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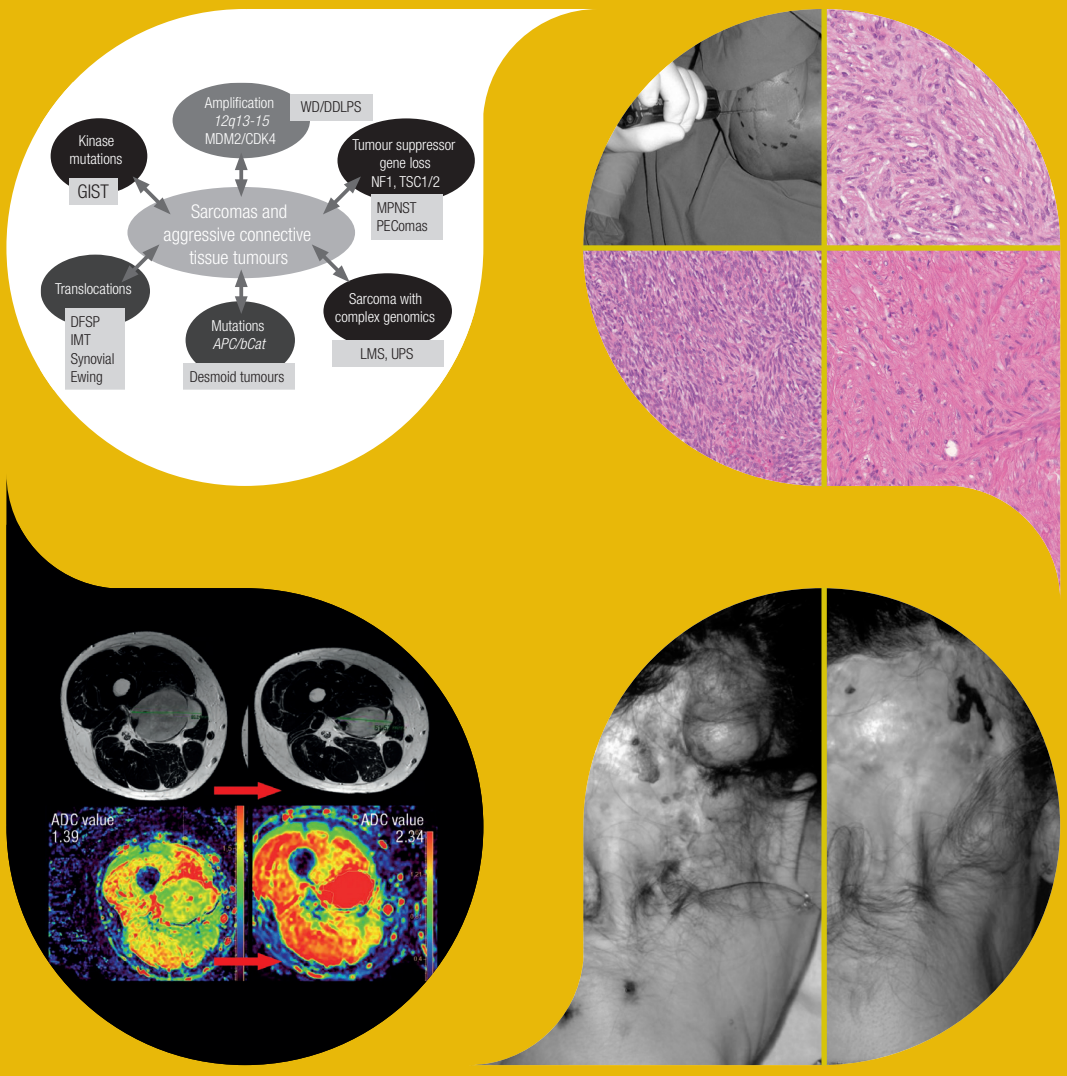
Iwona Lugowska
Jean-Yves Blay
Hans Gelderblom

SARCOMA & GIST

plus CANCER OF UNKNOWN PRIMARY SITE

ESSENTIALS *for* CLINICIANS



ESMO Press

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Sarcoma and Gastrointestinal Stromal Tumours plus Cancer of Unknown Primary Site Essentials for Clinicians

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Preface

The diagnosis and treatment of soft tissue sarcomas (STSs), including gastrointestinal stromal tumours (GISTs), has seen great progress in recent years. A new World Health Organization (WHO) classification was published this year and several novel drugs have shown activity in subsets of sarcoma and GIST. In addition to sarcoma and GIST, the book also provides information about diagnosis and therapy of cancer of unknown primary site (CUP), with an emphasis on the value of gene-profiling microarray diagnosis in this indication.

This first edition of *Sarcoma and Gastrointestinal Stromal Tumours plus Cancer of Unknown Primary Site: Essentials for Clinicians* encompasses the whole spectrum of current knowledge and provides clinicians with an easily accessible overview as well as a focus on key developments in the treatment of STS, GIST and CUP. The topics range from pathology to the current therapeutic options in these indications.

Sarcoma, representing <2% of all tumours with >50 different subtypes, is a true (ultra) rare condition that should be treated under the guidance of reference centres to ensure quality of care. For this reason, in Europe, EURACAN was founded. This network of hospitals includes all rare cancers including STS and GIST.

Concise text together with many colour illustrations provide the reader with a simple and engaging way to acquire information. Under our editorial supervision, all chapters have been contributed by experts in sarcoma, GIST and CUP, highly regarded in their field.

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Professor Jean-Yves Blay
Lyon, France

Professor Hans Gelderblom
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Professor Iwona Lugowska is Plenipotentiary Director for International Affairs, Head of the Early Phase Clinical Trials Unit, Leader of the Centre of Excellence for Precision Oncology, Coordinator of the Centre for Research and Development and Consultant in Oncology in the Department of Soft Tissue/Bone Sarcoma and Melanoma at the Maria Skłodowska-Curie National Research Institute of Oncology (MSCI), Warsaw, Poland.

Professor Lugowska is a board member of the European Organisation for Research and Treatment of Cancer (EORTC), Chair of the European Society for Medical Oncology (ESMO) Educational Publications Working Group and a member of the Ethics Committee at MSCI. She received an award from the American Society of Clinical Oncology (ASCO) IDEA Program 2010, visited the Memorial Sloan Kettering Cancer Center, New York (mentor, Robert Maki), and undertook a fellowship at the Sir Bobby Robson Cancer Trials Research Centre, Newcastle, UK (mentor, Ruth Plummer).

Her main fields of interest are sarcoma, melanoma research, immunotherapy, precision oncology and early phase clinical trials. She also developed a Clinical Support System for the management of gastrointestinal stromal tumour (GIST).

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Professor Jean-Yves Blay is a medical oncologist, General Director of the Centre Léon Bérard, the Comprehensive Cancer Centre of Lyon, France, researcher and a Professor at the University Claude Bernard, France. Since 2019, he has been the President of the French Federation of Cancer Centres: UNICANCER.

His work focuses on sarcoma, genomics and targeted treatment of cancer, immuno-oncology and the relationship between tumour immunological microenvironment and malignant cells, with the goal of clinical applications in the field of diagnosis, prognosis and treatment.

Professor Blay has been the Director of the LYriCAN SIRIC (previously LYRIC) since 2018. He has also been President of the French Sarcoma Group and Network Director of NETSARC+ network of sarcoma reference centres for the INCA since 2019. He serves as the Network Director of European Reference Network-EURACAN, designated by the EU Commission. Previously, he served as EORTC President (2009-2012). He has co-authored over 1000 peer-reviewed articles and book chapters and was distinguished as a Highly Cited Researcher in 2019.

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Professor Dr Hans (André Johan) Gelderblom is Chair of the Department of Medical Oncology at Leiden University Medical Center (LUMC), Netherlands. His department has a research lab focused on the immunotherapy of cancer and his personal interests, aside from sarcoma, involve targeted therapy, pharmacokinetics and pharmacogenomics of cancer medication.

He is co-principal investigator of the Drug Rediscovery Protocol (DRUP trial), a nationwide study using approved matched targeted drugs off-label. He is Chair of the EORTC Soft Tissue and Bone Sarcoma group and member of the Dutch Committee of Bone Tumours. LUMC is a national and European reference centre for GIST, bone and soft tissue sarcoma and has an established oncology bench-to-bedside infrastructure and track record.

Professor Gelderblom has co-authored approximately 400 papers, of which more than 200 are in the field of GIST and sarcoma. His personal aim is to improve the outcome for patients with these rare tumours.

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Abbreviations

Ab	Antibody
ADC	Apparent diffusion coefficient
AFP	Alpha-foetoprotein
ALK	Anaplastic lymphoma kinase
ARMS	Alveolar rhabdomyosarcoma
ASPS	Alveolar soft part sarcoma
AYA	Adolescent and young adult
β-HCG	Beta-human chorionic gonadotropin
BMI	Body mass index
CCS	Clear cell sarcoma
ChT	Chemotherapy
CNS	Central nervous system
CSF	Cerebrospinal fluid
CSF1	Colony stimulating factor 1
CSF1R	CSF1 receptor
CT	Computed tomography
CTNNB1	Beta catenin 1
CUP	Cancer of unknown primary site
DDLPS	Dedifferentiated liposarcoma
DFS	Disease-free survival
DFSP	Dermatofibrosarcoma protuberans
DSRCT	Desmoplastic small round cell tumour
dTGCT	Diffuse type tenosynovial giant cell tumour
DWI	Diffusion-weighted imaging
EFS	Event-free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EpSSG	European paediatric Soft tissue sarcoma Study Group
ER	Oestrogen receptor
ERMS	Embryonal rhabdomyosarcoma
ERN	European Reference Network
EWSR1	Ewing sarcoma breakpoint region 1
FDA	Food & Drug Administration
FDG	Fluorodeoxyglucose
FISH	Fluorescent *in situ* hybridisation
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
GCTB	Giant cell tumour of bone
GIST	Gastrointestinal stromal tumour
HHV	Human herpes virus
HIV	Human immunodeficiency virus
HPF	High-power field
ICF	International Classification of Functioning, Disability and Health
ICI	Immune checkpoint inhibitor
IFS	Infantile fibrosarcoma
IHC	Immunohistochemistry
IL	Interleukin
IMT	Inflammatory myofibroblastic tumour
LDH	Lactate dehydrogenase
MAP	Methotrexate/doxorubicin/cisplatin
MDP	Methylene diphosphonate
MDT	Multidisciplinary team
MLPS	Myxoid liposarcoma
MPNST	Malignant peripheral nerve sheath tumour
MRI	Magnetic resonance imaging
MSTS	Musculoskeletal Tumor Society
mTOR	Mammalian target of rapamycin
MUC4	Mucin 4
NF1	Neurofibromatosis type 1
NGS	Next-generation sequencing
NP	Neuropathic pain
NTRK	Neurotrophic tyrosine receptor kinase
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD-1	Programmed cell death protein 1
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PDGFRA	Platelet-derived growth factor receptor alpha
PD-L1	Programmed death-ligand 1
PEComa	Perivascular epithelioid cell tumour
PET	Positron emission tomography
PFS	Progression-free survival
PM	Parameningeal
PR	Progesterone receptor
PS	Performance status
PSA	Prostate-specific antigen
PVNS	Pigmented villonodular synovitis
QoL	Quality of life
R	Resection
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RFS	Relapse-free survival
RMS	Rhabdomyosarcoma
RR	Response rate
RT	Radiotherapy
SDH	Succinate dehydrogenase
SFT	Solitary fibrous tumour
SS	Synovial sarcoma
SSG	Scandinavian Sarcoma Group
STS	Soft tissue sarcoma
TCCD	Tetrachlorodibenzodioxin
TESS	Toronto Extremity Salvage Score
TKI	Tyrosine kinase inhibitor
TNM	Tumour, node, metastasis
ToO	Tissue of origin
TRK	Tyrosine receptor kinase
UICC	Union for International Cancer Control
UPS	Undifferentiated pleomorphic sarcoma
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2
WDLPS	Well-differentiated liposarcoma
WHO	World Health Organization
WT	Wild-type

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Iwona Lugowska, Jean-Yves Blay and Hans Gelderblom

A

What every oncologist should know

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

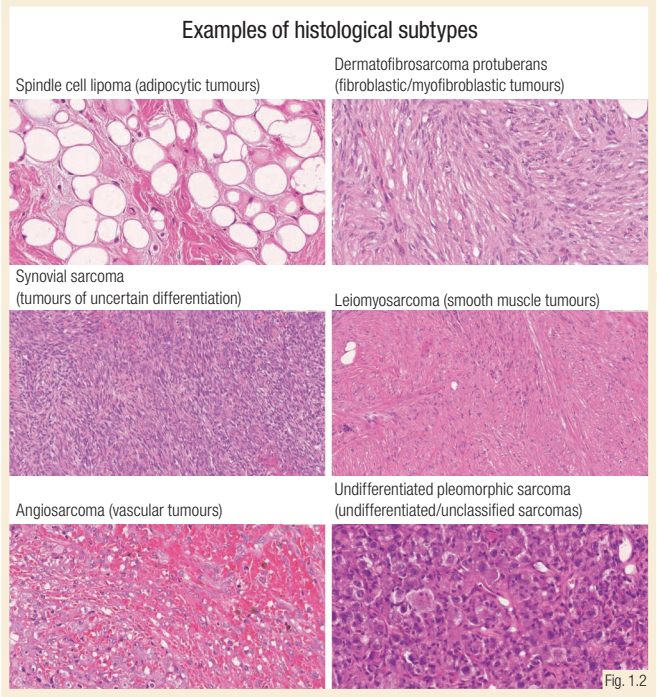


Fig. 1.2

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

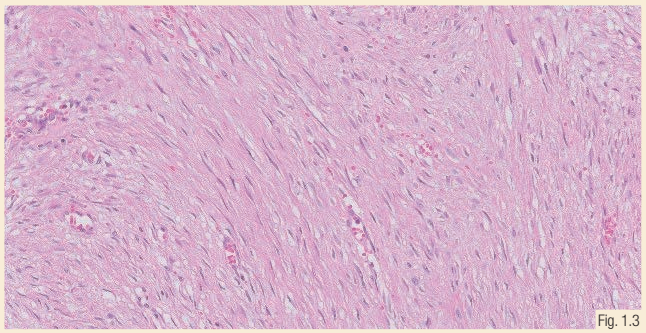


Fig. 1.3

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.

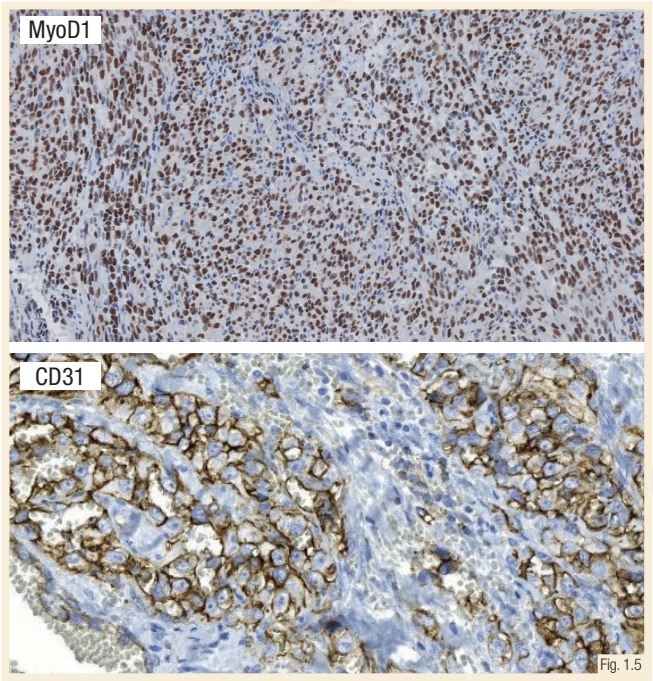


Fig. 1.5

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).

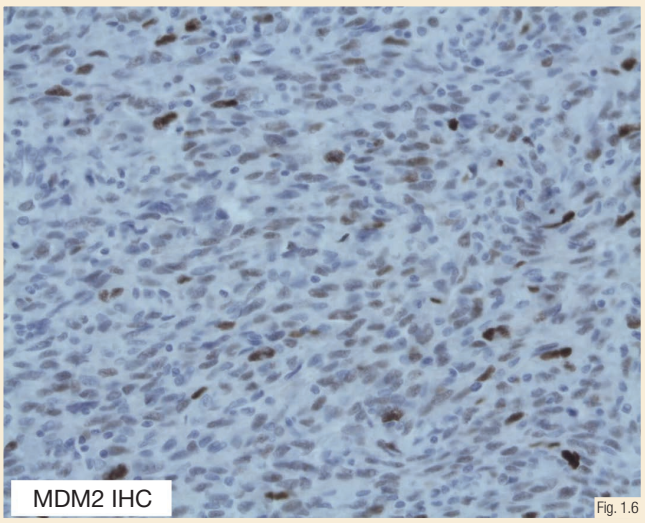


Fig. 1.6

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.

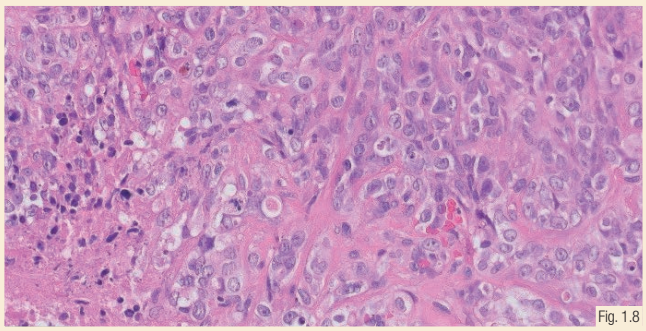


Fig. 1.8

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.

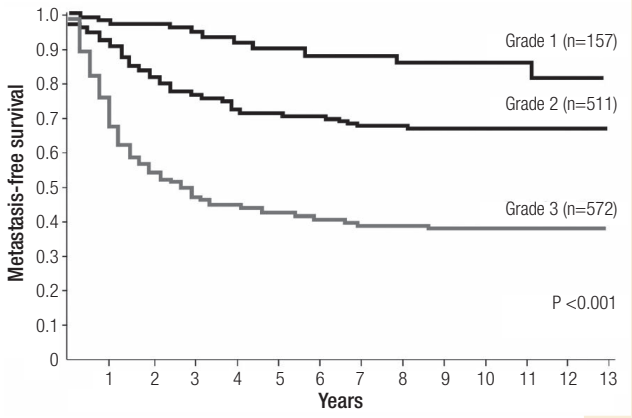


Fig. 1.9

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.

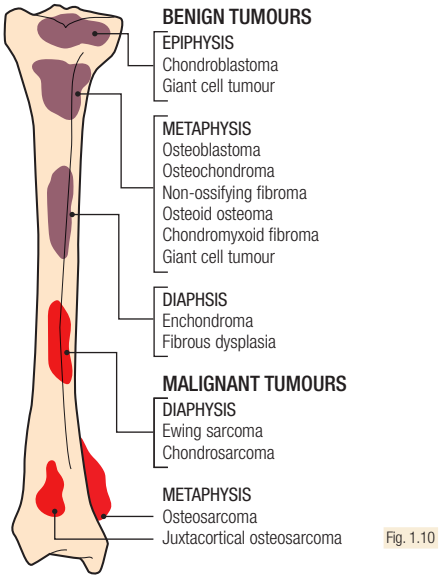


Fig. 1.10

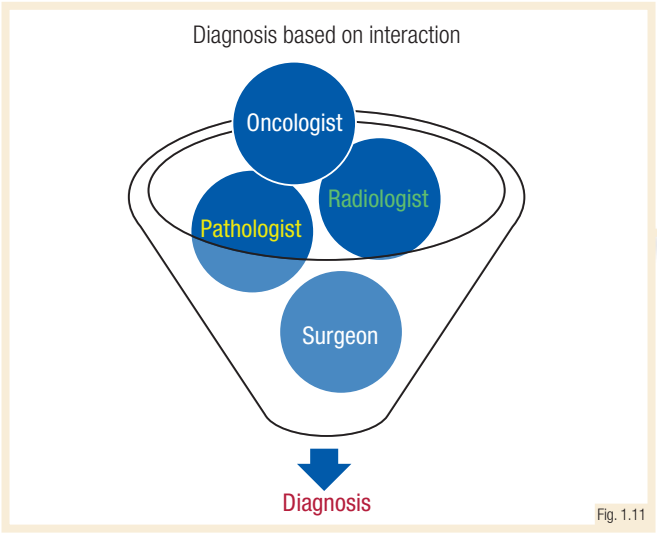


Fig. 1.11

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.

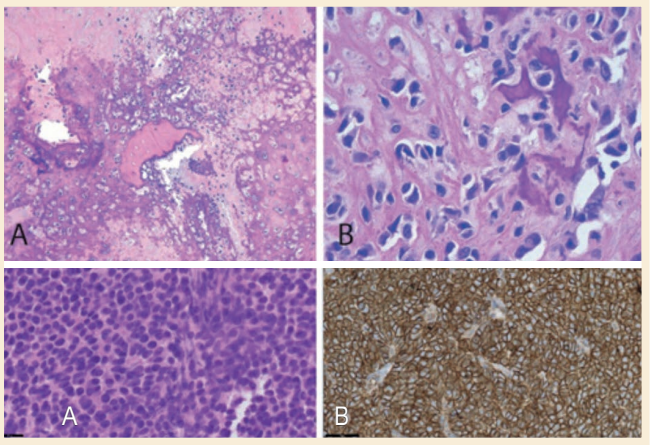


Fig. 1.13

Osteosarcoma resection specimen, good response after chemotherapy

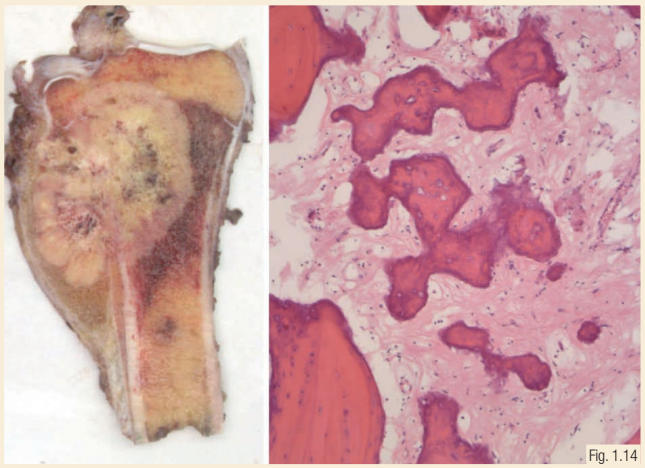


Fig. 1.14

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.

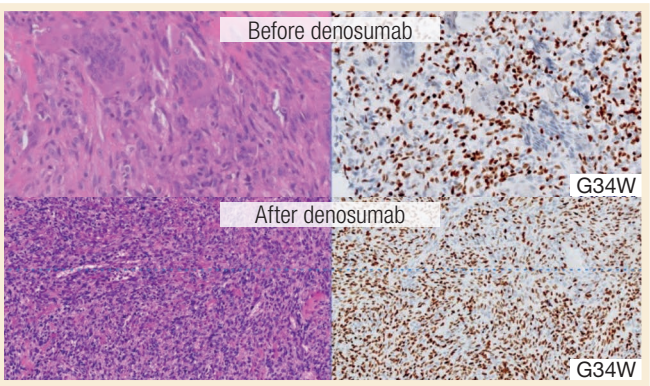


Fig. 1.15

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.

WHO Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours; WHO Classification of Tumours, 5th Edition, Volume 3. France: IACR; 2020.

2 Clinical presentation, staging and response assessment

Clinical presentation and diagnostic procedures

Soft tissue sarcomas (STSs) of the extremities usually present as painless lumps. Deep seated, recent growth or lumps >5 cm are alarm signs that require further investigations to rule out sarcoma.

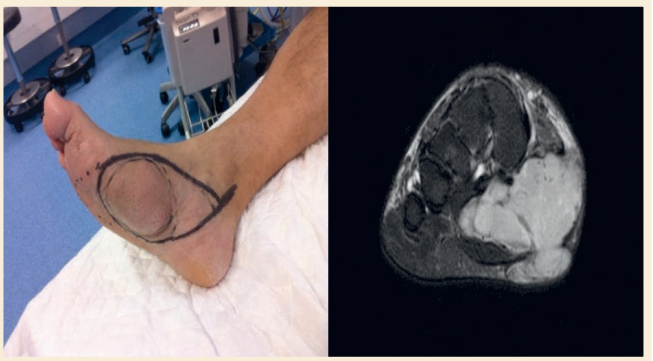


Fig. 2.1

Patients with sarcoma suspicion referred to expert centres with multidisciplinary teams (MDTs) have been shown to achieve better clinical outcomes. Heterogeneity (>70 subtypes) and ubiquity are issues in sarcoma care.

Core biopsy constitutes the cornerstone for sarcoma diagnosis. If adequately sampled (at least 6-8 14G needle Tru-Cut), the pathologist can report histological and grading diagnosis.

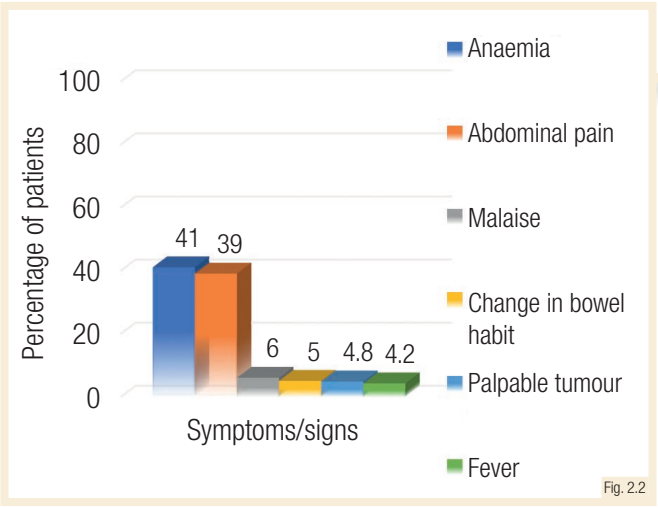


Fig. 2.2

In gastrointestinal stomal tumours (GISTs), although symptoms depend on location, most reported cases have non-specific findings, such as anaemia, postprandial fullness or abdominal distension.

Most cases of *KIT* or platelet-derived growth factor receptor alpha *(PDGFRA)* wild-type (WT) GIST are related to succinate dehydrogenase (SDH) deficiency. They present most frequently in female patients, young age, gastric location, with epithelioid or mixed histology, frequent involvement of lymph nodes, and often show an indolent course.

Many SDH mutations found in *KIT/PDGFRA* WT GIST are also present in the germline, which may require genetic counselling (Carney-Stratakis syndrome).

CD117 *(KIT)* is the immunohistochemical marker most widely used in the diagnosis of GIST, with positive staining being recorded in 95% of cases. DOG1 (Anoctamin 1) identifies *KIT*-negative GIST patients while *KIT* and DOG1-negative GISTs are exceptional.

Core biopsy with sufficient tissue sample is paramount in GIST. Histological diagnosis, mitotic count per 50 high-power fields (HPFs) and genotype are required for adequate treatment planning.

Although traditionally expressed as number of mitoses per 50 HPFs, it is advisable to count mitosis in areas of 5 mm^2, equivalent to 25 HPFs with a 20x lens, or 21 HPFs with a 22x lens (this corresponds to 50 HPFs in Miettinen risk classification).

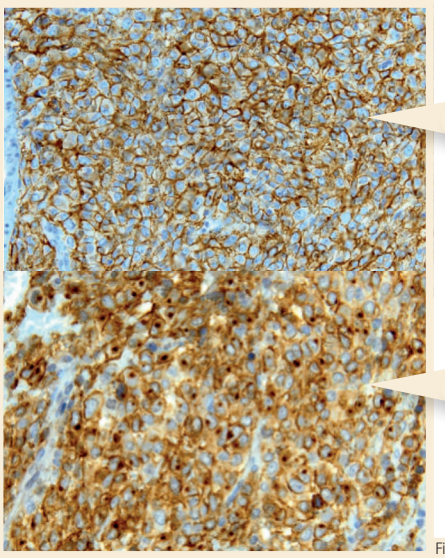


Fig. 2.3

REVISION QUESTIONS

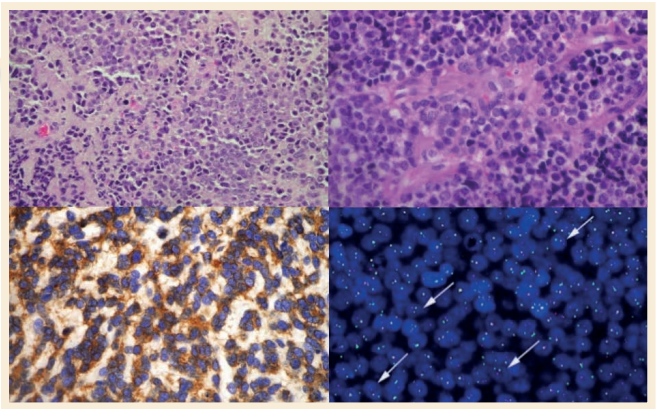
1. What alarm signs must be considered to suspect sarcoma?
2. What are the most relevant immunostainings in GIST diagnosis?
3. Is a young female GIST patient without *KIT/PDGFRA* mutations a candidate for SDH mutation analysis in tumour and germline?

Pathology and molecular tests

A third of STSs have reciprocal translocations that encode fusion genes, which can act as at least three types of oncogenic mediator: aberrant transcription factors, involving constitutive activation of tyrosine receptor kinases (TRKs), and constitutive activation of growth factors.

Around 50% of translocation-related STSs have fusion genes that involve TET genes (*TLS/FUS, EWSR1* and *TAFII68*), including Ewing sarcoma, clear cell sarcoma (CCS), desmoplastic small round cell tumour, myxoid chondrosarcoma, myxoid liposarcoma (MLPS), low-grade fibromyxoid sarcoma and angiomatoid fibrous histiocytoma.

Top: haematoxylin-eosin staining of a small round cell sarcoma. Bottom left: CD99 staining. Bottom right: FISH of EWSR1



FISH, Fluorescent *in situ* hybridisation.

Fig. 2.4

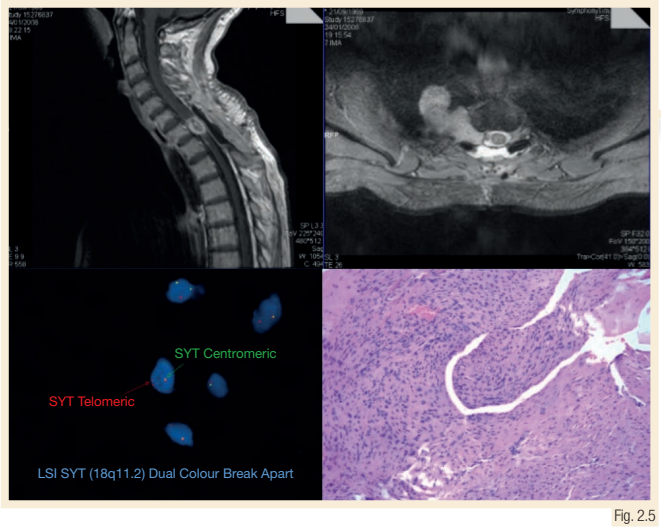


Fig. 2.5

Opposite, monophasic synovial sarcoma (SS) (*SYT-SSX* positive) in close relationship with root nerve and spinal cord, in a 38-year-old female patient. Vimentin++, CD34+, epithelial membrane antigen -/+; isolated CK and S-100. This case was clinicopathologically difficult to differentiate from malignant peripheral nerve sheath tumour.

The fingerprint of SS is the reciprocal (X,18) translocation, creating fusion genes, with *SYT-SSX* being the most frequent. Fluorescent *in situ* hybridisation (FISH) positive for *SYT* is a helpful diagnostic tool is these cases.

A study analysing the concordance in sarcoma pathology diagnosis between non-expert and expert found complete discordance (other subtype) in 19% of cases.

In GIST, each type of mutation in exon 11 of the KIT gene clusters in different positions: (5´ region) deletions involve codons 550-572, duplications in codons 573-591 and missense mutations predominate in codons 559 and 560.

According to several GIST guidelines, genotype is mandatory at diagnosis time due to its prognostic and predictive value. Secondary mutations do not guide clinical decisions.

Patients harbouring D842V mutation in exon 18 of the PDGFRA gene do not respond to imatinib, sunitinib or regorafenib. Emerging drugs such as crenolanib or avapritinib show relevant activity in this mutant type.

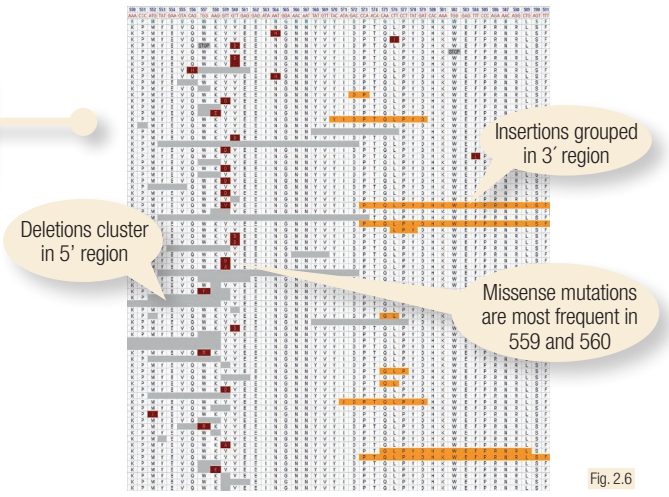


Fig. 2.6

REVISION QUESTIONS

1. Which genes are more frequently involved in translocation-related sarcomas?
2. How can FISH analysis help in the pathological diagnosis of sarcomas?
3. Why is genotype mandatory in GIST diagnosis?

