WHO Classification of Soft Tissue Tumours

This new WHO classification of soft tissue tumours, in line with other volumes in this new series, incorporates detailed clinical, histological and genetic data. The explosion of cytogenetic and molecular genetic information in this field over the past 10-15 years has had significant impact on soft tissue tumour classification and also on our understanding of their biology.

The major changes which are reflected in the new classification include a revised categorization of biological behaviour which allows for two distinct types of intermediate malignancy, identified respectively as 'locally aggressive' and 'rarely metastasizing'. The new classification, most importantly, acknowledges the poorly defined nature of the categories known as malignant fibrous histiocytoma (MFH) (which in reality represents undifferentiated pleomorphic sarcoma) and haemangiopericytoma (most examples of which are closely related to solitary fibrous tumour). The uncertain line of differentiation in so-called angiomatoid MFH and extraskeletal myxoid chondrosarcoma has resulted in their reclassification into the chapter of Tumours of uncertain differentiation. However, the Working Group has avoided changes in nomenclature until these tumour types are better understood, for fear of causing confusion in routine clinical practice. Multiple newly recognized entities, which have become established since the 1994 classification, are now included and it seems likely that this trend of clinically relevant and carefully defined subclassification of soft tissue tumours will continue in the future.

WHO classification of soft tissue tumours

ADIPOCYTIC TUMOURS

Benign

Lipoma	8850/0*
Lipomatosis	8850/0
Lipomatosis of nerve	8850/0
Lipoblastoma / Lipoblastomatosis	8881/0
Angiolipoma	8861/0
Myolipoma	8890/0
Chondroid lipoma	8862/0
Extrarenal angiomyolipoma	8860/0
Extra-adrenal myelolipoma	8870/0
Spindle cell/	8857/0
Pleomorphic lipoma	8854/0
Hibernoma	8880/0

Intermediate (locally aggressive)

Atypical lipomatous tumour/	
Well differentiated liposarcoma	8851/3

Malignant

Dedifferentiated liposarcoma	8858/3
Myxoid liposarcoma	8852/3
Round cell liposarcoma	8853/3
Pleomorphic liposarcoma	8854/3
Mixed-type liposarcoma	8855/3
Liposarcoma, not otherwise specified	8850/3

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Benign

Nodular fasciitis	
Proliferative fasciitis	
Proliferative myositis	
Myositis ossificans	
fibro-osseous pseudotumour of digits	
Ischaemic fasciitis	
Elastofibroma	8820/0
Fibrous hamartoma of infancy	
Myofibroma / Myofibromatosis	8824/0
Fibromatosis colli	
Juvenile hyaline fibromatosis	
Inclusion body fibromatosis	
Fibroma of tendon sheath	8810/0
Desmoplastic fibroblastoma	8810/0
Mammary-type myofibroblastoma	8825/0
Calcifying aponeurotic fibroma	8810/0
Angiomyofibroblastoma	8826/0
Cellular angiofibroma	9160/0
Nuchal-type fibroma	8810/0
Gardner fibroma	8810/0
Calcifying fibrous tumour	
Giant cell angiofibroma	9160/0

Intermediate (locally aggressive)

Superficial fibromatoses (palmar / plantar)	
Desmoid-type fibromatoses	8821/1
Lipofibromatosis	

Intermediate (rarely metastasizing)

Solitary fibrous tumour	8815/1
and haemangiopericytoma	9150/1
(incl. lipomatous haemangiopericytoma)	
Inflammatory myofibroblastic tumour	8825/1
Low grade myofibroblastic sarcoma	8825/3
Myxoinflammatory	
fibroblastic sarcoma	8811/3
Infantile fibrosarcoma	8814/3

Malignant

Adult fibrosarcoma	8810/3
Myxofibrosarcoma	8811/3
Low grade fibromyxoid sarcoma	8811/3
hyalinizing spindle cell tumour	
Sclerosing epithelioid fibrosarcoma	8810/3

SO-CALLED FIBROHISTIOCYTIC TUMOURS

Benign

Giant cell tumour of tendon sheath	9252/0
Diffuse-type giant cell tumour	9251/0
Deep benign fibrous histiocytoma	8830/0

Intermediate (rarely metastasizing)

Plexiform fibrohistiocytic tumour	8835/1
Giant cell tumour of soft tissues	9251/1

Malignant

Pleomorphic 'MFH' / Undifferentiated	
pleomorphic sarcoma	8830/3
Giant cell 'MFH' / Undifferentiated	
pleomorphic sarcoma	
with giant cells	8830/3
Inflammatory 'MFH' / Undifferentiated	
pleomorphic sarcoma with	
prominent inflammation	8830/3

* Morphology code of the International Classification of Diseases for Oncology (ICD-O) {726} and the Systematize Nomenclature of Medicine (http://snomed.org).

