SSG XVII

Recommendations for
the Diagnosis and Treatment of Abdominal,
Pelvic and Retroperitoneal Sarcomas
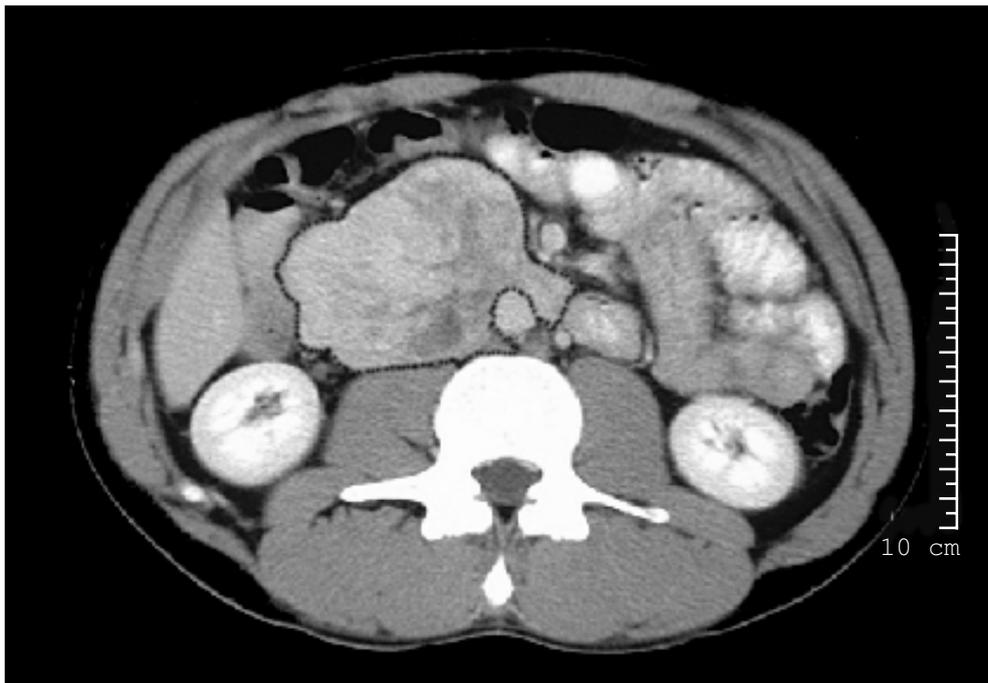
May 2002

Version for Internet

Purpose of the current draft

Soft tissue sarcomas arising in the retroperitoneal space or in the intraabdominal cavity traditionally carry a poor prognosis. Many factors contribute to the fact that both the local disease free survival and overall survival figures are poor among patients with this subgroup of sarcomas (see sections 2.0 and 3.0).

The management of abdominal, pelvic and retroperitoneal soft tissue tumours is complex and prognosis of patients with such tumours can be affected from the earliest stages of work-up.

With the goal of increasing the survival of this group of sarcoma patients, the subsequent recommendations will focus on the:
1) anatomical evaluation
2) pathological diagnosis
3) surgical management
4) adjuvant therapy
5) clinical trials
6) follow-up

More importantly, the need for centralisation of the management of patients to specialised institutions will be emphasised.

These recommendations are based on proposals made by various Scandinavian Sarcoma Group (SSG) members and represent the state of the art management of patients with abdominal, pelvic and retroperitoneal tumours. They will be updated periodically in accordance to the current knowledge of this disease entity.

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

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Contents

1.0 Introduction

Sarcomas that arise in the retroperitoneum or in the abdominal cavity are relatively rare tumours 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 fullness are referred, and approximately half of the patients will report pain. Because of their anatomic location and the non-specific symptoms, tumours 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 abdominal pain, bleeding or obstruction.

For most patients the prognosis has historically been poor (Herman et al. 1999). Overall survival in most retrospective series is approximately 55 % at five years with a range of 3075 %. Recurrence after 5 years is not uncommon and despite 5 years disease-free survival, 40 % will recur in the subsequent 5 years.

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). Furthermore, it has been shown that surgical treatment at a specialised centre, where a relatively greater number of similar cases are treated, confers the patient a significantly better prognosis. Complete resection can also be attained for recurrent disease, but the likelihood of achieving clear margins declines significantly as the number of recurrences increases.

