of radiation enteritis. Neither group experienced a survival advantage.

The use of radiation therapy following en bloc resection has been used in a number of institutions without a clear prospective definition of the selection of patients for adjuvant treatment. Those patients receiving adjuvant radiation, details regarding dose and volume are not uniform, and frequently not even reported. These retrospective studies are all relatively

small (<25 patients) and definitive conclusions cannot be drawn (van Doorn et al., 1993, Fein et al., 1995).

The most obvious advantage of postoperative instead of preoperative radiation therapy is having a full pathologic evaluation of stage, grade and margin status before treatment. This advantage is offset by the difficulty in clearly identifying the region at risk and by the return of normal tissues, including bowel, to these areas.

A dose response relationship has been suggested by several retrospective reviews and improved rates of local control have been observed with doses >55-60 Gy (Catton et al., 1994, Fein et al., 1995). Unfortunately, this dose escalation is frequently related to gastrointestinal toxicity and other radiation-induced complications. Three-dimensional treatment planning, merging advanced computer graphics to CT scan data sets, may improve the delivery of higher doses with acceptable toxicity, though these techniques are still heavily dependent on the difficulty of identifying the region at greatest risk so that the volume to be irradiated can be more clearly established. A close working relationship between surgeon and radiation oncologist is helpful and the intraoperative placement of clips can radiographically suggest the area of previous resection. Nonetheless, the difficulty in identifying the area of concern postoperatively cannot be overcome completely. These techniques have yet to be studied and validated in a prospective fashion.

Although some reviews have found a delay in local recurrence after adjuvant external beam radiotherapy and after IORT and external beam radiation, this gain did not prevent local recurrence and more importantly, it did not translate into a survival benefit (Sindelar et al., 1993, Catton et al., 1994, Alektiar et al., 2000, Pirayesh et al., 2001).

The lack of effect on survival by radiotherapy can at least partially be explained by the frequent transperitoneal spread of these tumors. This mode of spread and subsequent recurrence is at least as significant, and possibly even more, as local recurrence at sites of marginal resection.

Therefore, the routine use of adjuvant radiation therapy for abdominal, pelvic and retroperitoneal sarcomas cannot at present be recommended.

Nevertheless, we suggest the consideration of a clinical trial for a well defined subgroup to be treated with adjuvant radiation therapy. Discussions are on-going and participation in a proposed forth-coming European study may be an alternative for SSG. Outside from a clinical study, only individual patients operated for tumors of malignancy grade 3 or 4, where macroscopic tumor tissue is left behind, or where the resection margins are microscopically involved with tumor, should be considered for postoperative external radiotherapy.

Uterine sarcomas

The role of adjuvant radiotherapy in uterine sarcoma is controversial. All available data are retrospective and usually including all histological types (even carcinosarcoma). A number of institutions have reported outcomes of all uterine sarcomas combined (Olah et al., 1991, Salazar et al., 1978). Salazar et al. reviewed more than 900 cases. They noted increased local control with the addition of radiotherapy. Some other studies have noted similar results (Knocke, 1998, Livi, 2003, Ferrer et al., 1999). However, as these studies are retrospective there might be a selection bias with respect to treatment when patients receiving adjuvant radiotherapy are compared to patients treated with surgery alone. Despite this limitation, there is still some evidence that radiotherapy can be of importance in the curative therapy of uterine sarcoma. The only randomised study on adjuvant radiotherapy in stage I and II uterine sarcomas so far has not shown any benefit for radiotherapy. (EORTC, preliminary results).

Studies that only have looked at ESS have seen long disease-free intervals in absence of specific therapy and do not recommend adjuvant radiotherapy (Mansi, 1990).

8.0 Chemotherapy

8.1 Adjuvant/Neoadjuvant treatment

Little data exist to support the use of adjuvant chemotherapy as a means to improve distant control or survival in patients with resectable intraabdominal or retroperitoneal sarcoma. Most of the studies have been small non randomized trials that have been subject to selection bias. No benefit has been demonstrated, but may on the other hand not be excluded.

