1 Pathology and classification

Classification of soft tissue sarcomas

Soft tissue sarcomas (STSs) represent less than 1% of all malignant tumours and benign mesenchymal tumours are at least 100 times more frequent than sarcomas.

The World Health Organization (WHO) classification recognises >50 histological sarcoma types. The diagnosis should be made by a multidisciplinary team and the histological diagnosis should be confirmed by an expert pathologist.

Histological classification of soft tissue tumours is based on the line of differentiation (resemblance to normal tissue counterpart) of the tumour.

Histological subtypes
Adipocytic tumours
Fibroblastic and myofibroblastic tumours
Fibrohistiocytic tumours
Vascular tumours
Pericytic (perivascular) tumours
Smooth muscle tumours
Skeletal muscle tumours
Gastrointestinal stromal tumours
Chondro-osseous tumours
Peripheral nerve sheath tumours
Tumours of uncertain differentiation
Undifferentiated small round cell sarcomas

Fig. 1.1

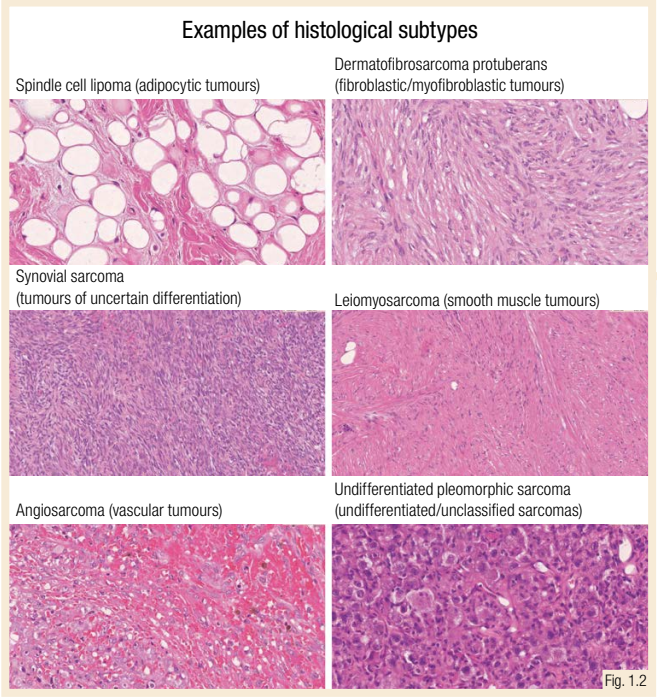

Fig. 1.2

Each histological subgroup is divided into:

- benign: low rate of non-destructive local recurrence, no metastasis
- intermediate, locally aggressive: no metastatic potential, but high rate of local recurrence, with destructive growth pattern, requiring wide excision, e.g. desmoid-type fibromatosis
- intermediate, rarely metastasising: locally aggressive, and well-documented metastatic potential (<2% distant metastases)
- malignant (sarcoma): locally destructive and significant risk of distant metastases (most often 20%–100%).

Note that the intermediate category does NOT correspond to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) histological intermediate grade (Grade 2) of malignancy.

The aetiology of most benign and soft tissue tumours is unknown.

Soft tissue tumours can occur on a familial or inherited basis. Examples of hereditary syndromes with soft tissue tumours include: desmoid-type fibromatosis in patients with familial adenomatous polyposis, peripheral nerve sheath tumours and gastrointestinal stromal tumours (GISTs) in patients with neurofibromatosis, and sarcomas in Li-Fraumeni syndrome.

Rarely, sarcomas are associated with previous radiation, viral infection or immunodeficiency.