Staging

Prognostic factors in GISTs include mitotic count (expressed as the number of mitoses on a total area of 5 mm^2), tumour size and tumour site (extra-gastric location entails worse outcome).

Tumour rupture (spontaneous or iatrogenic) results in poor prognostic outcomes and most authors consider it a peritoneal disease requiring imatinib up to progression.

Molecular biomarkers, such as *KIT* mutants involving codons 557-558 in exon 11, are not yet implemented in the risk classification but are an independent prognostic factor in gastric GISTs.

Risk group	Size (cm)	Mitotic count (5 mm^2)	Location
Very low risk	2-5	≤5	Gastric
Low risk	>5 and ≤10 ≤5	≤5 ≤5	Gastric Intestinal
Intermediate risk	>10 >5 and ≤10 2-5	≤5 ≤5 >5	Gastric Intestinal Gastric
High risk	2-5 >10 >5 and ≤10 >10 >5 and ≤10 >10	>5 ≤5 >5 >5 >5 >5	Intestinal Intestinal Gastric Gastric Intestinal Intestinal

Fig. 2.7

AJCC/UICC Cancer Staging Manual 8th edition.
T1 ≤5 cm; T2 >5 cm and ≤10 cm; T3 >10 cm and ≤15 cm;
T4 >15 cm. G: grading according to FNCLCC

Stage	T	N	M	G
IA	T1	N0	M0	G1
IB	T2-4	N0	M0	G1
II	T1	N0	M0	G2-3
IIIA	T2	N0	M0	G2-3
IIIB	T3-4	N0	M0	G2-3
IV	Any T Any T	N1 Any N	M0 M1	Any G Any G

AJCC, American Joint Committee on Cancer, FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; M, metastasis; N, node; T, tumour; UICC, Union for International Cancer Control.

Fig. 2.8

Despite the proposed TNM (tumour, node, metastasis) classification in STSs, the variables do not have the same impact across different histological subtypes and among different prognostic variables, making clinical application difficult.

Typically, G2 or G3 are considered high-grade tumours, but the impact of perioperative chemotherapy (ChT) may only be restricted to G3.

A time-dependency has been described for prognostic factors in STS, thus grade and size affect prognosis earlier than microscopic margins.

Magnetic resonance imaging (MRI) of primary tumours and thoraco-abdominal computed tomography (CT) scan for staging are the most relevant imaging tests in STS of limbs.

Bone-marrow biopsy is standard procedure in the staging of Ewing sarcoma and rhabdomyosarcoma (RMS).

Lymph-node involvement occurs in <5% of STSs and is mainly seen in the context of CCS, alveolar soft tissue sarcoma (ASPS), epithelioid sarcoma, RMS and angiosarcomas.

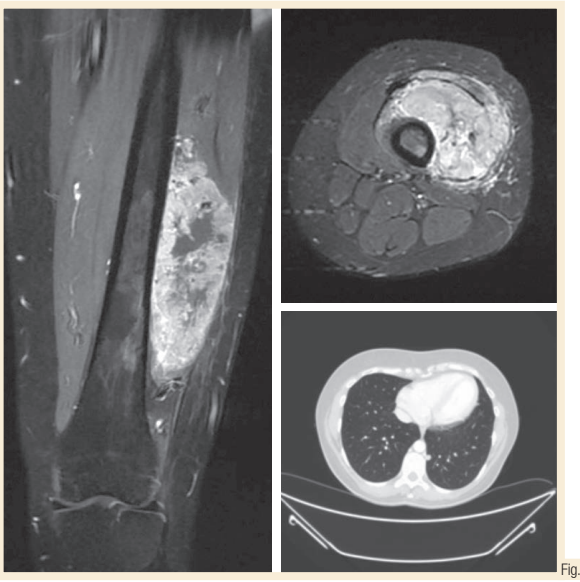


Fig. 2.9

REVISION QUESTIONS

1. Which prognostic factors are relevant in localised GIST?
2. Why could it be harsh to apply TNM staging to localised STS?
3. What are the most recommended imaging tests for somatic STS?

Response evaluation (radiological)

Evaluation of response is essential for assessing the efficacy of therapy and is key for clinical decision-making processes. RECIST (Response Evaluation Criteria in Solid Tumours) has the most validated criteria (considering only dimensional changes).

Non-dimensional responses (density changes) are often seen in sarcoma and frequently present earlier than dimensional variations. Choi criteria (which consider both dimensional and density changes, measured in Hounsfield units) have been validated in GIST to evaluate response to imatinib.

Choi criteria have shown more accuracy in predicting patient outcomes in GIST and in some sarcoma subtypes, such as solitary fibrous tumour treated with antiangiogenic therapy.

Top: example of RECIST response. Bottom: example of Choi response.

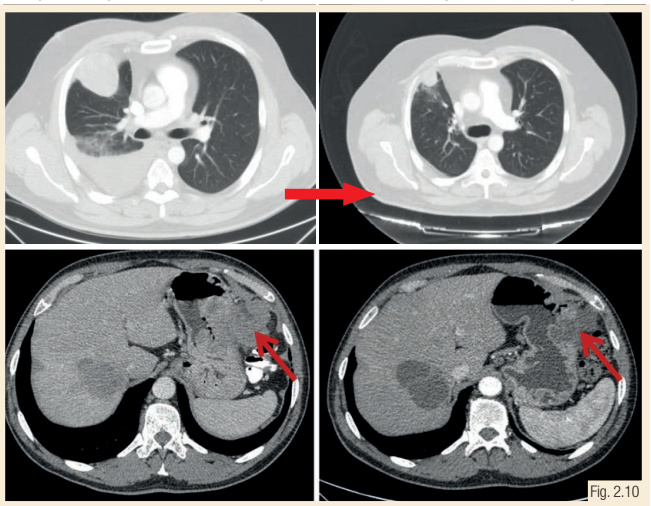


Fig. 2.10

RECIST, Response Evaluation Criteria in Solid Tumours

Evaluation of response in sarcoma can be challenging. It should be performed by expert radiologists with experience in sarcoma, using the same techniques to ensure comparable images.

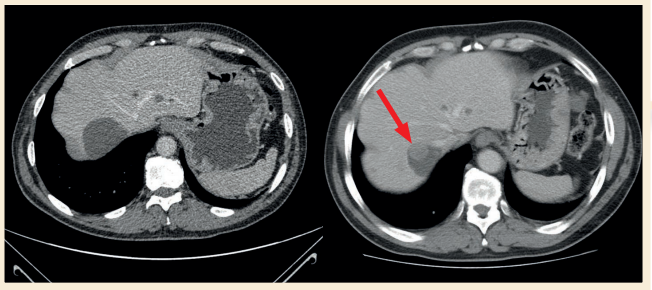


Fig. 2.11

Patterns of progression may also be non-dimensional, such as the 'nodule within a mass' phenomenon: the appearance of solid nodules in a previously responding lesion.

The natural history of different sarcomas should be considered in the radiological examinations (i.e. propensity to central nervous system [CNS] spread in CCS or ASPS).

Functional MRI studies such as diffusion-weighted imaging (DWI), using the quantitative value of apparent diffusion coefficient (ADC), may also be useful to identify early tumoural changes in response to therapy.

Increasing ADC values frequently translate to increases in necrosis as a result of a good response to therapy.

A complete MRI is relevant in the context of primary osteosarcoma, and it should include the two nearest joints. This will allow examination of the bone axis in order to detect skip dissemination.

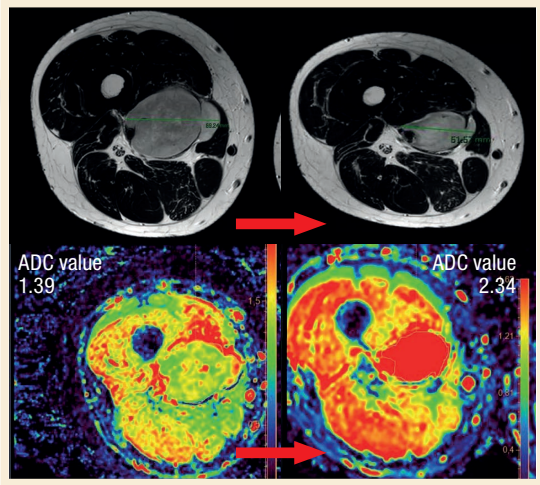


Fig. 2.12

ADC, apparent diffusion coefficient.

REVISION QUESTIONS

1. In sarcoma, are dimensional responses the only pattern of response to therapy?
2. In which histological subtype are Choi criteria more validated?
3. Which pattern of response is identified earlier in sarcoma: dimensional or density changes?

Response evaluation (non-radiological)

Pathological response after neoadjuvant ChT (measured in surgical specimen, analysed in the whole tumour, using a grid) correlates with patient outcome in both osteosarcoma and Ewing sarcoma.

Evaluation of pathological response must be performed by an expert pathologist.

A good response is defined as a tumour with <10% of viable tumour (therapy-induced necrosis >90%).

Response description	Response grade
Osteosarcoma (Huvos system)	
No vital tumour cells	IV
Less than 10% vital tumour tissue	III
10%-50% vital tumour tissue	II
No effect of chemotherapy	I
Ewing sarcoma (Picci)	
At least one residual macroscopic nodule of viable tumour (>10x)	I
Only isolated microscopic nodules of viable tumour cells are identified (<10x)	II
No viable nodules of tumour cells can be identified within the specimen	III

Fig. 2.13

In STS, the prognostic impact of preoperative therapy-induced changes is not so well established. Ongoing prospective studies will evaluate its possible prognostic role.

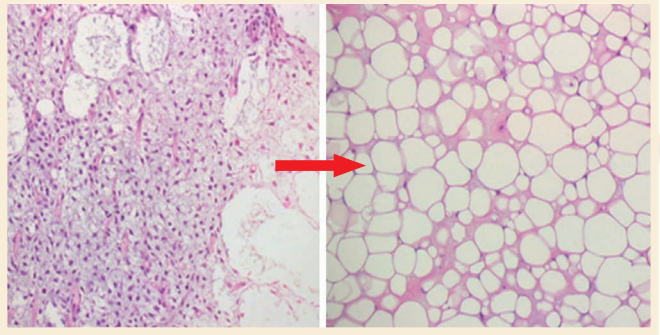


Fig. 2.14

Different histological changes can be found: necrosis, sclero-hyalinosis, fibrosis and mature adipocytic differentiation (in the case of liposarcoma, as shown in the image).

There are recommendations for pathological examination protocols after neoadjuvant treatment in STS such as those proposed by the Soft Tissue and Bone Sarcoma Group of the European Organisation for Research and Treatment of Cancer (EORTC).

Metabolic response can be detected by positron emission tomography (PET) scan in the context of high-grade sarcoma and GIST.

In some specific cases (to rule out M1 spread or to detect an early response), PET can be helpful.

In the case of high-grade MLPS, PET scan can detect substantial metabolic response. Interestingly, even in the context of complete pathological response, the fusion gene alteration was still present.

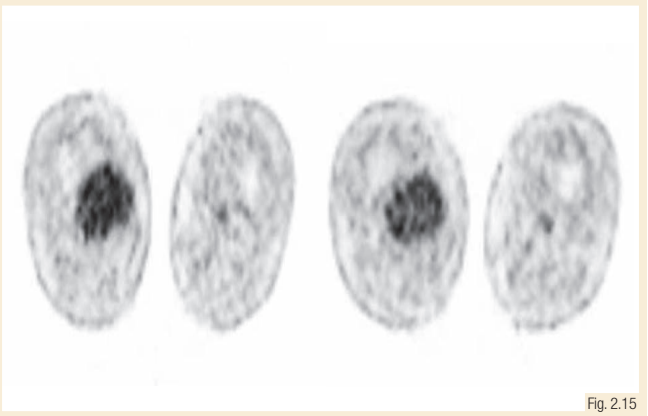


Fig. 2.15

REVISION QUESTIONS

1. What prognostic information can we obtain from pathological examination of a bone sarcoma after neoadjuvant ChT?
2. Which method is used to evaluate pathological changes in osteosarcoma?
3. In which contexts could metabolic evaluation by PET scan be useful?

Summary: Clinical presentation, staging and response assessment

- Referral of patients to expert MDTs is crucial in sarcoma
- Alarm signs (recently growing, deep or >5 cm masses) can be helpful for early referral of sarcoma patients
- A correct diagnosis, based on core biopsy, is essential to take therapeutic decisions in an MDT context
- One third of sarcomas are associated with genetic translocation and their fusions can be helpful as an ancillary diagnostic tool
- Imaging tests should be adapted to the natural history of different sarcomas: CNS spread is more frequent in ASPS and CCS, retroperitoneal in MLPS, breast in RMS
- Dynamic MRI can detect histological changes occurring in the tumour due to neoadjuvant treatment
- Although PET scan is not a standard in sarcoma, it can be useful in some contexts: to rule out M1 spread before metastasectomies or when early response assessment is required
- Although evaluation of size change (RECIST) is the most validated response assessment method, non-dimensional responses are frequently seen in sarcoma
- Pathological response after neoadjuvant ChT correlates with patient outcome in osteosarcoma and Ewing sarcoma

Further Reading

Blay JY, Bonvalot S, Casali P, et al. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. Ann Oncol 2005; 16:566–578.

Casali PG, Abecassis N, Aro HT, et al. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29(Supplement_4):iv267.

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.

Choi H, Charnsangavej C, de Castro Faria S, et al. CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. AJR Am J Roentgenol 2004; 183:1619–1628.

Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet Oncol 2017; 18:812–822.

Lurkin A, Ducimetière F, Vince DR, et al. Epidemiological evaluation of concordance between initial diagnosis and central pathology review in a comprehensive and prospective series of sarcoma patients in the Rhone-Alpes region. BMC Cancer 2010; 10:150.

Morosi C, Stacchiotti S, Marchianò A, et al. Correlation between radiological assessment and histopathological diagnosis in retroperitoneal tumors: analysis of 291 consecutive patients at a tertiary reference sarcoma center. Eur J Surg Oncol 2014; 40:1662–1670.

Stojadinovic A, Leung DH, Allen P, et al. Primary adult soft tissue sarcoma: time-dependent influence of prognostic variables. J Clin Oncol 2002; 20:4344–4352.

3 Treatment strategy for soft tissue and visceral sarcomas

Localised disease

In case of localised soft tissue sarcoma (STS), wide surgical excision with negative margins (R0), followed by radiotherapy (RT) up to 66 Gy, if compartmental resection was not performed, and in case of Grade 2-3 lesions >5 cm, is the current standard of care.

Pre-operative RT can be considered if it is anticipated that wound complication rates will be low; this depends on many factors such as patient condition and location of the sarcoma. Pre-operative RT leads to lower late toxicity and thus better functional outcome and quality of life.

The addition of pre- or post-operative RT provides better local control and can avoid amputation in some cases, but it has not proven to increase survival.

Forest plot for local recurrence with pre- or post-operative radiotherapy

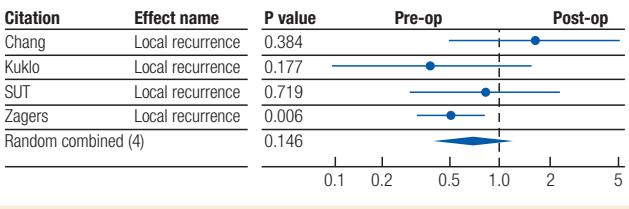


Fig. 3.1

Pooled overall survival data of two phase III trials, radical vs marginal

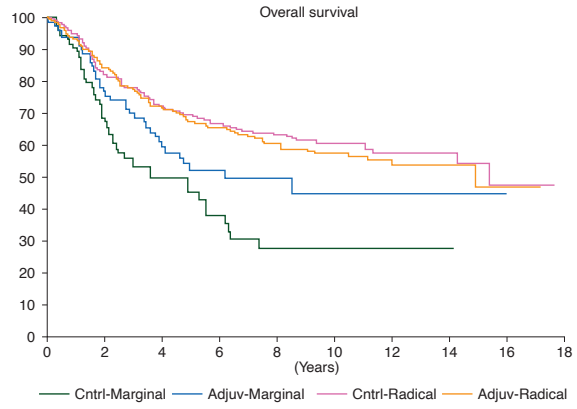


Fig. 3.2

Adjuvant treatment of STS with chemotherapy (ChT) is a controversial topic. Study outcomes of relapse-free survival (RFS) and overall survival (OS) are conflicting. The only OS and RFS benefit were seen in the subgroup that underwent a marginal (R1) resection.

The best choice of ChT agent is another point of discussion. The combination of doxorubicin (or epirubicin) and ifosfamide will achieve the greatest risk reduction.

Based on these limited data, adjuvant treatment should not be routine practice. It should only be offered to high-risk patients likely to show benefit (e.g. based on histology), in clinical trials or on an individual basis after shared decision-making with the patient.

One large randomised phase III study (NCT00003052) evaluated regional hyperthermia in addition to adjuvant ChT in patients with Grade 2-3, deep STS >5 cm.

It showed a disease-free survival (DFS) advantage compared with ChT alone.

Isolated limb perfusion for extremity STS has shown good overall response rates (ORRs) and significant limb salvage rates.

Disease-free survival of phase III trial, addition of hyperthermia to adjuvant ChT

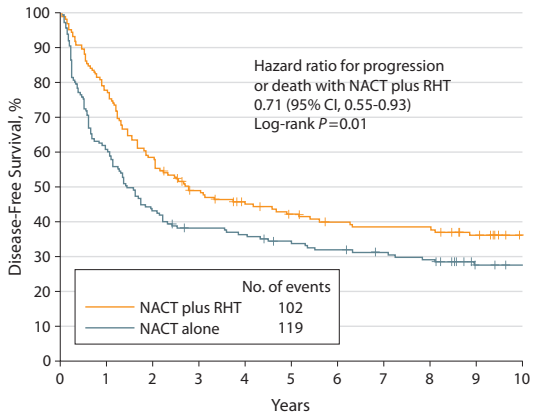


Fig. 3.3

ChT, chemotherapy; CI, confidence interval; NACT, neoadjuvant chemotherapy; RHT, regional hyperthermia.

REVISION QUESTIONS

1. In which patients can pre-operative RT be considered?
2. What is the optimal dose level for adjuvant RT in STS?
3. What are the main considerations regarding the decision whether to start adjuvant ChT?

Advanced and metastatic disease – first-line treatment

In the advanced or metastatic setting, palliative systemic treatment can be given primarily for symptom palliation, to prevent or slow down disease progression, and in some cases to improve OS at 5 years.

Both doxorubicin and ifosfamide have shown activity against STS and have been used for over 3 decades.

Doxorubicin is considered the current standard first-line treatment, with response rates (RRs) of 16%-27%. The dose-limiting toxicity of doxorubicin is myelosuppression and (cumulative) cardiomyopathy.

Remissions according to tumour type (partial or complete)

	No. remissions (total patients)	Percent remissions
Sarcoma		
Osteogenic sarcoma	5/9	
Leiomyosarcoma	3/8	
Fibrosarcoma	2/14	
Rhabdomyosarcoma	3/11	
Ewing sarcoma	2/7	
Chondrosarcoma	1/3	
Liposarcoma	1/3	
Haemangiosarcoma	2/3	
Haemangiopericytoma	1/2	
Neuroepithelioma	1/1	
'Others'	0/3	
	21/64	33%

Fig. 3.4

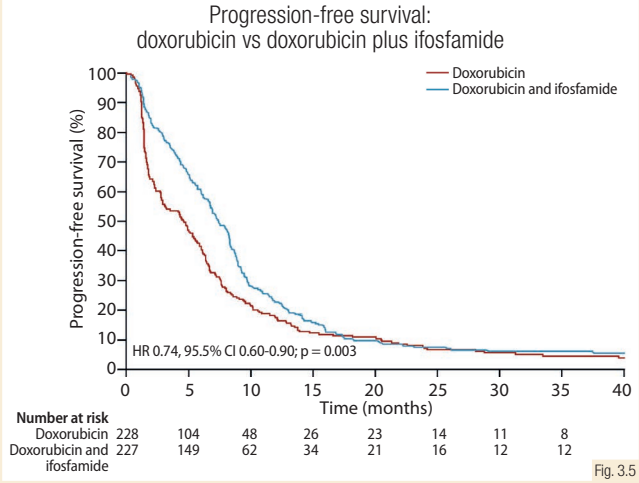


Fig. 3.5

CI, confidence interval; HR, hazard ratio.

Ifosfamide should be given in doses of at least 9-10 g/m^2, reaching RRs of around 25%. Common toxicities of ifosfamide include neurotoxicity, myelosuppression and haemorrhagic cystitis.

The addition of ifosfamide to the standard doxorubicin regimen is subject to discussion. Different randomised controlled trials (RCTs) report better RRs with combination treatment; however, this is accompanied by increased toxicity, especially myelotoxicity.

Furthermore, the combination does not improve survival rates.

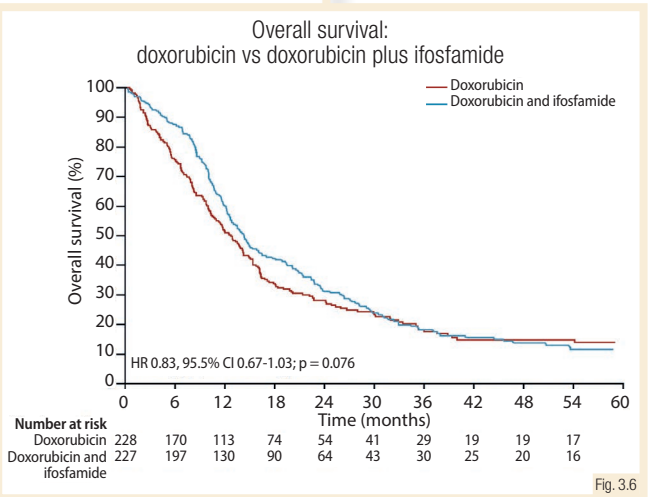


Fig. 3.6

CI, confidence interval; HR, hazard ratio.

In general, the decision whether to give combination or (sequential) monotherapy should be made on a patient-by-patient basis.

Combination treatment can be considered in the neoadjuvant setting, for example, where downstaging of the tumour is the main goal of therapy.

Patients over 60 years old were not included in the main study (NCT00061984). Given the myelotoxicity of the combination regimen, this patient category is less suitable for combination treatment.

REVISION QUESTIONS

1. Which two ChT agents are considered in first-line treatment of STS?
2. What are the main dose-limiting toxicities for doxorubicin treatment?
3. What are the considerations with regard to the addition of ifosfamide to standard treatment with doxorubicin?

Advanced and metastatic disease – first-line treatment (continued)

Prognostic factor analysis gave us insight on the chemosensitivity of specific histological subtypes.

For example: synovial sarcomas show better RRs to ChT, especially ifosfamide-containing regimens, compared with other STS subtypes.

Among ifosfamide-treated patients, the leiomyosarcoma and liposarcoma group showed worse outcomes compared with doxorubicin monotherapy.

Response rates of different STS types for doxorubicin vs ifosfamide-containing regimen

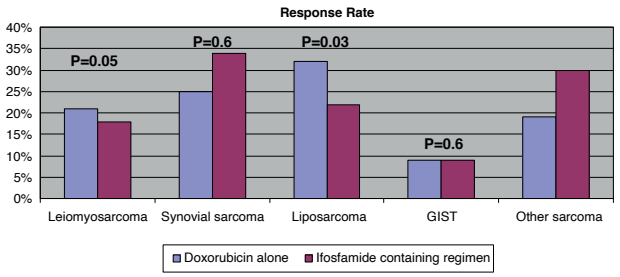


Fig. 3.7

GIST, gastrointestinal stromal tumour; STS, soft tissue sarcoma.

Ifosfamide metabolism

Advantages of slow continuous infusion of ifosfamide with mesna include:

- More total exposure to the active metabolite of ifosfamide (IPM)
- Lower peak concentrations of chloroacetaldehyde (less neurotoxicity)
- Convenience

However, to avoid bladder toxicity and haemorrhagic cystitis, mesna is required during the infusion

If present, mesna is highly effective and vigorous hydration is unnecessary

IPM, isophosphoramide mustard.

Fig. 3.8

An alternative to the commonly used regimen of ifosfamide in three daily divided doses of 3-4 g/m² is continuous infusion of ifosfamide over a period of 3-14 days in the outpatient setting.

Two studies suggested better tolerability and less cytotoxicity with a prolonged infusion time (Martin-Liberal et al, 2013; Sanfilippo et al, 2014).

However, a significant incidence of neurotoxicity (encephalopathy) was seen in one study.

Angiosarcomas are a distinct group of STSs when it comes to treatment with cytotoxic agents.

They are the only subtype to have shown a response to paclitaxel.

Whether or not the response to paclitaxel is superior to that of doxorubicin is unclear, but both agents can be considered.

Overall survival of angiosarcoma according to treatment regimen

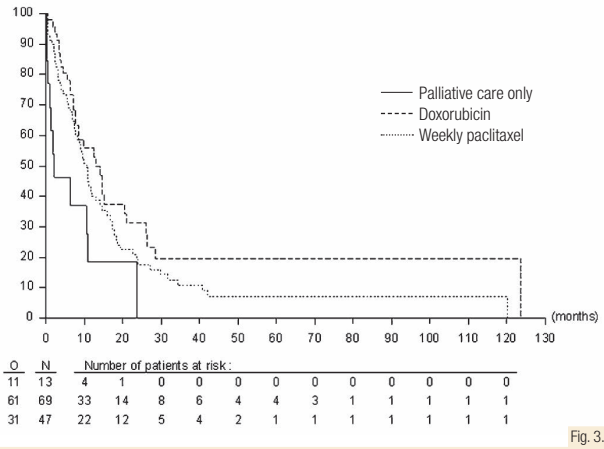


Fig. 3.9

REVISION QUESTIONS

1. Which STS subtypes are known to show limited benefit from standard doxorubicin-containing regimens compared with other subtypes?
2. Which STS subtype shows more benefit from doxorubicin-containing regimens?
3. Which agent should be considered for metastatic angiosarcoma in the first line?

Advanced and metastatic disease – second- and further-line treatment

Ifosfamide is a good choice for second-line treatment, if it has not yet been used in a first-line regimen.

Other cytotoxic agents besides doxorubicin and ifosfamide have been used in STS, for example: epirubicin, dacarbazine, cyclophosphamide, eribulin, trabectedin, docetaxel and gemcitabine.

Gemcitabine/docetaxel combination treatment is commonly used as second-line treatment after doxorubicin and/or ifosfamide.

Efficacy of trabectedin vs dacarbazine in leiomyosarcoma and liposarcoma

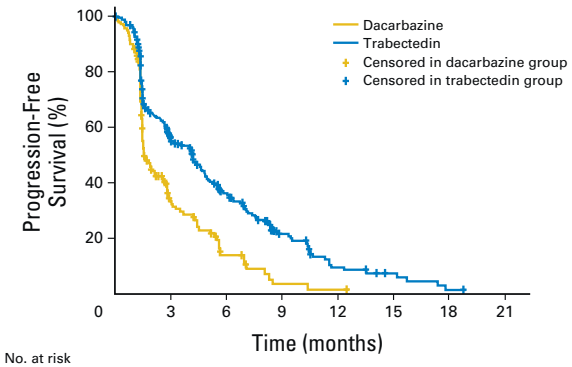


Fig. 3.10

Gemcitabine/docetaxel: no superiority over doxorubicin

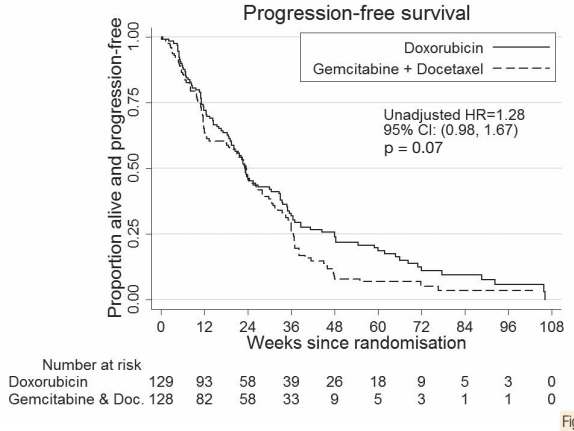


Fig. 3.11

CI, confidence interval; Doc, docetaxel; HR, hazard ratio.

Gemcitabine plus docetaxel has shown RRs of 14%-24% in the second-line treatment of leiomyosarcoma.

A trial comparing gemcitabine/docetaxel with doxorubicin alone even showed a 32% RR for undifferentiated pleomorphic sarcoma in both groups combined.

No superiority over doxorubicin-based treatments was seen in STS in general.

One of the recently approved agents for second- or third-line treatment of STS is pazopanib, a tyrosine kinase inhibitor (TKI) with activity against vascular endothelial growth factor (VEGF) 1, 2, 3 and platelet-derived growth factor (PDGF).

Pazopanib significantly increased progression-free survival (PFS) of non-adipocytic STS in second or further line compared with placebo in the PALETTE study.

The main adverse events were fatigue, hypertension, anorexia and diarrhoea.

Pazopanib vs placebo

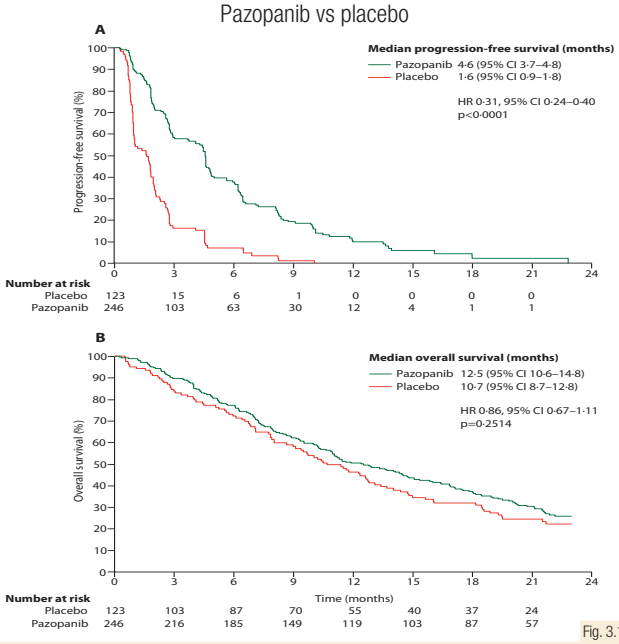


Fig. 3.12

CI, confidence interval; HR, hazard ratio.

REVISION QUESTIONS

1. What treatment modalities should be considered in second- or further-line treatment of STS?
2. How does combination therapy with gemcitabine/docetaxel compare with doxorubicin?
3. For which distinct STS subgroup should pazopanib be considered as second-line treatment?

Advanced and metastatic disease – second- and further-line treatment (continued)

Trabectedin is the preferential second/third-line option for liposarcomas and leiomyosarcomas, though this agent has also shown activity in other STS types. Trabectedin works among other mechanisms by sticking to the minor groove of DNA, thereby blocking DNA repair mechanisms and inducing apoptosis.

A large phase III study by Demetri et al (2016) in leiomyosarcoma and liposarcoma patients previously treated with an anthracycline therapy and at least one additional systemic regimen, resulted in a 45% risk reduction of disease progression or death, versus dacarbazine.

Observed toxicity with trabectedin consists mainly of myelosuppression and elevated transaminases.

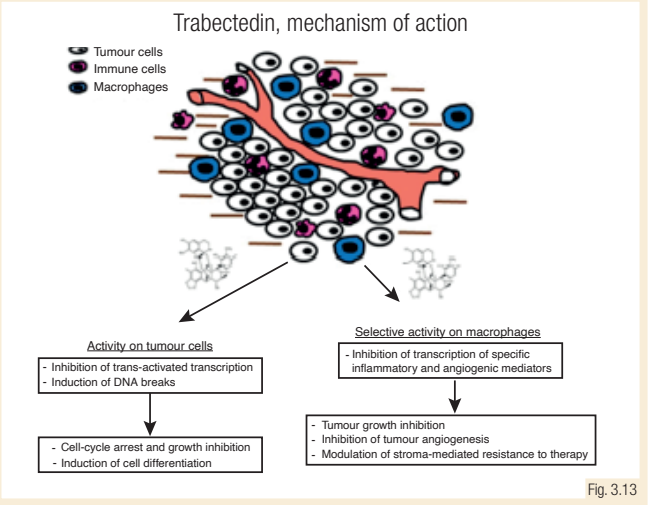


Fig. 3.13

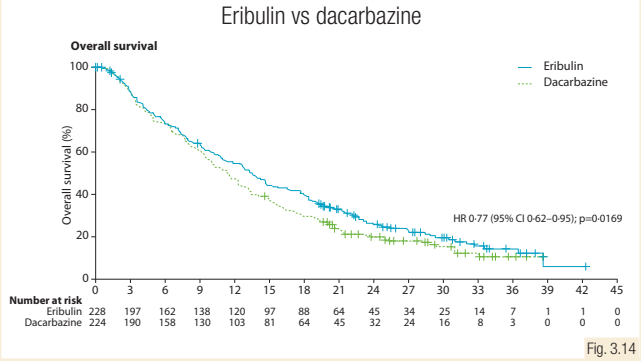


Fig. 3.14

CI, confidence interval; HR, hazard ratio.