Introduction of tyrosine kinase inhibitors in the treatment of GIST has dramatically changed the course of this disease. GIST will be discussed separately, see chapter 9.8.

Studies of neoadjuvant chemotherapy in soft-tissue sarcoma have also been performed. In a retrospective study Meric et al., (2000) reported on the safety of such a strategy. In this study 105 patients received neoadjuvant chemotherapy, 34 of whom had retroperitoneal or intraabdominal sarcomas. No significant difference in morbidity rates when compared to patients who had primary surgery was found. In a subsequent study, 23 patients with retroperitoneal sarcoma, potentially operable at time point for diagnosis, were treated with doxorubicin/ ifosfamide-based neoadjuvant chemotherapy (Meric et al., 2002). 16 patients had no radiographic response, and of these 5 (31%) had unresectable or only partially resectable disease upon exploration. In contrast, all seven patients who had radiographic response to preoperative chemotherapy had resectable disease.

The potential role of chemotherapy in patients with resectable retroperitoneal sarcoma, whether delivered pre- or postoperatively, is currently undefined and may not be generally recommended outside of clinical trials.

Combined chemo- and radiation therapy preoperatively have demonstrated that this treatment strategy for retroperitoneal sarcoma is feasible with low toxicity rates. There have been pilot and phase I studies utilizing iododeoxuridine- or doxorubicin-based chemoradiation (Eilber et al., 1995, Robertson et al., 1995, Pisters et al., 2003). Phase II studies will be necessary to clarify response rates and toxicity profiles.

8.2 Treatment for advanced disease

Systemic chemotherapy should be considered in the treatment of unresectable or metastatic disease in which it may be used for palliation of symptoms and control of disease progression (see SSG XIX; Recommendations for treatment of metastatic soft-tissue sarcoma in adult patients). Currently, doxorubicin and ifosfamide are mostly used as the first line chemotherapeutic regimen for all localizations of soft tissues sarcoma. However, there are no data specifically analyzing the effect in advanced disease with abdominal origin.

Trabectedin (Yondelis[®]), a marine-derived antineoplastic agent, has recently received marketing authorization for the treatment of metastatic or advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide. Clinical benefit has especially been shown in patients with leiomyosarcoma and liposarcoma. In three Phase II studies involving 189 previously treated patients a pooled analysis of data showed that trabectedin induced tumor control (objective responses plus disease stabilization) in approximately 50% of the patients; median overall survival was 10.3 months and progression-free survival at 6 months was 19.8 months

with 29.3 % of patients alive at 2 years. (Garcia-Carbonero et al., 2004, Le Cesne et al., 2005, Yovine et al., 2004). The effect of Yondelis in abdominal located sarcoma was not specified in these studies.

In other studies of newer drugs abdominal sarcomas were included, but not separately studied. Thus, Leu et al., (2004) reported a retrospective review of 35 patients with various types of sarcoma who received gemcitabine sequentially followed by docetaxel as second-line therapy. Six patients had retroperitoneal leiomyosarcoma. Of the 12 patients with leiomyosarcoma, two had complete response, five partial response, three stable disease, and two had progressive disease. The overall response rate for the entire cohort was 43%, and median survival was 13 months. Furthermore, Bay et al., (2006) evaluated the combination of docetaxel and gemcitabine for advanced soft-tissue sarcomas. Of 133 patients 23 patients had primary retroperitoneal soft-tissue sarcomas. The overall response rate for all patients (133) was 18%, three patients had a complete response, and 18 patients experienced a partial response. No statistical difference was found with respect to the initial localization.

