Common Soft Tissue Sarcomas- a brief outline

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Introduction

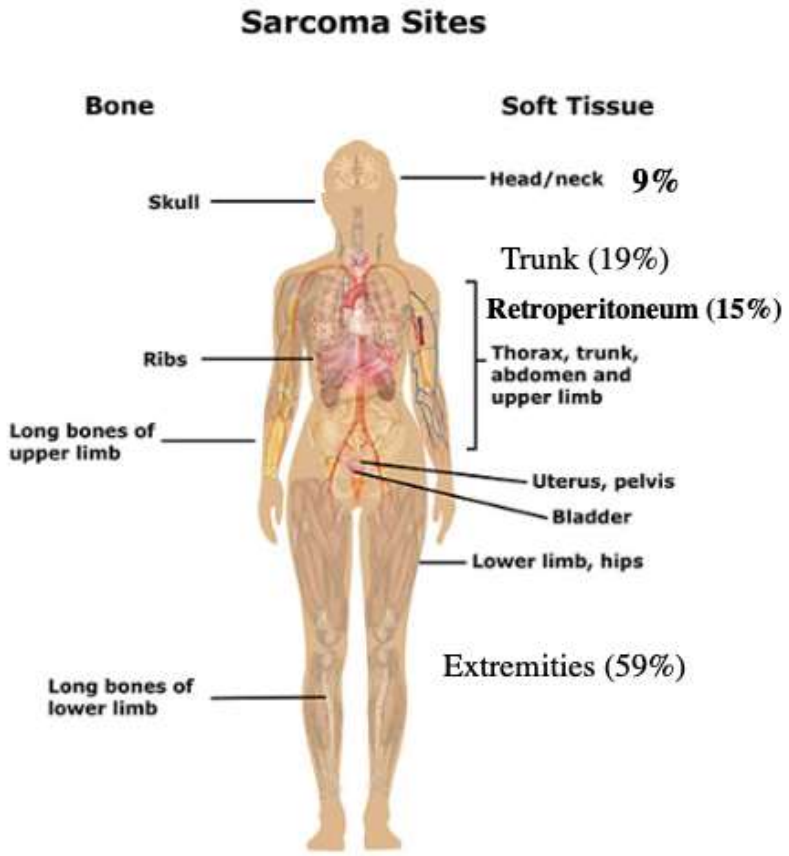
Soft-tissue sarcomas (STS) are a diverse group of rare malignant tumors which arise from mesenchymal tissue.

- Approx .11,000 new cases of STS are diagnosed each year in US, accounting for <1% of all cancers
- Can occur over all age ranges, median age at diagnosis is 56–65 years, peaking in 8th decade

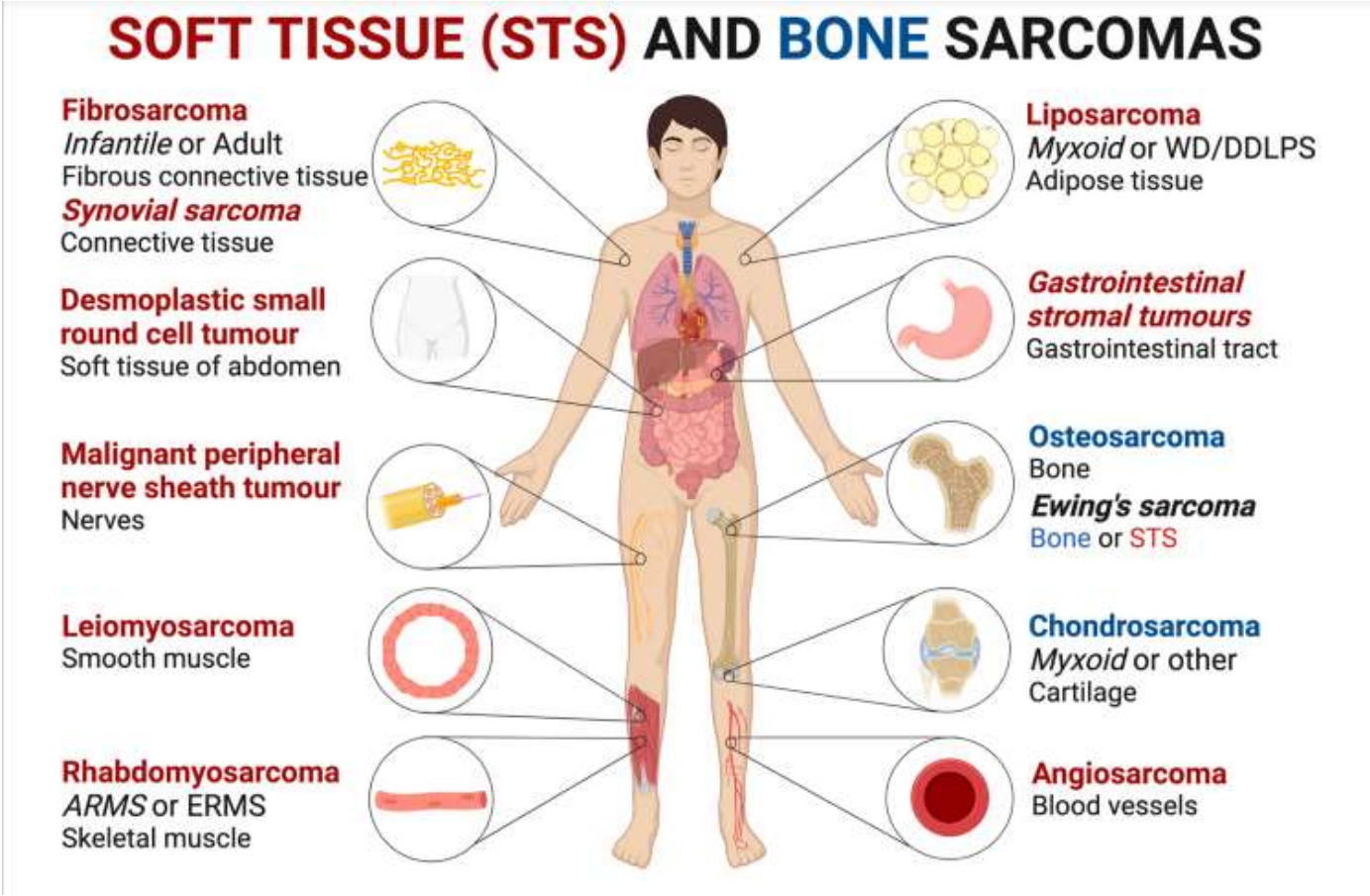
❖Account for <1% of adult malignancies

❖ More common in children- represent up to 15% of paediatric malignancies

- Can arise anywhere in body-extremities account for 60% of cases



Soft Tissue Sarcomas



- Adipocytic
- Chondro-osseous
- Fibroblastic or myofibrobla
- Fibrohistiocytic
- Nerve sheath
- Pericystic
- Skeletal muscle
- Smooth muscle
- Uncertain differentiation
- Vascular

- Extra skeletal tissues such as muscles, fat, blood vessels, nerves, & synovial tissues
- Typically, high grade &, if diagnosed at an advanced stage, survival rates are poor

Biologic behaviour of a tumor

Indicated by tumor grade -.