Nevertheless, due to anatomical considerations and the often extensive size of the tumours, 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 lung and liver in no more than one third of patients. Extensive locoregional tumour growth is usually the cause of death.

In addition to complete surgical resection, also malignancy grade (high), tumour size (>10 cm), histological subtype (leiomyosarcoma unfavourable, liposarcoma favourable), and age (>60 years), have been found to be related to survival (worst) 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 more recently in two series (Sindelar et al., 1993, Willett et al., 1991). In the first study from the NCI, 35 patients were randomised to receive IORT followed by low-dose external beam radiation versus high-dose external beam radiotherapy only. Though local control could be improved in the IORT arm, there was no survival advantage in either of the treatment arms and significant complications attributed to both (Sindelar et al., 1993). A study from the Massachusetts General Hospital evaluated combined preoperative high-dose external beam radiation given together with 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 the high complication rates of radiation to the retroperitoneum 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 Center. Of the 278 patients (56%) that presented with primary tumours, 168 (60%) had high grade tumours, 198 (71%) had lesions >10 cm, and 136 (49%) were operated with microscopic tumour-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 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 this report.

Gynaecological 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 in the present proposal be included in the discussion. These lesions mostly originate in the uterus, but may also occur in the ovary, the vagina or the vulva. Uterine sarcomas represent 2–6 % of all uterine malignancies. The prognosis has been extremely poor with a 5-year survival rate as low as 30 % (Nordal, 1998). Also in gynaecological sarcomas surgery has been the cornerstone of treatment and a tumour-free resection margin at primary surgery is the best predictor for survival.

2.0 Experience of the Scandinavian Sarcoma Group

In Scandinavia, multidisciplinary sarcoma groups within specialised centres have taken care of patients with soft tissue sarcomas of the extremities and trunk wall since the 1970s. It is without doubt that management of these patients has been improved by this practice and that treatment has led to an increase in survival.

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 tumour-free margins was attained in only 36% of cases and prognosis was found to be 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 tumour-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 centers 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 tumours in order to achieve better results and for the aim to refer such patients to a specialised sarcoma center before they are operated on. There, a multidisciplinary team, and specifically for these types of tumours, surgeons having a special interest and a relative greater experience in this field, can provide optimal treatment. Due to the rarity of these tumours expertise may be achieved in only a few centres. Furthermore, reporting of patients with abdominal, pelvic and retroperitoneal sarcomas to the SSG register is essential to gain further knowledge of these tumour types.

3.0 Pathology

3.1 Histological Types

Sarcomas of the abdominal region (retroperitoneal, abdominal and pelvic tumours) include a broad spectrum of histological entities with both low-grade and high-grade malignant tumours. The morphological classification is generally based on the WHO-classification system.

Retroperitoneal sarcomas:
A retroperitoneal tumour 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 retroperitoneal sarcomas according to histological subtype is listed below (adapted from Lewis et al., 1998):

Liposarcoma	41%
Leiomyosarcoma	27%
Malignant fibrous histiocytoma	7%
Fibrosarcoma	6%
Hemangiopericytoma	4%
Malignant peripheral nerve sheath tumour	3%
Others	14%

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

Gastrointestinal stromal tumours (GIST)
Leiomyosarcoma
Malignant fibrous histiocytoma
Intraabdominal desmoplastic small cell tumour
Rhabdomyosarcoma
Synovial sarcoma

Uterine and other gynaecological sarcomas:
The following list reveals the relative frequency of gynaecological sarcomas according to histological subtype (Nordal 1998):

Leiomyosarcoma	41%
Carcinosarcoma	35%
Endometrial stromal sarcoma	16%
Others	8%

3.2 Changes in histological classification

Gastrointestinal stromal tumours (GISTs) are probably the most common mesenchymal tumours in the gastrointestinal tract. They are not listed in the World Health Organisation's histological classification of tumours of 1994, but they have recently become a clear entity different from smooth muscle tumours in the gastrointestinal tract (Kindblom et al., 1998, Miettinen et al., 1999, 2001).

The majority of the GISTs are localised in the stomach (60–70%), 20–30% in the small intestine and 10% in other sites (oesophagus, colon, rectum, mesentery and omentum). These tumours are thought to arise from mesenchymal stem cells, which also give rise to the interstitial cells of Cajal within the GI tract. Histological examination shows a cellular tumour with spindle and epithelioid cells.