A multimodal approach involving surgery, chemotherapy and radiotherapy is necessary in the treatment of abdominal, pelvic and retroperitoneal rhabdomyosarcoma. For patients <21 years old with localized rhabdomyosarcoma protocol EpSSGRMS 2005 should be applied. Patients with desmoplastic small-cell tumors should be treated with intensive multiagent therapy. Most centres treat abdominal Ewing sarcoma according to protocols as used for bone tumors, with some modifications e.g avoidance of radiotherapy if large abdominal fields.

Uterine sarcomas

No studies so far have shown a benefit for adjuvant chemotherapy. In advanced and recurrent uterine sarcomas there is no standard therapy. Doxorubicin has been the most active single agent for leiomyosarcoma (Sarcoma Meta-analyse Collaboration (SMAC) 2000). Combination therapy is no more active than a single-agent for advanced or metastatic disease. Single-agent cisplatin, paclitaxel, docetaxel, doxorubicin/epirubicin, topotecan, ifosfamide, vepesid can be considered for advanced or metastatic disease. These agents have activity in other STS (Look KY-GOG, 2004). Recently the combination of gemcitabine and docetaxel seems to be active in a variety of sarcomas especial for leiomyosarcoma (Hensley et al., 2002, Leu et al., 2004, Bay et al., 2006).

Hormone therapy especially, medroxyprogesterone has been effective for recurrent or unresectable ESS and has even been proposed as adjuvant treatment.

9.0 Gastrointestinal stromal tumors, GIST

9.1 Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Although previously diagnosed as leiomyoma, leiomyoblastoma or leiomyosarcoma, GIST is now regarded as a tumor entity different from all other mesenchymal tumors. True smooth muscle tumors are rare in the GI tract. The breakthrough in knowledge of molecular pathological mechanisms and new targeted therapies has resulted in effective systemic treatment with Tyrosine kinase inhibitors and better prognosis for patients with GIST. Many novel agents are now being tested in the treatment of GIST.

9.2 Epidemiology of GIST

The incidence of clinically detected GIST in the western region of Sweden was estimated to be 15 cases per million per year, and the prevalence was 129 per million (Nilsson et al., 2005). In an Icelandic population-based series the reported annual incidence was 11 GISTs per million per year. Female/male ratio: 1/1. Median age at diagnosis: 63 to 68 years, but occur in all ages (range 0-92).

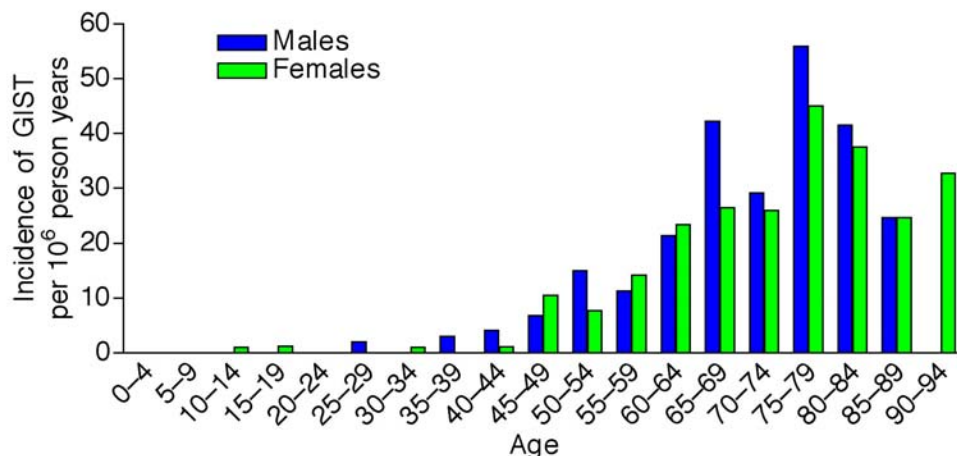


Fig. 1. Age- and sex-specific incidence of GIST in a Western Swedish population (n = 259).