Desmoid-type fibromatosis

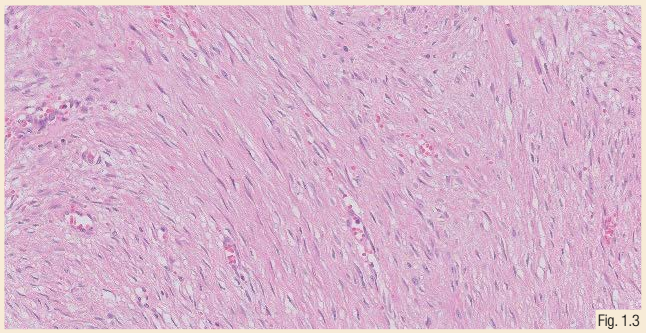

Fig. 1.3

REVISION QUESTIONS

1. To which histological subgroup do liposarcomas belong?
2. What is known about the aetiology of STSs?
3. What does it mean when a tumour is classified in the intermediate category?

WHO classification of soft tissue sarcomas: use of immunohistochemistry

In addition to histological features, immunohistochemistry (IHC) is used to determine line of differentiation in STS.

The different markers have different sensitivity and specificity.

Immunohistochemical markers used to determine line of differentiation	
Muscle differentiation	Melanocyte-inducing desmin, smooth muscle actin (SMA), muscle specific actin (HHF35), MyoD1, Myf4 (myogenin), heavy caldesmon, calponin
Nerve sheath differentiation	S100, SOX10
Melanocytic differentiation	HMB-45, Melan-A (MART-1), tyrosinase, *MITF*
Endothelial differentiation	ERG, CD34, CD31
Fibrohistiocytic differentiation	CD68, Factor 13A, vimentin
Epithelial differentiation	Cytokeratins, EMA

Fig. 1.4

EMA, epithelial membrane antigen; MITF, melanocyte inducing transcription factor.

Diffuse nuclear MyoD1 staining in case of rhabdomyosarcoma (RMS) indicates rhabdomyogenic differentiation.

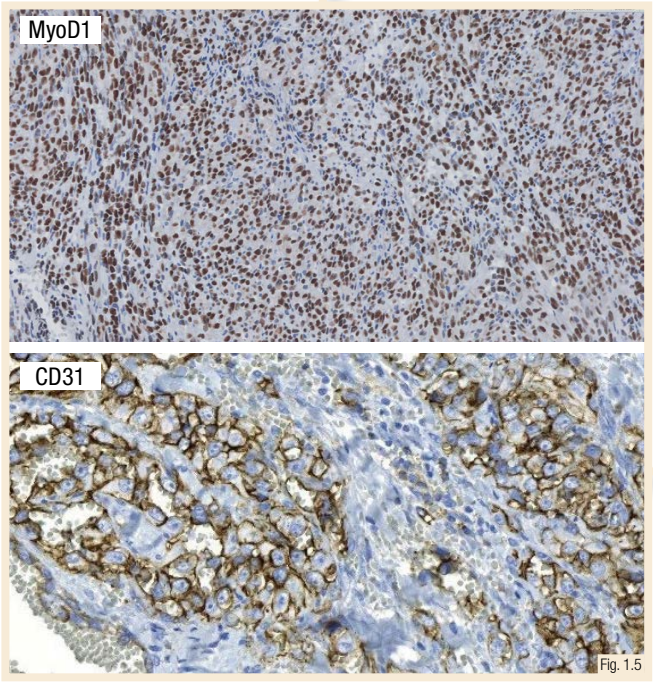

Fig. 1.5

Usually a panel of immunohistochemical markers is used.

Examples of second-line markers that are more specific include mucin 4 (MUC4) for low-grade fibromyxoid sarcoma/sclerosing epithelioid fibrosarcoma, loss of H3K27me3 in malignant peripheral nerve sheath tumour and ETV4 in *CIC*-rearranged round cell sarcoma.

Strong membranous staining of vascular marker CD31 in case of epithelioid angiosarcoma indicates endothelial differentiation.

IHC can also be used as a surrogate to identify specific molecular alterations.