The GISTs have a certain immunoprofile, which helps to separate them from leiomyomas and leiomyosarcomas. Generally there is a strong positive reaction with antibodies to CD117 (c-kit protein) and CD34, and negative findings for desmin and protein S-100. CD117 is the c-kit proto-oncogene protein, which is a transmembrane receptor for a growth factor, that has an internal tyrosine kinase component. In many tumours one can find a c-kit mutation in exon 11 in the long arm of chromosome 4. This will give a gain-of-function mutation leading to spontaneous tyrosine kinase activation.

There are not yet any established criteria to separate the benign tumours from the malignant ones, and it is also difficult to grade the malignant tumours. Spread of the tumour is a clear malignant sign (presence of omental-mesenteric or peritoneal metastasis at surgery). Size, mitotic count, cellularity, presence of necrotic areas, localisation, and proliferation index can be important features to evaluate.

A new drug imatinib (STI571, GLIVEC®) which is a phenylaminopyrimidine derivative, is a specific inhibitor of c-kit tyrosine kinase. The observed clinical activity of imatinib in surgically incurable GIST is an important therapeutic advance (see section 7.0).

3.3 Preoperative diagnosis

***Biopsy evaluation*:**
The method to use depends on the type of tumour and how much information the clinician needs. In cases where preoperative treatment is a possibility the diagnosis must be accurate, for instance in germinal cell tumours, lymphoma, or small round cell tumours. In other cases an unspecific diagnosis like spindle cell sarcoma can be sufficient. Fine needle aspiration biopsy, a core-needle biopsy or curettage (in uterine tumours) can be used. If possible an ultrasound guided fine needle aspiration biopsy is recommended as a first choice (see section 4.2).

Immunohistochemistry:
The panel of antibodies will be decided from the morphology. When possible, CD31, CD34, CD117, protein s-100, actin, desmin, smooth muscle actin, and vimentin should be evaluated.

Optional studies:
Electronmicroscopy
Cytogenetics
Molecular biology
DNA-measurements

3.4 Final diagnosis

Operation specimen:
1. Tumour site and depth: retroperitoneum, intraabdominal (stomach, small bowel, colon, rectum, mesentery, omentum etc), gynaecological (uterine, ovarian)
2. Type of resection: intralesional, marginal, wide
3. Status of margins: pushing or infiltrating
4. Histological type: take one slide per cm of tumour size
5. Tumour size: three dimensions, cm
6. Histological grade: four grade scale
7. Mitotic rate: mitotic figures/10 HPF
8. Necrosis: macroscopic and microscopic
9. Results of ancillary or special studies

It is recommended to take fresh tissue for cytogenetic analysis and molecular diagnostics whenever indicated.

3.5 Pathology Review

The morphology group within SSG has started a review of the retroperitoneal sarcomas listed in their database, which includes some, but not all intraabdominal sarcomas and no gynaecological sarcomas. The total number of patients with retroperitoneal sarcomas in the SSG register is 265, with over 65% of the cases from Norway. This work started in November 2000.

4.0 Anatomical evaluation

4.1 Preoperative anatomical evaluation

Computed Tomography (CT) and Magnetic Resonance Imaging (MR) are today the best studies available to evaluate soft tissue tumours of the retroperitoneum, intraabdominal cavity and gynaecological organs.

CT is preferred as a general screening tool for abdominal and retroperitoneal pathology. It has as the main advantages short scan times, limited motion artifacts and reproducible results. The introduction of helical CT and especially multi-slice technique has improved anatomical detail, quality of multi-planar reconstructions and reduced examination time considerably. CT is superior to MR in showing calcifications and abnormal gas collections, but lacks specificity in distinguishing some tumours from hematomas and abscesses. In patients with known retroperitoneal pathology

and especially neoplastic lesions, MR is a superb adjunct to CT and has significant advantages that make it the method of choice for secondary evaluation.