9.3 Pathology in GIST

9.3.1 Tumor biology

GISTs are thought to originate from a stem cell that may differentiate towards the interstitial cells of Cajal (ICC) (Kindblom et al., 1998) and are composed of either spindle (70%), epitheloid (15%) or mixed cell forms (15%). Thus they arise from the gastrointestinal tract (from the oesophagus to the anus), and rarely outside the GI-tract within the abdominal cavity. The most common site of origin is the stomach (55-65 %) followed by the small intestine (20-30%), colon/rectum (5-8%), other, including oesophagus (2-3%).

GISTs usually express the KIT oncogene that encodes the receptor tyrosine kinase KIT. GISTs therefore has a special.

9.3.2 Histopathological diagnosis

The diagnosis is based on morphology and immunophenotyping and in difficult cases also mutation analysis. Morphological GIST is characterized by a cellular tumor with spindle cells and/or epitheloid cell and sometimes also pleomorphic cells.

Immunohistochemical analysis is usually positive for CD117 and CD34, and sometimes also for smooth-muscle actin (SMA). Mitotic count should be expressed as number of mitotic figures per 50HPF. It is important to measure the size of the tumor.

Immunophenotype

KIT receptor (CD 117)	95%
CD 34	60–70%
Smooth muscle actin	30–40 %
S-100 protein	5%
Desmin	<5%
Ki67 (MIB 1)	<1–80%

9.3.3 Molecular Pathology/Genetics in GIST

Mutation analysis should always, if possible, be done.

Mutations in the tyrosine kinase receptor genes KIT or PDGFRA are characteristic. The mutations are activating (so called gain-of-function mutations) leading to ligand-independent dimerization, autophosphorylation and activation of downstream signalling pathways (Hirota et al., 1998). KIT exon 9 mutations are found in approximately 10% of GIST, exon 11 in 60-70%, exon 13 in 1%, and exon 17 in <1% of cases (Corless et al, 2004). Some tumors lacking KIT mutations have mutations in the closely related PDGFRA gene in exon 12, 14, and 18 (Heinrich et al., 2003). About 5 to 10% of GIST lack mutations in these genes.

Mutation analysis is a useful tool in the management of GIST patients not only in the diagnostic setting but also by providing prognostic information and sometimes by influencing therapy. The location of mutations has an impact on outcome in untreated patients and different mutations also correlate with response to treatment with imatinib mesylate (Andersson et al., 2006, Heinrich et al., 2003).

9.4 Symptoms

GIST gives usually sparse and/or late symptoms. These depend mostly on site of origin. Bleeding from the GI-tract is the most common symptom (in 50%), followed by abdominal pain/discomfort (20%) and obstruction (10%).

9.5 Prognosis

No GIST can be regarded as truly benign, although patients with small tumors with low proliferation have the same survival as the normal population. In retrospective studies, patients with high-risk GIST have a 3-year survival of about 20-30%. Since the introduction of imatinib, this has changed dramatically and the median survival in the metastatic group today exceeds 5 years.

Size and proliferation are the most important prognostic factors in GIST. In general, large tumors and tumors with high cell proliferation (mitotic count, mitosis per 50 high power fields) have a high risk for recurrence (Fletcher et al., 2002). However, follow up data shows that site also is of great importance. Tumors in the stomach seem to have a better prognosis with proliferation more important than size, and tumors in the small intestine and rectum mostly have a worse outcome. The risk classification made by Miettinen and Lasota (2006) is therefore very likely to replace the presently used classification by Fletcher. Other prognostic factors include tumor rupture.

Risk assessment (modified from Fletcher et al., 2002).