- Well-differentiated (low grade)
- Moderately differentiated (intermediate grade)
- Poorly differentiated (high grade)

Stratification is based on various histopathologic features—

- Degree of cytologic atypia
- Mitotic rate
- Presence or absence of necrosis

Histological Types of Tumors The following histological types are included, with ICD-O morphology codes:

Alveolar soft part sarcoma	9581/3
Epithelioid sarcoma	8804/3
Extraskeletal chondrosarcoma	9220/3
Extraskeletal osteosarcoma	9180/3
Extraskeletal Ewing sarcoma	9260/3
Primitive neuroectodermal tumour (PNET)	9473/3
Fibrosarcoma	8810/3
Leiomyosarcoma	8890/3
Liposarcoma	8850/3
Malignant fibrous histiocytoma	8830/3
Malignant haemangiopericytoma	9150/3
Malignant mesenchymoma	8990/3
Malignant peripheral nerve sheath tumour	9540/3
Rhabdomyosarcoma	8900/3
Synovial sarcoma	9040/3
Sarcoma, not otherwise specified (NOS)	8800/3

The following histological types are not included:

Kaposi Sarcoma

Dermatofibrosarcoma (protuberans)

Fibromatosis (desmoid tumour)

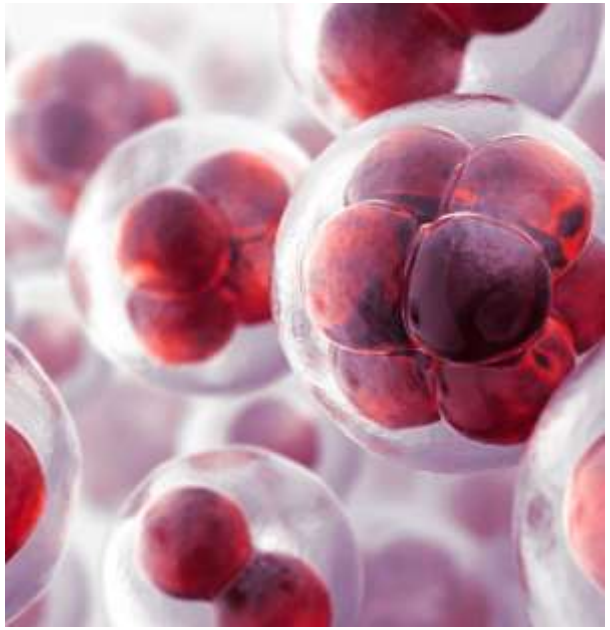
Sarcoma arising from the dura mater, brain, hollow viscera, or parenchymatous organs (with the exception of breast sarcomas).

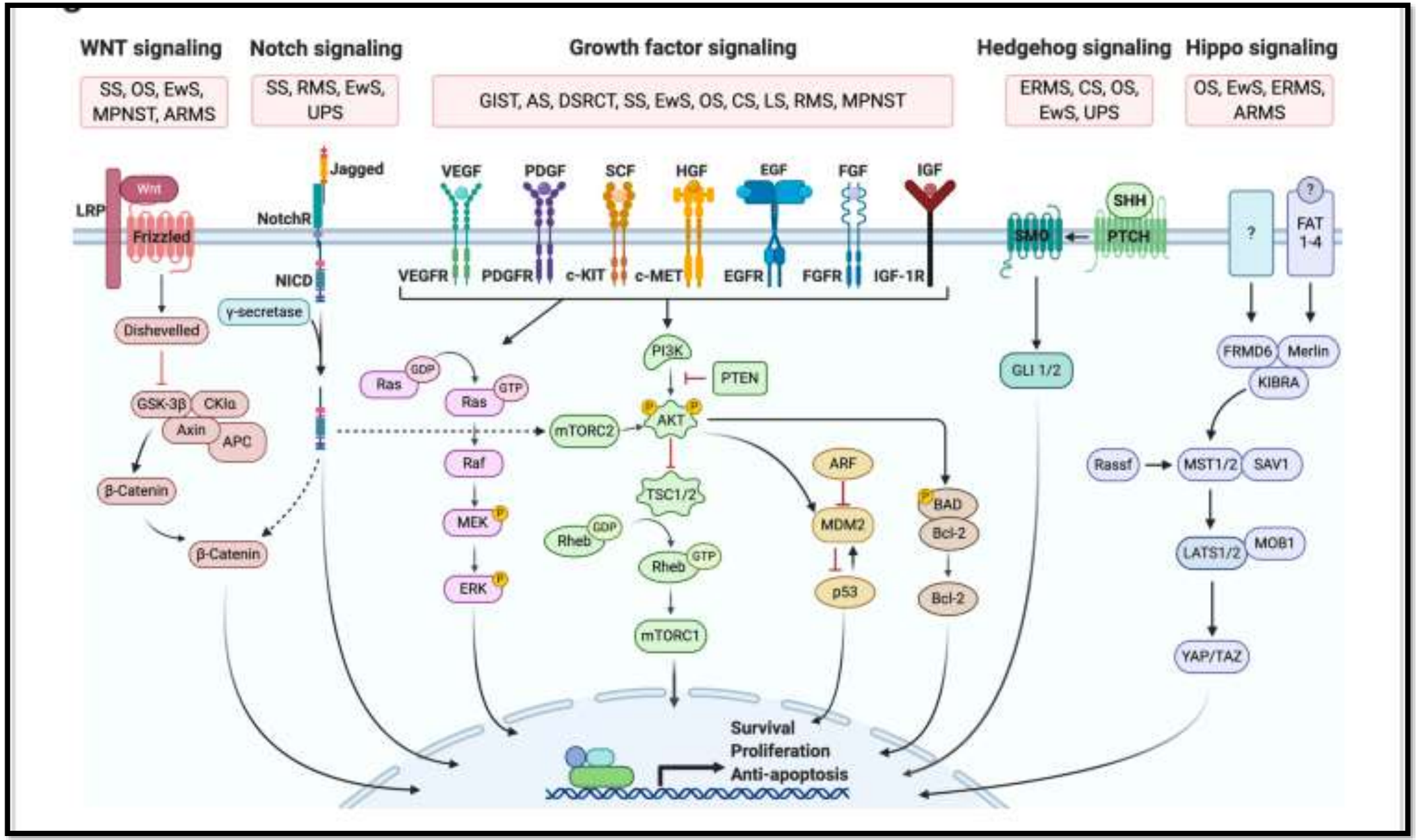
Angiosarcoma, an aggressive sarcoma, is excluded because its natural history is not consistent with the classification.

Gastrointestinal stromal tumours are separately classified in the Digestive System Tumours section..