SMOOTH MUSCLE TUMOURS

Angioleiomyoma	8894/0
Deep leiomyoma	8890/0
Genital leiomyoma	8890/0
Leiomyosarcoma (excluding skin)	8890/3

PERICYTIC (PERIVASCULAR) TUMOURS

Glomus tumour (and variants)	8711/0
malignant glomus tumour	8711/3
Myopericytoma	8713/1

SKELETAL MUSCLE TUMOURS

Benign

Rhabdomyoma	8900/0
adult type	8904/0
fetal type	8903/0
genital type	8905/0

Malignant

Embryonal rhabdomyosarcoma	8910/3
(incl. spindle cell,	8912/3
botryoid, anaplastic)	8910/3
Alveolar rhabdomyosarcoma	
(incl. solid, anaplastic)	8920/3
Pleomorphic rhabdomyosarcoma	8901/3

VASCULAR TUMOURS

Benign

Haemangiomas of	
subcut/deep soft tissue:	9120/0
capillary	9131/0
cavernous	9121/0
arteriovenous	9123/0
venous	9122/0
intramuscular	9132/0
synovial	9120/0
Epithelioid haemangioma	9125/0
Angiomatosis	
Lymphangioma	9170/0

Intermediate (locally aggressive)

Kaposiform haemangioendothelioma	9130/1

Intermediate (rarely metastasizing)

Retiform haemangioendothelioma	9135/1
Papillary intralymphatic angioendothelioma	9135/1
Composite haemangioendothelioma	9130/1
Kaposi sarcoma	9140/3

Malignant

Epithelioid haemangioendothelioma	9133/3
Angiosarcoma of soft tissue	9120/3

CHONDRO-OSSEOUS TUMOURS

Soft tissue chondroma	9220/0
Mesenchymal chondrosarcoma	9240/3
Extraskeletal osteosarcoma	9180/3

TUMOURS OF UNCERTAIN DIFFERENTIATION

Benign

Intramuscular myxoma	8840/0
(incl. cellular variant)	
Juxta-articular myxoma	8840/0
Deep ('aggressive') angiomyxoma	8841/0
Pleomorphic hyalinizing	
angiectatic tumour	
Ectopic hamartomatous thymoma	8587/0

Intermediate (rarely metastasizing)

Angiomatoid fibrous histiocytoma	8836/1
Ossifying fibromyxoid tumour	8842/0
(incl. atypical / malignant)	
Mixed tumour/	8940/1
Myoepithelioma/	8982/1
Parachordoma	9373/1

Malignant

Synovial sarcoma	9040/3
Epithelioid sarcoma	8804/3
Alveolar soft part sarcoma	9581/3
Clear cell sarcoma of soft tissue	9044/3
Extraskeletal myxoid chondrosarcoma	9231/3
("chordoid" type)	
PNET / Extraskeletal Ewing tumour	
pPNET	9364/3
extraskeletal Ewing tumour	9260/3
Desmoplastic small round cell tumour	8806/3
Extra-renal rhabdoid tumour	8963/3
Malignant mesenchymoma	8990/3
Neoplasms with perivascular epithelioid	
cell differentiation (PEComa)	
clear cell myomelanocytic tumour	
Intimal sarcoma	8800/3

Soft tissue tumours: Epidemiology, clinical features, histopathological typing and grading

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The large majority of soft tissue tumours are benign, with a very high cure rate after surgical excision. Malignant mesenchymal neoplasms amount to less than 1% of the overall human burden of malignant tumours but they are life-threatening and may pose a significant diagnostic and therapeutic challenge since there are more than 50 histological subtypes of STS, which are often associated with unique clinical, prognostic and therapeutic features. Over the past decade, our understanding of these neoplasms has increased significantly, both from a histopathological and genetic point of view. The close interaction of surgical pathologists, surgeons and oncologists has brought about a significant increase in disease-free survival for tumours which were previously almost invariably fatal {1960}, the overall 5-year survival rate for STS in the limbs now being in the order of 65-75% {1960}. Careful physical examination and radiographic evaluation to evaluate the size, depth and location of the mass, along with signs of neurovascular involvement are essential for designing the best therapeutic approach.approach.

Epidemiology

Benign mesenchymal tumours outnumber sarcomas by a factor of at least 100. The annual clinical incidence (number of new patients consulting a doctor) of benign soft tissue tumours has been estimated as up to 3000/million population {1830} whereas the annual incidence of soft tissue sarcoma is around 30/million {861,1663}, i.e. less than 1 percent of all malignant tumours. There are no data to indicate a change in the incidence of sarcoma nor are there significant geographic differences.