Examples include nuclear staining of STAT6 in solitary fibrous tumour, loss of *INI1* in epithelioid sarcoma, nuclear CAMTA1 in epithelioid haemangioendothelioma and TFE3 in alveolar soft part sarcoma (ASPS).

IHC is used to detect *MDM2* amplification in well-differentiated/dedifferentiated liposarcoma. Amplification can be confirmed using fluorescent *in situ* hybridisation (FISH).

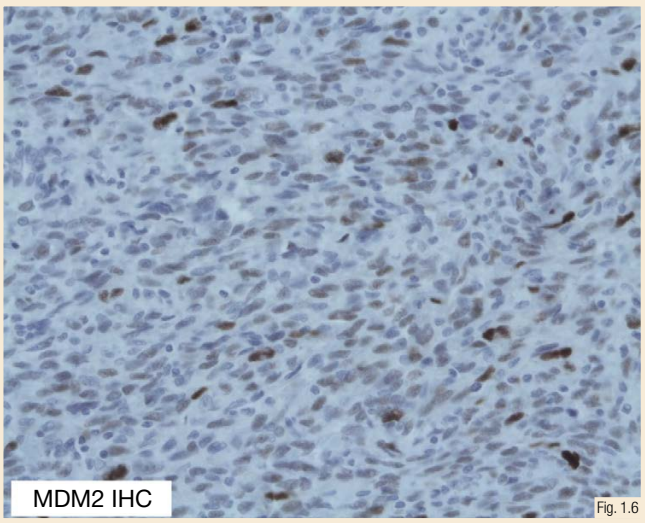

Fig. 1.6

IHC, immunohistochemistry.

REVISION QUESTIONS

1. What is the purpose of IHC in STSs?
2. Which markers are used to demonstrate endothelial differentiation?
3. Which tumour is characterised by amplification of *MDM2*?

Classification of soft tissue sarcomas: histological grading

Histological grading of STS (Grade 1, 2 or 3) is performed according to FNCLCC.

Three parameters are evaluated: tumour differentiation, mitotic count and tumour necrosis.

The main value of grading is to predict the probability of distant metastases and overall survival (OS). It does not predict local recurrence.

Histological grading according to FNCLCC	
Tumour differentiation	
Score 1	Closely resembling normal tissue
Score 2	Histological typing is certain
Score 3	Embryonal or undifferentiated sarcomas
Mitotic count (per 1.7 mm^2)	
Score 1	0-9 mitoses per 1.7 mm^2
Score 2	10-19 mitoses per 1.7 mm^2
Score 3	>19 mitoses per 1.7 mm^2
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**

Fig. 1.7

FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer.

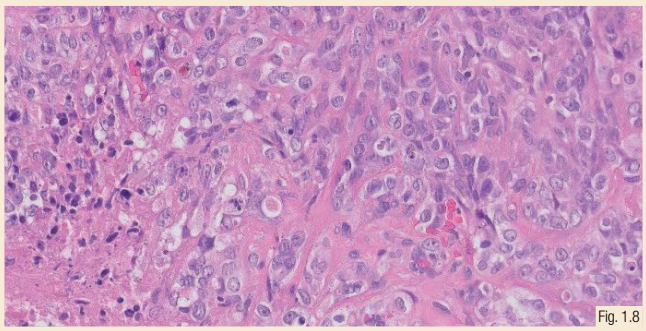

Fig. 1.8

FNCLCC grading is less informative in RMS, Ewing sarcoma, ASPS, epithelioid sarcoma and clear cell sarcoma; these are by definition high grade.

Epithelioid sarcoma is by definition high grade. Note the area of necrosis on the left.

In myxoid liposarcoma, the percentage of hypercellular round cell component determines the grade: >5% is considered high grade.

For adult patients with localised STS, metastasis-free survival correlates with histological grade (from the French Sarcoma Group database).

Histological grading cannot be performed after neoadjuvant therapy.