Risk	Size (cm)	Mitotic Count (per 50 HPF)
Very low-risk	<2	<5
Low-risk	2–5	<5
Intermediate-risk	<5	6–10
	5–10	<5
High-risk	>5	>5
	>10	Any mitotic rate
	Any tumor	>10
Overtly malignant	Metastases	

Assessment of the risk of recurrence in resectable GIST based on GIST patient follow-up data

Tumor features		Risk of progressive disease			
Size	Mitotic count	Stomach	Duodenum	Jejunum/Ileum	Rectum
<2 cm	<5/50 HPF	None (0%)			
>2 <5 cm		Very low (2%)	Low (4%)	Low (8%)	Low (9%)
>5 <10 cm		Low (4%)	Moderate (24%)	(Insufficient data)	(Insufficient data)
>10 cm		Moderate (12%)	High (52%)	High (52%)	High (57%)
<2 cm	>5/50 HPF	None?†	High?†	(Insufficient data)	High (54%)
>2 <5 cm		Moderate (16%)	High (73%)	High (50%)	High (52%)
>5 <10 cm		High (55%)	High (85%)	(Insufficient data)	(Insufficient data)
>10 cm		High (86%)	High (90%)	High (86%)	High (71%)

†Denotes tumor categories with very small number of cases. HPF, High power field

Modified from Miettinen M and Lasota J. Semin Diagn Pathol 2006; 23: 70-83

9.6 Preoperative diagnosis

Ultrasound-guided fine-needle biopsy is the method of choice for preoperative diagnosis of GIST, (see chapters 3, 5). A reliable diagnosis is mandatory before surgery or start of treatment. The aim is to get answer of mesenchymala tumor, morphological suspicion, confirming immunohistochemistry of GIST and proliferation. Endoscopic ultrasound is of high diagnostic value if possible to perform.

Fine needle aspiration biopsy should, if possible be performed without passing the abdominal cavity e.g. through endoscopy or through a retroperitoneal route. Core-needle biopsy is rarely indicated and should be used only if fine needle aspiration gives insufficient information.

If neoadjuvant treatment with tyrosine kinase inhibitor is planed, the need for mutation analysis prior to start has to be discussed as finding of exon 9 mutation might change the treatment dose. For mutation analysis core-needle biopsy is needed.

Open biopsy should never be performed as this procedure will mimic tumor rupture and significantly influence the prognosis. For postoperative diagnosis and risk assessment, (see chapters 3, 9.3.1, 9.5).

9.7 Anatomical evaluation

For detailed description of anatomical evaluation, see chapter 4. Preoperative CT or MRI is often used in tumor evaluation to demonstrate the anatomical extent of the tumor, and presence of intra-abdominal tumor implants or metastases. GIST is suspected if there is an endophytically growing mass, often with necrosis, closely related to the stomach or the small intestine.

Endoscopic ultrasound may be a useful method to investigate a tumor in the stomach, duodenum or colon/rectum, by which the layer of origin of the tumor in the gastrointestinal wall, the depth of tumor infiltration and infiltration into adjacent organs can usually be determined.

PET is often a useful tool in GIST. GISTs show heterogenic hypermetabolism; areas with strongly hypermetabolic foci are mixed with areas of lower activity within the tumor volume. Staging of GIST involvement with PET are comparable to CT. Staging accuracy is most likely to be enhanced, however, when combined PET-CT are used. Strikingly early metabolic effects of treatment with tyrosine kinase inhibitors in GIST have been noted with PET, in some cases within days of treatment start (Stroobants et al., 2003, van den Abbele et al., 2002), furthermore early metabolic response correlates to progression-free survival. In order to evaluate response and exclude false positive findings, a baseline, pre-treatment PET scan is essential. PET is especially valuable when an early assessment is needed during pre-operative imatinib therapy.

9.8 Treatment of GIST

9.8.1 Surgery

Surgery is the main treatment for non-metastatic GIST. Surgery should be planned and performed in accordance to surgery for other kinds of visceral and retroperitoneal sarcomas aiming at achieving R0 resection (Bumming et al., 2006), and should if necessary include adjacent organs that are adherent to the tumor (see chapter 6). A careful dissection is necessary as most of the GISTs have an infiltrative growth pattern and a ruptured tumor will give the patient approximately the same prognosis as metastatic disease. Lymph node resection is not indicated.