Etiology

- Etiology of most cases remains unknown
- Environmental factors/ genetic predispositions which have been associated.
- Hereditary syndromes such as Li Fraumeni syndrome, familial retinoblastoma harbour mutations affecting tumor suppressor genes - TP53 tumor suppressor gene, RB1, or CHK2
- Exposure to chemical carcinogens-- phenoxy-acetic acid in herbicides
- Radiation induced DNA damage or chromosomal instability as a result of radiation-induced alterations in telomere functions




WNT signaling
SS, OS, EwS, MPNST, ARMS
Notch signaling
SS, RMS, EwS, UPS
Growth factor signaling
GIST, AS, DSRCT, SS, EwS, OS, CS, LS, RMS, MPNST
Hedgehog signaling
ERMS, CS, OS, EwS, UPS
Hippo signaling
OS, EwS, ERMS, ARMS
Wnt
LRP
Frizzled
Dishevelled
GSK-3β
CKIα
Axin
APC
β-Catenin
β-Catenin
Jagged
NotchR
NICD
γ-secretase
VEGF
PDGF
SCF
HGF
EGF
FGF
IGF
VEGFR
PDGFR
c-KIT
c-MET
EGFR
FGFR
IGF-1R
Ras
GDP
Ras
GTP
Raf
MEK
P
ERK
P
PI3K
PTEN
mTORC2
AKT
P
P
TSC1/2
Rheb
GDP
Rheb
GTP
mTORC1
ARF
MDM2
p53
BAD
Bcl-2
Bcl-2
SHH
PTCH
SMO
GLI 1/2
?
FAT 1-4
?
FRMD6
Merlin
KIBRA
Rassf
MST1/2
SAV1
LATS1/2
MOB1
YAP/TAZ
Survival
Proliferation
Anti-apoptosis

Clinical presentation

Vary depending on tumor site, subtype & grade

- Extremities and superficial trunk (60%): Painless primary soft tissue mass
- Retroperitoneum(15%) :Abdominal mass, Pain, grows to large size before symptoms.
- Viscera (15%) :Anaemia, melena, abdominal pain, wt loss, painless P/V bleed
- H&N (10%): Smaller, Mechanical problems: compression or invasion of adjacent critical structures.

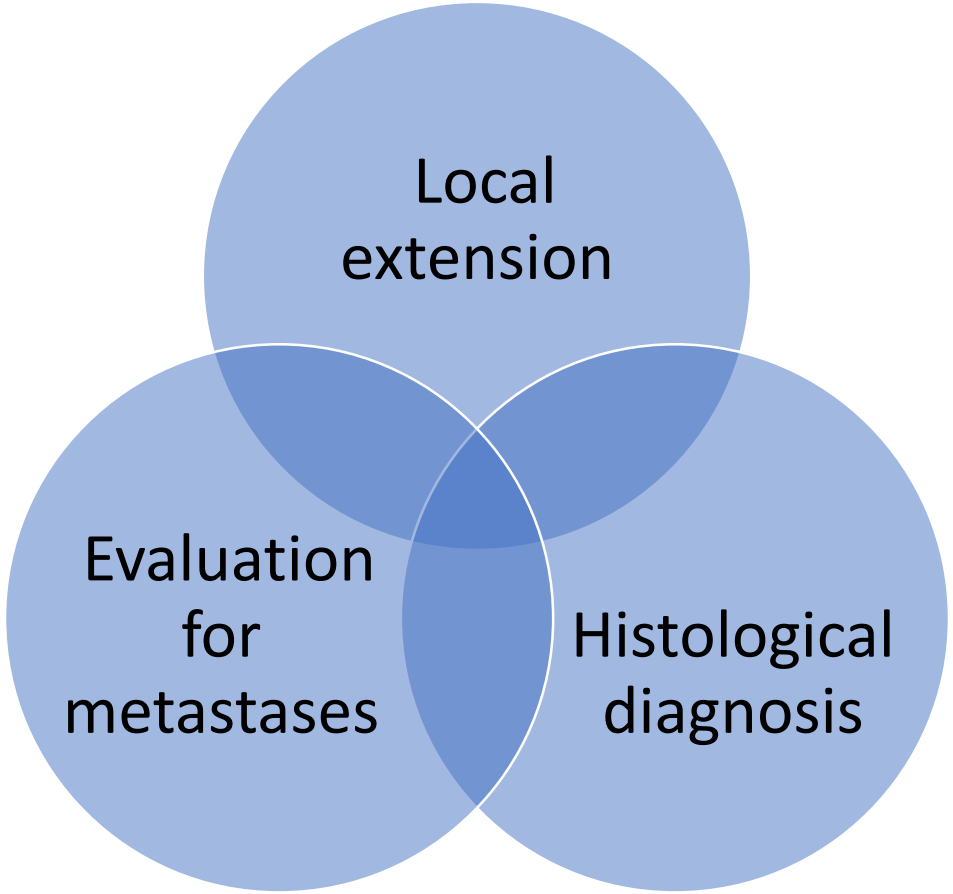
Anatomic locations:

- Liposarcoma is more common in lower extremity
- Synovial sarcoma, epithelioid sarcoma & fibrosarcoma are encountered more often in upper extremity

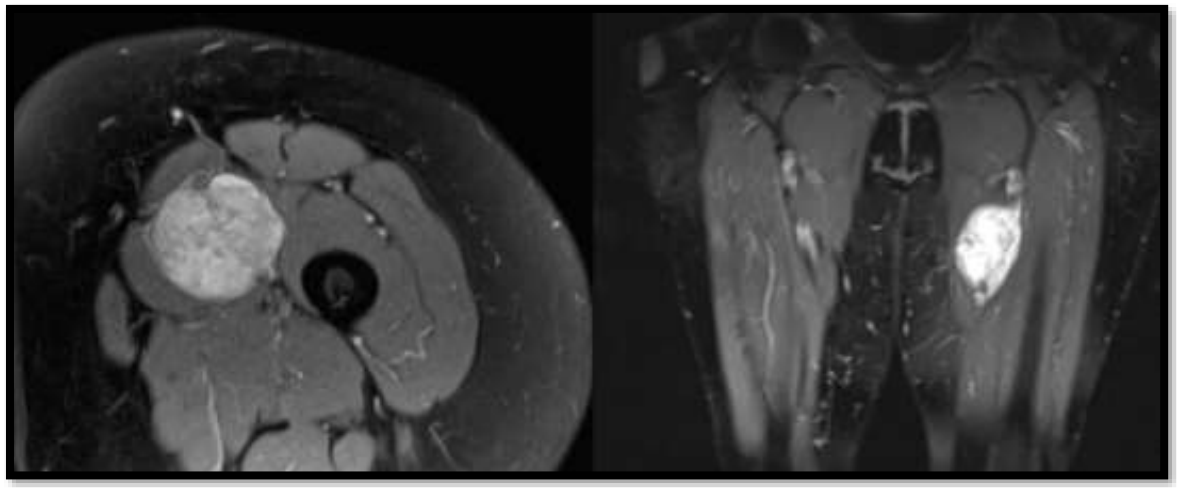
Rarely (<5%) STS metastasize to lymph nodes
SS, RMS, epithelioid sarcoma, clear cell sarcoma & angiosarcoma have a higher propensity for lymphatic spread