Histological grading is not a substitute for a histological diagnosis.

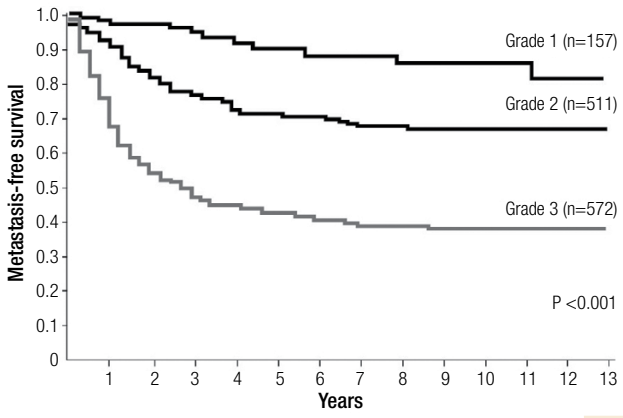

Fig. 1.9

REVISION QUESTIONS

1. Which criteria are used for histological grading?
2. For which tumours is FNCLCC grading not applicable?
3. What is the purpose of histological grading?

WHO classification of bone sarcomas

Primary tumours of bone are relatively rare and bone sarcomas account for only 0.2% of all neoplasms. ~58 different bone tumours are recognised by the WHO.

Most bone tumours show a specific anatomical bone distribution and affect specific age groups.

Approximately 43% of bone sarcomas arise around the knee. The second most common site is the pelvis.

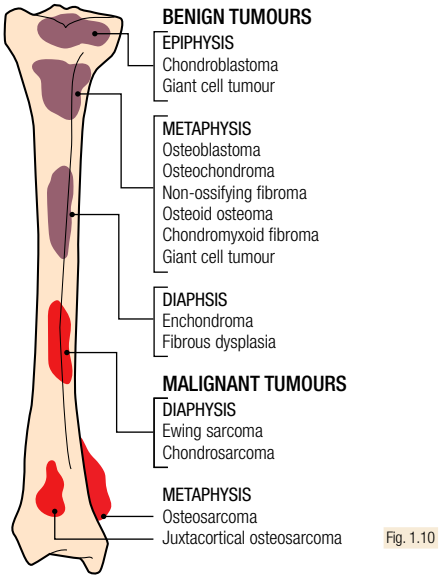

Fig. 1.10

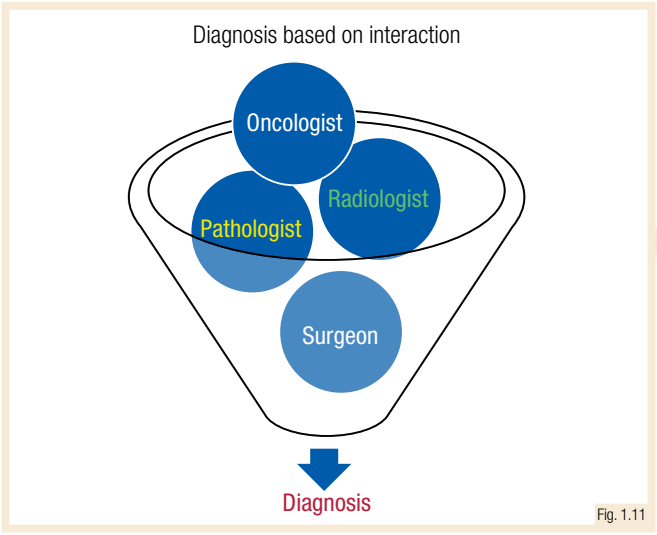

Fig. 1.11

A multidisciplinary approach with correlation between radiological features and morphology is mandatory for correct diagnosis, since the morphology of different tumours (benign and malignant) may show considerable overlap.

Bone tumours vary widely in their biological behaviour and are grouped in concordance with STSs into benign, intermediate (locally aggressive/rarely metastasising) or malignant.