Eribulin was recently approved for second-line treatment of metastatic liposarcoma in the USA and Europe. A phase III study (Schoffski et al, 2016) reported a median OS of 8.4 months, compared with 15.6 months with dacarbazine.

Side effects of eribulin are neutropaenia, fatigue, nausea and alopecia.

Eribulin inhibits microtubule dynamics and was previously approved for use in breast cancer.

Many other targeted therapies such as imatinib, sirolimus, sunitinib and cediranib were empirically studied in STS, and some are approved for rare types of STS. In the REGOSARC trial, regorafenib demonstrated improved PFS in non-liposarcomas, and improved PFS and OS in pazopanib-treated patients.

Sirolimus can be considered in later-line treatment for perivascular epithelioid cell tumours (PEComas) (e.g. angiomyolipoma and lymphangioleiomyomatosis). Mutations in the TSC1/2 genes can lead to dysregulated activation of the mammalian target of rapamycin (mTOR) pathway in these tumour types.

In liposarcomas, eribulin and trabectedin are approved, whereas pazopanib is not.

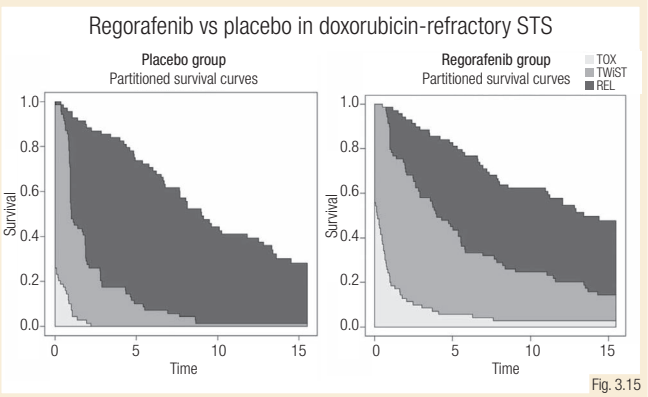


Fig. 3.15

REL, time spent without disease progression; STS, soft tissue sarcoma; TOX, time with a grade 3 or 4 adverse event; TWiST, time spent without toxicity or disease progression.

REVISION QUESTIONS

1. What is the preferred second-line treatment for the L-sarcomas (leiomyosarcoma/liposarcoma)?
2. What is the mechanism of action of trabectedin and eribulin?
3. For which STS subtype should sirolimus be considered in later-line treatment?

Summary: Treatment strategy for soft tissue and visceral sarcomas

Localised disease

- Surgical excision with negative margins is the current standard of care for localised STS
- The addition of pre- or post-operative RT provides better local control and can avoid amputation in some cases, but has not proven to increase survival
- Adjuvant treatment of STS with ChT is a controversial topic. It should only be offered to high-risk patients likely to show benefit, or on an individual basis after shared decision-making with the patient

Advanced or metastatic disease

- Both doxorubicin and ifosfamide have shown activity against STS in first-line palliative treatment
- In general, the decision whether to give ifosfamide and doxorubicin combination or doxorubicin monotherapy should be made on a patient-by-patient basis. It can be considered in the neoadjuvant setting, for example, where downstaging of the tumour is the main goal of therapy
- Synovial sarcomas are more chemosensitive, especially to ifosfamide-containing regimens
- Leiomyosarcomas and liposarcomas showed better outcomes with doxorubicin monotherapy compared with ifosfamide-containing regimens
- Angiosarcomas are the only sarcoma subtype to show a response to paclitaxel
- In second-line treatment, ifosfamide and gemcitabine/docetaxel should be considered
- The TKI pazopanib is another second-line option for non-adipocytic STS
- Trabectedin is the preferred second- or third-line option for liposarcomas and leiomyosarcomas
- Eribulin can also be considered as second- or later-line treatment for liposarcomas

Further Reading

Al-Absi E, Farrokhyar F, Sharma R, et al. A systematic review and meta-analysis of oncologic outcomes of pre- versus postoperative radiation in localized resectable soft-tissue sarcoma. Ann Surg Oncol 2010; 17:1367–1374.

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(Suppl_4):iv268–iv269.

Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: Results of a phase III randomized multicenter clinical trial. J Clin Oncol 2016; 34:786–793.

Dickson MA, Schwartz GK, Antonescu CR, et al. Extrarenal perivascular epithelioid cell tumors (PEComas) respond to mTOR inhibition: clinical and molecular correlates. Int J Cancer 2013; 132:1711–1717.

Issels RD, Lindner LH, Verweij J, et al. Effect of neoadjuvant chemotherapy plus regional hyperthermia on long-term outcomes among patients with localized high-risk soft tissue sarcoma: The EORTC 62961-ESHO 95 randomized clinical trial. JAMA Oncol 2018; 4:483–492.

Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 2014; 15:415–423.

Neuwirth MG, Song Y, Sinnamon AJ, et al. Isolated limb perfusion and infusion for extremity soft tissue sarcoma: a contemporary systematic review and meta-analysis. Ann Surg Oncol 2017; 13:3803–3810.

Pervaiz N, Colterjohn N, Farrokhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008; 113:573–581.

Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet 2016; 387:1629–1637.

Seddon B, Strauss SJ, Whelan J, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. Lancet Oncol 2017; 18:1397–1410.

Sleijfer S, Seynaeve C, Verweij J. Using single-agent therapy in adult patients with advanced soft tissue sarcoma can still be considered standard care. Oncologist 2005; 10:833–841.

van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012; 379:1879–1886.

4 Treatment strategy for bone sarcomas

Principles of multimodal therapy

Osteosarcoma and Ewing sarcoma commonly arise in adolescent or young adult patients. They require both local treatment and systemic chemotherapy (ChT).

Conventional chondrosarcoma is primarily a surgically treated disease, with limited options for other treatments.

Treatment strategies for other high-grade spindle-cell/pleomorphic sarcomas mimic those of osteosarcoma.

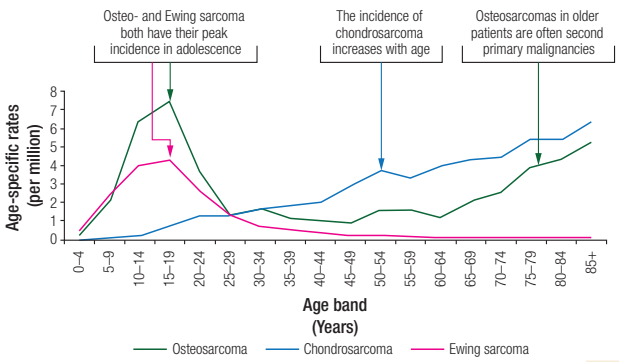


Fig. 4.1

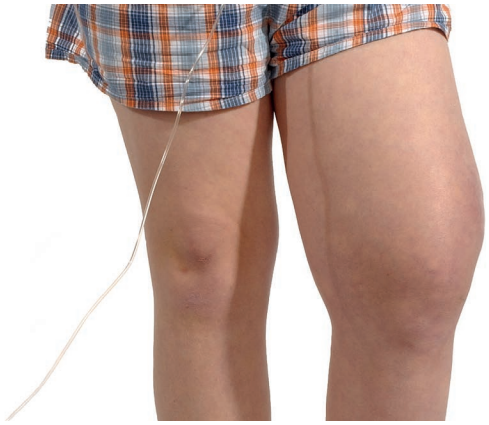


Fig. 4.2

Prior to biopsy, all patients with a suspected bone sarcoma should be referred to a reference centre or an institution belonging to a specialised network.

Pain, swelling, reduced joint mobility and pathological fractures are the most frequent presenting symptoms, while systemic signs of disease are rare.

All suspected bone sarcomas must be proven by histological evaluation, and suspected Ewing sarcomas should also be investigated for *EWSR1* translocations.

The diagnostic biopsy should be carried out at the reference centre by the team which will also carry out the definitive resection.

Both open or core-needle biopsies may provide sufficient tissue for light microscopy, immunohistochemistry and molecular studies.

Biopsy tracts must result in minimal tissue contamination, as they must later be removed *en bloc* with the primary tumour during definitive surgery.

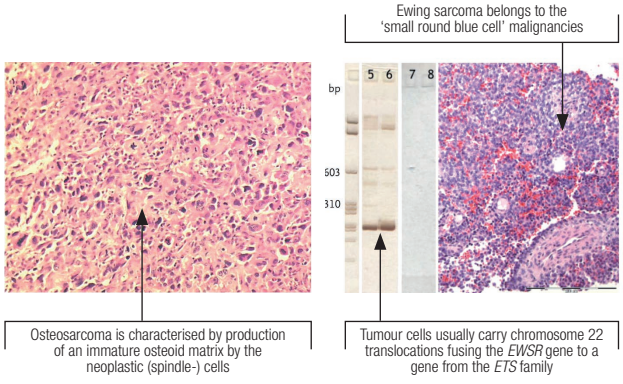


Fig. 4.3

REVISION QUESTIONS

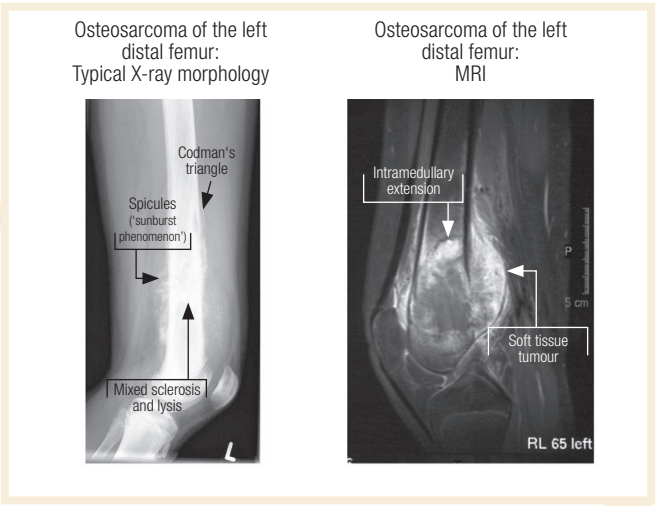
1. What are the three most common types of bone sarcoma?
2. When should suspected bone sarcoma patients be referred to specialists?
3. How must biopsy tracts be placed?

Imaging

Conventional X-ray is the method of choice for bony changes. For intramedullary and soft tissue extension and the relation to vessels and nerves, magnetic resonance imaging (MRI) is indicated.

MRI should show the whole involved bone, to ensure that skip metastases are not missed, as well as the neighbouring joints.

When it comes to imaging the primary tumour, additional imaging is rarely needed.



MRI, magnetic resonance imaging. Fig. 4.4

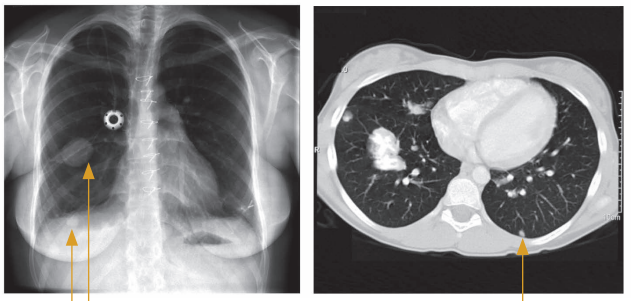


Fig. 4.5

Lung metastases make up >80% of all osteosarcoma metastases and 50% of those from Ewing sarcoma, with chest computed tomography (CT) as the most sensitive imaging technique.

It is often difficult to classify small pulmonary lesions <0.5-1 cm as metastatic or benign by imaging alone.

^{99m}Technetium-methylene-diphosphonate (MDP) bone scans were long considered standard to detect bone metastases, but both positron emission tomography (PET)-CT and whole-body MRI may be more sensitive.

Sites other than lungs or bone (in case of Ewing sarcoma: also bone marrow) are only rarely affected by primary bone sarcoma metastases.

Reduce radiation exposure: CT of the abdomen and other regions apart from the chest is NOT part of the routine bone sarcoma work up!

The Union for International Cancer Control (UICC) TNM (Tumour, Node, Metastasis) staging system can be used to describe the extent of disease. It allows distinguishing of skip metastases (T3) and sites of distant metastases.

TX		Primary tumour cannot be assessed			
T0		No evidence of primary tumour			
Appendicular skeleton, trunk, facial bones			**Pelvis**		
T1		Tumour ≤8 cm	T1		Tumour confined to 1 pelvic segment with no extraosseous extension
T2		Tumour >8 cm		T1a	Tumour ≤8 cm
T3		Discontinuous tumours in the primary bone site		T1b	Tumour >8 cm
Spine			T2		Tumour confined to 1 pelvic segment with extraosseous extension or 2 segments without extension
T1		Tumour confined to 1 vertebral segment or 2 adjacent segments		T2a	Tumour ≤8 cm
T2		Tumour confined to 3 adjacent vertebral segment		T2b	Tumour >8 cm
T3		Tumour confined to 4 or more adjacent vertebral segments or any non-adjacent segments	T3		Tumour spanning 2 pelvic segments with extraosseous extension
T4		Extension into the spinal canal or great vessels		T3a	Tumour ≤8 cm
	T4a	Extension into the spinal canal		T3b	Tumour >8 cm
	T4b	Evidence of gross vascular invasion or tumour thrombus in the great vessels	T4		Tumour spanning 3 pelvic segments or crossing the sacroiliac joint
					Tumour ≤8 cm
					Tumour >8 cm
NX		Regional lymph nodes cannot be assessed			
N0		No regional lymph node metastases			
N1		Regional lymph node metastases			
MX		Distant metastases cannot be assessed			
M0		No distant metastases			
M1		Distant metastases			
	M1a	Lung			
	M1b	Secondary bone or other distant sites			

Fig. 4.6

REVISION QUESTIONS

1. Which imaging techniques are required to describe the primary tumour?
2. Which organs are those most likely to be affected by primary bone sarcoma metastases?
3. What is a skip metastasis?

Local therapy

Surgery is the local treatment of choice for most bone sarcomas. It is essential for osteo- and chondrosarcoma and is the preferred method for Ewing sarcoma.

Definitive surgery must strive to achieve 'wide' resection margins, which is particularly challenging when the tumour is located in the axial skeleton.

Inadequate margins result in a substantially increased local failure rate. Local failure results in death far more often than not.

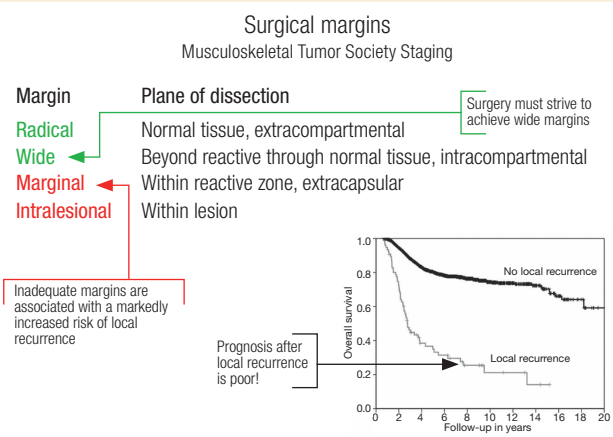


Fig. 4.7

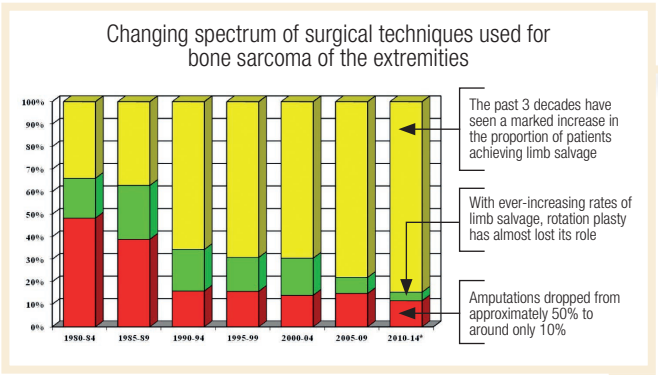


Fig. 4.8

Today, most patients with bone sarcomas of the extremities are candidates for limb salvage, but some still require other techniques to achieve wide margins.

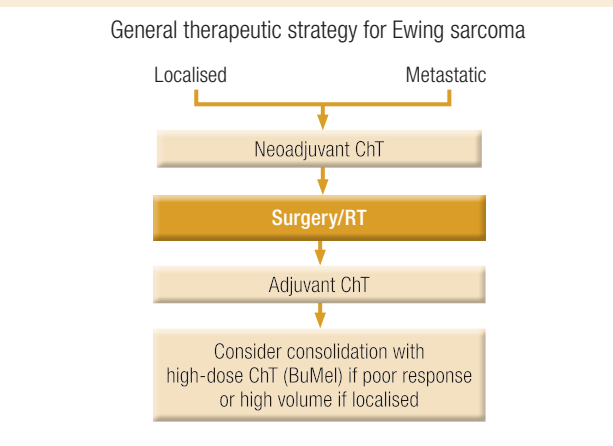
A variety of techniques, most notably endoprosthetic joint replacement, are available for reconstruction following tumour removal.

Technical advances such as 'self-expanding endoprostheses' may allow limb reconstruction even in patients who have not yet reached skeletal maturity.

Definitive radiotherapy (RT) has a role in treating selected Ewing sarcomas, inoperable osteosarcomas and inoperable chondrosarcomas.

RT added to surgery is indicated in bone sarcomas operated with inadequate margins and should be considered in Ewing sarcomas, at least those with a poor ChT response.

Innovative techniques such as proton and heavy ion RT may be considered for particularly challenging situations.



BuMel, busulfan and melphalan; ChT, chemotherapy; RT, radiotherapy.

Fig. 4.9

REVISION QUESTIONS

1. What is the definition of a wide margin?
2. Must bone sarcoma patients undergo amputation?
3. When is postoperative RT indicated?

Multimodal treatment of osteosarcoma

High-grade osteosarcoma is treated by surgery plus ChT. Some low- or intermediate-grade variants (peri-/parosteal, low-grade central) are treated by surgery alone.

Treatment is usually given over a period of about 6-10 months and generally includes several months of preoperative, 'neoadjuvant' induction ChT.

High-dose methotrexate with leucovorin rescue, doxorubicin and cisplatin (MAP regimen) often forms the basis of osteosarcoma ChT.

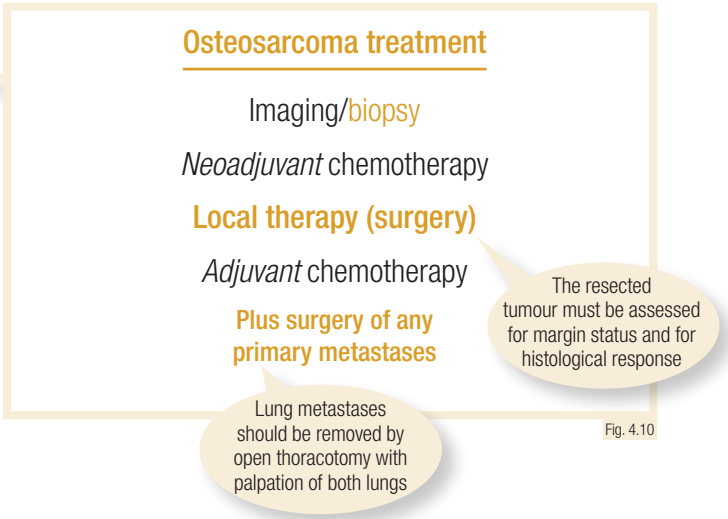


Fig. 4.10

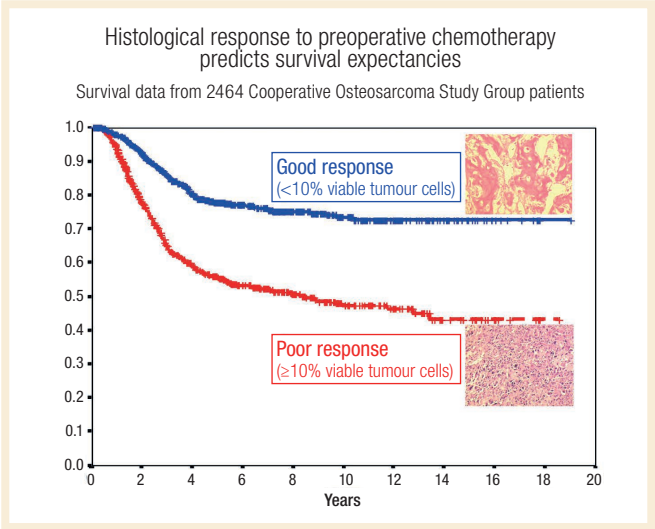


Fig. 4.11

A small primary tumour and localised disease correlate with a more favourable prognosis, as does a good histological response to preoperative ChT.

There is no evidence that altering postoperative ChT in case of poor histological response to induction treatment will improve outcomes.

Patients with primary (lung) metastases receive the same treatment as those with localised disease, plus surgery of the metastases (usually open thoracotomy).

Only 20% of patients with osteosarcoma recurrence survive long-term. A long disease-free interval and a low number of lesions correlate with better outcomes.

Complete surgical removal of each and every lesion at recurrence is considered a prerequisite for cure.

Second-line ChT is associated with limited survival prolongation in unresectable recurrence. Its role for resectable recurrence is still debated.

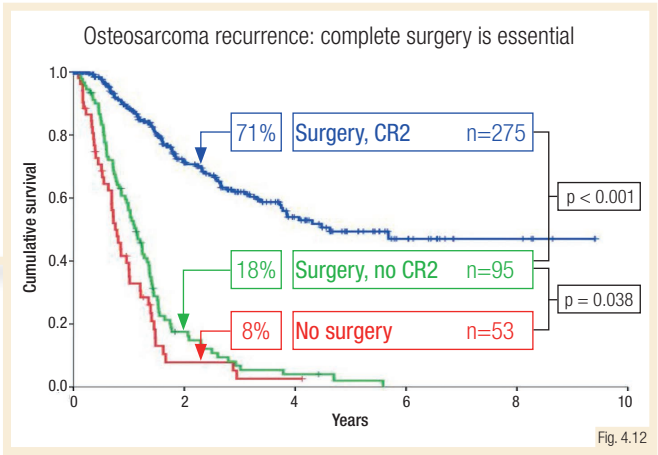


Fig. 4.12

CR2, second complete remission.

REVISION QUESTIONS

1. Which three drugs form the basis of most osteosarcoma ChT protocols?
2. Should postoperative ChT be modified in case of poor response to preoperative ChT?
3. Which type of treatment confers a chance of cure for patients with osteosarcoma recurrence?

Multimodal treatment of Ewing sarcoma

Ewing sarcoma treatment is usually given over around 10-12 months and includes several months of induction ChT prior to local treatment.

ChT generally incorporates vincristine, doxorubicin and oxazaphosphorines (cyclophosphamide or ifosfamide), and often also actinomycin D and etoposide.

Primary metastases (particularly those outside the lungs) confer inferior outcomes. Tumour size and ChT response are also prognostic.

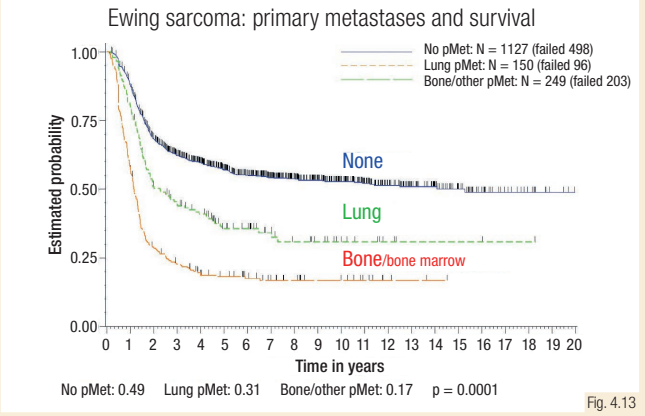


Fig. 4.13

pMet, primary metastases.

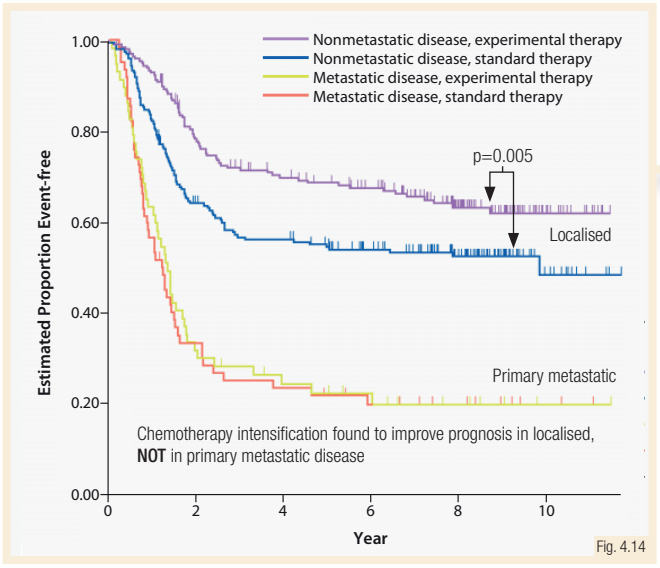


Fig. 4.14

ChT intensifications have resulted in improvements for patients with localised disease, but not for those with primary metastatic disease.

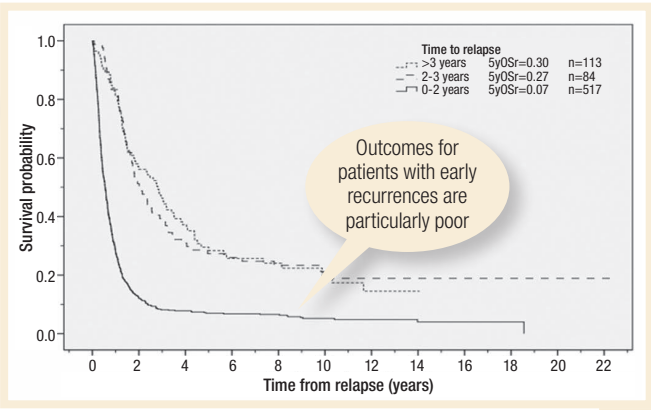
The use of high-dose ChT with peripheral blood stem-cell rescue may be indicated in selected patients with localised high-risk diseases.

Both whole-lung RT or high-dose ChT may confer similar survival advantages for patients with primary lung metastases.

The prognosis for patients with recurrent Ewing sarcoma remains poor, particularly in cases of early relapse.

Treatment at recurrence is not standardised, but often includes ChT with topoisomerase inhibitors and alkylators.

High-dose ChT with peripheral blood stem-cell rescue may have a role in consolidating a second complete remission.



5yOSr, 5-year overall survival rate.

Fig. 4.15

REVISION QUESTIONS

1. Which drugs are included in standard Ewing sarcoma protocols?
2. For which population was ChT intensification shown to be beneficial?
3. Is high-dose ChT with blood stem-cell rescue part of standard Ewing sarcoma treatment?

Summary: Treatment strategy for bone sarcomas

- All patients with a suspected bone sarcoma should be referred immediately to a reference centre or an institution belonging to a specialised network
- Osteosarcoma and Ewing sarcoma require multimodal approaches, while operable conventional chondrosarcoma is treated by surgery alone
- Conventional X-ray and MRI should be used to image the primary tumour
- Chest CT should be used to search for lung metastases and bone scans and/or whole-body MRI or PET/CT should be used to search for bone metastases
- Bone sarcoma ChT regimens generally include several months of induction ChT prior to local treatment of the primary tumour. This in turn is followed by several months of adjuvant ChT
- ChT for osteosarcoma is often based upon high-dose methotrexate/doxorubicin/cisplatin
- ChT for Ewing sarcoma is generally based upon oxazaphosphorines, doxorubicin and vincristine, often augmented by etoposide and actinomycin D
- Surgery with 'wide' margins is the local treatment of choice for most bone sarcomas
- RT has a role in selected Ewing sarcomas as well as in inoperable osteo- and chondrosarcomas
- Outcomes for bone sarcomas which recur following multimodal therapy remain poor, but some patients may be cured by treatment measures which are adapted to the specific situation

Further Reading

Andritsch E, Beishon M, Bielack S, et al. ECCO essential requirements for quality cancer care: Soft tissue sarcoma in adults and bone sarcoma. A critical review. Crit Rev Oncol Hematol 2017; 110:94–105.

Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. J Clin Oncol 2002; 20:776–790.

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(Suppl 4):iv79–iv95.

Gorlick R, Janeway K, Marina M, et al. Osteosarcoma. In: Pizzo PA, Poplack DG (Eds). Principles and Practice of Pediatric Oncology, seventh edition. Alphen aan den Rijn, Netherlands: Wsolters Kluwer, 2016; pp. 877–898

Hawkins DS, Brennan B, Bölling T, et al. Ewing sarcoma. In: Pizzo PA, Poplack DG (Eds). Principles and Practice of Pediatric Oncology, seventh edition. Alphen aan den Rijn, Netherlands: Wolters Kluver, 2016; pp. 855–876.

Marina NM, Smeland S, Bielack SS, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. Lancet Oncol 2016; 17:1396–1408.

Meyers PA, Schwartz CL, Krailo MD, et al. Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival – a report from the Children's Oncology Group. J Clin Oncol 2008; 26:633–638.

National Cancer Institute Physician Data Query (PDQ®). Osteosarcoma and Malignant Fibrous Histiocytoma of Bone Treatment / Ewing Sarcoma Treatment (PDQ®) – Health Professional Version. https://www.cancer.gov/types/bone/hp/osteosarcoma-treatment-pdq (11 August 2020, date last accessed) and https://www.cancer.gov/types/bone/hp/ewing-treatment-pdq (11 August 2020, date last accessed).

Whelan J, Le Deley MC, Dirksen U, et al; Euro-E.W.I.N.G.99 and EWING-2008 Investigators. High-dose chemotherapy and blood autologous stem-cell rescue compared with standard chemotherapy in localized high-risk Ewing sarcoma: results of Euro-E.W.I.N.G.99 and Ewing-2008. J Clin Oncol 2018; 36:3110–3119.

Wilhelm M, Dirksen U, Bielack SS, et al. ENCCA WP17-WP7 consensus paper on teenagers and young adults (TYA) with bone sarcomas. Ann Oncol 2014; 25:1500–1505.

Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. J Clin Oncol 2012; 30:4148–4154.

Acknowledgements

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B

More advanced knowledge

5 Epidemiology and prognostic factors

Incidence

Sarcomas are rare, accounting for approximately 1% of all cancers. The age-standardised incidence has been reported from between 1 to 6.4/100 000 population.

In the paediatric and young adult population, the incidence is even lower, ~1-2/100 000 population. However, proportionally, sarcomas represent up to 13% of all cancers in this age group.

Most sarcomas are soft tissue in origin, with bone sarcomas representing only 10% of all sarcomas.

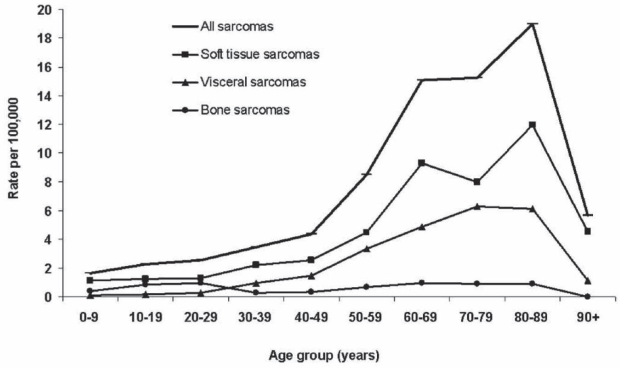


Fig. 5.1

Soft tissue sarcoma (STS) incidence increases with age, with a peak incidence between 80 and 89 years, and a mean age of diagnosis around 60 years old.

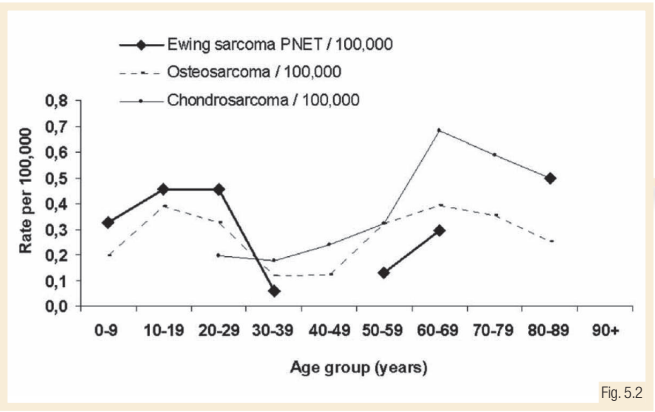


Fig. 5.2

PNET, primitive neuroectodermal tumour.

Bone sarcomas have a bimodal age distribution, with peak incidences between ages 10-30 and 60-90 years.

Gastrointestinal stromal tumour (GIST), leiomyosarcoma and angiosarcoma are more frequent in women, while undifferentiated pleomorphic sarcoma (UPS), liposarcoma, osteosarcoma and Kaposi sarcoma favour men. Overall there is no difference in sex distribution.

GIST, leiomyosarcoma, liposarcoma and UPS are the most common STSs. No other subtype accounts for more than 5%.

Osteosarcoma, Ewing sarcoma and chondrosarcoma are the most common bone sarcomas.

STS incidence has been growing slowly over recent years, whereas the incidence of bone sarcomas has remained static (Cancer Research UK).