Local recurrence in the abdomen should be regarded and treated as metastatic disease and in these cases imatinib treatment is needed. Whether surgery is beneficial in a responding locally recurrent disease is not known and must be regarded as experimental.

9.8.2 Treatment of advanced GIST

Imatinib is currently considered first-line systemic therapy in patient with metastatic or primarily non-operable disease. A daily dose of 400 mg is considered standard in most cases (Joensuu et al., 2001).

Approximately two thirds of GIST patients respond to treatment with imatinib, defined as >50% reduction in tumor volume. Another 20% have stabilized disease. The median time to progression exceeds 2 years. The maximum duration of response to imatinib is not yet known, but some patients may respond for longer than 5 years.

About 15% have primary resistant tumors. Patients with KIT exon 11 mutation respond best to imatinib treatment (Heinrich et al., 2003), but patients with GISTs with other types of mutations or those with wild-type GIST may also respond to imatinib. Present data, indicate that patients with exon 9 mutations need a higher initial dose of imatinib, 800 mg daily. In progressive disease, a fraction of patients respond to an increased dose to 600-800 mg daily or even higher. (Blanke et al. 2008).

Sunitinib is the approved second-line therapy for patients whose GIST has progressed during imatinib treatment or who are intolerant to imatinib. There is some data that sunitinib may be most effective for GISTs that harbour KIT exon 9 mutation, and in wild-type GISTs. Some GISTs with PDGFRA mutation are also sensitive to sunitinib. Nilotinib is one of several other newer drugs that presently are tested for resistant GIST.

9.8.3 Adjuvant treatment

Adjuvant imatinib following complete surgical removal of GIST is under investigation. Three randomized trials investigate the efficacy of adjuvant imatinib. The Scandinavian Sarcoma Group (SSG XVIII) trial compares 12 or 36 months imatinib in high risk GISTs. In the EORTC and ACOSOG Z9001 studies patients with lower risk tumors are included. Recently presented results from an interim analysis in the ACOSOG Z9001 demonstrates a significantly improved progression-free survival in the group who received one year of imatinib compared to placebo, but follow-up is short. This is in accordance with results from a study by Nilsson et al., 2007 were a series of patients with high-risk tumors treated with adjuvant imatinib after radical surgery was compared with historic controls. Only one of 23 patients (4%) in the adjuvant treatment group developed recurrent disease compared to 32/48 patients (67%) in the control group. Confirmation of these findings, including potential advantage in overall survival, awaits the results of ongoing randomised studies. It may be recommended that all patients with high risk tumors should be treated within adjuvant treatment protocols if possible, e.g., SSG XVIII (Nilsson et al., 2007).

9.8.4 Neoadjuvant treatment

Selected patients with primary inoperable tumors may benefit from the use of down-staging treatment with pre-operative imatinib administered under close surveillance. Evaluation with a PET in 6-12 months may, in some cases, show that a large primary tumor has become resectable or may allow less mutilating surgery (Bumming et al., 2003). Neoadjuvant treatment mainly given with the purpose to eradicate potential microscopic metastatic disease before surgery is under investigation in two small non-randomized phase II trials (RTOG S0132 and German neoadjuvant trial), but such treatment is considered experimental at the present time.

9.8.5 Interactions and side effects of imatinib

Since imatinib mesylate is metabolised in the liver by the enzyme family cytochrome P450, caution must be taken if the patient is treated with CYP3/4 inducers or inhibitors. Drugs that may interact with imatinib metabolism include paracetamol, warfarine, cimetidine, erythromycine, ketokonazole, dexomaethasone, barbiturates and fenytonine. The most common side effects of imatinib include oedema, muscle cramps, diarrhea, and fatigue, rarely intestinal/tumor bleeding or lung toxicity.