In contrast to the FNCLCC STS grading, the histotype determines the histological grade of most bone sarcomas.

Exceptions are chondrosarcoma and leiomyosarcoma, for which separate grading systems are used.

The significance of histological grading in chondrosarcoma is limited by interobserver variability.

Histotype determines grade in bone sarcoma
Low grade
Low-grade central osteosarcoma
Parosteal osteosarcoma
Clear cell chondrosarcoma
Intermediate grade
Periosteal osteosarcoma
High grade
Osteosarcoma (conventional, telangiectatic, small cell, secondary, high-grade surface)
Undifferentiated pleomorphic sarcoma
Ewing sarcoma
Dedifferentiated chondrosarcoma
Mesenchymal chondrosarcoma
Dedifferentiated chordoma
Poorly differentiated chondroma
Angiosarcoma
Variable grading
Conventional chondrosarcoma (Grade 1-3 according to Evans)
Leiomyosarcoma

Fig. 1.12

REVISION QUESTIONS

1. Is chondrosarcoma typically located in the metaphysis or epiphysis of the long bone?
2. What is mandatory for a correct diagnosis in bone tumours?
3. What is bone sarcoma grading based on?

WHO classification of bone sarcomas (continued)

Osteosarcoma is the most common primary bone sarcoma. Ewing sarcoma is relatively uncommon, but the second most common bone sarcoma in children.

The figure shows permeative growth pattern in high-grade osteosarcoma (A) with pleomorphic tumour cells producing osteoid (B). The diagnosis is based on morphology.

The figure shows typical undifferentiated small blue round cell morphology of Ewing sarcoma (A) with strong diffuse CD99 expression (B). The diagnosis is confirmed by molecular analysis demonstrating an *EWSR1-ETS* fusion.

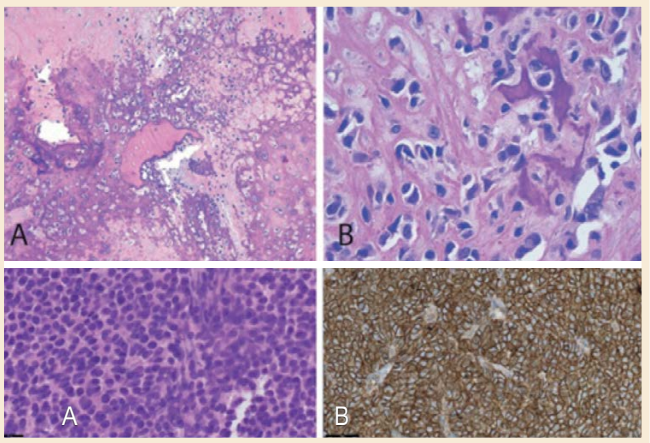

Fig. 1.13

Osteosarcoma resection specimen, good response after chemotherapy

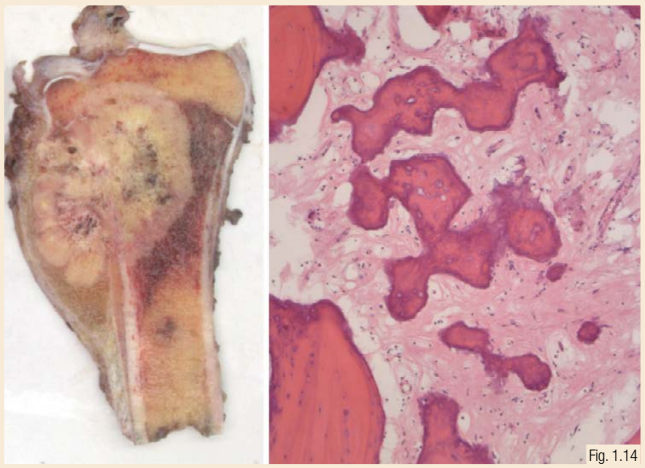
Fig. 1.14

After neoadjuvant chemotherapy (ChT) in Ewing sarcoma and osteosarcoma, response should be evaluated morphologically.