Age and site distribution

At least one-third of the *benign tumours* are lipomas, one-third fibrohistiocytic and fibrous tumours, 10 percent vascular tumours and 5 percent nerve sheath tumours. There is a relation between the type of tumour, symptoms, location and patient's age and gender. Lipomas are painless, rare in hand, lower leg and foot and very uncommon in children {1830}, multiple (angio)lipomas are sometimes painful and most common in young men, angioleiomyomas are often painful and common in lower leg of middle-aged women, whereas half of the vascular tumours occur in patients younger than 20 years {1524}. Of the benign soft tissue tumours 99% are superficial and 95% are less than 5 cm in diameter {1524}.

Soft tissue sarcomas may occur anywhere but three fourths are located in the extremities (most common in thigh) and 10 percent each in the trunk wall and retroperitoneum. There is a slight male predominance. Like almost all other malignancies, soft tissue sarcomas become more common with increasing age; the median age is 65 years. Of the extremity and trunk wall tumours one-third are superficial with a median diameter of 5 cm and two-thirds are deep-seated with a median diameter of 9 cm {861}. Retroperitoneal tumours are often much larger before they become symptomatic. One tenth of the patients have detectable metastases (most common in the lungs) at diagnosis of the primary tumour. Overall, at least one-third of the patients with soft tissue sarcoma die because of tumour, most of them because of lung metastases.

Three fourths of soft tissue sarcomas are histologically classified as high grade pleomorphic (malignant fibrous histiocytoma [MFH]-like) sarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumours and three fourths are highly malignant (histological malignancy-grades 2 and 3 in three-tiered grading systems, grades 3 and 4 in four-tiered systems) {861}. The distribution of histotypes varies over time and between researchers, probably because of changing definitions of histotypes (compare the evolution of the concept of MFH, page 120). The age-related incidences vary; embryonal rhabdomyosarcoma occurs almost exclusively in children, synovial sarcoma mostly in young adults, whereas pleomorphic high grade sarcoma, liposarcoma and leiomyosarcoma dominate in the elderly.

Aetiology

The aetiology of most benign and malignant soft tissue tumours is unknown. In rare cases, genetic and environmental factors, irradiation, viral infections and immune deficiency have been found associated with the development of usually malignant soft tissue tumours. There are also isolated reports of soft tissue sarcomas arising in scar tissue, at fracture sites and close to surgical implants {1125}. However, the large majority of soft tissue sarcomas seem to arise de novo, without an apparent causative factor. Some malignant mesenchymal neoplasms occur in the setting of familial cancer syndromes (see below and Chapter 21). Multistage tumourigenesis sequences with gradual accumulation of genetic alterations and increasing histological malignancy have not yet been clearly identified in soft tissue tumours.

Chemical carcinogens

Several studies, many of them from Sweden, have reported an increased incidence of soft tissue sarcoma after exposure to phenoxyacetic herbicides, chlorophenols, and their contaminants (dioxin) in agricultural or forestry work {607,608}. Other studies have not found this association. One explanation for different findings may be the use of herbicides with different dioxin contaminations {4,2333}.

Radiation

The reported incidence of post-irradiation sarcoma ranges from some few per thousand to nearly one percent. Most

incidence estimates are based on breast cancer patients treated with radiation as adjuvant therapy {1070}. The risk increases with dose; most patients have received 50 Gy or more and the median time between exposure and tumour diagnosis is about 10 years, although there is some evidence that this latent interval is decreasing. More than half of the tumours have been classified as so-called malignant fibrous histiocytoma, most often highly malignant. Patients with a germline mutation in the retinoblastomas gene (*RB1*) have a significantly elevated risk of developing post-irradiation sarcomas, usually osteosarcomas.

Viral infection and immunodeficiency

Human herpes virus 8 plays a key role in the development of Kaposi sarcoma and the clinical course is dependent on the immune status of the patient {2232}. Epstein-Barr virus is associated with smooth muscle tumours in patients with immunodeficiency {1368}. Stewart-Treves syndrome, development of angiosarcoma in chronic lymphoedema, particularly after radical mastectomy, has by some authors been attributed to regional acquired immunodeficiency {1895}.

Genetic susceptibility

Several types of benign soft tissue tumour have been reported to occur on a familial or inherited basis (for review see Chapter 21 and reference {2242}). However these reports are rare and comprise an insignificant number of tumours. The most common example is probably hereditary multiple lipomas (often angiolipomas) {1062}. Desmoid tumours occur in patients with the familial Gardner syndrome (including adenomatous polyposis, osteomas and epidermal cysts) {859}. Neurofibromatosis (types 1 and 2) is associated with multiple benign nerve tumours (and sometimes also non-neural tumours). In around 2% of the patients with neurofibromatosis type1 malignant peripheral nerve sheath tumours develop in a benign nerve sheath tumour {1997}. The Li-Fraumeni syndrome {954} is a rare autosomal dominant disease caused by germline mutations in the *TP53* tumour suppressor gene, which seems to be of importance for sarcomagenesis. Half of the patients have already developed malignant tumours at age 30, among them, in more than 30% of cases, soft tissue and bone sarcomas. The inherited, or bilateral form of retinoblastoma, with a germline mutation of the *RB1* locus, may also be associated with sarcoma development.