Diagnosis of a soft-tissue sarcoma

Three factors which need to be evaluated as part of the investigation



Assessment of local extension

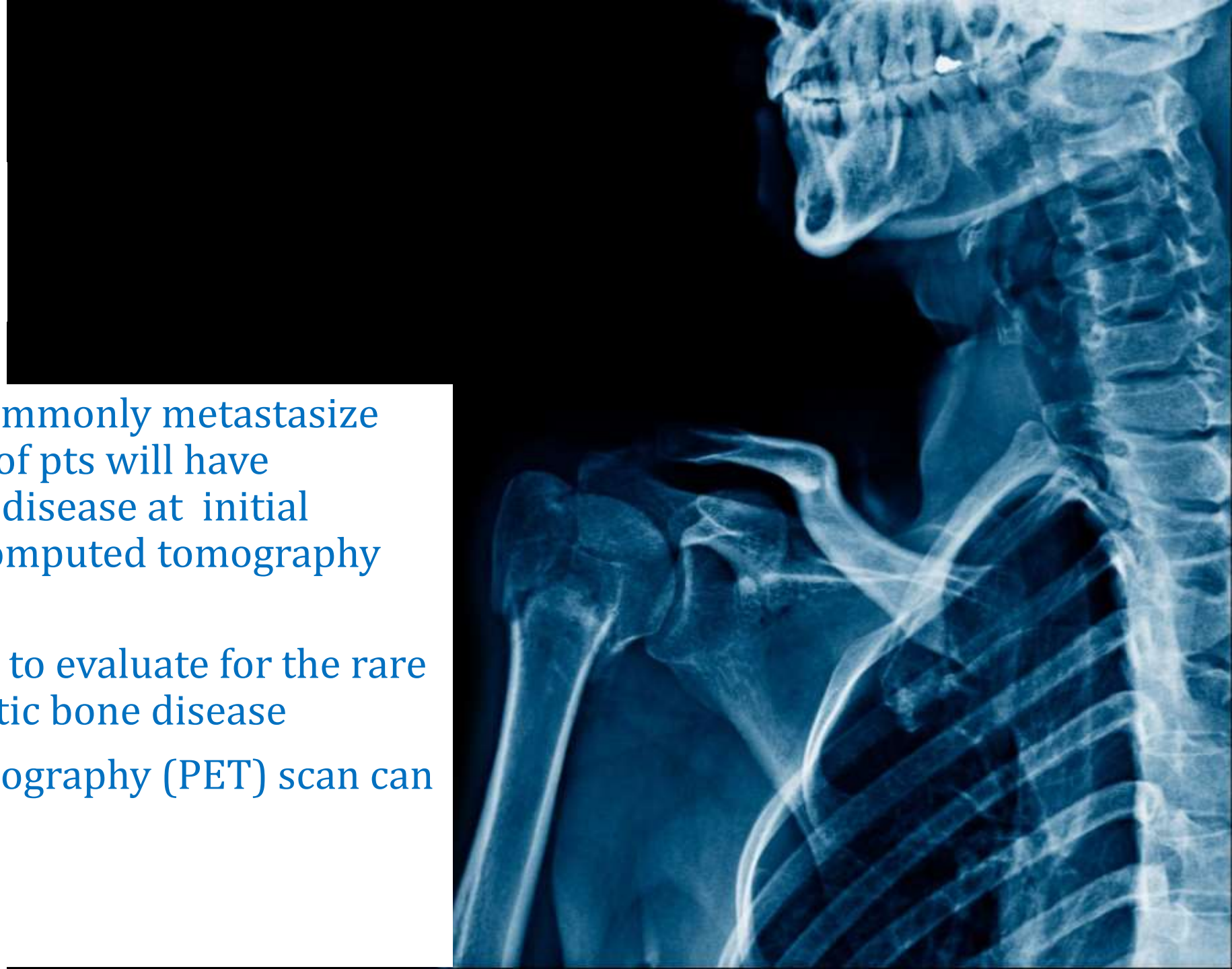


MRI demonstrating a heterogeneous mass with predominantly low signal intensity on T1-weighted images, high signal intensity on T2-weighted images & post-gadolinium contrast enhancement is very characteristic of a STS .

- MRI - “gold standard” for defining local extent of tumor & surrounding edema .
- Reconstruct a 3D model from cross-sectional images & provides anatomic information related to tumor & its proximity to critical neurovascular structures & bone.
- Addition of contrast differentiates between cystic areas representing hemorrhage or necrosis based on peripheral rim enhancement & solid viable areas of tumor.
- Spread along tissue planes, compressing surrounding tissues & typically do not violate anatomic barriers such as fascia or bone.
- Rarely Radiographs may be required

Investigations

- Extremity STS most commonly metastasize hematogenous &10% of pts will have detectable pulmonary disease at initial presentation - chest computed tomography (CT)-scan
- Bone scan can be used to evaluate for the rare occurrence of metastatic bone disease
- Positron emission tomography (PET) scan can be helpful in staging



Staging of STSs

- Two systems are available -
  - ❖ Musculoskeletal Tumour Society (MSTS) staging system
  - ❖ GTNM (grading, tumor, nodes, metastases) staging system

Both systems utilize the local extent of the tumor (size and depth for AJCC vs. compartment status for MSTS), histologic grade, and the presence or absence of metastases

TNM CLINICAL CLASSIFICATION

T- Primary Tumour: TX- Primary tumour cannot be assessed, T0- No evidence of primary tumour, T1- Tumour 5cm or less in greatest dimension, T1a- Superficial tumour*, T1b Deep Tumour*,T2-Tumour more than 5cm in greatest dimension, T2a- Superficial tumour*, T2b Deep tumour*

N- Regional Lymph Nodes:

NX - Regional lymph nodes cannot be assessed, N0 - No regional lymph node metastasis, N1 Regional lymph node metastasis

M- Distant Metastasis: M0- No distant metastasis, M1-Distant metastasis,

G- Histopathological Grading

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

TNM Two-grade System	Three-grade System	Four-grade System
Low grade	Grade 1	Grade 1
	Grade 2	Grade 2
High grade	Grade 2	Grade 3
	Grade 3	Grade 4