In osteosarcoma, response to ChT is one of the most important prognostic factors for OS and disease-free survival; <10% viable tumour cells is considered a good response.

In Ewing sarcoma, histopathological assessment of tumour response also has prognostic value, though it is more difficult to evaluate due to volume changes.

Giant cell tumour of bone (GCTB) is locally aggressive. The peak incidence is between 20 and 45 years of age.

GCTB is characterised by the presence of neoplastic mononuclear stromal cells admixed with reactive multinucleated osteoclast-type giant cells. It has a mutation in *H3F3A* at the G34 position, which can be demonstrated using IHC.

GCTB can be treated with denosumab (a RANKL antibody) that targets and binds with high affinity and specificity to RANKL, preventing activation of the osteoclast-type giant cells. At histology, no more giant cells are seen.

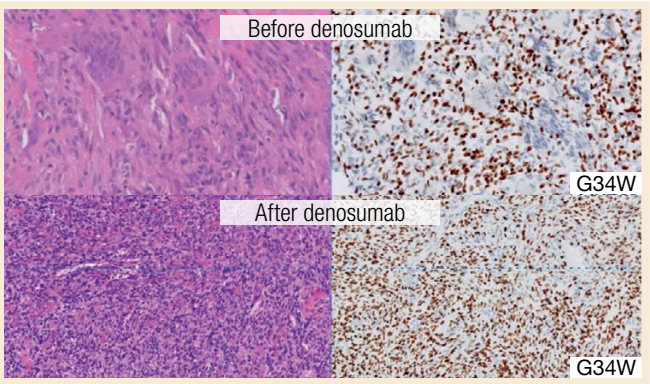

Fig. 1.15

REVISION QUESTIONS

1. What is the function of denosumab?
2. What is the most common bone sarcoma?
3. What is the morphological hallmark of osteosarcoma?

Summary: Pathology and classification

- STSs represent <1% of all malignant tumours
- Histological classification of STSs is based on the line of differentiation
- IHC is used to determine line of differentiation in STSs
- IHC can also be used as a surrogate for specific molecular alterations
- Most STSs are histologically graded (Grade 1, 2 or 3) according to FNCLCC
- Primary bone sarcomas account for only 0.2% of all neoplasms
- A multidisciplinary approach with correlation between radiological features and morphology is mandatory for a correct diagnosis in bone tumours
- Grading of most bone sarcomas is determined according to histological subtype

Further Reading

Blay JY, Sleijfer S, Schoffski P, et al. International expert opinion on patient-tailored management of soft tissue sarcomas. Eur J Cancer 2014; 50:679–689.

Blay JY, Soibinet P, Penel N, et al. Improved survival using specialized multidisciplinary board in sarcoma patients. Ann Oncol 2017; 28:2852–2859.

Casali PG, Abecassis N, Aro HT, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29(Supplement_4):iv268–iv269.

Casali PG, Bielack S, Abecassis N, et al. Bone sarcomas: ESMO–PaedCan–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29(Supplement_4):iv79–iv95.

Demicco EG, Lazar AJ. Clinicopathologic considerations: how can we fine tune our approach to sarcoma? Semin Oncol 2011; 38 Suppl 3:S3–18.

Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. Cancer 1977; 40:818–831.

Ray-Coquard I, Montesco MC, Coindre JM, et al. Sarcoma: concordance between initial diagnosis and centralized expert review in a population-based study within three European regions. Ann Oncol 2012; 23:2442–2449.

Trojani M, Contesso G, Coindre JM, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. Int J Cancer 1984; 33:37–42.

van der Heijden L, Dijkstra PD, van de Sande MA, et al. The clinical approach toward giant cell tumor of bone. Oncologist 2014; 19:550–561.

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