Clinical features

Benign soft tissue tumours outnumber sarcomas by at least 100 to 1, although it is almost impossible to derive accurate numbers in this regard. Most benign lesions are located in superficial (dermal or subcutaneous) soft tissue. By far the most frequent benign lesion is lipoma, which often goes untreated. Some benign lesions have distinct clinical features but most do not. Some non-metastasizing lesions, such as desmoid-type fibromatosis or intramuscular haemangioma, require wide excision comparable to a sarcoma, otherwise local recurrence is very frequent. Since excisional biopsy or 'shelling out' of a sarcoma is inappropriate and often may cause difficulties in further patient management, then it is generally advisable to obtain a diagnostic biopsy (prior to definitive treatment) for all soft tissue masses >5 cm (unless a very obvious subcutaneous lipoma) and for all subfascial or deep-seated masses, almost irrespective of size.

Most soft tissue sarcomas of the extremities and trunk wall present as painless, accidentally observed tumours, which do not influence function or general health despite the often large tumour volume. The seemingly innocent presentation and the rarity of soft tissue sarcomas often lead to misinterpretation as benign conditions. Epidemiological data regarding size and depth distribution for benign and malignant soft tissue tumours in Sweden have been used to formulate simple guidelines for the suspicion of a sarcoma: superficial soft tissue lesions that are larger than 5 cm and all deep-seated (irrespective of size) have such a high risk (around 10 percent) of being a sarcoma {1524,1830} that such patients should ideally be referred to a specialized tumour centre before surgery for optimal treatment {143,862,1831}.

Imaging of soft tissue tumours

Magnetic resonance imaging (MRI) is the modality of choice for detecting, characterizing, and staging soft tissue tumours due to its ability to distinguish tumour tissue from adjacent muscle and fat, as well as to define relationships to key neurovascular bundles. Additionally, it aids in guiding biopsy, planning surgery, evaluating response to chemotherapy, restaging, and in the long-term follow-up for local recurrence. Although MR imaging may not always reliably predict the histological diagnosis of a mass or its potential biologic activity, several conditions can be reliably diagnosed based on their characteristic pathological and signal pattern, location of mass, relationship to adjacent structures, multiplicity, and clinical history. MR imaging accurately defines tumour size, relationship to muscle compartments, fascial planes, and bone and neurovascular structures in multiple planes; it provides information on haemorrhage, necrosis, oedema, cystic and myxoid degeneration, and fibrosis.

MR imaging provides better tissue discrimination between normal and abnormal tissues than any other imaging modality. Most masses show a long T1 and long T2. However, there are a group of lesions that show a short T1 and short T2. Masses with relatively high signal intensity on T1 are lipoma, well-differentiated liposarcoma, haemangioma, subacute haemorrhage, and some examples of Ewing sarcoma/peripheral PNET. Clumps or streaks of high signal within the low signal intensity mass on T1-weighted sequences might be encountered in haemangioma, myxoid liposarcoma, infiltrative intramuscular lipoma, and lipomatosis of nerve. Tumours that may have a low signal on T2 include diffuse-type giant cell tumour, clear-cell sarcoma and fibromatosis. Soft tissue masses that do not demonstrate tumour-specific features on MR imaging should be considered indeterminate and biopsy should always be obtained to exclude malignancy.

MRI-guided biopsy. Radiologists should be cautious when asked to perform biopsies of indeterminate soft tissue tumours. Caution has to be exercised in three respects: Selection of an appropriate pathway, coordination with the treating surgeon, and participation of a pathologist comfortable with interpreting percutaneous biopsies. The radiologist should undertake biopsies only at the request of the treating surgeon and not necessarily at the request of the patient's initial physician. In collaboration with the treating

surgeon, the needle tract (which needs to be excised with the tumour) can be established and the patient well served.

Spiral CT is preferable for examining sarcomas of the chest and abdomen, since air / tissue interface and motion artefacts often degrade MRI quality. A baseline chest CT scan at the time of diagnosis for evidence of lung metastasis is important, particularly for sarcomas >5 cm, for accurate staging of patients. Early studies suggest that *positron emission tomography (PET)* has clinical potential by determining biological activity of soft tissue masses {522,565,700,1293}. The technique is selectively used for distinguishing benign tumours from high grade sarcomas, pretreatment grading of sarcomas, and evaluation of local recurrence. Its role, vis-à-vis, MR imaging which remains the mainstay, is yet to be defined.