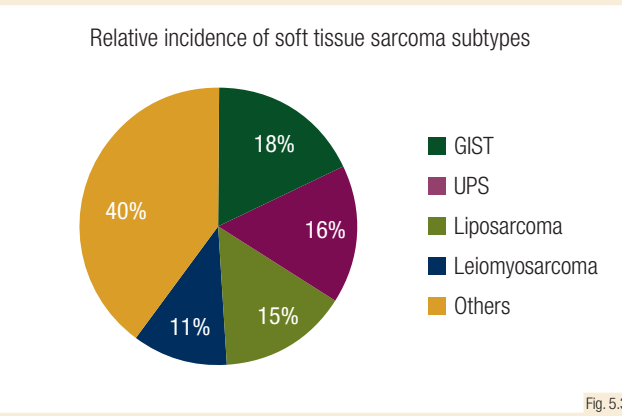


Fig. 5.3

GIST, gastrointestinal stromal tumour; UPS, undfferentiated pleomorphic sarcoma.

REVISION QUESTIONS

1. Which age group has the highest incidence of sarcoma?
2. The incidence of sarcomas in the paediatric population is less than in the adult population, but accounts for a higher percentage of cancers. Why might this be the case?
3. What is a possible explanation for the bimodal distribution of bone sarcomas?

Location and risk factors

Sarcomas may develop in any part of the body but most locations in the body will have certain subtypes that occur more frequently as primary tumours.

Sarcomas in the abdomen or retroperitoneum are more frequently liposarcomas or leiomyosarcoma. In the limbs, pleomorphic sarcoma, liposarcomas and synovial sarcoma are the most common.

The majority (approximately 80%) of bone sarcomas will develop in the limbs.

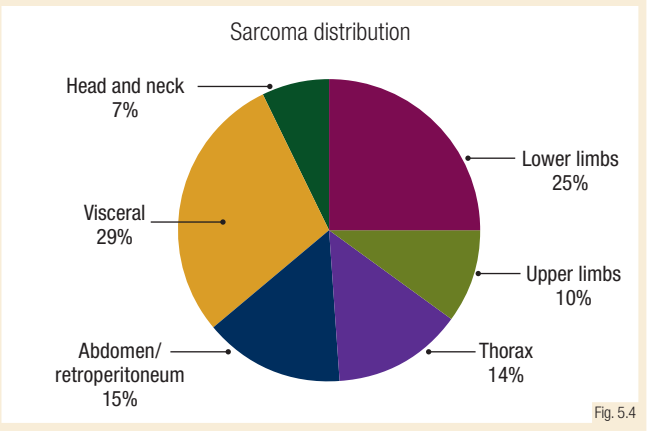


Fig. 5.4

Genetic syndrome	Sarcoma	Gene
Neurofibromatosis type 1	MPNST, GIST	*NF1*
Retinoblastoma	STS, osteogenic	*Rb-1*
Li-Fraumeni syndrome	STS, osteogenic	*TP53*
Gardner syndrome	Fibromatosis, Fibrosarcoma	*APC*
Werner syndrome	STS	*WRN*
Gorlin syndrome	Fibrosarcoma, Rhabdomyosarcoma	*PTC*
Tuberous sclerosis	Rhabdomyosarcoma	*TSC1/TSC2*
Carney-Stratakis syndrome	GIST	*SDH* subunit genes

APC, adenomatous polyposis coli; GIST, gastrointestinal stromal tumour; MPNST, malignant peripheral nerve sheath tumour; SDH, succinate dehydrogenase; STS, soft tissue sarcoma; TSC1/2, tuberous sclerosis 1/2.

Fig. 5.5

The majority of sarcomas are sporadic and not identified with any particular genetic syndrome or environmental trigger.

There are, however, a number of risk factors that do predispose to the development of sarcoma in a small percentage of cases.

A number of genetic syndromes have been associated with sarcomas. Genetic predisposition may play an important role, especially in paediatric sarcoma.

Radiation is a proven risk factor for sarcomas. Environmental radiation doubles the risk for every 1 Gy exposure.

More commonly, sarcomas develop after radiotherapy for a previous cancer, with a latency of 3-30 years (median 11 years). Radiation for breast cancer increases the risk of angiosarcoma 16-fold.

Other risk factors include human immunodeficiency virus (HIV)/human herpes virus 8 (HHV8) (Kaposi sarcoma), chemical exposure (TCCD [tetrachlorodibenzodioxin], polychlorophenols), previous cancers, increased BMI (body mass index), trauma/surgery – fibromatosis.

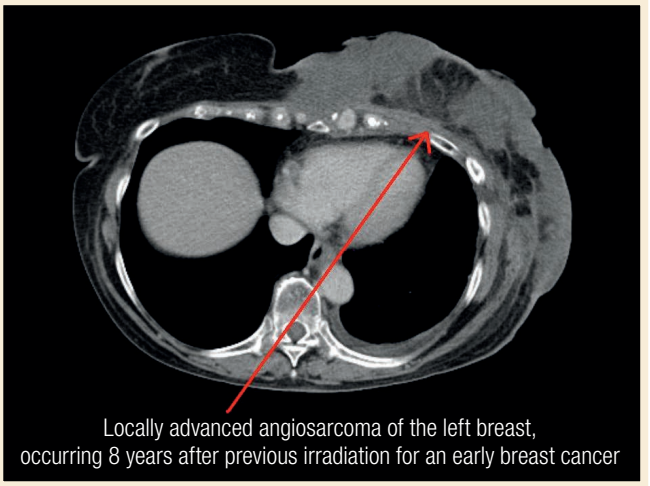

Locally advanced angiosarcoma of the left breast, occurring 8 years after previous irradiation for an early breast cancer

Fig. 5.6

REVISION QUESTIONS

1. Where are the most common sites for a sarcoma to develop?
2. What is the most common reason that a patient with a past history of malignancy will develop a sarcoma?
3. What is the usual time frame for the development of a radiation-induced sarcoma?

Prognostic factors

Prognosis varies greatly. Many sarcomas can be cured with surgery alone; some, however, are highly aggressive with poor outcomes.

Extremity tumours have a better prognosis than visceral/retroperitoneal sarcomas, partly because they are detected earlier, at smaller size, and because truly radical surgery is more easily performed.

Patients older than 65 years have a poorer prognosis than younger patients.

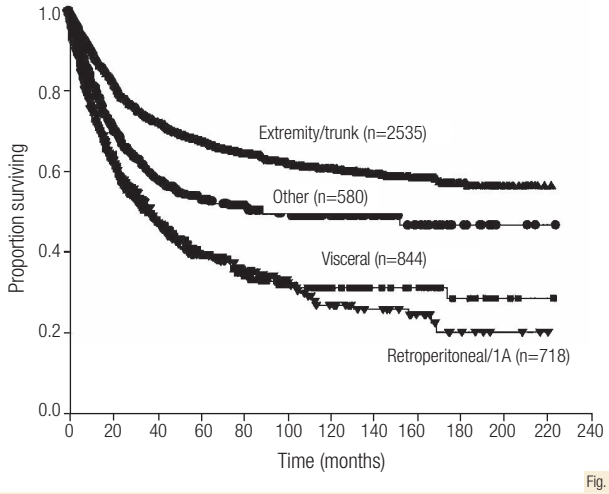
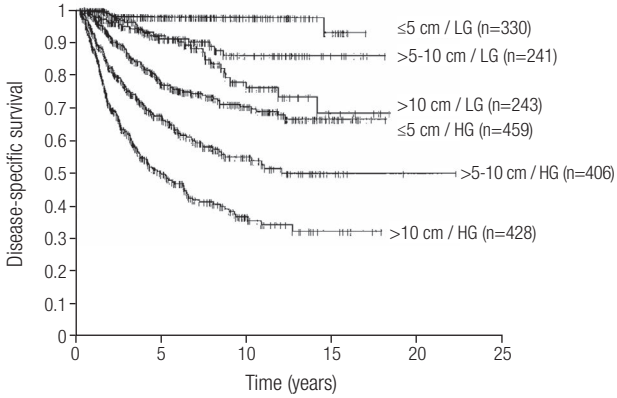


Fig. 5.7



HG, high grade; LG, low grade.

Fig. 5.8

Stage of sarcoma is a very important prognostic factor with a 5-year survival of 91%, 74%, 43% and 16% for stage I to stage IV, respectively.

The size of the sarcoma helps determine stage, but is an important risk factor in its own right, with larger tumours having a worse prognosis.

The histological grade is a very important factor in the prognosis, with high-grade tumours having a higher risk of distant metastasis.

Prognosis varies markedly depending on histological subtype, due to differences in the underlying biology. Some subtypes rarely/never metastasise, or progress slowly. Others behave highly aggressively.

Patients with metastatic disease (stage IV) generally have a poor prognosis, with median survival of ~12 months.

Some subtypes, such as endometrial stromal tumour or alveolar soft part sarcoma, may have long survival times, even with metastatic disease.

5-year metastasis-free survival by grade of sarcoma (percentage)

	Grade 1	Grade 2	Grade 3
Pleomorphic	89.8	76.5	48.1
Liposarcoma	93.8	71.6	58.7
Leiomyosarcoma	92.9	66.6	44.7
Synovial sarcoma		74.8	35.1
MPNST	77.8	56.1	52.1
Rhabdomyosarcoma		74.9	42.1
UPS		69.9	40.3
Others	82	69	36.5

MPNST, malignant peripheral nerve sheath tumour; UPS, undifferentiated pleomorphic sarcoma.

Fig. 5.9

REVISION QUESTIONS

1. What are the important determinants of prognosis in sarcoma?
2. Which primary sarcoma location has a better outcome and why?
3. In terms of prognosis, which is more important: the grade or the size of a sarcoma?

Summary: Epidemiology and prognostic factors

- Sarcomas are very rare, accounting for only 1% of all cancers
- The incidence of STS increases with age
- Bone sarcomas have a bimodal distribution of incidence
- STSs account for 90% of sarcomas, with the most common subtypes being GIST and leiomyosarcoma
- STSs may develop in any part of the body, but more commonly on extremities or in the abdomen
- A number of genetic syndromes and environmental risk factors have been described; however, they account for only a small proportion of sarcomas
- Radiation is a well-defined risk factor for sarcoma
- Prognosis varies greatly depending on underlying histology, stage and grade of the sarcoma
- The majority of small low-grade sarcomas are cured with surgery
- Most patients with metastatic sarcoma have a poor prognosis with short survival times

Further Reading

Amankwah EK, Conley AP, Reed DR. Epidemiology and therapies for metastatic sarcoma. Clin Epidemiol 2013; 5:147–162.

Ballinger ML, Goode DL, Ray-Coquard I, et al. Monogenic and polygenic determinants of sarcoma risk: an international genetic study. Lancet Oncol 2016; 17:1261–1271.

Borden EC, Baker LH, Bell RS, et al. Soft tissue sarcomas of adults: state of the translational science. Clin Cancer Res 2003; 9:1941–1956.

Burningham Z, Hashibe M, Spector L, Schiffman JD. The epidemiology of sarcoma. Clin Sarcoma Res 2012; 2:14.

Chen C, Borker R, Ewing J, et al. Epidemiology, treatment patterns, and outcomes of metastatic soft tissue sarcoma in a community-based oncology network. Sarcoma 2014; 2014:145764.

Coindre JM, Terrier P, Guillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 2001; 91:1914–1926.

Corey RM, Swett K, Ward WG. Epidemiology and survivorship of soft tissue sarcomas in adults: a national cancer database report. Cancer Med 2014; 3:1404–1415.

Ducimetière F, Lurkin A, Ranchère-Vince D, et al. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. PLoS ONE 2011; 6:e20294.

Garg PK, Kumar A. Radiation induced sarcoma: Everything comes with a price. Urol Ann 2014; 6:250–251.

National Cancer Registration and Analysis Service. Sarcomas. Available at: http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/sarcomas/ (date last accessed 11 August 2020).

Singer S, Maki RG, O'Sullivan B. Soft tissue sarcoma. In: DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2011, pp 1533–1577.

Stojadinovic A, Leung DH, Allen P, et al. Primary adult soft tissue sarcoma: time-dependent influence of prognostic variables. J Clin Oncol 2002; 21:4344–4352.

6 Pathogenesis and molecular biology

Molecular alterations in sarcomas

Based on molecular features, sarcomas can be subdivided as a conceptual framework into sarcomas with complex karyotype (most frequent), and sarcomas with a relatively simple karyotype (with specific translocations or with specific gene mutations or amplifications).

Translocations usually result in highly specific gene fusions.

In combination with clinical and histological features they provide a useful diagnostic tool in sarcoma classification.

Molecular subgroup	Tumour type
Complex karyotype	Osteosarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma
Simple karyotype with specific translocation	Ewing sarcoma, DFSP, alveolar rhabdomyosarcoma, myxoid liposarcoma, clear cell sarcoma, mesenchymal chondrosarcoma
Specific gene mutations or amplifications	GIST, well-differentiated and dedifferentiated liposarcoma

DFSP, dermatofibrosarcoma protuberans; GIST, gastrointestinal stromal tumour. Fig. 6.1

Translocations resulting in chimeric transcription factors

Tumour type	Translocation	Gene(s)
Ewing sarcoma	*t(11;12)(q24;q12)* *t(21;22)(q22;q12)* *t(16;21)(p11;q22)*	*EWSR1-FLI1* *EWSR1-ERG* *FUS-ERG*
Angiomatoid fibrous histiocytoma	*t(12;22)(q13;q12)* *t(2;22)(q33;q12)*	*EWSR1-ATF1* *EWSR1-CREB1*
Clear cell sarcoma	*t(12;22)(q13;q12)* *t(2;22)(q33;q12)*	*EWSR1-ATF1* *EWSR1-CREB1*
Low-grade fibromyxoid sarcoma	*t(7;16)(q33;p11)* *t(11;16)(p11;p11)*	*FUS-CREB3L2* *FUS-CREB3L1*
Desmoplastic small round-cell tumour	*t(11;22)(p13;q12)*	*EWSR1-WT1*
Extraskeletal myxoid chondrosarcoma	*t(9;22)(q22;q12)* *t(9;17)(q22;q11)*	*EWSR1-NR4A3* *TAF2N-NR4A3*

EWSR1, Ewing sarcoma breakpoint region 1. Fig. 6.2

Ewing sarcoma is an example of a high-grade sarcoma that in 90%-95% of cases harbours a Ewing sarcoma breakpoint region 1 *(EWSR1)-FLI1* gene fusion, encoding a chimeric transcription factor.

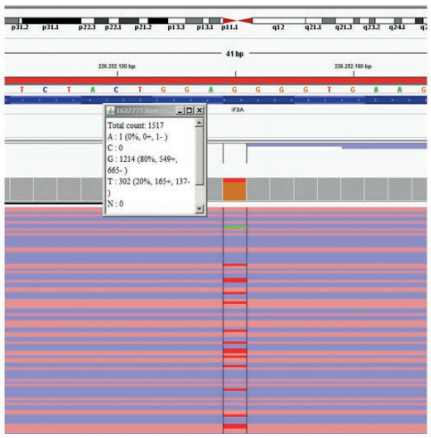
Different types of sarcomas may have overlapping fusion partners; e.g. *EWSR1* is involved in fusions in Ewing sarcoma, clear cell sarcoma, extraskeletal myxoid chondrosarcoma and myoepithelioma. Detection of a break in *EWSR1* is therefore not specific.

In contrast, *SS18-SSX* fusions are exclusive to synovial sarcoma.

Single gene mutations are important findings with diagnostic and therapeutic implications.

For instance: hotspot mutations at the G34 position in the histone 3.3 gene *H3F3A* are helpful to distinguish giant cell tumour of bone (GCTB) from its histological mimics.

Another example is gastrointestinal stromal tumour (GIST) with mutations in *KIT*, platelet-derived growth factor receptor alpha *(PDGFRA)*, *BRAF*, succinate dehydrogenase (SDH) or neurofibromatosis type 1 *(NF1)*.



H3F3A p.Gly34Trp (G34W) in 20% of the reads

Fig. 6.3

REVISION QUESTIONS

1. What is the most frequent molecular subgroup of sarcomas?
2. To which molecular subgroup does myxoid liposarcoma belong?
3. Which tumour is characterised by mutations in *KIT*?

Indications for molecular testing in sarcomas

Molecular testing in sarcomas is performed:

- for diagnosis: for confirmation, if a specific pathological diagnosis is doubtful, or if the clinical pathological presentation is unusual
- for prognosis (e.g. *PAX-FOXO1* fusion type in rhabdomyosarcoma)
- for response prediction (e.g. *KIT* mutation in GIST)
- to rule out hereditary syndrome (in case of a somatic beta catenin 1 [*CTNNB1*] mutation in desmoid-type fibromatosis)

With the exception of GIST, most molecular analysis is used for diagnosis.

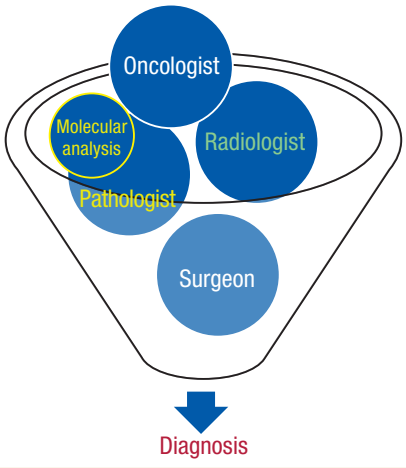


Fig. 6.4

Tumour type	Translocation	Drug
Gastrointestinal stromal cell tumour	*ETV6-NTRK*	Tropomyosin receptor kinase inhibitors
Dermatofibrosarcoma protuberans	*COL1A1-PDGFB*	Imatinib
Tenosynovial giant cell tumour	*COL6A3-CSF1*	Anti-CSF1
Inflammatory myofibroblastic tumour	*ALK* rearrangement	Crizotinib
Myxoid liposarcoma	*FUS-DDIT3*	Trabectedin
Alveolar rhabdomyosarcoma	*PAX3-FOXO1*	TKIs
Alveolar soft part sarcoma	*ASPSCR1-TFE3*	TKIs

Fig. 6.5

ALK, anaplastic lymphoma kinase; CSF1, colony stimulating factor 1; NTRK, neurotrophic tyrosine receptor kinase; PDGFB, platelet-derived growth factor beta; TKI, tyrosine kinase inhibitor.

Most fusion products resulting from translocations are difficult to target therapeutically.

However, some fusions involve tyrosine kinases, or provide sensitivity to specific therapy in another way.

For example, in case of locally advanced or metastatic dermatofibrosarcoma protuberans, imatinib may be used as systemic therapy.

Imatinib and sunitinib are examples of selective tyrosine kinase inhibitors (TKIs).

Selective TKIs are used in the treatment of GISTs, whose targets include KIT and PDGFRA.

Imatinib treatment achieves a partial response or stable disease in the majority of GIST patients (unless the *PDGFRA* D842V mutation is found, which confers resistance to imatinib).

Frequencies of *KIT* and *PDGFRA* mutations in GIST and sensitivity (S) or resistance (R) to tyrosine kinase inhibitors imatinib and sunitinib

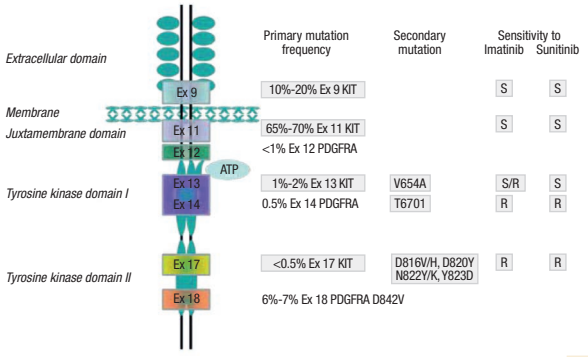


Fig. 6.6

GIST, gastrointestinal stromal tumour; PDGFRA, platelet-derived growth factor receptor alpha.

REVISION QUESTIONS

1. What are the indications for molecular testing in sarcomas?
2. Which type of sarcoma can be treated with a selective TKI?
3. Which specific mutation in GIST confers resistance to imatinib?

Methods for detecting translocations in sarcomas

In molecular diagnostics, translocation detection can be performed by fluorescent *in situ* hybridisation (FISH).

FISH is a sensitive and fast method to detect translocations. The pitfall is that the fusion partner remains unknown. As some genes (*EWSR1, FUS*) are highly promiscuous, a definitive diagnosis can only be made within the appropriate morphological and immunohistochemical context by an expert pathologist.

FUS FISH shows a split signal (red and green) in case of a *FUS*-translocated tumour (such as low-grade fibromyxoid sarcoma, Ewing sarcoma, acute myeloid leukaemia, myxoid liposarcoma).

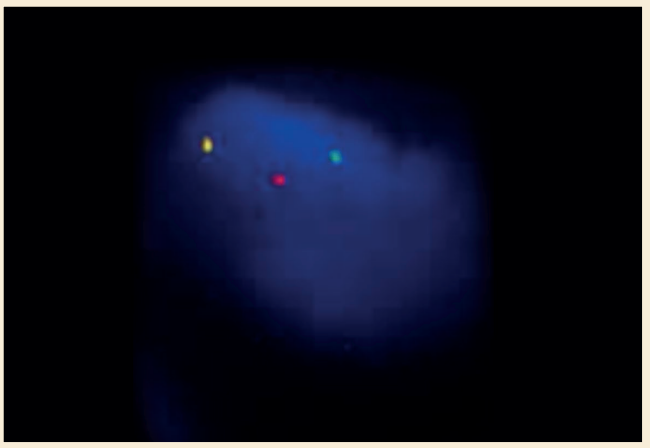


Fig. 6.7

Fig. 6.8

EWSR1, Ewing sarcoma breakpoint region 1; NGS, next-generation sequencing; SNP, single-nucleotide polymorphism; VCF, variant call format.

Using next-generation sequencing (NGS) multiple specific gene fusions can be detected with a single test.

Most NGS approaches also reveal the fusion partner.

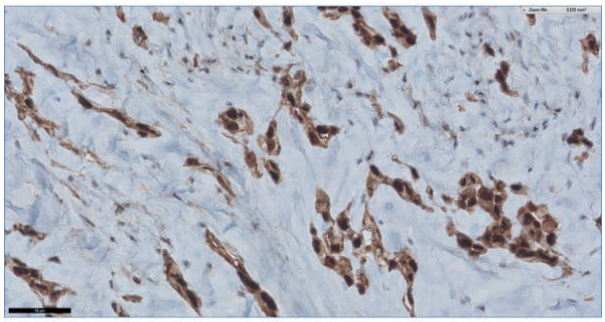
Here, the example shows an *EWSR1-FLI1* fusion in a Ewing sarcoma using anchored multiplex polymerase chain reaction (PCR)-based targeted NGS.

For some fusions, immunohistochemistry (IHC) can be used as a surrogate for molecular testing.

Example of CAMTA1-positive staining in case of an epithelioid haemangioendothelioma harbouring a *WWTR1-CAMTA1* fusion.

Example of nuclear staining for STAT6 in case of a solitary fibrous tumour with a *NAB2-STAT6* fusion.

CAMTA1 in epithelioid haemangioendothelioma



Nuclear STAT6 in solitary fibrous tumour

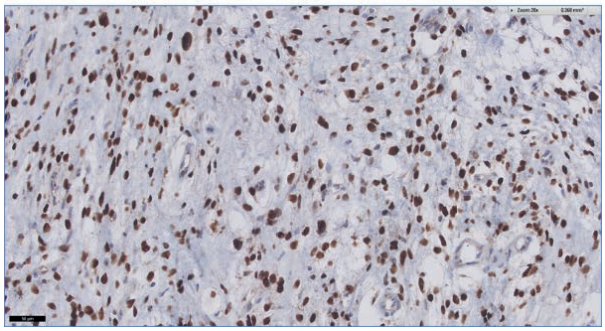


Fig. 6.9

REVISION QUESTIONS

1. Can FISH detect more than one fusion product?
2. Which test can detect multiple gene fusions?
3. Which tumour type is characterised by nuclear CAMTA1 staining?

Summary: Pathogenesis and molecular biology

- Molecular subgroups of sarcomas include those with complex karyotype and those with a relatively simple karyotype. In the latter group, specific translocations, gene mutations or amplifications can be found
- These specific molecular alterations can be used as a diagnostic tool
- Different types of sarcomas may have overlapping fusion partners
- Single translocation detection can be performed by FISH
- Using NGS, multiple specific gene fusions can be tested for in a single test
- Some IHC markers stain a specific mutant protein or fusion product
- Molecular testing in sarcomas is performed mostly for diagnosis or to predict response to therapy (e.g. GIST)
- Few molecular alterations in sarcomas are targetable

Further Reading

Anderson WJ, Hornick JL. Immunohistochemical correlates of recurrent genetic alterations in sarcomas. Genes Chromosomes Cancer 2019; 58:111–123.

Lam SW, Cleton-Jansen AM, Cleven AHG, et al. Molecular analysis of gene fusions in bone and soft tissue tumors by anchored multiplex PCR-based targeted next-generation sequencing. J Mol Diagn 2018; 20:653–663.

Lam SW, van IJzendoorn DGP, Cleton-Jansen AM, et al. Molecular pathology of bone tumors. J Mol Diagn 2019; 21:171–182.

Mariño-Enriquez A, Bovée JV. Molecular pathogenesis and diagnostic, prognostic and predictive molecular markers in sarcoma. Surg Pathol Clin 2016; 9:457–473.

Zhao X, Yue C. Gastrointestinal stromal tumor. J Gastrointest Oncol 2012; 3:189–208.

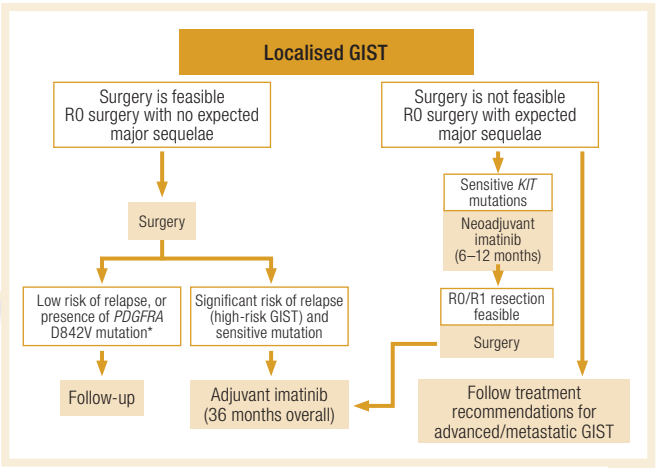
7 Treatment of gastrointestinal stromal tumours

Multidisciplinary management of localised disease

Gastrointestinal stromal tumours (GISTs) are rare tumours of the gastrointestinal tract. They can be asymptomatic (detected incidentally), or cause abdominal pain, bleeding and chronic anaemia. Most arise in the stomach (60%) and small bowel (30%).

The treatment of localised GIST is complete surgical excision of the lesion without the need for dissection of clinically negative lymph nodes. Laparoscopy is discouraged in large tumours due to the risk of tumour rupture.

If R0 surgery is not feasible, or could be achieved through less mutilating/function-sparing surgery, neoadjuvant imatinib is standard. Surgery is carried out after maximal tumour response (~6–12 months).



* Mutational analysis is critical to make a clinical decision about adjuvant therapy
PDGFRA D842V-mutated GISTs should not be treated with any adjuvant therapy
GIST, gastrointestinal stromal tumour; *PDGFRA*, platelet-derived growth factor receptor alpha. Fig. 7.1

Tumour parameters		Risk for progressive disease*(%), based on site of origin			
Mitotic rate (HPF)	Size	Stomach	Jejunum/ ileum	Duodenum	Rectum
≤5/50	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2 cm, ≤5 cm	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
	>5 cm, ≤10 cm	Low (3.6%)	Moderate (24%)	Insufficient data	Insufficient data
	>10 cm	Moderate (10%)	High (52%)	High (34%)	High (57%)
>5/50	≤2 cm	None[1]	High[1]	Insufficient data	High (54%)
	>2 cm, ≤5 cm	Moderate (16%)	High (73%)	High (50%)	High (52%)
	>5 cm, ≤10 cm	High (55%)	High (85%)	Insufficient data	Insufficient data
	>10 cm	High (86%)	High (90%)	High (86%)	High (71%)

*Defined as metastasis or tumour-related death.
[1]Denotes small number of cases.
Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GISTs.
GIST, gastrointestinal stromal tumour; HPF, high-power field. Fig. 7.2

Decisions about adjuvant therapy depend on prognostic factors such as resection margin, tumour size and location, mitotic index, tumour rupture, and the presence of platelet-derived growth factor receptor alpha (*PDGFRA*) D842V mutation.

Molecular biomarkers such as *KIT* mutations (codons 557-558 in exon 11) are not yet implemented in risk classification but have an independent prognostic value in gastric GISTs. Secondary mutations do not guide clinical decisions.

Adjuvant imatinib for 3 years is the standard for patients with a significant risk of relapse (except *PDGFRA* D842V-mutated, neurofibromatosis type 1 [NF1]-related and succinate dehydrogenase [SDH] expression-negative GISTs).

Study protocol	Dose	Duration	Risk groups	Population	Outcomes	P
ACOSOG Z9001 Randomised, phase III, placebo-controlled	400 mg a day vs placebo	1 year	All risk groups	Any *KIT*, R0, tumour size ≥3 cm	1-year RFS: 98% with imatinib vs 83% in the control	HR 0.35; p <0.001
ACOSOG Z9000 Single arm, open-label, phase II	400 mg a day	1 year	High risk of relapse	Any *KIT*, R0, tumour size ≥10 cm, or tumour rupture or intraperitoneal metastases <5 cm	1-year OS: 99%, 3-year OS: 97%	n/a
SSG XVIII/AIO Randomised, open-label, phase III	400 mg a day	1 year vs 3 years	High risk of relapse	Any *KIT*, tumour size >10 cm or MI >10/50 HPFs or MI >5/50 HPFs and tumour size >5 cm or tumour rupture	5-year RFS: 65.6% after 3 years vs 47.9% after 1 year of imatinib	HR 0.46; p <0.001
EORTC 62024 Randomised, phase III	400 mg a day vs observation	2 years	Intermediate/high risk of relapse	Any *KIT*, R0, tumour size >5 cm or MI >5/50 HPFs	5-year imatinib failure-free survival (IFFS): 87% with imatinib vs 84% in the control	HR 0.80; p = 0.23

ACOSOG, American College of Surgeons Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; HPF, high-power field; HR, hazard ratio; MI, mitotic index; OS, overall survival; RFS, recurrence-free survival; SSG, Scandinavian Sarcoma Group. Fig. 7.3

REVISION QUESTIONS

1. What is the recommended approach in operable GIST?
2. What is the indication for adjuvant therapy?
3. What type of GIST mutations are contraindicated for adjuvant therapy?

Treatment of advanced/metastatic disease

Unresectable/metastatic disease is detected in 20% of patients at presentation, and in 30% of patients during follow-up after radical treatment. Metastases are mainly to the liver and/or peritoneum.

First-line therapy is imatinib (400 mg/day, or 800 mg daily in exon 9 *KIT*-mutated GISTs). Median progression-free survival (PFS) was 2 years for imatinib. In case of progression, dose should be increased to 800 mg/day. Imatinib is well tolerated.

Second-line therapy is sunitinib (50 mg/day: 4 weeks on/2 weeks off, or with a daily dose of 37.5 mg). Median PFS was 24.1 weeks for sunitinib, and 6.0 weeks for placebo. In wild-type (WT) SDH-deficient GIST, benefit from sunitinib is significantly higher than observed with imatinib.

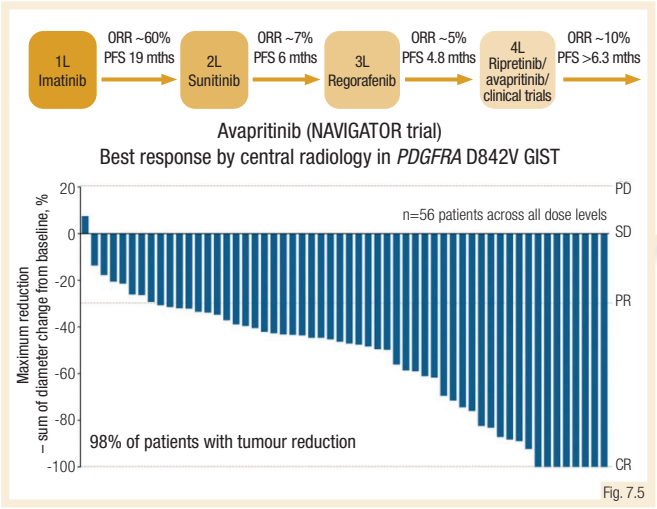


Fig. 7.5

CR, complete response; GIST, gastrointestinal stromal tumour; ORR, overall response rate; PD, progressive disease; *PDGFRA*, platelet-derived growth factor alpha; PFS, progression-free survival; PR, partial response; SD, stable disease.

Early progression should be confirmed by an experienced team. If oligometastatic disease becomes resectable, complete excision of residual metastatic disease has been shown to be associated with clinical benefit.

'Nodule within the mass' (when a portion of a responding lesion becomes hyperdense) is a typical GIST progression pattern. Surgical excision may give clinical benefit.

Patients should be alerted to the importance of compliance with therapy, as well as interactions with concomitant medications and foods (CYP3A4).