Summary - Soft Tissue Sarcoma

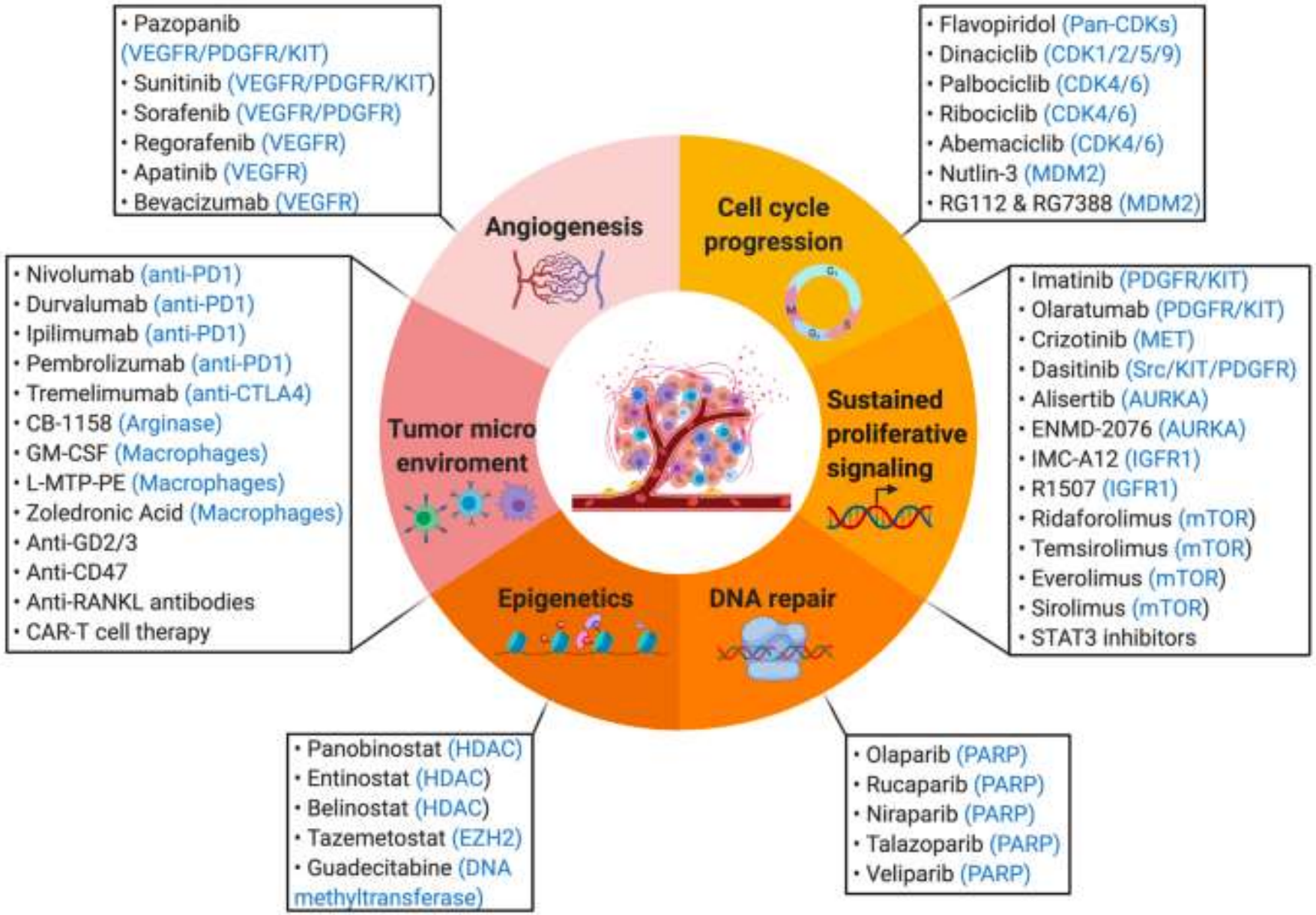
T1	< 5cm
T1a	Superficial
T1b	Deep
T2	> 5cm
T2a	Superficial
T2b	Deep
N1	Regional lymph nodes
	Low grade
	High grade

*Physical examination, diagnostic radiology and biopsy provide the AJCC criteria input data needed to stage STS. *The AJCC system uses 4 histologic grades whilst the recommended UK system (FNCLCC) uses 3. The matching grades are G1 = low grade, G2 = intermediate grade and G3 and G4 = high grade.Reproduced from Sobin L, Gospodarowicz M, Wittekind C (Eds.). TNM classification of malignant tumors (seventh edition). Wiley-Blackwell, Delhi press, Delhi 2009; 157-61.*

Treatment

- Treatment involves a **multidisciplinary team decision** - surgical resection with or without adjuvant radiation for successful limb salvage.
- **Goals of treatment** --provide the patient with a functional extremity without local tumor relapse
- Localized extremity STS are best treated surgically with/ without radiation therapy.
- Chemotherapy reserved for management of patients with metastatic disease
- Chemotherapy is also utilised in attempting to facilitate local tumor down-staging for very extensive lesions which might not otherwise be amenable to limb sparing surgery.

Current Targeted Therapies for Sarcomas



Common STS

Malignant peripheral Nerve Sheath Tumours

Mutations	*NF1*	87.5
	CDKN2A	75
	TP53	40.3
	EED, SUZ12	Common

- ❖Malignant form of benign schwannoma
- ❖Sporadic = as part of NF1
- ❖Age: 20 – 50 yrs
- Often painless but aggressive
- 20 % local recurrence

Prognostic factors

- Tumor size at presentation
- Tumor grade

Treatment : margin negative resection

Adjuvant RT : decreased local recurrence in extremity & superficial trunk lesions

Angiosarcoma

Origin – Endothelial lining of blood vessels

Sites –

- Trunk
- H & N (Scalp)
- Viscera

- Maximum - sporadic
- 40% are radiation associated
- Other association - lymphedema
- 7th – 8th decade
- High regional node involvement

Mutations	*TP53, PTPRB*	66, 26
Overexpression	*VEGF*	80

Angiosarcoma

Metastasis

- 20% at presentation
- Commonest – lung; breast angiosarcoma - liver

Histology

- Extremely well differentiated to very poorly differentiated
- IHC – CD31 & FLI-1

Poor prognostic factors

- Tumor > 5 cm
- Epitheloid component on histology

Angiosarcoma-Treatment

Often locally advanced & unresectable at presentation

- Margin negative resection whenever possible
- Poor outcome – 5 yr disease free survival is 53%
- Distant failure more common than local failure
- Chemo & radio-responsive

Unresectable/ metastatic disease

- Paclitaxel + doxorubicin f/by RT(except when RT is the etiological factor)

Future

- TKIs; Angiogenesis inhibitors + cytotoxic agents

Dermatofibrosarcoma Pertubrans

- Uncommon
- Equal incidence in males and females
- African Americans afflicted more than whites
- 4th – 7th decade
- Translocation t(17;22)(q22;q13)
- PDGFB overexpression
- Trunk = upper extremity = lower extremity > H & N
- Reddish/ brown, firm, indurated nodules
- Usually painless – can be large at presentation
- May be mistaken for keloid/ hypertrophic scar