Biopsy

Given the prognostic and therapeutic importance of accurate diagnosis, a biopsy is necessary (and appropriate) to establish malignancy, to assess histological grade, and to determine the specific histological type of sarcoma, if possible. A treatment plan can then be designed that is tailored to a lesion's predicted pattern of local growth, risk of metastasis, and likely sites of distant spread. A large enough sample from a viable area of sarcoma is usually required for definitive diagnosis and accurate grading. Most limb masses are generally best sampled through a longitudinally oriented incision, so that the entire biopsy tract can be completely excised at the time of definitive resection. An incisional biopsy with minimal extension into adjacent tissue planes is the ideal approach for most extremity masses. Excisional biopsy should be avoided, particularly for lesions greater than 2 cm in size, since such an approach will make definitive re-excision more extensive due to the contamination of surrounding tissue planes. For deep-seated lesions, a core biopsy approach may be used to establish a diagnosis, however, the limited tissue obtained with this technique may make definitive grading and prognostication difficult. Fine needle aspiration (FNA) cytology is generally best limited to those centres with a high case volume and with a well-integrated multidisciplinary team, since careful clinicoradiologic correlation and considerable experience are required in order to make accurate diagnoses. A particular problem with needle biopsies and FNA is the inevitability of limited sampling, which impacts not only diagnostic accuracy but also the possibility of triaging tissue for ancillary diagnostic techniques such as cytogenetics and electron microscopy.

Terminology regarding biological potential

As part of this new WHO classification of Soft Tissue Tumours, the Working Group wished to address the problems which have existed regarding definition of a lesion's biological potential, particularly with regard to the current ambiguity of such terms as 'intermediate malignancy' or 'borderline malignant potential.' With this goal in mind, it is recommended to divide soft tissue tumours into the following four categories: benign, intermediate (locally aggressive), intermediate (rarely metastasizing) and malignant. Definitions of these categories are as follows:

Benign

Most benign soft tissue tumours do not recur locally. Those that do recur do so in a non-destructive fashion and are almost always readily cured by complete local excision. Exceedingly rarely (almost certainly <1/50,000 cases, and probably much less than that), a morphologically benign lesion may give rise to distant metastases. This is entirely unpredictable on the basis of conventional histological examination and, to date has been best documented in cutaneous benign fibrous histiocytoma.

Intermediate (locally aggressive)

Soft tissue tumours in this category often recur locally and are associated with an infiltrative and locally destructive growth pattern. Lesions in this category do not have any evident potential to metastasize but typically require wide excision with a margin of normal tissue in order to ensure local control. The prototypical lesion in this category is desmoid fibromatosis.

Intermediate (rarely metastasizing)

Soft tissue tumours in this category are often locally aggressive (see above) but, in addition, show the well-documented ability to give rise to distant metastases in occasional cases. The risk of such metastases appears to be <2% and is not reliably predictable on the basis of histomorphology. Metastasis in such lesions is usually to lymph node or lung. Prototypical examples in this category include plexiform fibrohistiocytic tumour and so-called angiomatoid fibrous histiocytoma.

Malignant

In addition to the potential for locally destructive growth and recurrence, malignant soft tissue tumours (known as soft tissue sarcomas) have significant risk of distant metastasis, ranging in most instances from 20% to almost 100%, depending upon histological type and grade. Some (but not all) histologically low grade sarcomas have a metastatic risk of only 2-10%, but such lesions may advance in grade in a local recurrence, and thereby acquire a higher risk of distant spread (e.g., myxofibrosarcoma and leiomyosarcoma).

FNCLCC grading system: definition of parameters

Tumour differentiation	
Score 1:	sarcomas closely resembling normal adult mesenchymal tissue (e.g., low grade leiomyosarcoma).
Score 2:	sarcomas for which histological typing is certain (e.g., myxoid liposarcoma).
Score 3:	embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, osteosarcomas, PNET.
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
Tumour necrosis	
Score 0:	no necrosis
Score 1:	<50% tumour necrosis
Score 2:	≥50% tumour necrosis
Histological grade	
Grade 1:	total score 2,3
Grade 2:	total score 4,5
Grade 3:	total score 6, 7, 8

Modified from Trojani et al. {2131}.
PNET: primitive neuroectodermal tumour
*A high power field (HPF) measures 0.1734 mm^2

It is important to note, that in this new classification scheme, the intermediate categories do not correspond to histologically determined intermediate grade in a soft tissue sarcoma (see below), nor do they correspond to the ICD-O/1 category described as uncertain whether benign or malignant. The locally aggressive subset with no metastatic potential, as defined above, are generally given ICD-O/1 codes , while the rarely metastasizing lesions are given ICD-O/3 codes.

Histological grading of soft tissue sarcomas

The histological type of sarcomas does not always provide sufficient information for predicting the clinical course and therefore for planning therapy. Grading, based on histological parameters only, evaluates the degree of malignancy and mainly the probability of distant metastasis. Staging, based on both clinical and histological parameters, provides information on the extent of the tumour.