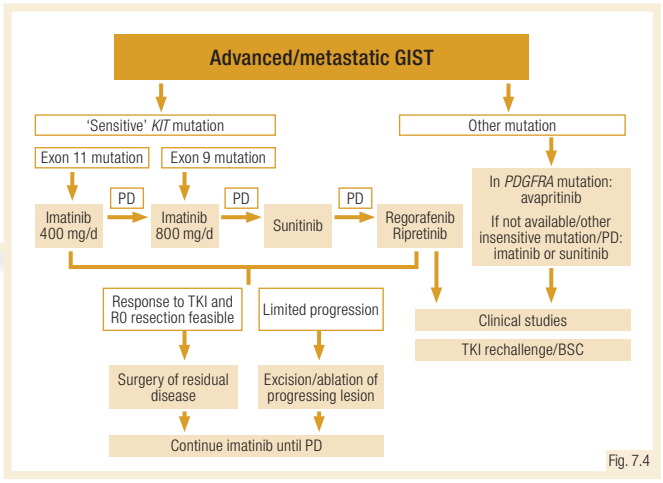


Fig. 7.4

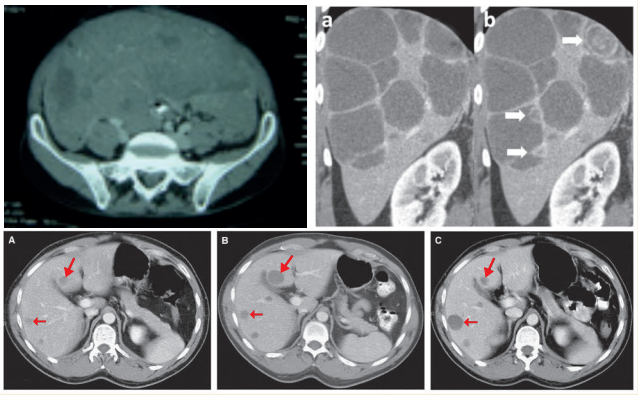
BSC, best supportive care; GIST, gastrointestinal stromal tumour; PD, progressive disease; *PDGFRA*, platelet-derived growth factor receptor alpha; TKI, tyrosine kinase inhibitor.

The standard third-line therapy is regorafenib (160 mg daily, 3 weeks on/1 week off). Median PFS was 4.8 months for regorafenib vs 0.9 months for placebo.

Emerging fourth-line therapy is ripretinib (150 mg orally, once daily). Avapritinib is an option for patients with *PDGFRA* exon 18 mutation regardless of the line of therapy. Common side effects are oedema, nausea, fatigue, cognitive impairment and increased lacrimation.

The most frequent adverse events on tyrosine kinase inhibitors (TKIs) are fatigue, diarrhoea and hand-foot syndrome. Sunitinib causes hypothyroidism, but hypertension induced by sunitinib predicts better response.

Top left. CT scan of GIST liver metastases. Top right: Disease progression: a 'nodule within the mass.' Bottom: Disease response to imatinib, changes in tumour density: A) baseline; B) 8 weeks; C) 16 weeks



CT, computed tomography; GIST, gastrointestinal stromal tumour.
Fig. 7.6

REVISION QUESTIONS

1. What are the first, second and third lines of systemic therapy used in standard practice?
2. What type of patients may benefit from avapritinib?
3. When should surgery in metastatic GIST be considered?

Multidisciplinary management of non-operable/metastatic disease

GIST treatment strategy is driven by presence of *KIT* (85%) and *PDGFRA* (10%) mutations. There are also WT GISTs, which are mostly related to SDH deficiency.

GIST with *KIT* mutation in exon 11 is the most sensitive to standard imatinib (400 mg/day). In *KIT* exon 9 – due to lower response – the imatinib dose of 800 mg/day is recommended.

The most common mutation in *PDGFRA*, D842V, is known to be imatinib resistant, but sensitive to avapritinib. Almost all other *PDGFRA* mutations are imatinib sensitive.

Molecular profile	Clinical characteristics
Mutations of the *KIT* gene	80%-85% GISTs
Exon 11	The best response to imatinib; the most common mutation in sporadic GIST and in the GIST family
Exon 9	Limited response to imatinib (a starting dose of imatinib 800 mg is recommended); good response to sunitinib, more common in GISTs originating from the small intestine and the colon
Exon 13 and 17	Clinical responses to imatinib possible but these are very rare mutations
PDGFRA gene mutations	5%-8% of GIST
Exon 12	Possible clinical response to imatinib
Exon 14	Possible clinical response to imatinib, very rare mutation
Wild-type – or no *KIT* or *PDGFRA* mutations	Poor response to imatinib, better response to sunitinib; 12%-15% of cases; in paediatric GISTs, related to NF1, SDHB or Carney triad, possible *BRAF* mutations

GIST, gastrointestinal stromal tumour; NF1, neurofibromatosis type 1; *PDGFRA*, platelet-derived growth factor receptor alpha. Fig. 7.7

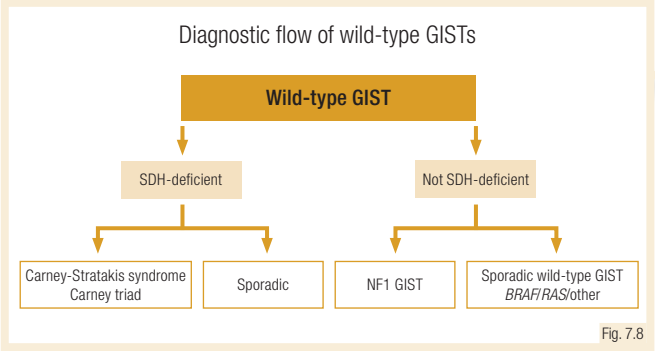


Fig. 7.8

GIST, gastrointestinal stromal tumour; NF1, neurofibromatosis type 1; SDH, succinate dehydrogenase.

WT GIST is observed in 10% of adult GISTs and is commonly found in the paediatric population. WT GISTs may have several different driver mutations: SDH-deficient, *BRAF*-mutated, and NF1-associated.

WT GISTs have indolent clinicopathological features and are insensitive to imatinib.

Syndromes linked to GISTs are: Carney triad (gastric GISTs, paraganglioma, pulmonary chondromas), Carney-Stratakis syndrome (GIST + paraganglioma) and NF1 WT, multicentric GIST, predominantly in the small bowel.

Patients harbouring a resistant mutation of *PDGFRA* D842V may also benefit from crenolanib; in *BRAF*-mutated GIST, *BRAF/MEK* inhibitors had a synergistic effect with imatinib.

There are no European Medicines Agency (EMA)/Food & Drug Administration (FDA)-approved immunotherapies for GISTs and few preclinical studies investigating the immunological profile. There is also no effective treatment for SDH-deficient GIST.

The follow-up schema in high-risk GIST is imaging every 3 months for 2 years, then every 6 months for 3 years, then once a year. In low-risk GIST, it should be less frequent.

Inhibitors of receptor tyrosine kinases	Molecular target	Trial
Ripretinib	*KIT, PDGFRA*	NCT03673501
Crenolanib	*PDGFRA* (not D842V)	NCT01243346
Ponatinib	*KIT, PDGFRA*	NCT03171389
Cabozantinib	*KIT, MET, VEGFRs*	NCT02216578
Avapritinib	*KIT, PDGFRA* (also D842V)	NCT02508532
Sorafenib	*VEGFR, PDGFRB, KIT, BRAF, FLT-3, FLT*	NCT01091207

PDGFRA/B, platelet-derived growth factor receptor alpha/beta; *VEGFR*, vascular endothelial growth factor receptor. Fig. 7.9

REVISION QUESTIONS

1. How does mutation status in GIST guide therapeutic decisions?
2. What are the novel promising compounds in GIST treatment?
3. What is the role of immunotherapy in GIST?

Summary: Treatment of gastrointestinal stromal tumours

Management of localised disease

- The standard treatment of localised GISTs is R0 surgical excision, avoiding tumour rupture, without dissection of clinically negative lymph nodes
- Preoperative imatinib is recommended when R0 surgery implies major functional sequelae
- Adjuvant therapy with imatinib for 3 years is the standard treatment of patients with a significant risk of relapse, peritoneal relapse or tumour rupture. The contraindications are presence of *PDGFRA* D842V mutation and SDH- and NF1-related GISTs

Management of advanced/metastatic disease

- Imatinib, 400 mg daily, is the standard treatment of locally advanced inoperable and metastatic disease, except in patients with *KIT* exon 9 mutation (here the recommended dose is 800 mg daily)
- In the case of tumour progression on 400 mg of imatinib, the dose can be increased to 800 mg daily
- In the case of further progression or imatinib intolerance (rare), standard second-line treatment is sunitinib, and third-line, regorafenib. Ripretinib is an FDA-approved option for the treatment of adult patients in fourth-line GIST
- GIST patients harbouring a *PDGFRA* exon 18 mutation benefit from avapritinib (ORR 84%); however, careful monitoring of side effects such as fatigue/asthenia, cognitive impairment or brain haemorrhages is mandatory
- Patients should be treated in referral centres with access to clinical trials at every stage of disease

Further Reading

Bauer S, Rutkowski P, Hohenberger P, et al. Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib – analysis of prognostic factors (EORTC-STBSG collaborative study). Eur J Surg Oncol 2014; 40:412–419.

Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol 2008; 26:626–632.

Blay J-Y, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2020; 21:923–934.

Brierley JD, Gospodarowicz MK, Wittekind C (eds). TNM Classification of Malignant Tumours, 8th edition. Oxford: John Wiley & Sons, Inc. 2016.

Casali PG, Abecassis, Bauer S, et al. Gastrointestinal stromal tumours: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29(Suppl 4):iv68–iv78.

Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol 2007; 25:1753–1759.

Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381:295–302.

Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006; 368:1329–1338.

George S, Blay JY, Casali PG, et al. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. Eur J Cancer 2009; 45:1959–1968.

Gronchi A, Judson I, Nishida T, et al. Adjuvant treatment of GIST with imatinib: solid ground or still quicksand? A comment on behalf of the EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, the NCRI Sarcoma Clinical Studies Group (UK), the Japanese Study Group on GIST, the French Sarcoma Group and the Spanish Sarcoma Group (GEIS). Eur J Cancer 2009; 45:1103–1106.

Joensuu H, Vehtari A, Riihimäki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 2012; 13:265–274.

Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23:70–83.

8 Specific management in common and rare sarcomas

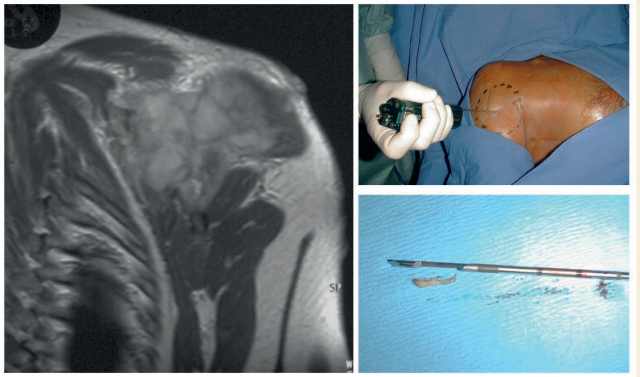
Specific management in common sarcomas – adult soft tissue sarcoma of limbs or superficial trunk

Soft tissue sarcomas (STSs) are ubiquitous, without specific symptoms. A progressive mass arising in an irritated field or in a patient with neurofibromatosis requires active diagnosis.

Magnetic resonance imaging (MRI) is the best imaging option. Core-needle biopsy is recommended in case of deep mass or superficial lesions of >5 cm. Consider retaining frozen tissue for further molecular analysis.

Pathological and molecular diagnosis of STS is challenging – a second opinion from an expert is mandatory (30% rate of misdiagnosis).

MRI and biopsy



MRI, magnetic resonance imaging.

Fig. 8.1

Large *en-bloc* resection

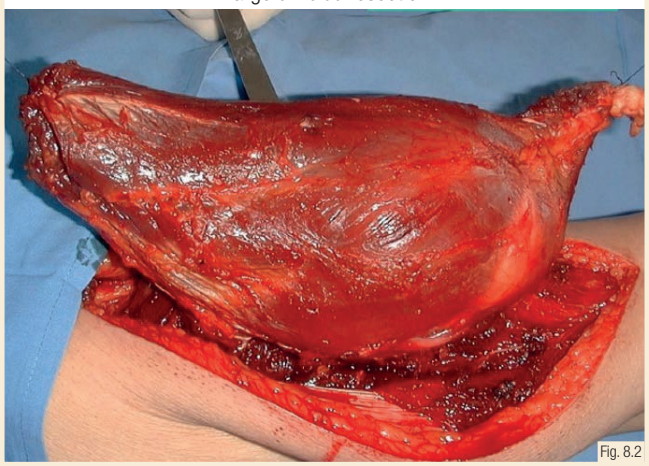


Fig. 8.2

Management of STS requires multidisciplinary expertise, ideally in a referral centre. Initial STS check-up requires a chest computed tomography (CT) scan.

Localised STS is best treated by large *en-bloc* surgery and in most cases (neo)adjuvant radiotherapy (RT). The role of neoadjuvant chemotherapy (ChT) in high-risk STS is debated.

Local control depends mostly on surgical margins. Risk of metastases (about 40%) depends on histological grade.

Resectable lung metastases without extra-pulmonary metastases are best treated with polyChT (doxorubicin-based) and surgical resection. About 2%-5% of patients achieve long-term survival in this case.

In cases of multiple lung metastases or extra-pulmonary metastasis, the primary aim is palliation with the use of doxorubicin alone. The median overall survival is 18 months.

After failure of first-line, optimal palliative care must be offered to patients. Treatment is histology-tailored.

Second-line treatment according to histology

Main histological subtypes	Second line and further lines
Angiosarcoma	**Weekly paclitaxel** or pazopanib or gemcitabine
Leiomyosarcoma	**Trabectedin or pazopanib**, dacarbazine or gemcitabine
Liposarcoma	Trabectedin or eribulin
Undifferentiated pleomorphic sarcoma	Pazopanib or dacarbazine
Synovial sarcoma	Ifosfamide or pazopanib

Fig. 8.3

REVISION QUESTIONS

1. Before a second opinion by an expert pathologist, what is the rate of STS misdiagnosis?
2. Is open biopsy recommended for initial diagnosis of STS?
3. Is doxorubicin/ifosfamide combination recommended as first-line treatment in leiomyosarcoma with lung, bone and liver metastasis?

Specific management in common sarcomas – management of some particular locations

Retroperitoneal sarcomas represent <10% of all adult STSs; they include mostly leiomyosarcoma and liposarcoma.

At diagnosis most tumours are huge. The risk of local relapse is very high, requiring management by an expert surgeon.

Uterine sarcomas are rare and heterogeneous.

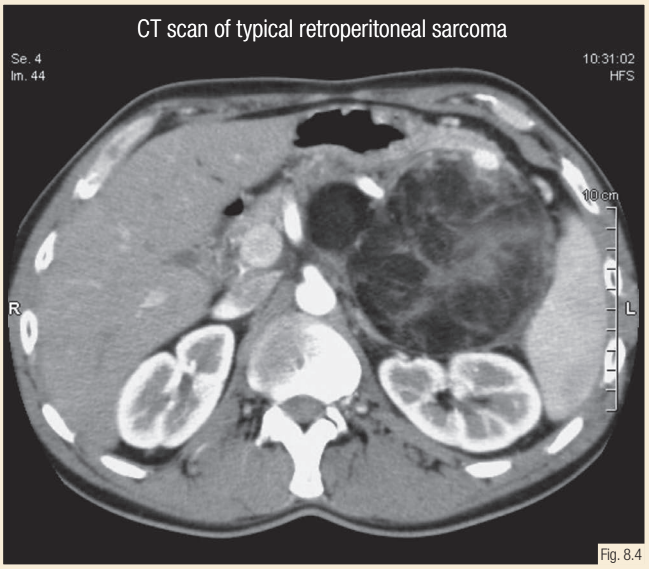


Fig. 8.4

CT, computed tomography.

Recommended management of specific locations

Location	Recommended management
Localised retroperitoneal sarcoma	Thoracic and abdominopelvic CT scan Percutaneous CT scan-guided core-needle biopsy (posterior and lateral approach) **Large *en-bloc* resection by an expert surgeon in an expert centre** No adjuvant treatment Preoperative RT is an option for retroperitoneal liposarcoma
Localised uterine leiomyosarcoma	Thoracoabdominal CT scan and pelvic MRI **Total abdominal hysterectomy and salpingo-oophorectomy** No systematic lymphadenectomy Adjuvant pelvic RT could be discussed No systematic adjuvant ChT Careful follow-up because of high risk of metastatic recurrence
Localised low-grade endometrial stromal sarcoma	Thoracoabdominal CT scan and pelvic MRI **Total abdominal hysterectomy and salpingo-oophorectomy** No adjuvant treatment Contraindication to oestrogens (in case of relapse: anti-aromatase)
Localised high-grade endometrial stromal sarcoma	Thoracoabdominal CT scan and pelvic MRI **Total abdominal hysterectomy and salpingo-oophorectomy** No systematic lymphadenectomy Adjuvant pelvic RT could be discussed No systematic adjuvant ChT Careful follow-up because of high risk of metastatic recurrence

Fig. 8.5

ChT, chemotherapy; CT, computed tomography; MRI, magnetic resonance imaging; RT, radiotherapy.

REVISION QUESTIONS

1. Is surgical biopsy the recommended method for diagnosis of retroperitoneal sarcoma?
2. Is neoadjuvant ChT recommended for management of localised uterine sarcoma?
3. Is adjuvant hormonal therapy with tamoxifen recommended for management of low-grade endometrial stromal sarcoma?

Management of rare sarcomas – alveolar soft part sarcoma

Within the sarcoma family, there are several ultra-rare mesenchymal tumour subtypes, each accounting for <1 case/1 000 000 people/year.

Each subtype represents a particular entity with a specific morphology, biology and natural history, and a different sensitivity to medical agents.

One of these subtypes is alveolar soft part sarcoma (ASPS). ASPS mostly affects young patients and, despite its indolent behaviour, is marked by >60% metastatic risk.

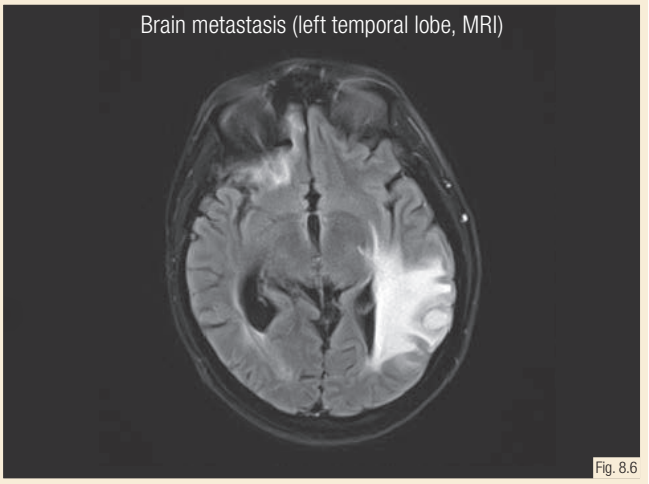
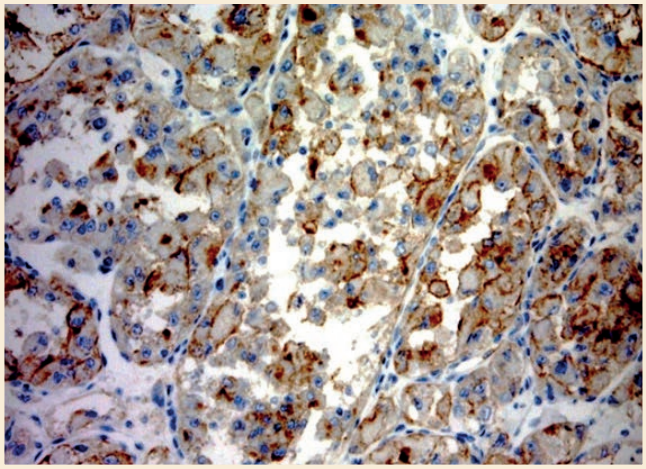


Fig. 8.6

MRI, magnetic resonance imaging.

ASPS arising from the retroperitoneum: MET immunostaining positivity



ASPS, alveolar soft part sarcoma.

Fig. 8.7

ASPS carries a typical chromosomal rearrangement, *t(X;17)(p11;q25)* that leads to the upregulation of several key genes, in particular *MET*, by means of the transcription factor *ASPL-TFE3*.

The general principles for treatment of ASPS and other rare sarcoma subtypes do not vary from what is required in more common STSs.

However, ASPS is known to be poorly responsive to conventional cytotoxic ChT. MET inhibitors, including crizotinib, were evaluated in clinical studies and showed limited antitumour activity. At present, they are not suggested for ASPS treatment.

Antiangiogenic agents can be effective in ASPS. There are retrospective reports on the activity of sunitinib, bevacizumab, regorafenib, anlotinib and pazopanib, which is the only antiangiogenic agent approved in STS from second line after failure on anthracyclines.

Cediranib was evaluated in a single-arm prospective phase II trial (35% partial response by RECIST [Response Evaluation Criteria In Solid Tumours] and 60% stable disease) and in a randomised phase III trial, in which it showed superiority to placebo.

Preliminary evidence of response to programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors are being confirmed in prospective studies.

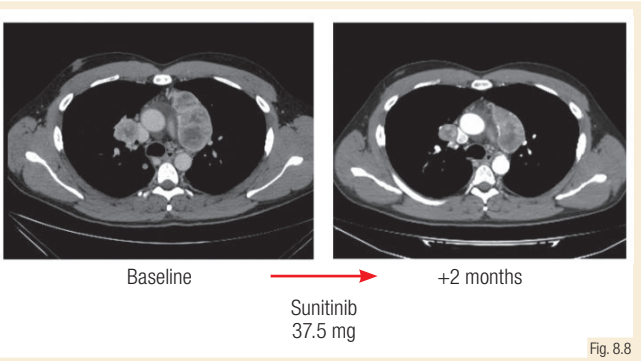


Fig. 8.8

REVISION QUESTIONS

1. What is the metastatic risk of ASPS?
2. Is cytotoxic ChT active in ASPS?
3. Are there any potentially active drugs approved for the treatment of ASPS?

Management of rare sarcomas – solitary fibrous tumour

Another rare STS is solitary fibrous tumour (SFT), formerly called haemangiopericytoma. SFT can arise at any site of the body.

SFT is marked by the *NAB2-STAT6* gene fusion, which is responsible for the activation of nuclear transcription factor: STAT6. Nuclear immunoreactivity for STAT6 is of major help in SFT diagnosis.

The standard treatment of localised SFT is wide excision surgery, followed by RT in selected cases.

STAT6 nuclear positive immunostaining

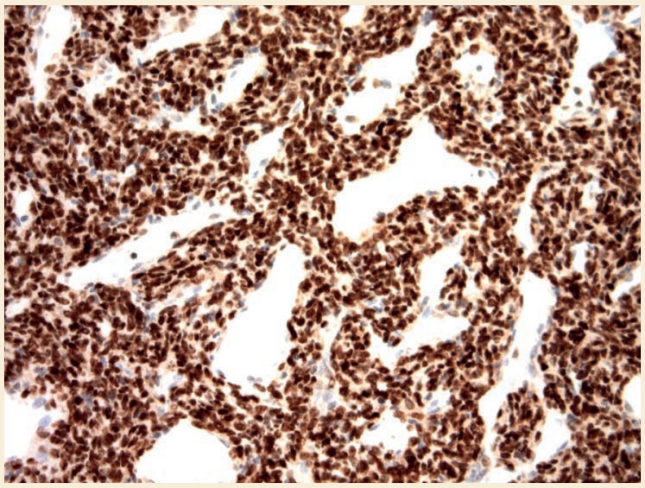


Fig. 8.9

Completely resected solitary fibrous tumour arising from retroperitoneum

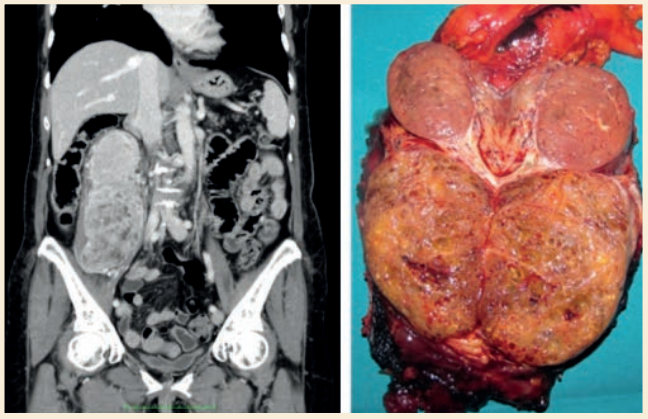


Fig. 8.10

Completely resected SFTs are characterised by a favourable outcome. Rarely, unexpected recurrences with high-grade morphology and aggressive behaviour are observed.

Medical therapy is needed in advanced-disease patients. As for all ultra-rare sarcoma, their rarity makes it very difficult to run high-power randomised clinical trials.

The evidence available often comes from uncontrolled studies, case series analyses or case reports.

The response rate to ChT with doxorubicin is low (roughly 20%), but it may be higher in more aggressive cases. There are also reports on dacarbazine and trabectedin.

The efficacy of antiangiogenic agents such as bevacizumab in combination with temozolomide, sorafenib, sunitinib, axitinib or pazopanib has been described. Only pazopanib is an approved agent.

Responses are non-dimensional in the majority of patients and marked by a decrease in tumour density that is detectable by CT scan.

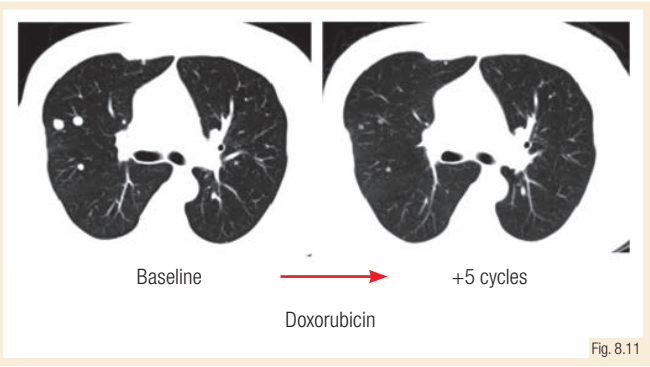


Fig. 8.11

REVISION QUESTIONS

1. What is the diagnostic marker for SFT diagnosis?
2. What is the standard approach to localised SFT?
3. Which systemic agents can be active in SFT?

Summary: Specific management in common and rare sarcomas

Common sarcomas

- A second pathologist's opinion is key to confirming STS diagnosis
- Management by referral centres provides the best chance of STS patients' survival
- Some metastatic STSs can be cured by thoracic surgery and combination ChT
- Interpretation of CT scan under treatment requires expertise
- Retroperitoneal sarcoma requires management by an expert surgeon

Rare sarcomas

- Each ultra-rare sarcoma subtype accounts for <1 case/1 000 000 population/year
- In recent years, many improvements have been made in the knowledge of rare sarcoma biology, which have led to better diagnosis and sarcoma subtype classification
- This has allowed a more reliable prediction of the natural history of each sarcoma subtype, and this is particularly true for the rarest histologies
- It also allowed the identification of new active medical treatments, among both old and new drugs
- General principles for the treatment of rare sarcomas do not vary from what is required in more common sarcomas
- Rarity makes it very difficult to run high-power randomised clinical trials
- The evidence available often comes from uncontrolled studies, case series analyses and case reports
- ASPS and SFT provide good examples of recent improvements in both diagnosis and treatment

Further Reading

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

Blay JY, van Glabbeke M, Verweij J, et al. Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy. Eur J Cancer 2003; 39:64–69.

Bonvalot S, Gaignard E, Stoeckle E, et al. Survival benefit of the surgical management of retroperitoneal sarcoma in a reference center: a nationwide study of the French Sarcoma Group from the NetSarc database. Ann Surg Oncol 2019; 26:2286–2293.

Casali PG, Abecassis N, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29(Suppl_4):iv51–iv67.

Chi Y, Fang Z, Hong X, et al. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft-tissue sarcoma. Clin Cancer Res 2018; 24:5233–5238.

Hensley ML, Barrette BA, Baumann K, et al. Gynecologic Cancer InterGroup (GCIG) consensus review: uterine and ovarian leiomyosarcomas. Int J Gynecol Cancer 2014; 24(9 Suppl 3):S61–66.

Kummar S, Allen D, Monks A, et al. Cediranib for metastatic alveolar soft part sarcoma. J Clin Oncol 2013; 31:2296–2302.

Martin-Broto J, Stacchiotti S, Lopez-Pousa A, et al. Pazopanib for treatment of advanced malignant and dedifferentiated solitary fibrous tumour: a multicentre, single-arm, phase 2 trial. Lancet Oncol 2019, 20:134–144.

Stacchiotti S, Simeone N, Lo Vullo S, et al. Activity of axitinib in progressive advanced solitary fibrous tumour: results from an exploratory, investigator-driven phase 2 clinical study. Eur J Cancer 2019; 106:225–233.

Stiller CA, Trama A, Serraino D, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. Eur J Cancer 2013; 49:684–695.

All authors contributed equally to this chapter

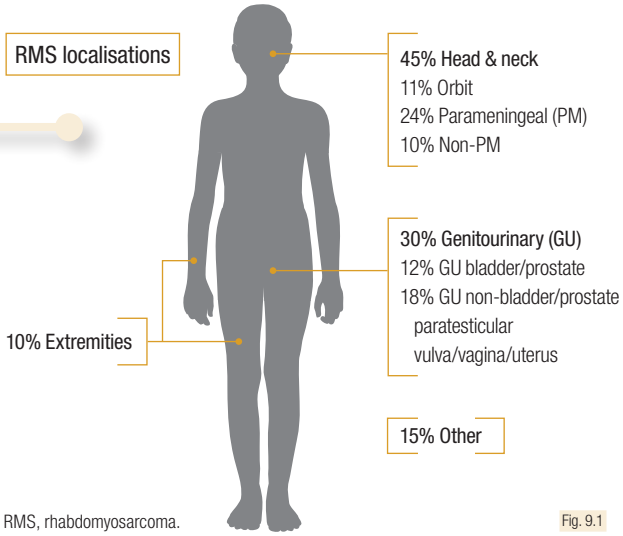
Sarcomas in children

Rhabdomyosarcomas – diagnosis, pathology and biology

Rhabdomyosarcoma (RMS), the most common childhood soft tissue sarcoma (STS), is a fast-growing, chemosensitive malignant tumour, developing in almost any part of the body where mesenchymal tissue is present.

Incidence is 4.5/1 000 000 children under the age of 20. Two thirds of RMSs arise before the age of 6, but there is a second peak in adolescents and young adults (AYAs).

Clinical presentation is strongly influenced by site: nerve palsy, nasal obstruction, urinary obstruction, scrotal mass, vaginal polyp, muscle mass, etc.



RMS, rhabdomyosarcoma. Fig. 9.1

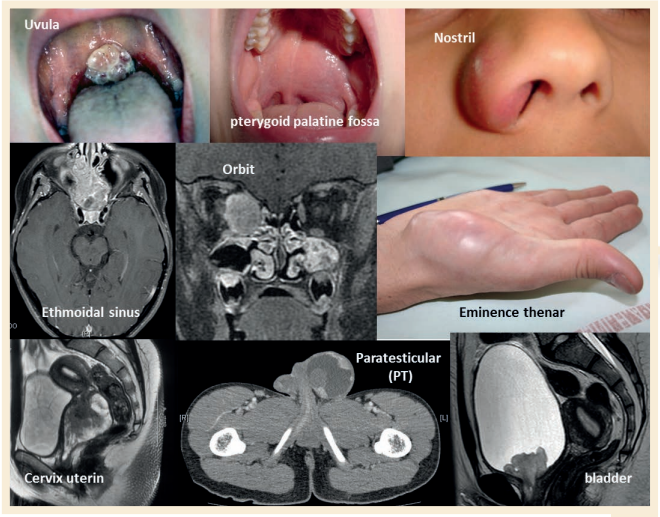


Fig. 9.2

Fast diagnosis requires adequate imaging before biopsy and is completed by accurate assessment of extension (nodes, lung, bone and bone marrow, cerebrospinal fluid [CSF]). In 20% of cases the RMS is metastatic.

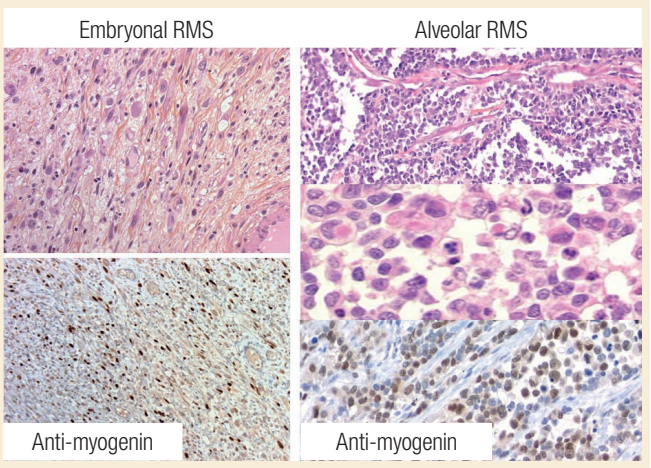
Work-up: magnetic resonance imaging (MRI) for the primary tumour and assessment of distant extension by lung computed tomography (CT) scan, positron emission tomography (PET) scan, bone marrow puncture and CSF analysis for parameningeal (PM) locations.

Tru-Cut/open biopsy is the first step in diagnosis following a decision by a multidisciplinary team (MDT). Primary surgery is not recommended if microscopically complete resection without mutilation is not possible.

Histological examination must be carried out quickly, since the tumour grows rapidly and some organs could be damaged irreversibly. Freezing is mandatory.

Myogenin positivity is mandatory to diagnose RMS (myogenic differentiation). Two main entities are defined: embryonal RMS (ERMS) (70%) and alveolar RMS (ARMS) (20%).

Currently, ARMS is biologically characterised by two transcripts: *FKHR-PAX3* from *t(2;13)(q35;q14)* and *FKHR-PAX7* from *t(1;13)(p36;q14)*.