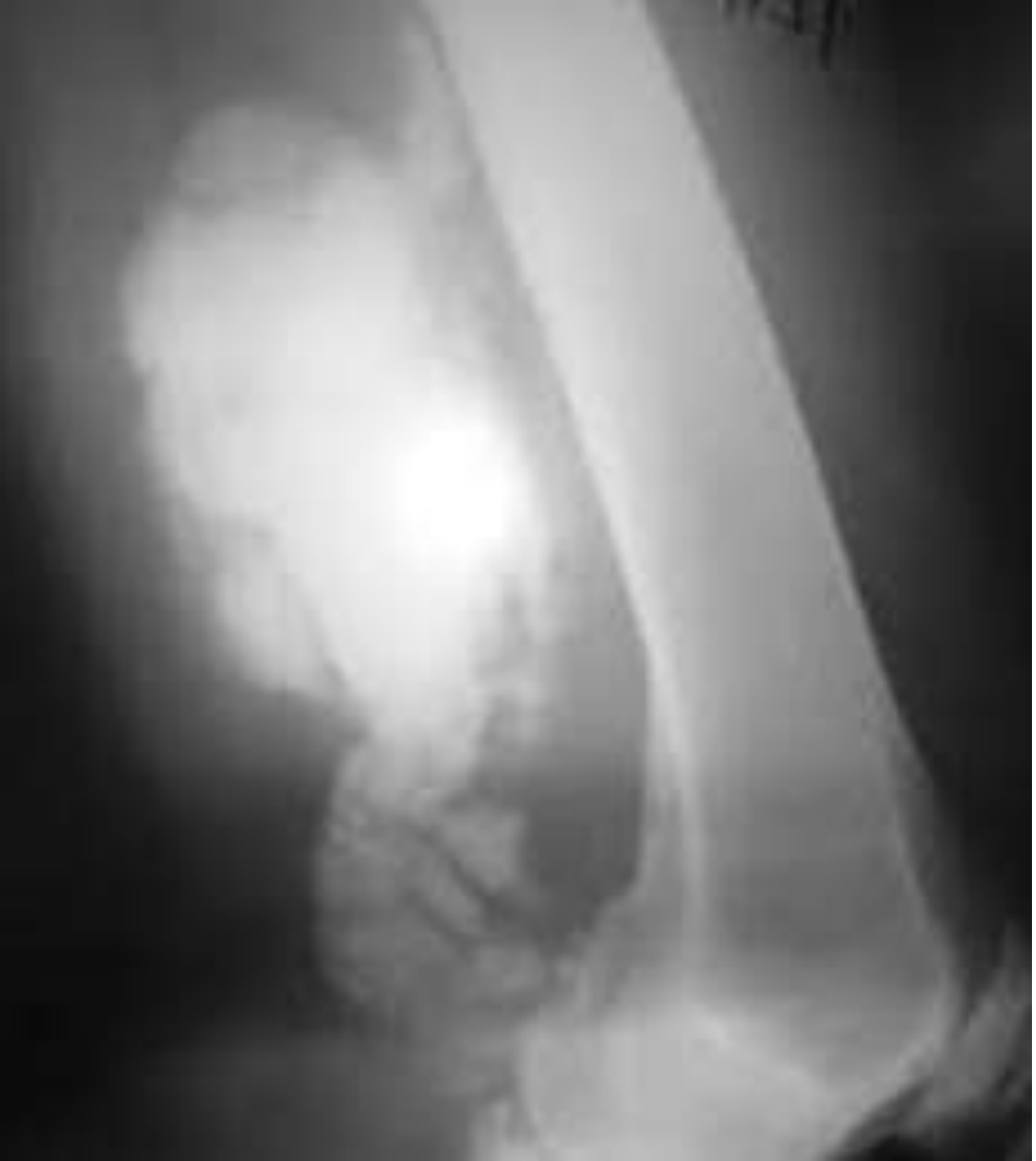
Dermatofibrosarcoma Pertubrans

Treatment: margin negative resection

- PDGFB overexpression: Neoadjuvant Imatinib may be useful
- Recurrence: re-resection
- 5 yr survival – 92%

Metastasis

- Rare
- Implies degeneration to fibrosarcoma



Extraosseous Osteosarcoma

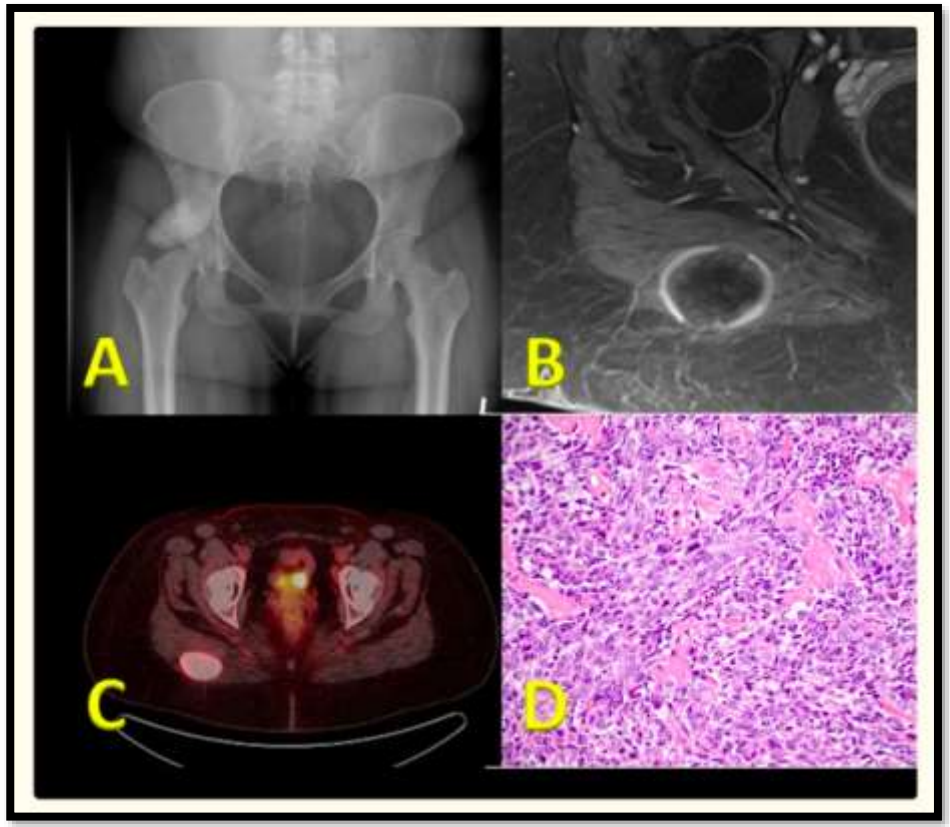
- High-grade tumors-comprising nearly 1-1.2% of all osteosarcomas.
- Most commonly affected sites- extremities, thorax & abdomen

Variants:

- Osteoblastic
- Chondroblastic
- Fibroblastic

Prognosis is poor, with 5- year survival ranging from 12 to 25%

Extraosseous Osteosarcoma



(a) Plain radiographic image demonstrating an ossific mass in the region of the right hip.
(b) Axial T1 CEMRI demonstrating mass arising from right gluteal musculature with a thin peripheral rim of enhancement.
(c) PETCT demonstrating mass with very high SUV