The retroperitoneum is well suited for MR imaging because its contents are relatively stationary (Engelken et al., 1997). Retroperitoneal sarcomas are usually large at diagnosis and reduce movement artefacts by compressing the surrounding structures. Even without contrast media, MR improves recognition of blood vessels, evaluation of blood flow, and detection of thrombosis when compared to CT. Superior soft tissue contrast helps to more clearly identify adipose tissues (normal fat versus a well-differentiated liposarcoma), necrosis (most frequent in leiomyosarcomas), fibrous components, and intratumoral hemorrhage. Multiplanar imaging improves definition of anatomical structures. However, motion artifacts can significantly reduce image quality and occasionally, patients cannot lie still for the time required to complete the examination.

As a general rule, CT of the chest, abdomen and pelvis should always be performed in patients with abdominal or retroperitoneal tumours. These examinations may be done at local hospitals. Oral contrast medium is mandatory in order to distinguish tumour from intestine. A pre-contrast series may be useful to identify tumour calcification, but increases radiation dose. Intravenous contrast medium should always be used. Supplementary MR should however, be performed at, or in close co-operation with the centralised sarcoma centre where 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 tumour depending on the specific anatomical site.

The optimal examination protocol for MR depends on the machine. Minimum field strength should be 1.0 Tesla. Phased array coils must be available. Basic sequences should comprise coronal T2-weighted single shot, axial T2, and T1 with and without fat sat and intravenous gadolinium. Additional sequences may be added depending on tumour characteristics and anatomical site.

MR angiography may be useful, especially to evaluate venous invasion, mapping of the vessels in proximity of the tumour and the tumour 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 tumour, 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.

Gastroscopy can be used to evaluate the extension of tumours in the esophagus or the stomach and it can allow needle cytology to be performed at the same time.

Endoscopic ultrasound is a useful method for investigation of the esophagus or the stomach as it can determine the depth of the tumour infiltration into the wall and adjacent tissue.

4.2 Diagnosis

Cytology by fine needle 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 grade of the tumour. When additional information is needed a core needle biopsy can be performed.

A retroperitoneal puncture route for retroperitoneal lesions may decrease the conceivable risk for dissemination of tumour cells into the abdominal cavity. A transperitoneal approach is usually indicated for intraabdominal lesions. In tumours of the stomach or esophagus needle cytology can frequently be taken through the gastroscope. Unlike the needle biopsy, a forceps biopsy through the gastroscope is often unreliable as the tumours 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 (see section 5.0).

5.0 Surgical aspects

5.1 Surgical goal

Surgery is today the mainstay treatment for patients with abdominal, pelvic and retroperitoneal sarcomas. It is the only potential curative treatment and the goal is complete surgical resection with microscopic tumour-free margins.

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, Bevilacqua et al., 1991, Sæter et. al., 1999). Resectability rates for primary tumours 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).

5.2 Surgical considerations

The large size attained by retroperitoneal and intraabdominal tumours before diagnosis, the biologic growth characteristics, and the close relationship to vital organs and structures in the retroperitoneum and in the abdominal cavity make 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.

Preoperative planning is essential. Defining the location, the extent, and the relationship of the tumour to adjoining structures and organs is imperative for adequate surgery. Compression of normal tissues around the lesion versus direct invasion of the tumour 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 tumour need to be defined and when necessary, organs adjoining the tumour 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 tumours if this is to achieve complete resection of the lesion and a potential cure.

5.3 Technical aspects

The preferred surgical incision for resection of abdominal, pelvic or retroperitoneal tumours 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 tumour-free resection plane can be determined.

Contiguous organs that are tightly adherent or infiltrated by the tumour must be resected en-bloc with the tumour. 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 tumours are also frequently considered for resection. With tumours 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 adherances. Vascular structures, like the vena cava and aorta are seldom infiltrated by tumour 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, autologous or synthetic grafts must be used for vessel replacement.

The expansive growth of sarcomas in the retroperitoneum and abdominal cavity often cause compression of surrounding structures without direct invasion, and an anatomical tumour-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 tumour pseudocapsule. Even the smallest of openings into the pseudocapsule may lead to tumour cell spillage and affect the prognosis negatively.

Resection of sarcomas is usually carried out in a circumferential manner. The tumour 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 tumour.

Reconstruction of anatomical structures resected during complex sarcoma surgery may involve grafts for abdominal wall defects or diaphragm resections. The latter can more often be repaired primarily or left alone. 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.

5.4 Surgical treatment report

In order to be able to evaluate the results of surgical treatment of sarcomas of the retroperitoneum 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 tumour removed or not) and any event that may have led to tumour cell spillage. For the pathologist, it is important to describe the resection margins.