RMS, rhabdomyosarcoma. Fig. 9.3

REVISION QUESTIONS

1. Why is fast diagnosis of RMS important?
2. What kind of puncture do you perform only for PM RMS?
3. Can molecular biology differentiate between ERMS and ARMS?

Rhabdomyosarcomas – prognostic factors, treatment and outcome

The main prognostic factors are histology (ERMS>ARMS), age (<10 years), size of the tumour (≤5 cm), nodes, metastasis and location(s).

Post-surgical status should be taken into account. If R0 is possible (in a few cases) as the first step, primary R1 microscopically incomplete excision should not be performed, and R2 as result of simple biopsy is recommended.

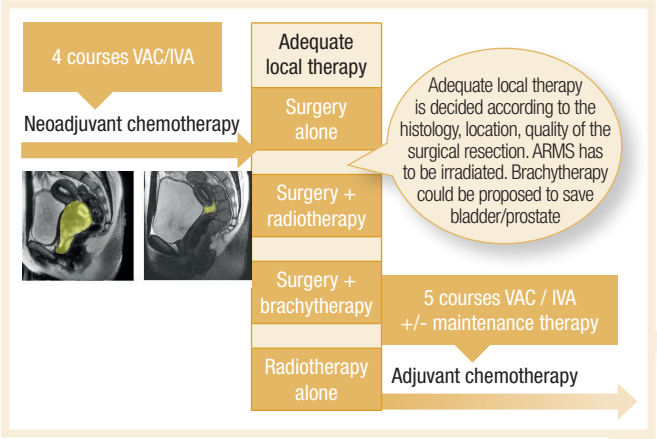
A staging system of low, standard, high and very high risk considers the above risk factors, resulting in a risk-adapted treatment strategy (European paediatric Soft tissue sarcoma Study Group [EpSSG]).

EpSSG classification (RMS 2005)						
Risk	**Groups**	**Histology**	**Surgery**	**Site**	**Nodes**	**Size and age**
LR	A	ERMS	I (R0)	Any	N0	Favourable
SR	B	ERMS	I (R0)	Any	N0	Unfavourable
	C	ERMS	II/III (R1/R2)	Favourable	N0	Any
	D	ERMS	II/III (R1/R2)	Unfavourable	N0	Favourable
HR	E	ERMS	II/III (R1/R2)	Unfavourable	N0	Unfavourable
	F	ERMS	II/III (R1/R2)	Any	N1	Any
	G	ARMS	I/II/III (R0/R1/R2)	Any	N0	Any
VHR	H	ARMS	II/III (R1/R2)	Any	N1	Any

Unfavourable site: parameningeal, extremities, genitourinary bladder-prostate; others. Unfavourable size and age: ≥5 cm or 10 years or both

ARMS, alveolar RMS; EpSSG, European paediatric Soft tissue sarcoma Study Group; ERMS, embryonal RMS; HR, high risk; LR, low risk; RMS, rhabdomyosarcoma; SR, standard risk; VHR, very high risk.

Fig. 9.4



ARMS, alveolar rhabdomyosarcoma; IVA, ifosfamide/vincristine/actinomycin D; VAC, vincristine/actinomycin D/cyclophosphamide.

Fig. 9.5

Neoadjuvant chemotherapy (ChT) is most often the first step. Cyclophosphamide or ifosfamide combined with actinomycin D and vincristine are currently the main combinations for RMS.

Maintenance therapy (vinorelbine/cyclophosphamide) in high-risk groups is beneficial. Irinotecan/vincristine is a possible second-line treatment.

Mutilating surgery should not be considered at primary resection. Delayed local therapy is mandatory and can combine surgery and/or radiotherapy (RT) (brachytherapy included) to decrease long-term sequelae.

According to the EpSSG RMS 2005 protocol, event-free survival (EFS) is around 70%. According to risk, survival ranges from 50% to 90% for localised disease. High-risk (HR) RMSs are the most numerous.

For metastatic disease, the prognosis is worse with a survival rate of 5%-50% according to age (≥10 years), number of sites of metastasis, bone and bone marrow involvement, and spread to extremities or other locations.

Relapses occur within 3 years and in two thirds of cases are local and/or regional (nodes). Salvage therapy depends on the possibility of secondary local control.

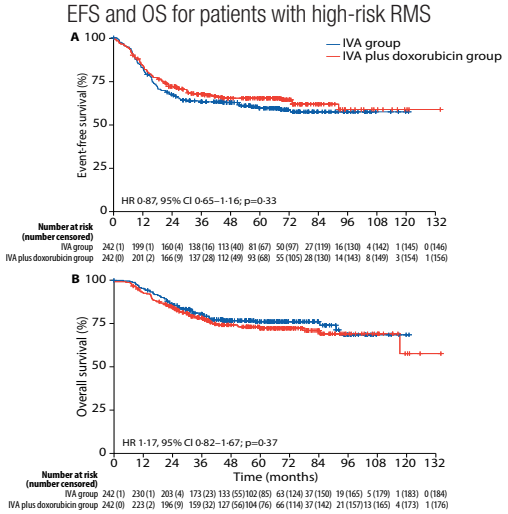


Fig. 9.6

CI, confidence interval; EFS, event-free survival; HR, hazard ratio; IVA, ifosfamide/vincristine/dactinomycin; OS, overall survival; RMS, rhabdomyosarcoma.

REVISION QUESTIONS

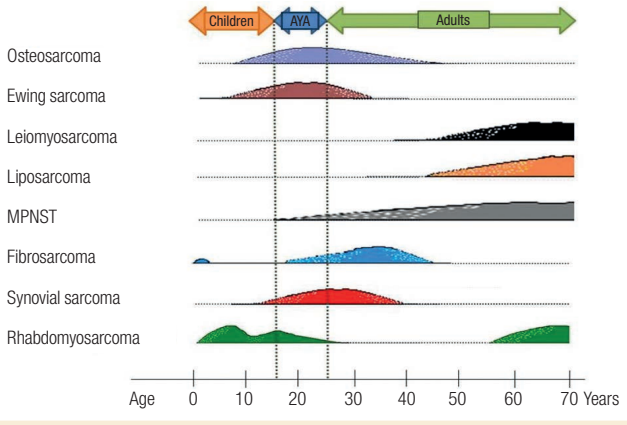
1. What are the principal risk factors to take into consideration for systemic treatment?
2. Why is surgery very rarely the first step of treatment?
3. Why is local treatment so important in RMS?

Other soft tissue sarcomas in children

Other STSs occur in the AYA population, except infantile fibrosarcoma (IFS), which appears in young children. Molecular profiling is now mandatory to better characterise the diagnosis.

Synovial sarcoma (SS) represents 8%-10% of all STSs in children. Less than 10% are metastatic. A biological hallmark of SS is *SYT-SSX* transcript.

Malignant peripheral nerve sheath tumour (MPNST) is the second most frequent STS in children and arises more frequently in patients affected by neurofibromatosis type 1 (NF1).



AYA, adolescent and young adult; MPNST, malignant peripheral nerve sheath tumour. Fig. 9.7

Infantile fibrosarcoma at day 3 of life treated by vincristine (VCR) alone and one course of VCR/actinomycin D at 3 months of life

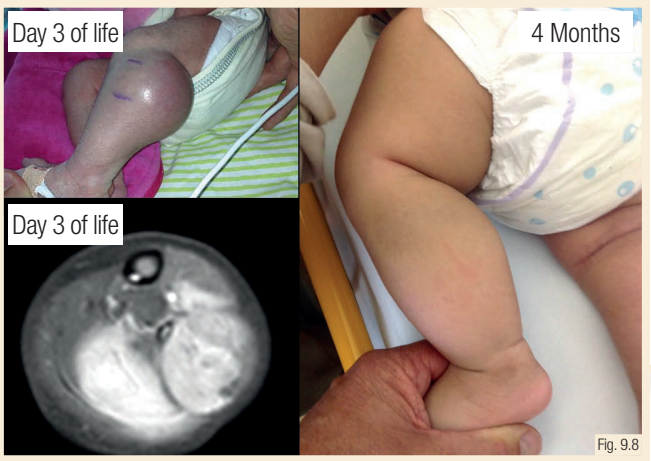


Fig. 9.8

IFS is a tumour of intermediate malignancy, mainly arising in the extremities in children under 2 years old. It is biologically characterised by the *ETV6-NTRK3* (neurotrophic tyrosine receptor kinase 3) transcript.

Initial biopsy is the first step. The chemosensitivity of IFS and good overall survival (OS) do not advocate mutilating resection or RT. Vincristine/actinomycin D regimen and/or NTRK inhibitors may reduce the volume to improve quality of surgery and decrease sequelae.

Extracranial rhabdoid tumours occur in infants and children as a fast-growing mass. A biallelic inactivating mutation of *SMARCB1* causes some defects in the cell cycle control (linked sometimes to constitutional condition). The outcome is bleak with current treatment.

As soon as sarcoma is mentioned, biopsy (after adequate imaging) is the mandatory first step. An MDT meeting is the second step.

From the outset, a child should be taken in charge by an oncological paediatric team. For AYAs, a paediatric oncologist must be part of the MDT to ensure the best pathway according to histology and staging.

Neoadjuvant ChT is often proposed with an ifosfamide/doxorubicin regimen. Local control with R0 resection is the goal. Adjuvant RT should be discussed.

Adult-type soft tissue sarcoma (EpSSG recommendations) (except synovial sarcomas)		
R0 and <5 cm:	→	Surgery alone
R0 and >5 cm:		
G1	→	Surgery alone
G2	→	Radiotherapy
G3	→	Ifo-doxo + radiotherapy
R1 N0:		
G1	→	Surgery alone
G2-G3, ≤5 cm	→	Radiotherapy
G2, >5 cm	→	Radiotherapy
G3, >5 cm	→	Ifo-doxo + radiotherapy
R2 N1:	→	Ifo-doxo, +/- surgery, +/- radiotherapy

Tumour grade is assessed according to the FNCLCC system Fig. 9.9

EpSSG, European paediatric Soft tissue sarcoma Study Group; FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; ifo-doxo, ifosfamide/doxorubicin.

REVISION QUESTIONS

1. What is usually the first step in the diagnostic process for suspicion of sarcoma?
2. Do you think complete imaging is always needed before biopsy or surgery?
3. Do you think an MTD meeting is mandatory before starting treatment of sarcoma?

Summary: Sarcomas in children

- RMS is a fast-growing tumour, so diagnosis should be organised as a matter of urgency
- RMS can be located anywhere in the body
- RMS is a highly chemosensitive tumour, which can benefit from neoadjuvant ChT
- Surgeons must ask themselves: Could my surgical action be inappropriate to cure the child?
- Let paediatric oncologists orchestrate the management of children with tumours
- Main prognostic factors are histology (ERMS/ARMS), age (<10 years), size of the tumour (≤5 cm), nodes, metastasis and location(s)
- ARMS should be biologically confirmed: *FKHR-PAX3* from *t(2;13)(q35;q14)* and *FKHR-PAX7* from *t(1;13)(p36;q14)*
- Biopsy is the best choice prior to primary surgery when faced with an STS
- IFSs are a special entity of sarcomas in children and have a very good prognosis
- SSs and MPNSTs are the most common sarcomas in AYAs
- Tumour molecular profiling is most often required for biological diagnosis and management of non-rhabdomyosarcoma soft tissue sarcomas (NRSTSs)
- Local control is mandatory for curative treatment in localised NRSTSs, but (neo)adjuvant ChT can help according to the different histological subgroups

Further Reading

Bisogno G, Jenney M, Bergeron C, et al. European paediatric Soft tissue sarcoma Study Group. Addition of dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma (EpSSG RMS 2005): a multicentre, open-label, randomised controlled, phase 3 trial. Lancet Oncol 2018; 19:1061–1071.

Bourdeaut F, Freneaux P, Thuille B, et al. Extra-renal non-cerebral rhabdoid tumours. Pediatr Blood Cancer 2008; 51:363–368.

DuBois SG, Laetsch TW, Federman N, et al. The use of neoadjuvant larotrectinib in the management of children with locally advanced TRK fusion sarcomas. Cancer 2018; 124:4241–4247.

Ferrari A, De Salvo GL, Brennan B, et al. Synovial sarcoma in children and adolescents: the European Pediatric Soft Tissue Sarcoma Study Group prospective trial (EpSSG NRSTS 2005). Ann Oncol 2015; 26:567–572.

Ferrari A, Gasparini P, Gill J, Gorlick R. Challenges of clinical management of adolescent and young adults with bone and soft tissue sarcoma. Cancer J 2018; 24:301–306.

Gallego S, Zanetti I, Orbach D, et al. Fusion status in patients with lymph node-positive (N1) alveolar rhabdomyosarcoma is a powerful predictor of prognosis: experience of the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). Cancer 2018; 124:3201–3209.

Merks JH, De Salvo GL, Bergeron C, et al. Parameningeal rhabdomyosarcoma in pediatric age: results of a pooled analysis from North American and European cooperative groups. Ann Oncol 2014; 25:231–236.

Oberlin O, Rey A, Lyden E, et al. Prognostic factors in metastatic rhabdomyosarcomas: results of a pooled analysis from United States and European cooperative groups. J Clin Oncol 2008; 10:2384–2389.

Orbach D, Brennan B, De Paoli A, et al. Conservative strategy in infantile fibrosarcoma is possible: the European paediatric Soft tissue Sarcoma Study Group experience. Eur J Cancer 2016; 57:1–9.

Orbach D, Mosseri V, Gallego S, et al. Nonparameningeal head and neck rhabdomyosarcoma in children and adolescents: Lessons from the consecutive International Society of Pediatric Oncology Malignant Mesenchymal Tumor studies. Head Neck 2017; 39:24–31.

Rogers T, Minard-Colin V, Cozic N, et al. Paratesticular rhabdomyosarcoma in children and adolescents–Outcome and patterns of relapse when utilizing a nonsurgical strategy for lymph node staging: Report from the International Society of Paediatric Oncology (SIOP) Malignant Mesenchymal Tumour 89 and 95 studies. Pediatr Blood Cancer 2017; 64:2384–2389.

Sarcoma: new drugs and novel treatment strategies

Driver genes in sarcoma

Sarcomas gather a group of rare heterogeneous mesenchymal malignancies, with >80 histological subtypes in the World Health Organization (WHO) classification. A grading system identifies three prognostic groups.

Genomic alterations of oncogenes (translocations [~20%], amplifications [~20%], missense mutations [~15%]) or suppressor gene losses refine the nosological classification.

These mutations define nosological subgroups and provide guidance for cytotoxic treatments (e.g. Ewing) but also targeted oncogene therapies (some are actionable drivers).

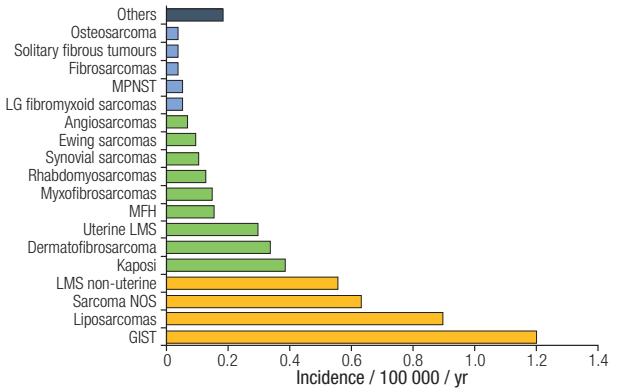


Fig. 10.1

GIST, gastrointestinal stromal tumour; LG, low grade; LMS, leiomyosarcoma; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumour; NOS, not otherwise specified.

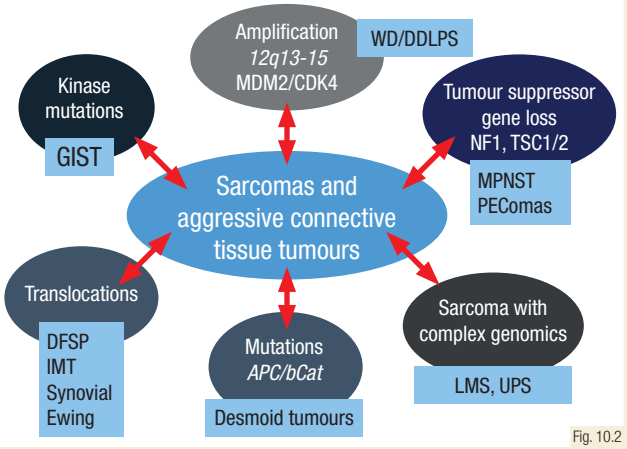


Fig. 10.2

APC; adenomatous polyposis coli; DFSP, dermatofibrosarcoma protuberans; GIST, gastrointestinal stromal tumour; IMT, inflammatory myofibroblastic tumour; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumour; NF1, neurofibromatosis type 1; PEComa, perivascular epithelioid cell tumour; TSC 1/2, tuberous sclerosis 1/2; UPS, undifferentiated pleomorphic sarcoma; WD/DDLPS; well-differentiated/dedifferentiated liposarcoma.

About 50% of sarcomas have canonical genomic alterations (e.g. *t(11;22)* in Ewing), encoding for an activated oncogene. Some of these oncogenes can be inhibited therapeutically.

Such targeted oncogene treatments can be active in several molecular and histological subtypes of sarcoma, e.g. KIT and platelet-derived growth factor receptor (PDGFR)A inhibitors (e.g. imatinib) in gastrointestinal stromal tumours (GISTs).

The biological alterations resulting from these genomic alterations guide the development of targeted treatments in sarcomas. We present examples hereunder.

Dermatofibrosarcoma protuberans (DFSP) is a rare skin sarcoma, characterised by a specific translocation encoding for a fusion protein containing platelet-derived growth factor (PDGF).

PDGFB, and more rarely PDGFD, is an autocrine growth factor for DFSP. Targeted therapies blocking the PDGFR block the oncogenic signal.

Relapsing non-operable, metastatic or locally advanced DFSP respond to PDGFR-tyrosine kinase inhibitors (TKIs), in particular imatinib. Trials in these rare sarcomas are challenging.

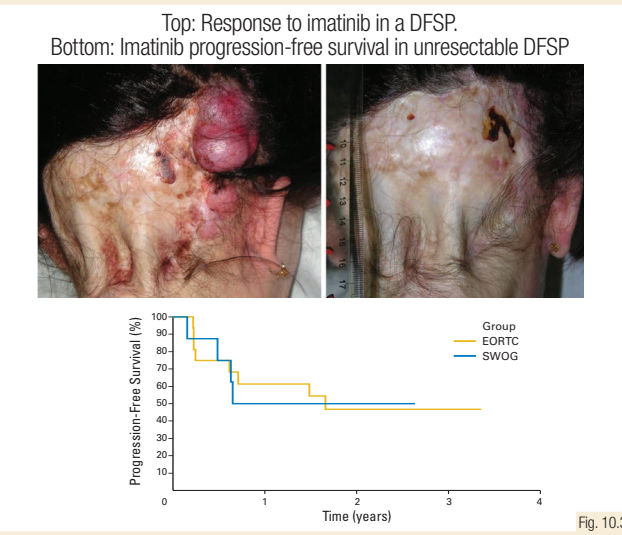


Fig. 10.3

DFSP, dermatofibrosarcoma protuberans; EORTC, European Organisation for Research and Treatment of Cancer; SWOG, Southwest Oncology Group.

REVISION QUESTIONS

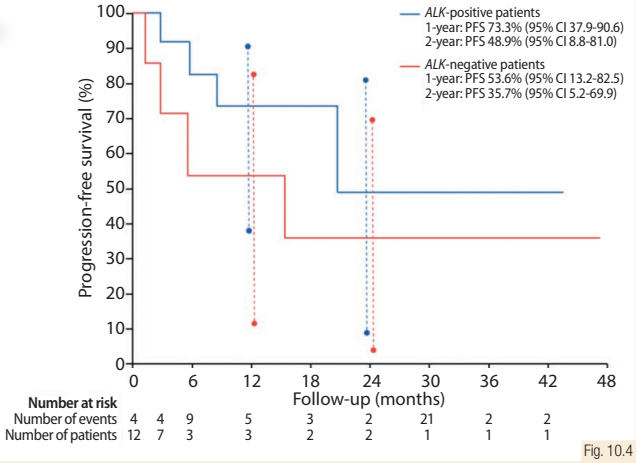
1. Is sarcoma classification based solely on histology?
2. Which genomic alterations are useful to classify sarcoma?
3. When does genomic alteration serve as a biomarker for treatment?

Targeting activated oncogenes

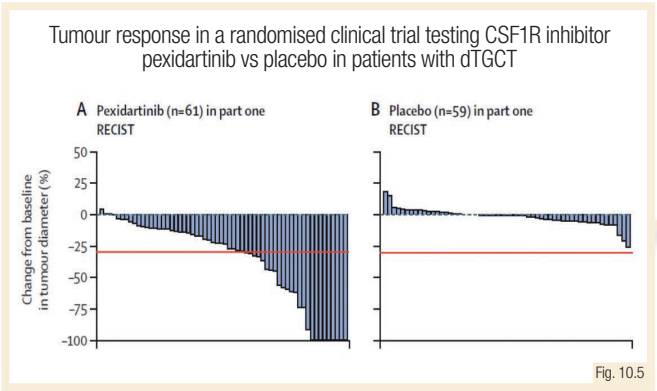
Inflammatory myofibroblastic tumours (IMTs) are rare sarcomas, often (50%) bearing translocations involving anaplastic lymphoma kinase (ALK), neurotrophic tyrosine receptor kinase (NTRK) or ROS1 receptor tyrosine kinases.

When locally advanced or metastatic, IMTs can be efficiently treated with TKIs blocking ALK, ROS1, or tyrosine receptor kinase (TRK) A/B/C.

In single-arm trials, durable (>5 years) remission was observed only in patients bearing one of these translocations. Randomised clinical trials may be unfeasible given the rarity.



ALK, anaplastic lymphoma kinase; CI, confidence interval; IMT, inflammatory myofibroblastic tumour; PFS, progression-free survival.



CSF1R, colony stimulating factor 1 receptor; dTGCT, diffuse-type tenosynovial giant cell tumour; RECIST, Response Evaluation Criteria in Solid Tumours.

Diffuse-type tenosynovial giant cell tumour ([dTGCT], a.k.a. pigmented villonodular synovitis [PVNS]) is a rare, locally aggressive tumour often bearing a translocation involving the colony stimulating factor 1 (CSF1) growth factor.

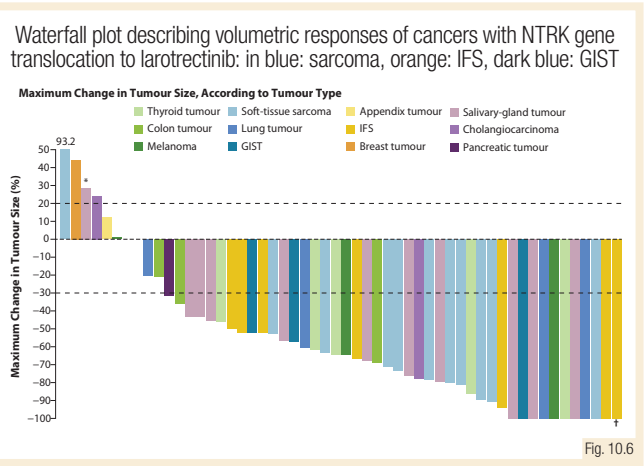
TKIs, small molecules and antibodies (Abs) blocking CSF1 receptor (CSF1R), are developed in dTGCT and have demonstrated anti-tumour efficacy in several clinical studies.

CSF1R TKIs are also active in dTGCT variants, with translocations involving other genes associated with an over-expression of CSF1 or interleukin (IL)-34 (another ligand of CSF1R).

Translocations involving NTRK1-3 genes are observed in infantile fibrosarcoma (IFS) and adult sarcomas (e.g. GIST, undifferentiated pleomorphic sarcoma [UPS], IMT). They are mutually exclusive from other translocations.

The NTRK1-3 genes have variable translocation partners. These translocations are found in 1% of all sarcomas, more frequently in specific rare histotypes (IFS, IMT, wild-type [WT] GIST).

High response rates to TRK A/B/C TKIs are reported in sarcomas (and any cancer) bearing these translocations. The strategy for the detection of the translocations is debated.



GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma; NTRK, neurotrophic tyrosine receptor kinase.

REVISION QUESTIONS

1. For a given sarcoma histotype, is there a single specific molecular alteration? Are these actionable?
2. Are TKIs active only when a translocation is detected in IMT?
3. What is the significance and impact of translocations involving one of the NTRK genes observed in sarcomas?

New targets, new challenges

Despite historical experience (Coley's toxin, mifamurtide) with immunotherapy in sarcoma, immune checkpoint inhibitors (ICIs) have provided low response rates and survival.

As expected, the different sarcomas have a different immune landscape with variable (often low, 5% high) tumour mutation burden, immune infiltrates and programmed death-ligand 1 (PD-L1) expression.

Low response rates to anti-programmed cell death protein 1 (PD-1) Abs have been reported in most sarcomas. Results are more encouraging in some molecular subtypes (e.g. alveolar soft part sarcomas, rhabdoids).

Response of a SMARCB1-deficient rhabdoid tumour to pembrolizumab

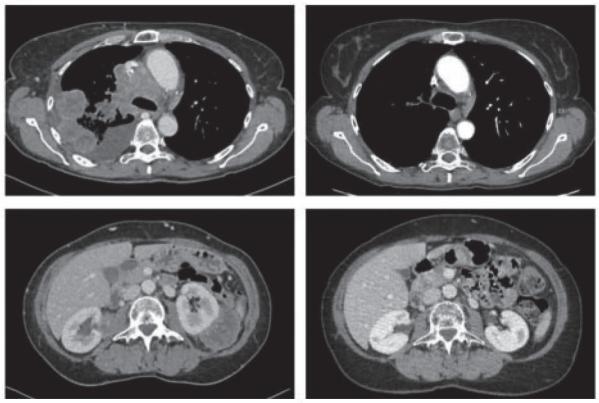


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Fig. 10.7

Response to denosumab in a giant cell tumour of the bone: reconstruction after 20 weeks for the primary tumour (upper panel), response of lung metastases after 40 weeks

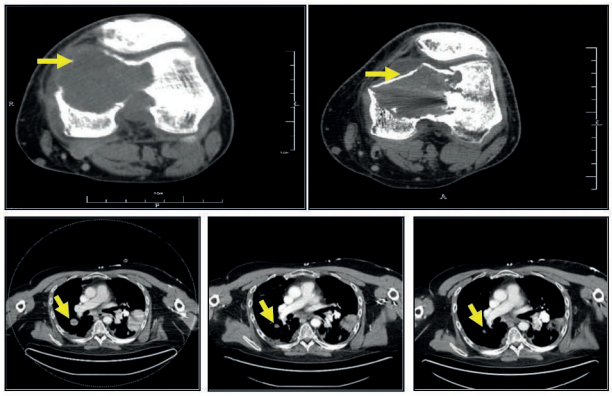

Fig. 10.8

Several sarcomas and related connective tissue tumours, such as desmoid tumours, are efficiently treated with targeted agents despite the lack of driver genomic alteration.

As examples, desmoid tumours and uterine low-grade endometrial stromal sarcoma have high tumour control rates to vascular endothelial growth factor receptor 2 (VEGFR2) inhibitors and aromatase inhibitors, respectively.

Empirical approaches for targeted therapy development should however be discouraged, as shown by the negative phase III trial of the anti-PDGFRA olaratumab in all sarcomas.

Well-differentiated and dedifferentiated liposarcomas (WD/DDLPSs) as well as other sarcoma subtypes present a *12q13-15* amplicon, containing the CDK4 and MDM2 genes.

Inhibitors of CDK4 and MDM2, as single agents, yield response and prolonged progression-free survival (PFS) only in a fraction of patients with inoperable WD/DDLPS.

Based on the rationale that this amplicon is consistent and often a unique genomic event in these sarcomas, phase I combinations of CDK4 and MDM2 inhibitors are ongoing. Mammalian target of rapamycin (mTOR) and EZH2 are also under investigation.

Description of the *12q13-15* amplicon present in well-differentiated and dedifferentiated liposarcomas, intimal sarcomas and low-grade superficial osteosarcoma

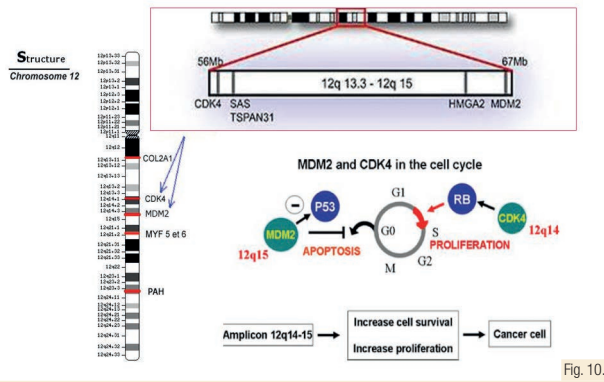

Fig. 10.9

REVISION QUESTIONS

1. What are the results of the immunotherapy trials with ICIs in sarcomas?
2. What are the limits of the paradigm that 'a genomic alteration of the targeted pathway is a prerequisite for response to a targeted oncogene treatment in sarcoma'?
3. Should CDK4 inhibitors be routinely prescribed in sarcomas with *CDK4* amplification?

Summary: Sarcoma: new drugs and novel treatment strategies

- Sarcoma is a very heterogeneous group of malignant connective tissue tumours with >80 histotypes
- About 50% of sarcomas present with specific genomic alterations: translocations (20%), *12q13-15* amplicon (with MDM2 and CDK4 gene amplification), missense mutation (e.g. *KIT*, *PDGFRA*), tumour suppressor gene losses (*NF1*, *p53*, *TSC1/2*, *Rb*, etc.)
- Histological subtypes of sarcoma do not consistently match with a specific genomic alteration: e.g. 80% of liposarcomas are associated with MDM2/CDK4 gene amplifications, 10% with translocations and 10% with complex genomic alterations
- Standard treatment and drug development in sarcoma are guided by histotype and molecular subtype
- All recently registered agents are registered for a given histotype or molecular subtype (eribulin, regorafenib, larotrectinib)
- Activated tyrosine kinases (KIT, PDGFRA, CSF1R, TRK A/B/C, ALK, ROS1, etc.), through missense mutation or translocation, are the most common actionable targets in sarcoma
- Other targets under study include MDM2, CDK4, mTOR and EZH2
- Targeted treatment of certain sarcoma subtypes is active despite the absence of direct genomic alteration of the targeted pathway (VEGFR2 in desmoids, oestrogen receptor in low-grade endometrial stromal sarcoma and RANKL in giant cell tumour of bone)
- Drug development in sarcoma is best guided by the molecular characterisation of the tumour
- Immunotherapy with ICIs has limited activity in unselected sarcoma histotypes

Further Reading

Chawla S, Henshaw R, Seeger L, et al. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. Lancet Oncol 2013; 14:901–908.

Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol 2018; 15:731–747.

D'Angelo SP, Mahoney MR, Van Tine BA, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol 2018; 19:416–426.

Dickson MA, Schwartz GK, Keohan ML, et al. Progression-free survival among patients with well differentiated or dedifferentiated liposarcoma treated with CDK4 inhibitor palbociclib: a phase 2 clinical trial. JAMA Oncol 2016: 2:937–940.

Dufresne A, Brahmi M, Karanian M, Blay JY. Using biology to guide the treatment of sarcomas and aggressive connective-tissue tumours. Nat Rev Clin Oncol 2018; 15:443–458.

Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. Pathology and genetics of tumours of soft tissue and bone. World Health Organization. IARC Press: Lyon, 2013.

Ray-Coquard I, Blay JY, Italiano A, et al. Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with MDM2-amplified, well-differentiated or dedifferentiated liposarcoma: An exploratory proof-of-mechanism study. Lancet Oncol 2012; 13:1133–1140.

Rutkowski P, Van Glabbeke M, Rankin CJ, et al. Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. J Clin Oncol 2010; 28:1772–1779.

Sanfilippo R, Jones RL, Blay JY, et al. Role of chemotherapy, VEGFR Inhibitors, and mTOR inhibitors in advanced perivascular epithelioid cell tumors (PEComas). Clin Cancer Res 2019; 25:5295–5300.

Schöffski P, Sufliarsky J, Gelderblom H, et al. Crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumours with and without anaplastic lymphoma kinase gene alterations (European Organisation for Research and Treatment of Cancer 90101 CREATE): a multicentre, single-drug, prospective, non-randomised phase 2 trial. Lancet Respir Med 2018; 6:431–441.

Tap WD, Gelderblom H, Palmerini E, et al; ENLIVEN investigators. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. Lancet 2019; 394:478–487.

Acknowledgements

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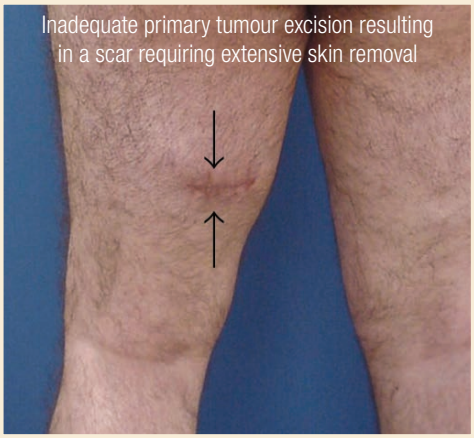
Difficult situations in sarcoma management

‘Whoops’ operation and its impact on treatment and prognosis

Sometimes, soft tissue lumps are not suspected to be a sarcoma and are inadvertently and inappropriately excised without imaging or treatment planning.