The concept of grading in STS was first properly introduced by Russell et al in 1977 {1826}, and was the most important factor of their clinico-pathological classification. Several grading systems, based on various histological parameters, have been published and proved to correlate with prognosis {401,1335,1525,2131, 2183}. The two most important parameters seem to be the mitotic index and the extent of tumour necrosis {401,2131, 2183}. A three-grade system is recommended, retaining an intermediate histological grade (grade 2) of malignancy. Grade particularly indicates the probability of distant metastasis and overall survival {50,155,385,773,930,1335,1711, 1833}, but is of poor value for predicting local recurrence which is mainly related to the quality of surgical margins. Moreover, the initial response to chemotherapy has been reported to be better in patients with a high grade tumour than in patients with a low grade one {385,672}.

The two most widely used systems are the NCI (United States National Cancer Institute) system {401,402} and the FNCLCC (French Fédération Nationale des Centres de Lutte Contre le Cancer) system {385,386,387,851,2131}.

According to the methodology defined in 1984 {401} and refined in 1999 {402}, the NCI system uses a combination of histological type, cellularity, pleomorphism and mitotic rate for attributing grade 1 or 3. All the other types of sarcomas were classified as either grade 2 or grade 3 depending on the amount of tumour necrosis, with 15% necrosis as the threshold for separation of grade 2 and grade 3 lesions.

The FNCLCC system is based on a score obtained by evaluating three parameters selected after multivariate analysis of several histological features: tumour differentiation, mitotic rate and amount of tumour necrosis {2131}. A score is attributed independently to each parameter and the grade is obtained by adding the three attributed scores. Tumour differentiation is highly dependent on histological type and subtype {851}. The reproducibility of this system was tested by 15 pathologists: the crude proportion in agreement was 75% for tumour grade but only 61% for histological type {387}.

Guillou et al. {851} performed a comparative study of the NCI and FNCLCC sys-

Comparison of the NCI and FNCLCC systems for the histological grading of soft tissue tumours

Histological type	NCI grading system	FNCLCC grading system
Well differentiated liposarcoma	1+(*)	1
Myxoid liposarcoma	1+	2
High grade myxoid liposarcoma	2-(**)	3
(round cell liposarcoma)	3	
Pleomorphic liposarcoma	2	3
	3	
Dedifferentiated liposarcoma		3
Fibrosarcoma		
Well differentiated	1+	1
Conventional	2	2
Poorly differentiated	3	3
Pleomorphic sarcoma (MFH, pleomorphic type)		
With storiform pattern	2	2
Patternless pleomorphic sarcoma	3	3
With giant cells		3
With prominent inflammation		3
Myxofibrosarcoma (MFH, myxoid-type)	1+	
	2	2
	3	
Leiomyosarcoma		
Well differentiated	1+	1
Conventional	2	2
Poorly differentiated / pleomorphic / epithelioid	3	3
Pleomorphic rhabdomyosarcoma	2	
	3	3
Embryonal / alveolar rhabdomyosarcomas	3	3
Myxoid chondrosarcoma	1	
	2	
	3	
Mesenchymal chondrosarcoma	3	3
Osteosarcoma	3	3
Ewing sarcoma / PNET	3	3
Synovial sarcoma	2	3
	3	
Epithelioid sarcoma	2	
	3	
Clear cell sarcoma	2	
	3	
Angiosarcoma	2	
	3	

Modified from Costa et al {401}, Costa {402} and Guillou {851}. The original diagnostic terms are shown in parentheses.
MFH: malignant fibrous histiocytoma; PNET: primitive neuroectodermal tumour.
(*) + grade is attributed by a combination of histological type, cellularity, pleomorphism and mitotic rate.
(**)- grade is attributed according to the extent of tumour necrosis (< or > 15%).