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

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

5.5 Recurrence and metastasis(es)

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 sarcomas is repeat surgical resection following the principles of treatment for primary tumours (Wang et al., 1994). Whenever feasible, the intention should still be curative and complete resection with tumour-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 more importantly on symptoms that the patient refers.

Complete resection of all macroscopic tumour 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 Center (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 tumour-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 tumour resection can often improve the quality of life. For GISTs however, treatment with imatinib (STI571, GLIVEC®) is always to be considered if curative intended surgery is not possible (see section 7.0).

6.0 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 tumour-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 tumour 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. In 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 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 all too 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 more clearly be established. A close working relationship between surgeon and radiation oncologist is helpful and the intraoperative placement of clips can radiografically 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 tumours. This mode of spread and subsequent recurrence is at least as significant a factor, and possibly even greater, 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 that individual patients from a well defined subgroup be included for adjuvant radiation therapy under prospective observation. Only patients operated for tumours of malignancy grade 3 or 4, where macroscopic tumour tissue is left behind, or where the resection margins are microscopically involved with tumour, should be considered for postoperative external radiotherapy (see section 9.0).

For gynaecological sarcomas, no studies so far have shown a benefit of either adjuvant radiotherapy or chemotherapy. Hence, the administration of adjuvant radiotherapy to patients with free resection margins outside randomised trials has been condemned by the Nordic Society of Gynaecological Oncology (NSGO) in this group of patients. A randomised trial on postoperative radiotherapy has recently been performed by the European Organisation of Research and Treatment of Cancer (EORTC), and patient accrual was terminated in May 2001. The NSGO has opted to await the results of that study before considering adjuvant radiation for gynaecological sarcomas within their confines.

7.0 Chemotherapy

Retrospective studies have not demonstrated any benefit of either neoadjuvant (Storm et al., 1981) or adjuvant chemotherapy (Glenn et al., 1985) for retroperitoneal or intraabdominal sarcomas. Doxorubicin-based regimens, historically shown to have significant activity in metastatic extremity sarcoma, have had no impact on survival in primary sarcomas of the retroperitoneum (Storm et al, 1991). Randomised prospective data to evaluate the effectiveness of adjuvant chemotherapy in retroperitoneal sarcomas does not exist.

The greater response rate of certain histologic types of soft tissue sarcoma have led to the current SSG-guided utilisation of pre- and post-operative chemotherapeutic regimens specifically for abdominal, pelvic and retroperitoneal rhabdomyosarcoma and desmoplastic small-cell tumours.

However, for other histological types the use of traditional adjuvant chemotherapy cannot be recommended.

New treatments have started to evolve from laboratory experience. One promising report on the use of the specific inhibitor of c-kit tyrosine kinase, imatinib (STI571, GLIVEC®), in metastatic GISTs prompted the EORTC to perform a phase III intergroup dose-finding study (Joensuu et al., 2001). Patient accrual was terminated in February 2002. Because of the promising preliminary results from this and a similar American study, it is not only possible but also recommended to prescribe imatinib in the dosage of 400 mg daily, to patients with metastatic GISTs where curative-intended surgery is not longer possible. Side-effects may be rather common but are usually mild. The treatment with imatinib has for now been centralised to specialised institutions.

8.0 Centralised management

Since sarcomas of the retroperitoneum and the abdominal cavity are uncommon tumours, no single individual or even institution is able to compile a large enough series when compared to other types of oncological cases. Experience is gained only when cases are collectively managed in individual centers and only over a long period of time.

It is well documented that sarcoma patients referred to specialised institutions, for diagnostic work-up, including biopsy taking, staging and treatment, have a significant better outcome than patients treated at multiple smaller institutions (Gustafson et al., 1994, Pollock et al, 1996, Pirayesh et al., 2001). Furthermore, the positive impact on the outcome of patients with sarcomas 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 importance of a multidisciplinary sarcoma group may be more apparent in bone or soft tissue sarcomas of the extremity where a multimodality treatment, combining surgery, radiation and chemotherapy is more useful. Nevertheless, the co-ordinated efforts of accurate anatomical definition, biopsy taking and preoperative planning, make also the management of patients with abdominal, pelvic or retroperitoneal lesions within a specialised sarcoma group essential.