This is referred to as a ‘whoops’ operation, because the surgeon begins to say ‘whoops’ at the time of the pathology report.

Subsequent radical surgery is required to remove the previous area of surgery with a margin of clearance.



Inadequate primary tumour excision resulting in a scar requiring extensive skin removal

Fig. 11.1

Inadequate primary tumour excision with scar formation requiring plastic reconstructive measures

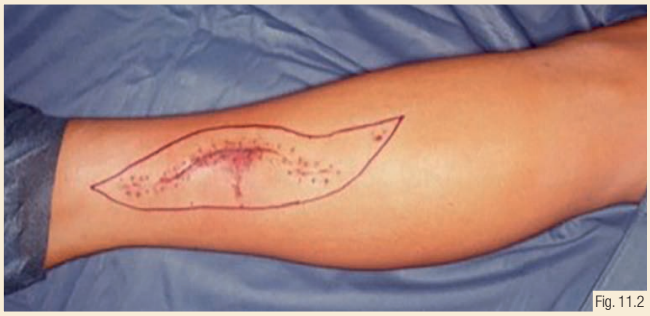


Fig. 11.2

Most commonly misdiagnosed soft tissue sarcomas (STSs) are 5 cm in size, painless and located above the fascia (superficial).

In bone tumours, the most often presumed diagnoses in unplanned resections are osteomyelitis, giant cell tumour of bone, bone cyst, osteonecrosis or metastatic disease.

Tumours that are >5 cm in any dimension, in the deep fascia or that are growing rapidly should be only diagnosed by a sarcoma specialist in a referral centre.

Microscopic tumour is found in up to 40% of re-excisions. A second opinion of the pathological specimen is recommended. This poses an additional financial burden to the health system and delays establishing the correct diagnosis and management.

Unplanned excisions have a major impact on subsequent therapy, yet they do not seem to affect negatively the long-term oncological outcome if patients are referred to a sarcoma centre immediately, and recommended therapy is applied.

Assessing residual macro-/microscopic disease after ‘whoops’ surgery on magnetic resonance imaging (MRI) as well as review of pathology by a reference sarcoma pathologist is mandatory before re-excision.

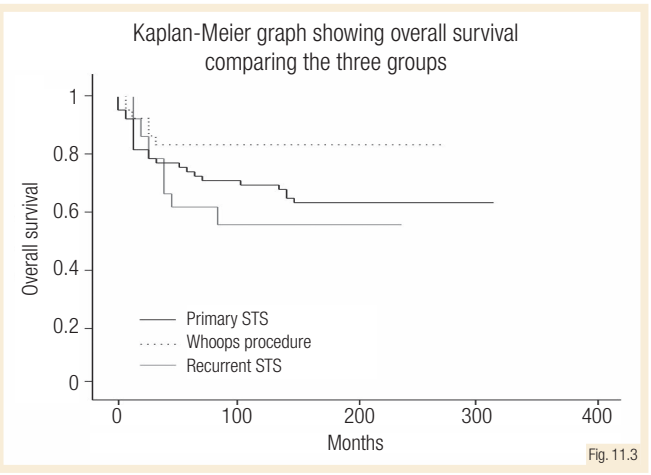


Fig. 11.3

STS, soft tissue sarcoma.

REVISION QUESTIONS

1. What is a ‘whoops’ operation?
2. What are the two essential management procedures after a ‘whoops’ operation, and before reoperation?
3. What is the recommended treatment following a ‘whoops’ operation?

European referral centres and EURACAN

European countries follow different ways in trying to establish the best-possible care for sarcoma patients. Many have their own sarcoma networks and have collaborated on several EU-funded research projects.

The Scandinavian Sarcoma Group (SSG), formed in 1979, set standards in defining reference centres and conducts important trials, e.g. SSG XVIII – leading to the approval of imatinib for 3-year adjuvant therapy in gastrointestinal stromal tumour (GIST).

NetSarc+ is the French clinical reference network for soft tissue and visceral sarcomas, bone sarcomas and rare bone tumours, contributing to a database with data on >50 000 sarcomas.

European sarcoma groups at national level

Fig. 11.4

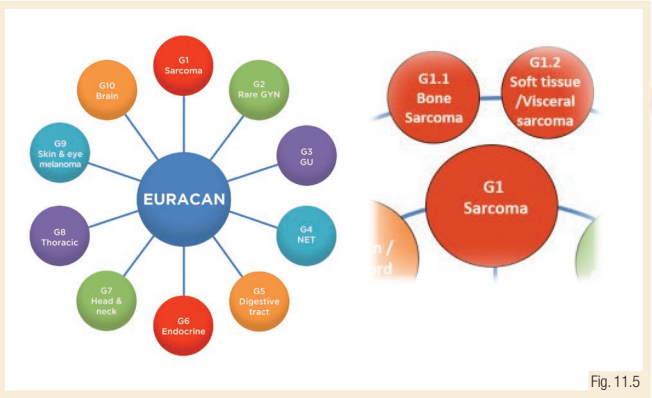


Fig. 11.5

GU, genitourinary; GYN, gynaecological; NET, neuroendocrine tumour.

EURACAN is the European Reference Network (ERN) for adult rare solid cancers, with the objective to improve the quality of care for all European citizens.

ERN EURACAN gathers the largest network of active European centres involved in the management of patients with adult rare solid cancers, grouping them into 10 domains corresponding to the RARECARE classification.

In the field of sarcomas there are two subdomains dealing with bone and soft tissue/visceral sarcomas.

The volume of sarcoma patients managed has been suggested to be a key characteristic to identify a hospital with better outcomes.

Reference sarcoma centres need to treat a certain number of sarcoma primary cases per year and require a trained interdisciplinary staff, with reference pathologists, dedicated radiologists and radiation and medical oncologists.

They contribute their data to prospectively kept disease registries and participate in clinical trials and research projects.

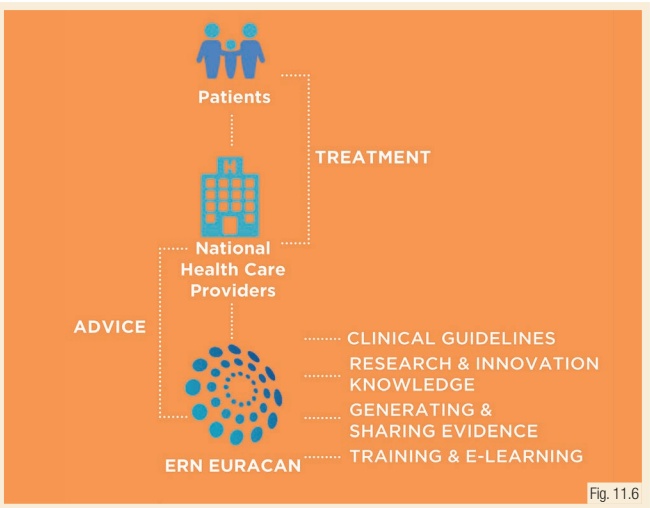


Fig. 11.6

ERN, European Reference Network.

REVISION QUESTIONS

1. How can a sarcoma centre be defined?
2. What kind of network is EURACAN?
3. What are the objectives of EURACAN?

Adolescents & Young Adults – age-specific sarcomas
Rhabdomyosarcoma, familial GIST and desmoplastic small round cell tumour

The adolescent and young adult (AYA) population (16-30 years of age) presents specific issues. They no longer belong to the 'protective' paediatric medicine and have disease with a worse prognosis than in children.

Rhabdomyosarcoma (RMS) is the most common STS in children and adolescents and represents a high-grade (G3) neoplasm of skeletal myoblast-like cells.

Two major subtypes, embryonal (ERMS) and alveolar (ARMS), show different molecular characteristics.

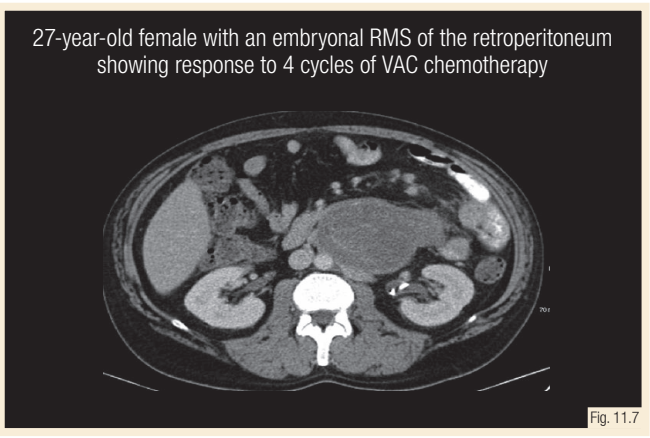
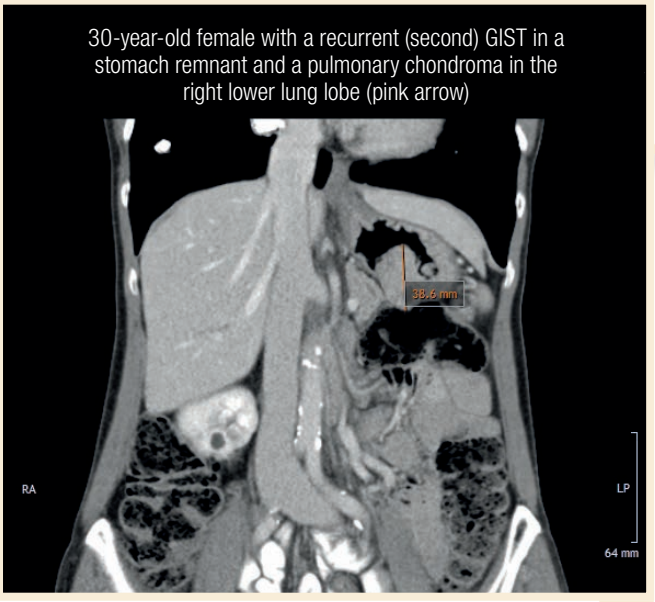


Fig. 11.7

RMS, rhabdomyosarcoma; VAC, vincristine/dactinomycin/cyclophosphamide.



GIST, gastrointestinal stromal tumour.

Fig. 11.8

Germline-determined (familial) GIST can occur as a typical component of neurofibromatosis type 1 (NF1) with a male preponderance, multi-focality and no *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) mutation.

Familial GIST outside of NF1 affects children or young females and tumours may spread to the regional lymph nodes.

Carney-Stratakis syndrome includes GIST plus pulmonary chondroma and paraganglioma. Families with inherited GIST syndromes have been described, presenting with *KIT* exon 8 or exon 11 mutations.

Desmoplastic small round cell tumour (DSRCT) is a rare, aggressive disease predominantly affecting AYA males. It is located in the abdomen, and is often associated with peritoneal, liver or lung metastasis.

Histologically, the tumour belongs to the wider Ewing sarcoma family and consists of small round blue cell nests harbouring a *t(11;22)(p13;q12)* chromosomal translocation. Treatment consists of primary systemic chemotherapy (ChT) and may be followed by surgery and/or radiotherapy (RT). Aggressive surgery, RT and ChT have all been used to treat DSRCT.

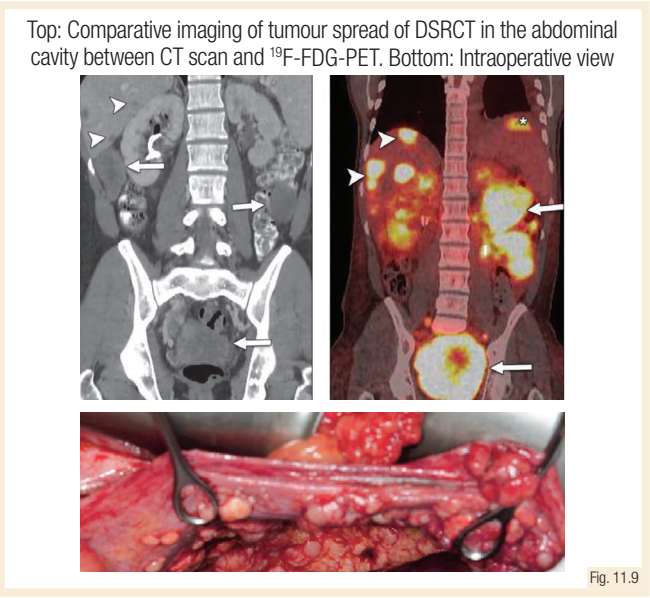


Fig. 11.9

CT, computed tomography, DSRCT, desmoplastic small round cell tumour; FDG-PET, fluorodeoxyglucose-positron emission tomography.

REVISION QUESTIONS

1. Which are the most common histological types of RMS and what does their treatment include?
2. How is familial GIST defined and what are the known germline mutations?
3. What are the characteristics of sarcomas in AYAs?

Social problems, rehabilitation and follow-up

Survivorship is the lived experience of individuals after cancer treatment. The recognised domains of survivorship are considered in three sections: physical, psychological and social.

Sarcoma treatment can lead to physical impairments (e.g. reduced joint movement), activity limitations (walking, dressing) and participation restrictions (e.g. sports or employment).

There are several models to assess the patient's functional impairment and its impact on daily life such as the Toronto Extremity Salvage Score (TESS) or the rating system of the Musculoskeletal Tumor Society (MSTS).

Correlation of functional disability impacts on the HRQoL of patients with extremity STS at 1-year post-surgery

Model	Predictors	*p*-value
A	Impairment	$p<0.001$
B	Activity limitations	$p<0.001$
C	Participation restrictions	$p<0.001$
D	Impairment	$p=0.002$

HRQoL, health-related quality of life; STS, soft tissue sarcoma.

Fig. 11.10

Oedema of the left arm and hand after isolated limb perfusion for sarcoma. Limits in making a fist interferes with the patient's ability to perform daily routines; colouration might be a stigma to other people

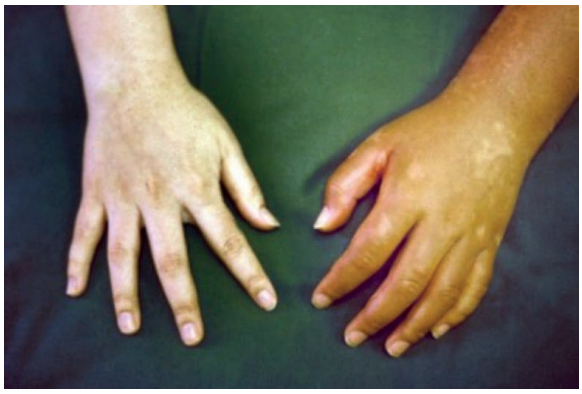


Fig. 11.11

Rehabilitation enables patients to reach and maintain optimal physical, sensory, intellectual and social functional levels. Good rehabilitation emphasises a return to normal psychosocial functioning.

Rehabilitation should begin early in treatment. Starting between diagnosis and first treatment ('prehabilitation') can reduce surgical complications and length of hospital stay. Postoperatively, extremity motion should start as early as possible.

Good communication between the surgeon and the rehabilitation team is crucial to agree an appropriate regimen, considering limb weakness, swelling, neurological injury and weight bearing.

The World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF) model provides a useful conceptual framework for understanding the multidimensional needs of patients. Almost one third of long-term surviving sarcoma patients report suffering from fatigue.

The ICF supports data compilation, analysis, policy monitoring, service provision and communication between health professional and has been used to develop rehabilitation models.

Physical rehabilitation and self-management programmes using the ICF framework can improve quality of life (QoL) in cancer survivors.

International Classification of Functioning, Disability and Health (ICF)

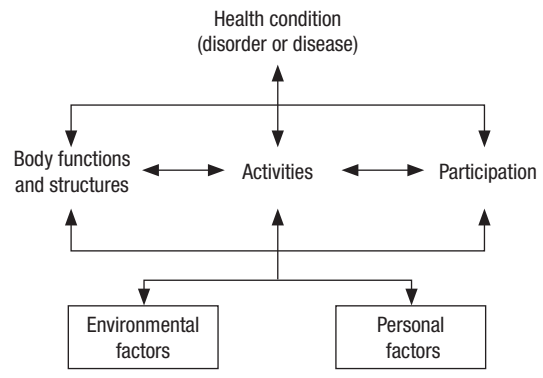


Fig. 11.12

REVISION QUESTIONS

1. What are the social problems, in terms of survivorship, caused after sarcoma surgery?
2. What are the targets of rehabilitation and how can they be achieved?
3. What is the ICF model and what is it used for?

Late events in sarcoma populations

Late disease recurrence is generally defined as recurrence that occurs >5 years after initial management.

Prognostic factors specific for late events, such as local recurrence or metastasis, are histological type, grading, tumour size, R (resection)-status and (adjuvant) RT.

The incidence of late events justifies prolonged long-term follow-up, especially in patients who need surveillance for the late side effects of cancer treatment.

Late sequelae of irradiation with 72 Gy resulting in acrocontracture and induration of cutaneous and subcutaneous tissues

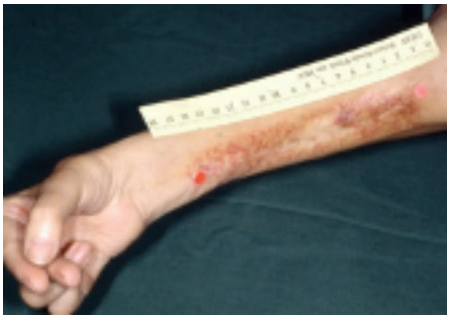


Fig. 11.13

Pathological fracture of the femur after neoadjuvant isolated limb perfusion, sarcoma resection and adjuvant radiation

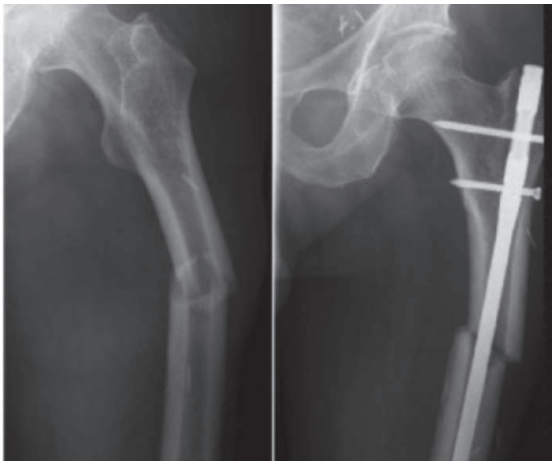


Fig. 11.14

Preoperative RT is advantageous over postoperative RT in terms of limb function.

However, if combined with periosteal stripping to achieve clear margins, the rate of RT-associated fractures is around 1.2%-9%.

RT impairs the proliferation of osteoblasts. Periosteal stripping decreases cortical bone perfusion. Fractures follow compromised biomechanical bone stability.

Persistent neuropathic pain (NP) is a major component of chronic postoperative pain.

Surgery for sarcoma of extremities or pelvis often requires extensive tissue dissection to achieve adequate surgical margins, including violation of the internervous planes.

Treatment of pain is often inadequate and requires a full initial assessment and regular reviews by a specialised team, alongside treatment of the cancer.

Patient after complex sarcoma treatment including ILP, chemotherapy and irradiation. Limb stiffness, oedema and desquamation contribute to chronic neuropathic pain

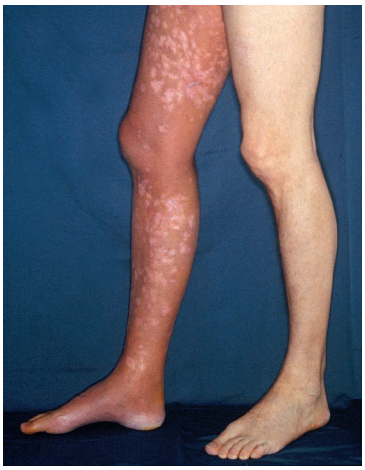


Fig. 11.15

ILP, isolated limb perfusion.

REVISION QUESTIONS

1. What changed in the complications of sarcoma surgery following the introduction of RT?
2. Why do pathological fractures occur more often after ILP?
3. Why do sarcoma patients often experience NP, and how can it be prevented?

Summary: Difficult situations in sarcoma management

- Situations after a 'whoops' operation require subsequent radical surgery with a margin of clearance. After 'whoops', microscopic tumour is found in up to 40% of re-excisions
- Sarcoma patients should be referred to a specialist centre, where a multidisciplinary team can assess the patient and determine the best treatment
- EURACAN is the ERN for adult rare solid cancers and gathers the largest network of active European centres involved in the management of these patients
- RMS represents the most common STS in children and adolescents and requires a multimodality therapy
- Germline-determined (familial) GIST can occur either as a typical component of NF1 with a male preponderance, or outside of NF1 in terms of Carney triad or Carney-Stratakis syndrome or inherited GIST syndromes
- DSRCT is an aggressive malignant neoplasm with a poor 5-year survival, despite different therapeutic options
- Sarcoma treatment can lead to physical impairments, activity and participation restrictions which are associated with lower HRQoL, especially when persistent NP occurs after surgery
- Rehabilitation enables patients to reach and maintain optimal physical, sensory, intellectual and social functioning levels

Further Reading

Abellan JF, Lamo de Espinosa JM, Duart J, et al. Nonreferral of possible soft tissue sarcomas in adults: a dangerous omission in policy. Sarcoma 2009; 2009:827912.

Agaimy A, Vassos N, Croner RS. Gastrointestinal manifestations of neurofibromatosis type 1 (Recklinghausen's disease): clinicopathological spectrum with pathogenetic considerations. Int J Clin Exp Pathol 2012; 5:852–862.

Benesch M, Wardelmann E, Ferrari A, et al. Gastrointestinal stromal tumors (GIST) in children and adolescents: a comprehensive review of the current literature. Pediatr Blood Cancer 2009; 53:1171–1179.

Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol 2005; 75:48–53.

Gerrand C, Furtado S. Issues of survivorship and rehabilitation in soft tissue sarcoma. Clin Oncol (R Coll Radiol) 2017; 29:538–545.

Livi L, Santoni R, Paiar F, et al. Late treatment-related complications in 214 patients with extremity soft-tissue sarcoma treated by surgery and postoperative radiation therapy. Am J Surg 2006; 191:230–234.

Michot A, Stoeckle E, Bannel J-D, et al. The introduction of early patient rehabilitation in surgery of soft tissue sarcoma and its impact on postoperative outcome. Eur J Surg Oncol 2015; 41:1678–1684.

Mussi C, Schildhaus HU, Gronchi A, et al. Therapeutic consequences from molecular biology for gastrointestinal stromal tumor patients affected by neurofibromatosis type 1. Clin Cancer Res 2008; 14:4550–4555.

Ng Kee Kwong T, Furtado S, Gerrand C. What do we know about survivorship after treatment for extremity sarcoma? A systematic review. Eur J Surg Oncol 2014; 40:1109–1124.

Park JW, Kim H-S, Yun JY, Han I. Neuropathic pain after sarcoma surgery: prevalence and predisposing factors. Medicine (Baltimore) 2018; 97:e10852.

Pasquali S, Bonvalot S, Tzanis D, et al. Treatment challenges in and outside a network setting: soft tissue sarcomas. Eur J Surg Oncol 2019; 45:31–39.

Scheer M, Vokuhl C, Blank B, et al. Desmoplastic small round cell tumors: multimodality treatment and new risks. Cancer Med 2019; 8:527–542.

Skapek SX, Ferrari A, Gupta AA, et al. Rhabdomyosarcoma. Nat Rev Dis Primers 2019; 5:1.

Storey L, Fern LA, Martins A, et al. A critical review of the impact of sarcoma on psychosocial wellbeing. Sarcoma 2019; 2019:9730867.

Toulmonde M, Le Cesne A, Mendiboure J, et al. Long-term recurrence of soft tissue sarcomas: prognostic factors and implications for prolonged follow-up. Cancer 2014; 120:3003–3006.

van der Graaf WTA, Orbach D, Judson IR, Ferrari A. Soft tissue sarcomas in adolescents and young adults: a comparison with their paediatric and adult counterparts. Lancet Oncol 2017; 18:e166–e175.

Weldon CB, Madenci AL, Boikos SA, et al. Surgical management of wild-type gastrointestinal stromal tumors: a report from the National Institutes of Health Pediatric and Wildtype GIST Clinic. J Clin Oncol 2017; 35:523–528.

Cancer of unknown primary site

Definition, incidence and biology

Cancer of unknown primary site (CUP) represents a heterogeneous group of metastatic tumours for which a standardised diagnostic approach fails to identify the site of origin at the time of diagnosis.

CUP accounts for 3%-5% of all human cancers worldwide. It is reported to be the seventh to eighth most frequent cancer and is the fourth most common cause of cancer death in both sexes.

Median age at presentation is 65-70 years and CUP is slightly more common in men than in women.

CUP might be a distinct clinical entity. Pictured: liver metastases harbouring adenocarcinoma from an unknown primary

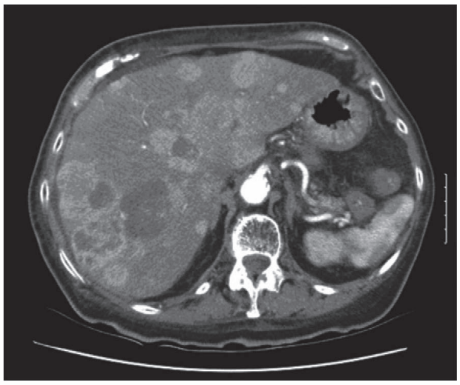


Fig. 12.1

CUP, cancer of unknown primary site.

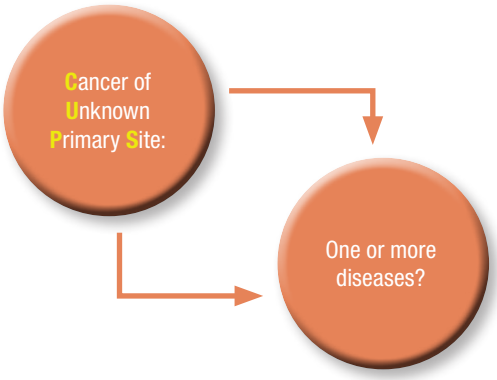


Fig. 12.2

CUP is an aggressive malignant entity metastasising early and possibly harbouring a pro-metastatic, CUP-specific biological signature.

The latter is the subject of ongoing research; however, it could include: metastatic propensity of cancer cells detached from the primary, homing and pro-survival adaptation of circulating tumour cells at secondary sites, and induction of oncogenes in tumour cells by surrounding stroma at metastatic sites.

Certain signalling pathways seem to be active in CUP and may have prognostic or predictive value. Active signalling pathways in CUP are: angiogenesis, stromal glutaminolytic activity, AKT/S6RP axis, β-catenin/Wnt axis and acquisition of the epithelial/mesenchymal phenotype.

The tumour global microRNA expression profile from CUP metastases biologically assigned to a primary tumour was found to harbour very few differences to that of metastases from a known primary.

Multi-gene expression profiler assays are available in order to biologically assign a CUP to a tissue of origin (ToO). However, no high-level evidence supports improvement of CUP patient survival by administration of ToO-tailored therapies.

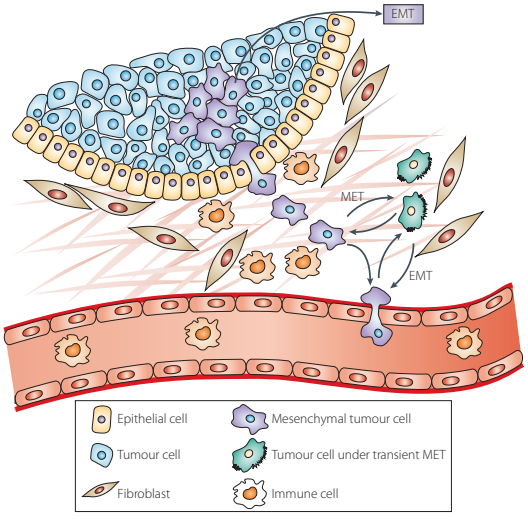


Fig. 12.3

EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition.

REVISION QUESTIONS

1. How is CUP defined?
2. How common is the diagnosis of CUP?
3. What are the biological hypotheses underlying the presentation of CUP?

Histological and molecular work-up

Immunohistochemistry (IHC) helps to identify the ToO and to exclude chemosensitive or potentially curable tumours (lymphomas and germ cell tumours).

Immunostaining for prostate-specific antigen (PSA) for males and oestrogen receptor (ER) and progesterone receptor (PR) for females is advisable to rule out hidden prostate and breast cancers.

Immunostaining for cytokeratins CK7 and CK20 could pinpoint a possible epithelial primary. Staining for chromogranin A and synaptophysin is a useful screen for neuroendocrine differentiation.

Primary markers		Additional markers
CK 7-/CK 20+	Colorectal and Merkel cell carcinoma	CEA and CDX-2
CK 7+/CK 20-	Lung, breast, thyroid, endometrial, cervical, and pancreatic carcinoma and cholangiocarcinoma	TTF-1, ER, PR, GCDFP-15, and CK 19
CK 7+/CK 20+	Urothelial, ovarian, and pancreatic cancer and cholangiocarcinoma	Urothelin and WT-1
CK 7-/CK 20-	Hepatocellular, renal cell, prostate, squamous cell	Hep Par-1 and PSA

Fig. 12.4

CEA, carcinoembryonic antigen; CK, cytokeratin; ER, oestrogen receptor; GCDFP-15, gross cystic disease fluid protein-15; Hep Par-1, hepatocyte paraffin 1; PR, progesterone receptor; PSA, prostate-specific antigen; TTF-1, thyroid transcription factor-1; WT-1, Wilms' tumour 1.

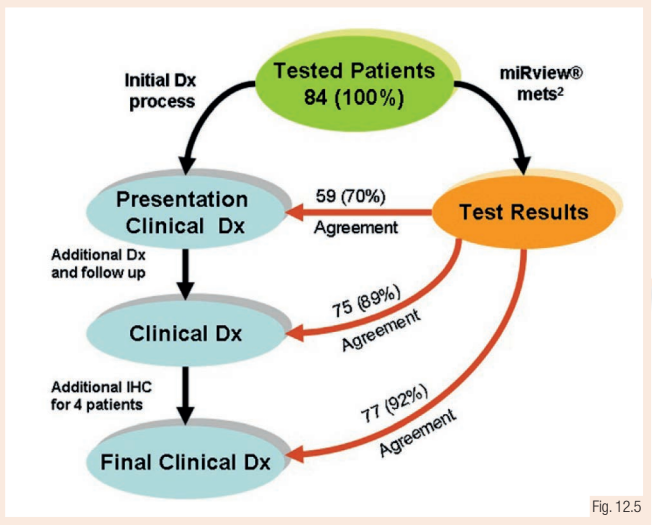


Fig. 12.5

IHC, immunohistochemistry.

Gene expression profiling assays for predicting the likely ToO are commercially available with accuracy rates of 75%-93%.

Only one such assay has been reviewed and cleared by the USA Food & Drug Administration (FDA) (1550 gene microarray-based Pathwork Tissue of Origin). The miRview mets test profiles tumour microRNA expression and has a reported accuracy of >90%.

Molecular assays may help in the identification of a putative primary tumour site but their utility in predicting the response to a primary site-specific therapy is not yet validated.

A suggested algorithm for the use of molecular assays is provided (Varadhachary, 2013).

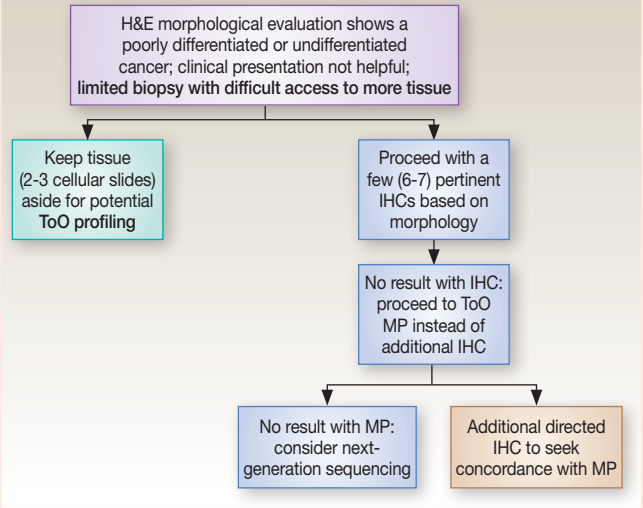


Fig. 12.6

H&E, haematoxylin and eosin; IHC, immunohistochemistry; MP, molecular profiling; ToO, tissue of origin.

REVISION QUESTIONS

1. What is the basic immunohistochemical staining for CUP?
2. What is the current use of molecular assays in CUP?
3. Is there high-level evidence that use of molecular assays results in improved patient survival?

Staging and risk assessment

A standard imaging work-up consists of chest and abdominopelvic computed tomography (CT), along with history, meticulous physical examination, basic blood and biochemistry screening.

The following serum markers should be assessed: alpha-foetoprotein (AFP), beta-human chorionic gonadotrophin (β-HCG), plasma chromogranin A and PSA (in males).

Specific work-up is advised for specific CUP subsets.