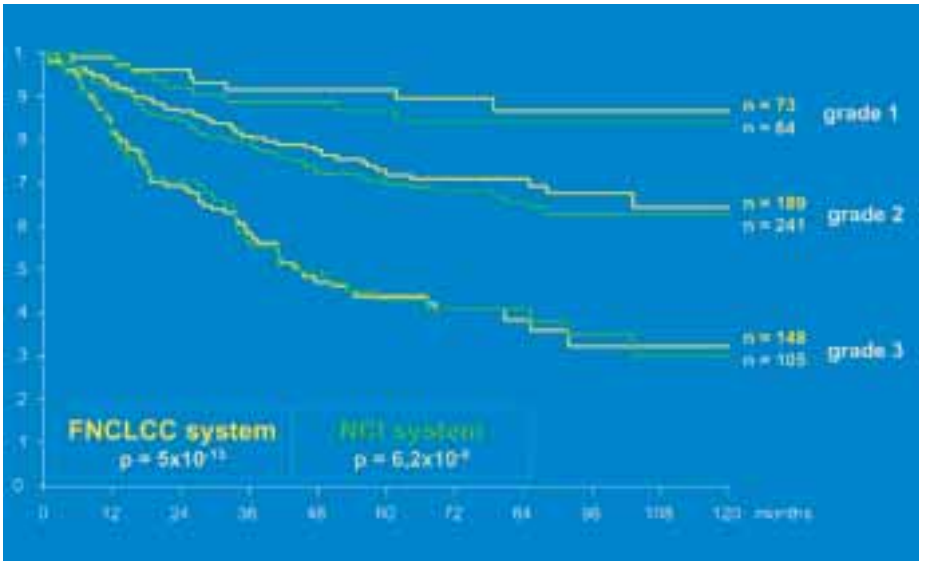

Fig. A.1 Comparison of overall survival curves for a cohort of 410 patients with soft tissue sarcomas graded according to the NCI and FNCLCC systems. Reproduced from Guillou et al {851}.

tems on a subgroup of 410 patients. In univariate analysis both systems were of good prognostic value, although grade discrepancies were observed in 34% of the cases. In the NCI system, there were more grade 2 tumours, and use of the FNCLCC resulted in a better correlation with overall and metastasis-free survival.
Because of some limitations and pitfalls of grading, some rules must be respected in order to get the highest performance and reproducibility of the system:
>Grading should be used only for untreated primary soft tissue sarcomas.
>Grading should be performed on representative and well processed material.
>Grading is not a substitute for a histological diagnosis and does not differentiate benign and malignant lesions, and, before grading a soft tissue lesion, one must be sure that one is dealing with a true sarcoma and not a pseudosarcoma.
>Grading is not applicable to all types of soft tissue sarcoma. Because of the over- all rarity of STS, grade is used on the whole group of sarcomas considered as a single entity, but the significance of the histological parameters used in grading systems differs for various sarcomas. Therefore, grade is of no prognostic value for some histological types, such as MPNST {386,902} and its use is not recommended for angiosarcoma, extraskeletal myxoid chondrosarcoma, alveolar soft part sarcoma, clear cell sarcoma and epithelioid sarcoma {5,851,1102} . In a recent study {386}, it was shown that the FNCLCC grading was the most important predictive factor for metastasis for pleomorphic sarcomas, unclassified sarcomas and synovial sarcomas and the second and third independent factor for leiomyosarcomas and liposarcomas.
Parameters of grading must be carefully evaluated and, particularly, mitosis counting should be done rigorously.

Staging

Staging of soft tissue sarcomas is based on both histological and clinical information. The major staging system used for STS was developed by the International Union against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) and appears to be clinically useful and of prognostic value. This TNM system incorporates histological grade as well as tumour size and depth, regional lymph node involvement and distant metastasis. It accommodates 2, 3, 4-tiered grading systems.

Therapy

Once the histological diagnosis and grade is established and the work-up for distant metastasis performed, a multidisciplinary team of surgeons, radiation oncologists and medical oncologists can design the most effective treatment plan for the patient.

Surgery

Although surgery remains the principal therapeutic modality in soft tissue sarcoma, the extent of surgery required, along with the optimum combination of radiotherapy and chemotherapy, remains controversial. In designing a treatment plan, the multidisciplinary team must balance the goal of minimizing local and distant recurrence with the aim of preserving function and quality of life. A properly executed surgical resection remains the most important part of the overall treatment. In general, the scope of the excision is dictated by the size of the tumour, its anatomical relation to normal structures (e.g. major neurovascular bundles) and the degree of function that would be lost after operation. If severe loss of function is likely, the key question is whether this can be minimized by use of adjuvant /neoadjuvant radiotherapy or chemotherapy. For subcutaneous or intramuscular high grade soft tissue sarcoma smaller than 5 cm, or any size low grade sarcoma, surgery alone should be considered if a wide excision with a good 1-2 cm cuff of surrounding fat and muscle can be achieved. If the excision margin is close, or if there is extramuscular involvement, adjuvant radiotherapy should be added to the surgical resection to reduce the probability of local failure. However, irrespective of grade, post-operative radiotherapy is probably used more often than strictly necessary. In fact, Rydholm et al. {1832} and Baldini et al. {115} have shown that a significant subset of subcutaneous and intramuscular sarcomas can be treated by wide margin excision alone, with a local recurrence rate of only 5-10%.