9.9 Follow-up

The optimal follow-up schedule after radical surgery has not been established but will depend on the risk classification. For high-risk GIST a CT, PET/CT or MRI of the abdomen should be performed at 6 month intervals during the first 5 years of follow-up, followed by once a year for an additional 5 years because of a high risk of late recurrence. Before the introduction of tyrosine kinase inhibitors only 20% of GIST patients remained recurrence free after 10 years. Some high-risk GIST may be followed every 3 month for the first 2 years. Patients with very low risk GIST (<2 cm in diameter) rarely have a recurrence, and may not benefit from longitudinally taken CTs (see chapter 12.0).

9.10 Conclusion

All suspected and verified GISTs, with the possible exception of very low risk tumors resected en passant, should be referred to a sarcoma centre in order to be evaluated and treated

by an experienced sarcoma team. If the diagnosis is a postoperative unexpected finding, the specimen should be evaluated by a pathologist experienced in sarcoma and the patient referred to a sarcoma centre. Questions to be dealt with at this centre include resectability, indication for preoperative treatment with tyrosine kinase inhibitors (TKI), adjuvant therapy within or outside studies, surgical approach, choice and dosage of TKI, indication for PET and mutation analysis etc. During the course of the treatment the patient must be regularly evaluated. At the time of any drug resistance or unacceptable toxicity different possibilities must be discussed, such as dosage and possible switch of TKI, surgery, radiotherapy, radiofrequency ablation etc.

10.0 Centralised management

Since sarcoma of the retroperitoneum and the abdominal cavity are uncommon tumors, no single institution is able to compile large series when compared to most other types of oncological cases. Experience is gained only when cases are collectively managed in specialized centres over a long period of time.

It is well documented that sarcoma patients referred to specialised institutions, for diagnostic work-up, including biopsy, staging and treatment, have a significant better outcome than patients treated at smaller institutions (Gustafson et al., 1994, Pollock et al., 1996, Pirayesh et al., 2001). Furthermore, the positive impact on the outcome of patients with sarcoma managed by a multidisciplinary group, including members from pathology, radiology, oncology and surgery, has also been firmly established (Lewis et al., 1996, Wiklund et al., 1996, Sæter et al., 1999). The complex surgical management of these tumors requires a surgeon with a special interest in sarcomas and special qualification in surgical oncology.

With the introduction of tyrosine kinase inhibitors also the management of GIST has become complex and the need for a multimodality treatment, combining surgery and tyrosine kinase inhibitors, is of utmost importance and the need for a multidisciplinary sarcoma group has been more apparent.

Therefore, to get a positive impact on the overall outcome of patients with intraabdominal or retroperitoneal sarcomas, the centralisation of management of these patients to specialised institutions is imperative. Centralisation is strongly recommended from the earliest stages of work-up, including special radiological studies and biopsy.

Uterine sarcomas

In gynaecological sarcoma patients the need for centralised management is the same as for retroperitoneal tumors. Uterine sarcoma patients often undergo operations after none or insufficient primary diagnostic work up for a presumed clinical diagnosis of leiomyoma which is far more frequent than its sarcoma counterpart. Intralesional surgery, including open biopsies, enucleation of lesions, and debulking procedures, is frequently the case before patients are referred to centres of competence. This practice must be avoided. If any, whatsoever, suspicion of anything but benign leiomyoma the patient should be referred. If this suspicion comes up during surgery, the operation should be terminated without open biopsy and the patient thereafter referred. For the improvement in diagnostic work-up, surgical and oncological treatment, it is strongly recommended that all these patients should be managed by a centralised multidisciplinary team with expertise in surgical and medical oncology for sarcoma.

11.0 Clinical trials

The uncommon nature of these tumors mandates that co-operative group multicentre clinical trials are performed in order to answer many of the outstanding questions in the treatment of retroperitoneal, intraabdominal and pelvic sarcomas. Such trials require the means to guarantee uniformity of protocol procedures which may be obtained at centralized sarcoma institutions.