Assessment suggested	Target patient population
Thorough medical history and physical examination	All patients
Basic blood and biochemistry analyses	All patients
CT scans of thorax, abdomen and pelvis	All patients
Mammography	Female patients
Work-up for CUP subsets	
Breast MRI	Females with axillary adenocarcinoma
Serum α-foetoprotein and human chorionic gonadotrophin	Patients with midline metastatic disease
Serum prostate-specific antigen	Males with adenocarcinomatous bone metastases
Head and neck CT/PET scan (optional)	Cervical squamous cell carcinoma
Endoscopies	Sign/symptom/laboratory-oriented
Octreoscan and plasma chromogranin A	Patients with neuroendocrine tumour CUP
Additional diagnostic pathology	Sign/symptom/laboratory-oriented

CT, computed tomography; CUP, cancer of unknown primary site; MRI, magnetic resonance imaging; PET, positron emission tomography. Fig. 12.7

Favourable subset

- Women with papillary adenocarcinoma of the peritoneal cavity
- Women with adenocarcinoma involving the axillary lymph nodes
- Poorly differentiated carcinoma with midline distribution
- Poorly differentiated neuroendocrine carcinoma
- Squamous cell carcinoma involving cervical lymph nodes
- Adenocarcinoma with a colon cancer profile (CK20+, CK7-, CDX2+)
- Men with blastic bone metastases and elevated prostate-specific antigen (adenocarcinoma)
- Isolated inguinal adenopathy (squamous cell carcinoma)
- Patients with one small, potentially resectable tumour

Unfavourable subset

- Adenocarcinoma metastatic to the liver or other organs
- Non-papillary malignant ascites (adenocarcinoma)
- Multiple cerebral metastases (adenocarcinoma or squamous carcinoma)
- Several lung or pleural metastases (adenocarcinoma)
- Multiple metastatic lytic bone disease (adenocarcinoma)
- Squamous cell carcinoma of the abdominopelvic cavity

CK, cytokeratin. Fig. 12.8

Based on clinical and pathological criteria, distinct subsets of patients with CUP have been recognised.

15%-20% of CUP patients belong to one of the favourable subsets (favourable-risk CUP).

Favourable-risk CUP patients have chemosensitive or potentially curable tumours and may experience long-term disease control.

80%-85% of CUP patients belong to unfavourable subsets with poor response to therapy and median overall survival (OS) of 6-10 months (unfavourable or poor risk CUP).

A simple prognostic model for poor-risk CUP patients is based on two prognostic parameters: lactate dehydrogenase (LDH) and performance status (PS).

Management of CUP patients depends on the recognition of specific subsets, exclusion of non-CUP neoplasms and the use of prognostic parameters.

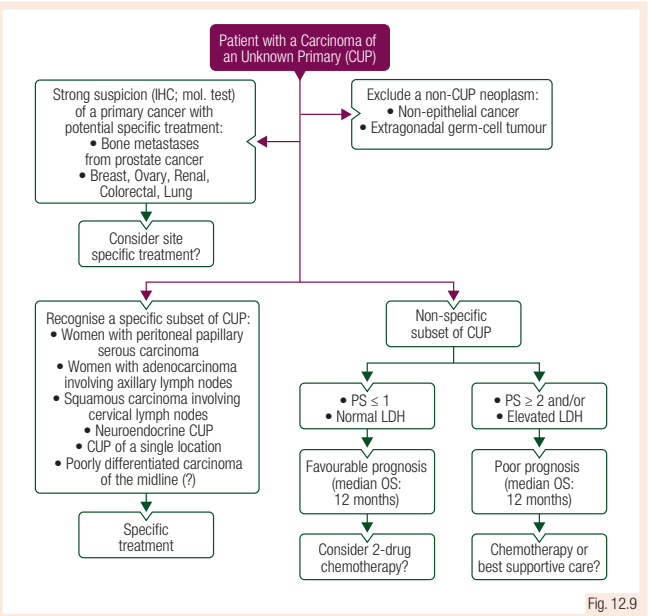


Fig. 12.9

IHC, immunohistochemistry; LDH, lactate dehydrogenase; OS, overall survival; PS, performance status.

REVISION QUESTIONS

1. What is the basic diagnostic work-up?
2. What are the clinicopathological subsets of CUP?
3. Are there any prognostic parameters or models to be used?

Treatment: favourable risk

Women with papillary serous adenocarcinoma of the peritoneal cavity: management is similar to that for stage III and stage IV ovarian cancer.

Poorly differentiated carcinoma with midline distribution: treatment is similar to that for poor-prognosis germ cell tumours.

CUP subtype	Proposed treatment	mORR	CR	mOS (months)
Peritoneal adenocarcinomatosis of a serous papillary histological type in female patients	Optimal surgical debulking followed by platinum/taxane-based ChT	80%	30%-40%	36
Poorly differentiated carcinoma with midline distribution	Platinum-based ChT	45%	25%	25

ChT, chemotherapy; CR, complete response; CUP, cancer of unknown primary site; mORR, median overall response rate; mOS, median overall survival.

Fig. 12.10

CUP subtype	Proposed treatment	mORR	CR	mOS (months)
Poorly differentiated neuroendocrine carcinomas of an unknown primary	Platinum/etoposide combination ChT	55%	21%	15.5
Isolated axillary nodal metastases in female patients	Axillary nodal dissection, mastectomy or breast irradiation and adjuvant chemohormonal therapy	NA	NA	>36
Squamous carcinoma involving non-supraclavicular cervical lymph nodes	Neck dissection and/or irradiation of bilateral neck and head-neck axis. For advanced stages, induction ChT with platinum-based combination or chemoradiotherapy.	NA	NA	>24

Fig. 12.11

ChT, chemotherapy; CR, complete response; CUP, cancer of unknown primary site; mORR, median overall response rate; mOS, median overall survival; NA, not applicable.

Poorly differentiated neuroendocrine carcinomas: treatment similar to that for poorly differentiated neuroendocrine tumours with a known primary.

Women with adenocarcinoma involving only axillary lymph nodes: treatment similar to that for women with stage II or stage III node-positive breast cancer.

Metastatic squamous cell carcinoma involving cervical lymph nodes: treatment similar to that for locally advanced head and neck cancer.

Isolated squamous cell carcinoma involving the inguinal lymph nodes or one metastatic lesion: treat as single metastasis (usually long disease-free survival).

Men with blastic bone metastases and serum or IHC PSA: treatment similar to that for hormone-sensitive metastatic prostate cancer.

Adenocarcinoma with a colon cancer profile (CK20+, CK7- and CDX2+): treatment similar to that for metastatic colorectal cancer.

CUP subtype	Proposed treatment	Potential equivalent tumour
Single metastatic deposit from unknown primary	Resection and/or RT +/- systemic therapy	Single metastasis
Men with blastic bone metastases and IHC/ serum PSA expression	Androgen deprivation therapy +/- RT	Prostate cancer
Adenocarcinoma with a colon cancer profile (CK20+, CK7- and CDX2+)	Fluoropyrimidine regimens with oxaliplatin or irinotecan and targeted therapies	Colon cancer; responses and survival similar to those obtained with colon cancer-specific therapies (mOS 20-24 months)

CK, cytokeratin; CUP, cancer of unknown primary site; IHC, immunohistochemistry; mOS, median overall survival; PSA, prostate-specific antigen; RT, radiotherapy.

Fig. 12.12

REVISION QUESTIONS

1. How should patients in the favourable-risk subsets be treated?
2. What is the level of evidence for the clinical recommendations for treatment of CUP subsets?
3. What is the suggested treatment of patients with poorly differentiated carcinoma with midline distribution?

Treatment: unfavourable risk

Patients with unfavourable-risk CUP subsets have a dismal prognosis despite treatment with any chemotherapeutic combination.

Non-randomised studies have shown that the introduction of platinum or platinum/taxane combinations is associated with a doubling of response rates and OS, which still lags behind the 1-year benchmark.

A meta-analysis has shown that no chemotherapy (ChT) regimen is superior to others in terms of survival. Generally, for fit patients, a platinum regimen with taxane or gemcitabine or vinca alkaloid is suggested as optimal empirical ChT.

Multiple treatments meta-analysis for death		
	HR[a]	95% CrI
nPnTc vs nPnTm	1.01	0.59-1.72
Platinum vs nPnTm	0.69	0.39-1.28
Taxane vs nPnTm	0.66	0.22-2.08
Platinum plus taxane vs nPnTm	0.81	0.34-1.89
Platinum vs nPnTc	0.69	0.43-1.15
Taxane vs nPnTc	0.66	0.23-2.00
Platinum plus taxane vs nPnTc	0.80	0.39-1.67
Taxane vs platinum	0.95	0.37-2.50
Platinum plus taxane vs platinum	1.16	0.56-2.38
Platinum plus taxane vs taxane	1.22	0.36-4.00

[a]A hazard ratio (HR) above one means that the risk of death is higher with the first rather than the second listed regimen

CrI, credible interval; HR, hazard ratio; nPnTc, non-platinum, non-taxane combination; nPnTm, non-platinum, non-taxane monotherapy.

Fig. 12.13

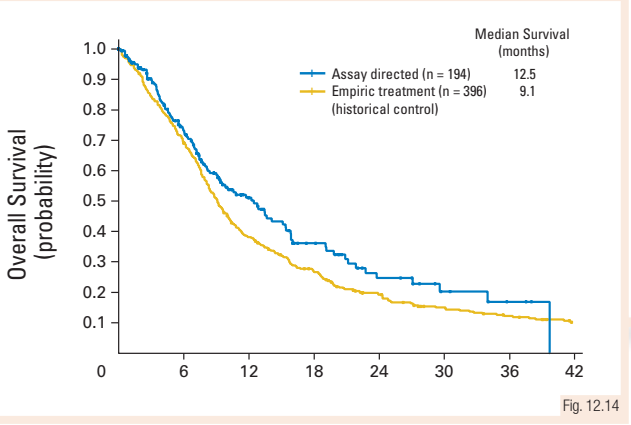


Fig. 12.14

The poor outcome of unfavourable-risk CUP patients has inevitably led to the application of molecular assays in order to a) pick the ToO or b) pick the target.

After inconclusive investigation, a molecular classifier assay can be used for biological assignment of a primary ToO: pick the tissue strategy.

The randomised phase III trial GEFCAPI04 failed to establish superiority of the pick the tissue-tailored therapeutic strategy over empirical ChT in patients with unfavourable CUP.

Ongoing studies are investigating the use of molecular assays to identify a targetable molecular alteration: pick the target strategy.

SHIVA, a randomised phase II study, assigned patients to receive targeted therapy or investigators' choice but failed to show progression-free survival (PFS) improvement.

Ongoing research is focusing on elucidating the molecular landscape of CUP and identifying effective biomarkers in order to improve patient outcome.

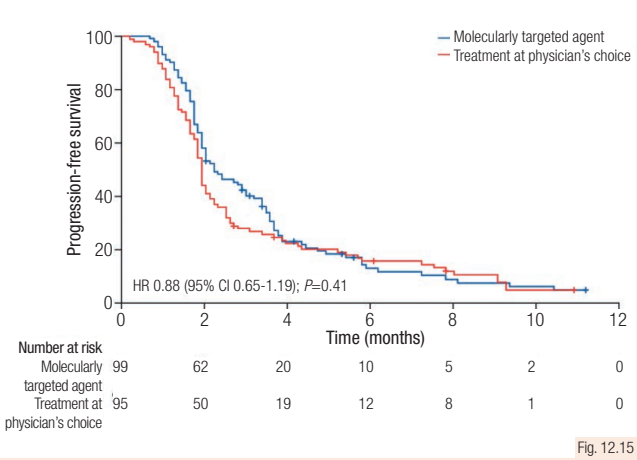


Fig. 12.15

CI, confidence interval; HR, hazard ratio.

REVISION QUESTIONS

1. What is the prognosis of CUP patients in the unfavourable-risk subsets?
2. Is there a role for targeted therapy in CUP?
3. What should be the focus of future research?

Summary: Cancer of unknown primary site

- CUP characteristics: early dissemination, clinical absence of primary at presentation, aggressiveness and unpredictable metastatic pattern
- CUP epidemiology: 3%-5% of all cancers, seventh to eighth most frequent cancer and the fourth most common cause of cancer death
- CUP biology: either disseminated disease from an occult primary tumour or true CUP where metastases harbour a unique CUP-specific biology
- Diagnosis (IHC): CK7; CK20; chromogranin A; synaptophysin; PSA for males; ER and PR for females with positive axilla
- Diagnosis (molecular): gene expression profile assays assist in the prediction of the putative primary, with unknown therapeutic implications
- CUP staging: a standard diagnostic work-up must be carried out
- The main aim should be to exclude a chemosensitive or curable tumour (e.g. germ cell, lymphoma, prostate cancer)
- Breast MRI should be done in women with positive axilla and whole-body fluorodeoxyglucose (FDG)-positron emission tomography (PET) CT scan is indicated for a solitary metastatic lesion and for occult head and neck cancer
- CUP treatment (favourable-risk subsets 10%-15%): similar to equivalent known metastatic primary tumours with long-term disease control in 30%-60% of cases
- CUP treatment (unfavourable-risk subsets): dismal prognosis, chemoresistant, ongoing research to fully elucidate the molecular basis of CUP and improve therapy application

Further Reading

Conway AM, Mitchell C, Kilgour E, et al. Molecular characterisation and liquid biomarkers in carcinoma of unknown primary (CUP): taking the 'U' out of 'CUP'. Br J Cancer 2019; 120:141–153.

Fizazi K, Greco FA, Pavlidis N, et al. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26(Suppl 5):v133–v138.

Greco FA, Lennington WJ, Spigel DR, Hainsworth JD. Molecular profiling diagnosis in unknown primary cancer: accuracy and ability to complement standard pathology. J Natl Cancer Inst 2013; 105:782–790.

Gross-Goupil M, Massard C, Lesimple T, et al. Identifying the primary site using gene expression profiling in patients with carcinoma of an unknown primary (CUP): a feasibility study from the GEFCAPI. Onkologie 2012; 35:54–55.

Hainsworth JD, Rubin MS, Spigel DR, et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon Research Institute. J Clin Oncol 2013; 31:217–223.

Hayashi H, Kurata T, Takiguchi Y, et al. Randomized phase II trial comparing site-specific treatment based on gene expression profiling with carboplatin and paclitaxel for patients with cancer of unknown primary site. J Clin Oncol 2019; 37:570–579.

Le Tourneau C, Delord JP, Gonçalves A, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol 2015; 16:1324–1334.

Oien KA. Pathologic evaluation of unknown primary cancer. Semin Oncol 2009; 36:8–37.

Pentheroudakis G, Briasoulis E, Pavlidis N. Cancer of unknown primary site: missing primary or missing biology? Oncologist 2007; 12:418–425.

Pentheroudakis G, Lazaridis G, Pavlidis N. Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence. Breast Cancer Res Treat 2010; 119:1–11.

Pentheroudakis G, Pavlidis N, Fountzilas G, et al. Novel microRNA-based assay demonstrates 92% agreement with diagnosis based on clinicopathologic and management data in a cohort of patients with carcinoma of unknown primary. Mol Cancer 2013; 12:57.

Pentheroudakis G, Pavlidis N. Serous papillary peritoneal carcinoma: unknown primary tumour, ovarian cancer counterpart or a distinct entity? A systematic review. Crit Rev Oncol Hematol 2010; 75:27–42.

Varadhachary G. New strategies for carcinoma of unknown primary: The role of tissue-of-origin molecular profiling. Clin Cancer Res 2013; 19:4027–4033.

Appendix 1: Soft Tissue and Bone Tumours, WHO Classification of Tumours, 5th Edition, Volume 3

Soft tissue tumours

Adipocytic tumours

- Lipoma
- Lipomatosis
- Lipomatosis of nerve
- Lipoblastoma and lipoblastomatosis
- Angiolipoma
- Myolipoma of soft tissue
- Chondroid lipoma
- Spindle cell lipoma and pleomorphic lipoma
- Hibernoma
- Atypical spindle cell / pleomorphic lipomatous tumour
- Atypical lipomatous tumour / well-differentiated liposarcoma
- Dedifferentiated liposarcoma
- Myxoid liposarcoma
- Pleomorphic liposarcoma
- Myxoid pleomorphic liposarcoma

Fibroblastic and myofibroblastic tumours

- Nodular fasciitis
- Proliferative fasciitis and proliferative myositis
  - Myositis ossificans and fibro-osseous pseudotumour of digits
- Ischaemic fasciitis
- Elastofibroma
- Fibrous hamartoma of infancy
- Fibromatosis colli
- Juvenile hyaline fibromatosis
- Inclusion body fibromatosis
- Fibroma of tendon sheath
- Desmoplastic fibroblastoma
- Myofibroblastoma
- Calcifying aponeurotic fibroma
  - *EWSR1-SMAD3*-positive fibroblastic tumour (emerging)
- Angiomyofibroblastoma
- Cellular angiofibroma
- Angiofibroma of soft tissue
- Nuchal-type fibroma
- Acral fibromyxoma
- Gardner fibroma
- Palmar fibromatosis and plantar fibromatosis
- Desmoid fibromatosis
- Lipofibromatosis
- Giant cell fibroblastoma
- Dermatofibrosarcoma protuberans
- Solitary fibrous tumour
- Inflammatory myofibroblastic tumour
- Low-grade myofibroblastic sarcoma
- Superficial CD34-positive fibroblastic tumour
- Myxoinflammatory fibroblastic sarcoma
- Infantile fibrosarcoma
- Adult fibrosarcoma
- Myxofibrosarcoma
- Low-grade fibromyxoid sarcoma
- Sclerosing epithelioid fibrosarcoma

So-called fibrohistiocytic tumours

- Tenosynovial giant cell tumour
- Deep fibrous histiocytoma
- Plexiform fibrohistiocytic tumour
- Giant cell tumour of soft tissue

Vascular tumours

- Haemangiomas
  - Synovial haemangioma
  - Intramuscular angioma
  - Arteriovenous malformation / haemangioma
  - Venous haemangioma
- Anastomosing haemangioma
- Epithelioid haemangioma
- Lymphangioma and lymphangiomatosis
- Tufted angioma and kaposiform haemangioendothelioma
- Retiform haemangioendothelioma
- Papillary intralymphatic angioendothelioma
- Composite haemangioendothelioma
- Kaposi sarcoma
- Pseudomyogenic haemangioendothelioma
- Epithelioid haemangioendothelioma
- Angiosarcoma

Pericytic (perivascular) tumours

- Glomus tumour
- Myopericytoma, including myofibroma
- Angioleiomyoma

Smooth muscle tumours

- Leiomyoma
- EBV-associated smooth muscle tumour
- Inflammatory leiomyosarcoma
- Leiomyosarcoma

Skeletal muscle tumours

- Rhabdomyoma
- Embryonal rhabdomyosarcoma
- Alveolar rhabdomyosarcoma
- Pleomorphic rhabdomyosarcoma
- Spindle cell / sclerosing rhabdomyosarcoma
- Ectomesenchymoma

Gastrointestinal stromal tumour

Chondro-osseous tumours

- Soft tissue chondroma
- Extraskeletal osteosarcoma

Peripheral nerve sheath tumours

- Schwannoma
- Neurofibroma
- Perineurioma
- Granular cell tumour
- Dermal nerve sheath myxoma
- Solitary circumscribed neuroma
- Ectopic meningioma and meningothelial hamartoma
- Benign triton tumour / neuromuscular choristoma
- Hybrid nerve sheath tumour
- Malignant peripheral nerve sheath tumour
- Malignant melanotic nerve sheath tumour

Tumours of uncertain differentiation

- Intramuscular myxoma
- Juxta-articular myxoma
- Deep (aggressive) angiomyxoma
- Atypical fibroxanthoma
- Angiomatoid fibrous histiocytoma
- Ossifying fibromyxoid tumour
  - Myoepithelioma, myoepithelial carcinoma, and mixed tumour
- Pleomorphic hyalinising angiectatic tumour of soft parts
- Haemosiderotic fibrolipomatous tumour
- Phosphaturic mesenchymal tumour
- *NTRK*-rearranged spindle cell neoplasm (emerging)
- Synovial sarcoma
- Epithelioid sarcoma
- Alveolar soft part sarcoma
- Clear cell sarcoma of soft tissue
- Extraskeletal myxoid chondrosarcoma
- Desmoplastic small round cell tumour
- Extrarenal rhabdoid tumour
- PEComa
- Intimal sarcoma
- Undifferentiated sarcoma

Undifferentiated small round cell sarcomas of bone and soft tissue

Ewing sarcoma
Round cell sarcoma with *EWSR1*-non-*ETS* fusions
CIC-rearranged sarcoma
Sarcoma with *BCOR* genetic alterations

Bone tumours

Chondrogenic tumours

Subungual exostosis
Bizarre parosteal osteochondromatous proliferation
Periosteal chondroma
Enchondroma
Osteochondroma
Chondroblastoma
Chondromyxoid fibroma
Osteochondromyxoma
Synovial chondromatosis
Central atypical cartilaginous tumour / chondrosarcoma, grade 1
Secondary peripheral atypical cartilaginous tumour / chondrosarcoma, grade 1
Central chondrosarcoma, grades 2 and 3
Secondary peripheral chondrosarcoma, grades 2 and 3
Periosteal chondrosarcoma
Clear cell chondrosarcoma
Mesenchymal chondrosarcoma
Dedifferentiated chondrosarcoma

Osteogenic tumours

Osteoma
Osteoid osteoma
Osteoblastoma
Low-grade central osteosarcoma
Osteosarcoma
Parosteal osteosarcoma
Periosteal osteosarcoma
High-grade surface osteosarcoma
Secondary osteosarcoma

Fibrogenic tumours

Desmoplastic fibroma of bone
Fibrosarcoma of bone

Vascular tumours of bone

Haemangioma of bone
Epithelioid haemangioma of bone
Epithelioid haemangioendothelioma of bone
Angiosarcoma of bone

Osteoclastic giant cell-rich tumours

Aneurysmal bone cyst
Giant cell tumour of bone
Non-ossifying fibroma

Notochordal tumours

Benign notochordal cell tumour
Conventional chordoma
Dedifferentiated chordoma
Poorly differentiated chordoma

Other mesenchymal tumours of bone

Chondromesenchymal hamartoma of chest wall
Osteofibrous dysplasia
Adamantinoma of long bones
Simple bone cyst
Fibrocartilaginous mesenchymoma
Fibrous dysplasia
Lipoma and hibernoma of bone
Leiomyosarcoma of bone
Undifferentiated pleomorphic sarcoma
Bone metastases

Haematopoietic neoplasms of bone

Solitary plasmacytoma of bone
Primary non-Hodgkin lymphoma of bone
Langerhans cell histiocytosis
Erdheim-Chester disease
Rosai-Dorfman disease

Genetic tumour syndromes of soft tissue and bone

Enchondromatosis
Li-Fraumeni syndrome
McCune-Albright syndrome
Multiple osteochondromas
Neurofibromatosis type 1
Rothmund-Thomson syndrome
Werner syndrome

Abbreviations:
EBV, Epstein-Barr virus; *EWSR1*, Ewing sarcoma breakpoint region 1; *NTRK*, neurotrophic tyrosine receptor kinase; PEComa, perivascular epithelioid cell tumour; WHO, World Health Organization.

Appendix 2: EURACAN: The European Reference Network (ERN) for Adult Rare Solid Cancers

European Reference Network
for rare or low prevalence complex diseases

Network Adult Cancers (ERN EURACAN)

European Reference Networks (ERNs) are virtual networks. They aim to improve access to care for patients affected by rare diseases across the European Union. **EURACAN is the ERN** for rare adult solid cancers. It is organised into 10 'domains', corresponding to the RARECARE list of rare cancers based on the International Classification of Diseases for Oncology (ICD-O) and gathers European centres of expertise across 23 Member States. Below, is a list of EURACAN centres whose area of expertise includes the management of sarcomas.

Institutions with expertise on sarcoma within EURACAN (Status at July 2020)		
Belgium	Institut Jules Bordet, Brussels	www.bordet.be
	Leuven Cancer Institut, Leuven	www.uzleuven.be
Czech Republic	Motol University Hospital, Prague	www.fnmotol.cz
	Masaryk Memorial Cancer Institute, Brno	www.mou.cz
Denmark	Aarhus University Hospital, Aarhus	www.auh.dk
Finland	Turku University Hospital, Turku	www.vsshp.fi
France	Centre Léon Bérard, Lyon	www.centreleonberard.fr
	Institut Curie, Paris	www.curie.fr
	Institut Gustave Roussy, Villejuif	www.gustaveroussy.fr
Germany	University Medical Center Manheim, Manheim	www.umm.de
	University Hospital Essen, Essen	www.wtz-essen.de; www.sarkomtherapie.de
Italy	Bologna University Hospital - Policlinico S. Orsola-Malpighi, Bologna	www.aosp.bo.it
	Careggi University Hospital, Florence	www.aou-careggi.toscana.it
	Azienda Ospedaliero - Universitaria Cita della Salute e della Scienza di Torino, Turin	www.unito.it
	Oncology Referral Centre Aviano, Aviano	www.cro.sanita.fvg.it
	Candiolo Cancer Institute - FPO IRCCS, Candiolo	www.irccs.com
	Istituto Ortopedico Rizzoli, Bologna	www.ior.it
	Istituto Fisioterapici Ospitalieri, Rome	www.ifo.it
	Fondazione IRCCS Istituto Nazionale dei Tumori, Milan	www.istitutotumori.mi.it
	Azienda ULSS 2 Marca Trevigiana, Treviso	www.aulss2.veneto.it
Netherlands	Erasmus MC, Rotterdam	www.erasmusmc.nl
	Leiden University Medical Center, Leiden	www.lumc.nl
	Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam	www.avl.nl
	Radboud University Medical Center, Nijmegen	www.radboudumc.nl
	University Medical Center Groningen, Groningen	www.umcg.nl
Norway	Oslo University Hospital - The Norwegian Radium Hospital, Oslo	www.oslo-universitetssykehus.no
Poland	Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw	www.pib-nio.pl
Portugal	Centro Hospitalar do Porto, Porto	www.chporto.pt
	Instituto Portugues de Oncologia de Lisboa - Francisco Gentil E.P.E, Lisbon	www.ipolisboa.min-saude.pt
Slovenia	Institute of Oncology of Ljubljana, Ljubljana	www.onko-i.si
Spain	Complejo Hospital Universitario (HUV) Virgen del Rocio, Seville	www.hospitaluvrocio.es
	Hospital de la Santa Creu I Sant Pau, Barcelona	www.santpau.cat
	Integrated unit ICO Hospitalet - HUB, Barcelona	http://ico.gencat.cat/ca/l_institut/centres/
United Kingdom	Oxford University Hospitals NHS Foundation Trust, Oxford	www.ouh.nhs.uk/hospitals/churchill/
	Royal Marsden Hospital, London	www.royalmarsden.org
	University College London Hospitals NHS Foundation Trust, London	www.uclh.nhs.uk

For a current list of centres and for further information on ERN EURACAN visit: https://euracan.ern-net.eu/

This project is cofunded by the European Union

Image sources

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Chapter 1
Figure 1. WHO Classification of Tumours Editorial Board (Eds). Soft Tissue and Bone Tumours, WHO Classification of Tumours, 5th Edition, Volume 3. Lyon: IACR Press, 2020; **2-6, 8, 11, 13, 14, 15.** courtesy of AHG Cleven & JVMG Bovée; **7, 12.** courtesy of Fédération Nationale des Centres de Lutte Contre le Cancer; **9.** Demicco EG & Lazar AJ. Semin Oncol 2011;38 Suppl 3:S3-S18; **10.** courtesy of PCW Hogendoorn, published in: Bosman TD, et al. World Health Organization Classification of Tumours. Lyon: IARC Press, 2013.

Chapter 2
Figures 1-5, 7, 9-15. courtesy of J Martin-Broto; **6.** Brierley JD, et al. Union for International Cancer Control TNM Classification of Malignant Tumours, 8th Edition. Oxford, UK: John Wiley & Sons; **8.** Martín J, et al. J Clin Oncol 2005;23:6190-6198.

Chapter 3
Figure 1. Al-Absi E, et al. Ann Surg Oncol 2010;17:1367-1374; **2.** Le Cesne A, et al. Ann Oncol 2014;25:2425-2432; **3.** Issels RD, et al. JAMA Oncol 2018;4:483-492; **4.** O'Bryan RM, et al. Cancer 1973;32:1-8; **5, 6.** Judson I, et al. Lancet Oncol 2014;15:415-423; **7.** Sleijfer S, et al. Eur J Cancer 2010;46:72-83; **9.** Penel N, et al. Ann Oncol 2012;23:517-523; **10.** Demetri G, et al. J Clin Oncol 2016;34:786-793; **11.** courtesy of B Seddon; **12.** van der Graaf WT, et al. Lancet 2012;379:1879-1886; **13.** D'Incalci M, et al. Br J Cancer 2014;111:646-650; **14.** Schoffski P, et al. Lancet 2016;387:1629-1637; **15.** Berry V, et al. Cancer 2017;123:2294-2302.

Chapter 4
Figure 1. NCIN. Bone Sarcomas: incidence and survival rates in England; http://ncin.org.uk/view?rid=59; **2.** Pizzo PA & Poplack DG (Eds). Principles and Practice of Pediatric Oncology, 6th Edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2011;1015-1044; **3 (left), 4, 11 (inserts).** Ritter J, et al. Osteosarkome. In: Hiddemann W & Bartram CR (Eds). Die Onkologie, 2nd Edition. Heidelberg: Springer Medizin Verlag, 2010;1351-1371; **3 (right).** Bielack SS, et al. N Engl J Med 2004;350:1364-1365; **5 (left & right)**. Marina M, et al. Pediatric osteosarcoma. In: Carrol WL, Finlay JL (Eds). Cancer in Children and Adolescents. Sudbury, MA: Jones and Bartlett Publishers, 2010;383-394; **6.** Brierly JD, et al (Eds). UICC TNM Classification of Malignant Tumours, 8th Edition. Oxford: John Wiley and Sons, 2016; **7 (bottom right).** Andreou D, et al. Ann Oncol 2011;22:1228-1235; **9.** adapted from Casali PG, et al. Ann Oncol 2018;29(Suppl 4):iv79-iv95; **11 (main).** Bielack S, et al. Osteosarcoma: The COSS experience. In: Jaffe N, Bruland O & Bielack S (Eds). Pediatric and Adolescent Osteosarcoma. Cancer Treatment and Research, Vol 152. Boston, MA: Springer, 2009; **13.** courtesy of H. Jürgens & M. Paulussen from the (European Intergroup) Cooperative Ewing Sarcoma Studies; **14.** Grier HE, et al. N Engl J Med 2003;348:694-701; **15.** Stahl M, et al. Pediatr Blood Cancer 2011;57:549-553.

Chapter 5
Figures 1, 2. Ducimetière F, et al. PLoS One 2011;6:e20294; **6.** courtesy of I Judson; **7.** Borden EC, et al. Clin Cancer Res 2003;9:1941-1956; **8.** Stojadinovic A, et al. J Clin Oncol 2002;20:4344-4352.

Chapter 6
Figures 1-5, 7-9. courtesy of AHG Cleven & JVMG Bovée; **6.** Zhao X & Yue C. J Gastrointest Oncol 2012;3:189-208.

Chapter 7
Figure 2. Miettinen M, et al. Semin Diagn Pathol 2006;23:70-83; **5 (bottom).** courtesy of M Heinrich; **6 (top left).** courtesy of Maria Skłodowska-Curie National Research Institute of Oncology; **(top right).** Kalkmann J. Cancer Imaging 2012;12: 126-135; **(bottom)** Demetri GD, et al. J Natl Compr Canc Netw 2007;5(Suppl 2): S1-S32.

Chapter 8
Figures 1, 2, 4. courtesy of Centre Oscar Lambret; **6-11.** courtesy of Fondazione IRCCS Istituto Nazionale dei Tumori.

Chapter 9
Figures 1-3, 5, 8. courtesy of C Bergeron; **6.** Bisogno G, et al. Lancet Oncol 2018;19:1061-1071; **7.** Gaspar N, et al. Oncologie 2016;18:216-229.

Chapter 10
Figure 1. adapted from Ducimetière F, et al. PLoS One 2011;6:e20294; **2, 8, 9.** courtesy of Centre Léon Bérard; **3.** Rutkowski P, et al. J Clin Oncol 2010;28:1772-1779; **4.** Schöffski P, et al. Lancet Respir Med 2018;6:431-441; **5.** Tap WD, et al. Lancet 2019;394:478-487; **6.** Drilon A, et al. N Engl J Med 2018;378:731-739; **7.** Henon C, et al. Ann Oncol 2019;30:1401-1403.

Chapter 11
Figures 1, 3. Abellan F, et al. Sarcoma 2009;2009:827912; **2, 7, 8, 11, 13, 15.** courtesy of P Hohenberger; **5, 6.** courtesy of EURACAN; **9 (top left and right).** Morani AC, et al. AJR Am J Roentgenol 2019;212:W45-W54; **(bottom).** Hayes-Jordan A, et al. Semin Pediatr Surg 2016;25:299-304; **10.** Schreiber D, et al. Qual Life Res 2006;15:1439-1446; **12.** World Health Organization: International Classification of Functioning, Disability and Health (ICF). Geneva: WHO, 2001; **14.** Seinen JM, et al. Eur J Surg Oncol 2018;44:1398-1405.

Chapter 12
Figures 1, 8. Pavlidis N & Pentheroudakis G. Lancet 2012;379:1428-1435; **3.** Peinado H, et al. Nat Rev Cancer 2007:7:415-428; **4, 7, 9.** Fizazi K, et al. Ann Oncol 2015;26:Suppl 5:v133-v138; **5.** Pentheroudakis G, et al. Mol Cancer 2013;12:57; **6.** Varadhachary G. Clin Cancer Res 2013;19:4027-4033; **13.** Golfinopoulos V, et al. Cancer Treat Rev 2009;35:570-573; **14.** Hainsworth JD, et al. J Clin Oncol 2013;31:217-223; **15.** Le Tourneau C, et al. Lancet Oncol 2015;16:1324-1334.

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