Adjuvant and neoadjuvant chemotherapy

For high grade sarcomas, greater than 5 cm, there are several possible approaches to treatment that are based on not only achieving good local control but also reducing the risk of developing subsequent systemic metastasis. The value of systemic chemotherapy depends on the specific histological subset of the sarcoma. Chemotherapy is usually indicated as primary "neoadjuvant" therapy in the treatment of Ewing sarcoma and rhabdomyosarcoma. Adjuvant chemotherapy is indicated for these specific tumour types, even if the primary site has been resected, because of the very high risk of metastasis. For other histological types

of soft tissue sarcoma the value of systemic chemotherapy remains controversial. The histological type and location of disease are important predictors of sensitivity to chemotherapy and thus may help in decisions on the potential benefit of chemotherapy. The majority of the randomized chemotherapy trials have shown no significant impact on overall survival; however they have found that chemotherapy does improve disease-free survival, with improved local and loco-regional control {3,51,64,245,612}. The majority of these trial data came from the era before the standard use of ifosfamide. A single randomized trial of adjuvant chemotherapy involving an anthracycline (epirubicin) plus ifosfamide has been performed in Italy. Although designed to detect only differences in disease-free survival (and with only relatively short follow-up), this trial is reported to show relapse-free and overall survival differences associated with systemic chemotherapy administration {3}. These results require confirmation before adjuvant chemotherapy for all sarcomas is accepted as standard practice. Given the limitations of the randomized trial data cited above and that the benefit in systemic disease control may be relatively small, the preoperative use of neoadjuvant chemotherapy with an anthracycline and ifosfamide can be justified in carefully selected patients with large, high grade tumours and in certain histological types most likely to respond to such chemotherapy (e.g. synovial sarcoma and myxoid/round cell liposarcoma).

Multimodal protocols

For the treatment of large, high grade extremity sarcomas several sequencing schedules of chemotherapy, radiation and surgery have been developed. There are three general approaches {1960}:

1. Neoadjuvant chemotherapy > surgery > adjuvant chemotherapy + post-operative radiotherapy.
2. Neoadjuvant chemotherapy interdigitated with preoperative radiotherapy > surgery > adjuvant chemotherapy
3. Neoadjuvant chemotherapy > preoperative radiotherapy > surgery > adjuvant chemotherapy

One major advantage to giving the chemotherapy alone and directly prior to surgery (approach 1) is the ability to determine if the sarcoma is progressing on therapy and thus avoid potential toxicity of additional adjuvant chemotherapy in those patients who have measurable disease that appears to be resistant to such therapy.

The retroperitoneal and visceral sarcomas represent a particularly complex challenge for the treating physician. Because of their large size, their tendency to invade adjacent organs, and the difficulty in achieving a clean margin surgical resection, the survival rate for

TNM Classification of soft tissue sarcomas

Primary tumour (T)	TX:	primary tumour cannot be assessed
	T0:	no evidence of primary tumour
	T1:	tumour ≤ 5cm in greatest dimension
		T1a: superficial tumour*
		T1b: deep tumour
	T2:	tumour > 5cm in greatest dimension
		T2a: superficial tumour
		T2b: deep tumour
Regional lymph nodes (N)	NX:	regional lymph nodes cannot be assessed
	N0:	no regional lymph node metastasis
	N1:	regional lymph node metastasis
Distant metastasis (M)	M0:	no distant metastasis
	M1:	distant metastasis

Note: Regional node involvement is rare and cases in which nodal status is not assessed either clinically or pathologically could be considered N0 instead of NX or pNX.

G Histopathological Grading

Translation table for three and four grade to two grade (low vs. high grade) system

TNM two grade system	Three grade systems	Four grade systems
Low grade	Grade 1	Grade 1
		Grade 2
High grade	Grade 2	Grade 3
	Grade 3	Grade 4

Stage IA	T1a	N0,NX	M0	Low grade
	T1b	N0,NX	M0	Low grade
Stage IB	T2a	N0,NX	M0	Low grade
	T2b	N0,NX	M0	Low grade
Stage IIA	T1a	N0,NX	M0	High grade
	T1b	N0,NX	M0	High grade
Stage IIB	T2a	N0,NX	M0	High grade
Stage III	T2b	N0,NX	M0	High grade
Stage IV	Any T	N1	M0	Any grade
	Any T	Any N	M1	Any grade

From references {831,1979}.
Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the superficial fascia, or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal and pelvic sarcomas are classified as deep tumours.

retroperitoneal sarcomas is 20-40% of that for extremity soft tissue sarcoma. The most important prognostic factors for survival in retroperitoneal sarcoma are the completeness of the surgical resection and the histological grade {1247, 1959}. Despite an aggressive surgical approach to eradicate tumour, local control is still a significant problem that ultimately leads to unresectable local disease and death in many cases. Well differentiated and dedifferentiated liposarcoma account for the majority of retroperitoneal sarcomas and they frequently recur locally and multi-focally within the retroperitoneum, with distant metastasis to lung only occurring in 20% of those patients who have dedifferentiated high grade liposarcoma {578,937}. In contrast, patients with retroperitoneal high grade leiomyosarcoma often (in greater than 50% of patients) develop distant metastasis to liver or lung, which is usually the limiting factor for outcome.