12.0 Follow-up

Follow-up of patients with intraabdominal, retroperitoneal, pelvic or uterine sarcomas is important for various reasons.

Patients treated operatively with resection of the tumor have relative high recurrence rates that are dependent on the completeness of resection and on possible intraoperative tumor-spillage (see chapters 2.0 and 3.0). Many patients will recur with limited disease in the abdomen or retroperitoneum and can still be considered candidates for curative surgery. Others with more extensive dissemination or distant metastasis to the liver and/or lungs may still benefit from palliative operative treatment. Those patients that succumb to the disease, do so predominantly from extensive tumor growth in the abdomen and from locoregional complications that this may cause.

It is not uncommon for intraabdominal, retroperitoneal, pelvic or uterine sarcomas, especially the low-grade tumors, to recur after many years, and a 5-year disease-free interval can therefore not be considered a cure. In one series, the 2 year survival of 34% had fallen to 17% at 5 years and 8% at 10 years (Storm et al., 1991).

It is recommended that all patients should be followed with pulmonary x-ray and CT or MRI of the abdomen and pelvis every 6 months up to 5 years and every 12 months for the next 5 years.

If a recurrence is clinically suspected and/or detected on routine abdominal CT, the feasibility and benefit of a new surgical resection always should be evaluated. Complete resection of all macroscopic tumor tissue is still a significant variable predicting outcome in patients with recurrent disease. In addition to that also combination therapy as surgery and chemotherapy/ other agents as tyrosine kinase inhibitors/ radiotherapy should be discussed.

13.0 Appendix – The French grading system

Tumor differentiation

- Score 1: Sarcomas closely resembling normal adult mesenchymal tissue
 Score 2: Sarcomas of certain histological types
 Score 3: Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcoma, osteosarcoma, PNET

Tumor differentiation score of sarcomas in the French Federation of Cancer Centres Sarcoma Group System*

Diagnosis	Score
Well-differentiated liposarcoma	1
Myxoid liposarcoma	2
Round cell liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Fibrosarcoma	2
Myxofibrosarcoma (myxoid MFH)	2
Typical storiform MFH (sarcoma, NOS)	3
Pleomorphic MFH (patternless pleomorphic sarcoma)	3
Giant cell and inflammatory MFH (pleomorphic sarcoma, NOS with giant cells or inflammatory cells)	3
Well-differentiated leiomyosarcoma	1
Conventional leiomyosarcoma	2
Poorly diff./epithelioid/pleomorphic leiomyosarcoma	3
Synovial sarcoma (biphasic, monophasic and poorly differentiated)	3
Pleomorphic rhabdomyosarcoma	3
Mesenchymal chondrosarcoma	3
Extraskeletal osteosarcoma	3
Ewing's sarcoma/PNET	3
Malignant rhabdoid tumor	3
Undifferentiated sarcoma	3

PNET= primitive neuroectodermal tumor; MFH= malignant fibrous histiocytoma

Note: Grading of malignant peripheral nerve sheath tumor, embryonal and alveolar rhabdomyosarcoma, angiosarcoma, extraskeletal myxoid chondrosarcoma, clear cell sarcoma and epithelioid sarcoma is not recommended.

*Modified from Guillou et al 1997 and Rubin et al 2006

Mitotic count:

Score 1: 0–9 mitoses per 10 HPF*

Score 2: 10–19 mitoses per 10 HPF

Score 3: ≥ 20 mitoses per 10 HPF

* A high power field (HPF) measures 0.1734 mm². Standardized HPF should be used.

Tumor necrosis:

Score 0: no necrosis

Score 1: <50% tumor necrosis

Score 2: $\geq 50\%$ tumor necrosis

Histological grade (FNCLCC)

Grade 1: total score 2, 3

Grade 2: total score 4, 5

Grade 3: total score 6, 7, and 8

14.0 References

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