- **Histopathologic diagnosis** -presence of osteoid a homogeneous, pink, structureless extracellular material produced by tumor cells.
- Extraosseous osteosarcomas - pleiotropic, containing small & round, clear, multinucleated, spindled, epithelioid, plasmacytoid, and/or fusiform cells

Extraosseous Osteosarcoma -**Etiology**

Most cases are sporadic , Environmental & genetic factors have been associated with osteosarcoma -

- RB1 & TP53 are two well-characterized genes implicated
- Up to 60% of high-grade EOS show TP53 mutations, compared with 1% of low grade osteosarcomas
- RB1, located at chromosome 13q14 encodes a 110-kDa protein that negatively regulates progression of cell cycle from G0/G1 into S phase

Extraosseous Osteosarcoma- **Treatment strategies**

- Best treatment strategy is surgical resection.
- Surgery combined with pre- and postoperative chemotherapy.
- With this multidisciplinary approach, long-term survival has increased to 70%.
- Patients who have recurrent disease or metastatic lesions (typically in lungs) at diagnosis have a lower survival rate of 20%

Liposarcoma (LPS)

- In adults, LPS is one of most frequent STS subtypes
- Arise from primitive mesenchymal cells
- Account for 14 -18% of all soft-tissue sarcomas
- Commonly arising in the deep soft tissues – thigh/ retroperitoneum, represents the most common variant accounting for ~10% of all adult soft tissue sarcomas
- Prognosis depends on histologic features, site, and size

Liposarcoma Subtypes

Morphological diversity correlated with their biologic behavior

Liposarcoma Subtype	Well-Differentiated	Dedifferentiated	Myxoid	Pleomorphic
Estimated proportion of liposarcoma (%)	40-50	15-20	20-30	5-10
Age of peak incidence (years)	50-60	50-60	30-50; can occur in childhood/ adolescence	≥ 50
Typical morphology	Proliferation of pleomorphic mature adipocytes, variable numbers of lipoblasts present	High-grade pleomorphic sarcoma on well-differentiated background	Round/oval mesenchymal cells plus signet ring lipoblasts within myxoid stroma	Variable number of pleomorphic lipoblasts on background of high-grade pleomorphic sarcoma
Typical sites of origin	Extremities Retroperitoneum Paratesticular (rare) Mediastinum (rare)	Retroperitoneum Extremities Paratesticular Mediastinum Head and neck	Thigh; other proximal extremities	Lower limb Upper limb
Patterns of recurrence	Local recurrence (retroperitoneum > extremities) Little to no metastatic potential	Local recurrence in approximately 40% Metastasis (lung) in approximtely 20%-30%	Local and/or metastatic (bone, soft tissue, serosa) in up to 40%	Local recurrence in 30%-50% Metastasis (lung) in 30%-50%
Response to available therapies	Poor	Poor	Typically sensitive to radiotherapy and chemotherapy	Variable chemosensitivity
Genomics	12q13-15 amplification	12q13-15 amplification plus other chromosomal abnormalities	t(12;16) with FUS-DDIT3 fusion	Complex, with multiple chromosomal abnormalities and higher mutation rate

Liposarcoma (LPS)-cytogenetics

WD/DDLPS

- Supernumerary ring and/or giant rod chromosomes with amplified segments from 12q13-15 region , harboring several oncogenes including HMGA2, MDM2, CDK4, HMGA2, TSPAN31, OS1, OS9, CHOP & GLI1
- In DDLPS-amplification involving c-Jun & apoptosis signaling kinase 1 (ASK1), located on 1p32 & 6q23 resp.

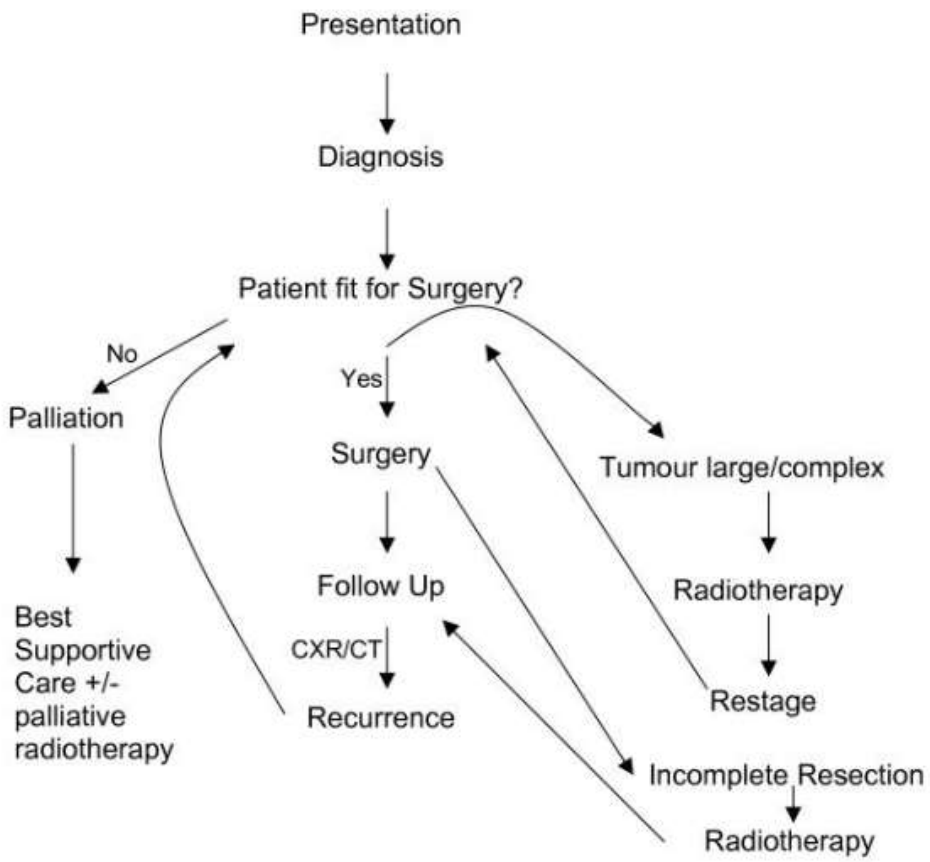
MLPS

Translocation, most commonly t(12;16)(q13;p11), fusing FUS (transcriptional regulatory domains interacting with the RNA polymeraseII complex) with DDIT3 (a DNA-binding leucine zipper transcription factor that plays a role in cell cycle control and adipocytic differentiation)