The complex surgical management of these tumours requires not only a surgeon with a special interest in these lesions, but also one with special qualification in surgical oncology and specifically in the treatment of sarcomas.

Therefore, if one is to have a positive impact on the overall outcome of patients with intraabdominal or retroperitoneal lesions, then 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 taking (see section 4.0).

In gynaecological sarcoma patients the need for centralised management is the same as for retroperitoneal tumours. 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 centers of competence. This practice has to be strongly condemned. Closer co-operation between SSG and The Nordic Society of Gynecological Oncology (NSGO) will be necessary for improvement in diagnostic work-up and surgical treatment of these patients.

9.0 Clinical trials

As mentioned previously, adjuvant radiotherapy and/or chemotherapy have yet to prove additional benefit over surgery alone in the treatment of abdominal, pelvic and retroperitoneal sarcomas. Institution of treatment using these modalities should exclusively be done within a prospective study.

Detailed guidelines for a prospective study for evaluating the efficacy of radiotherapy in a well defined patient group will be distributed to SSG-institutions in the near future. Many patients currently receive radiation therapy outside a protocol, and our recommendation is that only

patients operated for tumours of malignancy grade 3 or 4, where macroscopic tumour tissue is left behind or where the resection margins are microscopically involved with tumour should be considered for postoperative external radiotherapy.

For this subgroup of patients radiation treatment should strictly follow the following principles: The target volume should be defined by a multidisciplinary approach that involves a surgeon, an oncologist, a radiologist and a pathologist. Patients should be treated with irradiation to a total dose of 50 Gy where margins are microscopically involved and preferably to 60 Gy in smaller volumes where macroscopic tumour tissue is left behind using 2–4 treatment fields based on 3D simulation as determined by CT scan. The radiation therapy should be given 5 days a week. When a small volume containing macroscopic tumour tissue can be defined, the area should be delineated separately and given a boost of 2 Gy × 5. Selected institutions may want to use an intraoperative electron boost irradiation (Willet et al., 1991, Sindelar et al., 1993) or brachytherapy by high-dose rate after loading techniques. If a manifest peritoneal contamination occurs during the surgical procedure, or in case of established disseminated peritoneal disease, we do not recommend postoperative radiotherapy due to the questionable gain and the sequelae of irradiating the total abdominal compartment.

The uncommon nature of these tumours mandates that co-operative group multicenter clinical trials are performed in order to answer many of the outstanding questions in the adjuvant treatment of retroperitoneal and abdominal and pelvic sarcomas. These trials require that patient management be centralised to special institutions. In addition, they require the means to guarantee uniformity of treatment procedures as a prerequisite for evaluation of patients entered at all institutions. A major deviation from any protocol must be considered a failure to adhere to the intent of the study and may jeopardise the ability to answer the question in a given trial.

Clinical trials to evaluate old and/or new treatment modalities that will be difficult to establish within the confines of the SSG must find answers to their outstanding questions from trials carried out elsewhere (EORTC, NCI).

10.0 Follow-up

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

Patients treated operatively with resection of the tumour have relative high recurrence rates that are dependent on the completeness of resection and on possible intraoperative tumour-spillage (see sections 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 tumour growth in the abdomen and from locoregional complications that this may cause.

It is not uncommon for abdominal, pelvic or retroperitoneal sarcomas, especially the low-grade tumours, 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 patients should be followed every 6 months for the first 5 years and every 12 months for the next 5 years. A complete clinical evaluation should be complimented with a pulmonary X-ray and a CT of the abdomen and pelvis. If a recurrence is clinically suspected and/or detected on routine abdominal CT, the feasibility and benefit of a new operative resection should be evaluated. Further studies including MR, can then be undertaken.

Compression of an expanding tumour mass upon surrounding structures and organs may cause a multitude of symptoms in patients with recurrence. Nerve compression may cause pain, while pressure or direct invasion of intestinal loops may cause obstruction. Frequently, the expanding mass is the cause for an increasing abdominal girth associated with a decrease in lung capacity. In these symptomatic patients, prompt surgical intervention is indicated when feasible. In asymptomatic patients, on the contrary, surgery should be directed by the development of symptoms and not exclusively by the detection of a tumour mass by CT (see section 6.0). These patients should continue on a 6 month follow-up regime as described above.

11.0 References

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