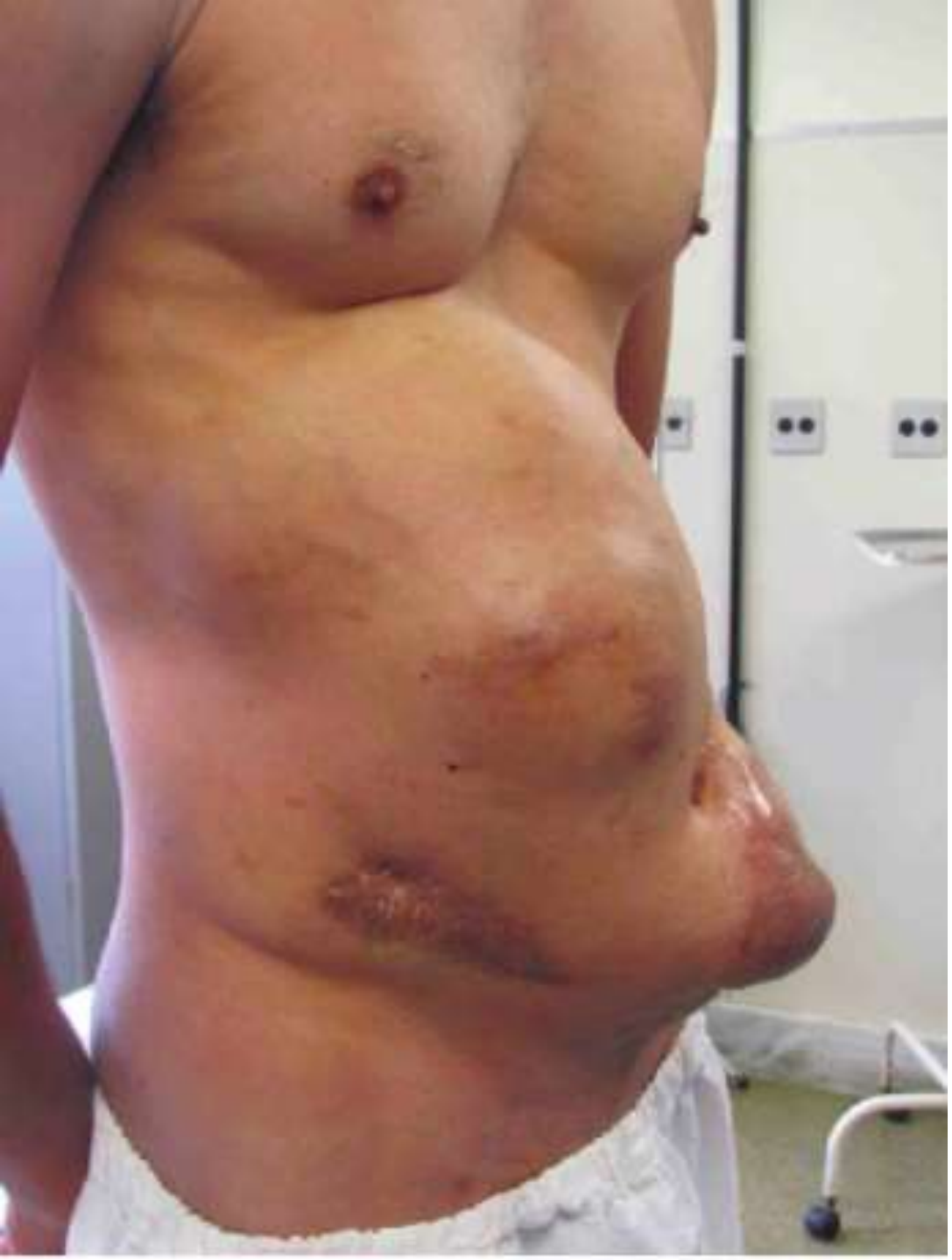
PLPS

Gains: 1p, 1q21-q32, 2q, 3p,3q, 5p12-p15, 5q, 6p21, 7p, 7q22,
Losses 1q, 2q, 3p, 4q, 10q, 11q, 12p13, 13q14, 13q21-qter, 13q23-24

Liposarcoma Treatment



Myxoid liposarcoma



Desmoid Tumours

- Aggressive fibromatosis
- Majority Sporadic (75-85%)
- Age: 30-40 yrs
- Recent pregnancy& Antecedent trauma
- Others – related to FAP
- Seen in 20% pts with FAP
- Preceded by colonic polyposis
- Occur at prior colectomy scar

Detailed family history to r/o unappreciated FAP

Consider screening colonoscopy

Desmoid Tumours

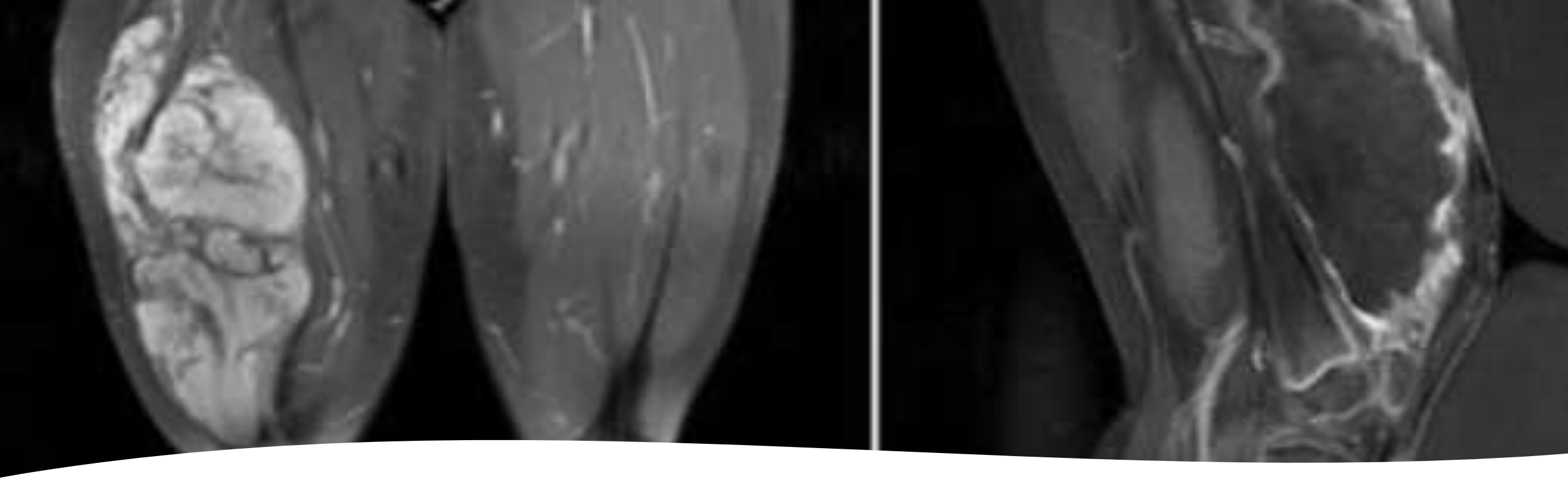
- Related to WNT signaling pathway
- Sporadic cases:
- CTNNB1 mutation
- Stabilized form of β-catenin
- Accumulates & transported to nucleus
- Activated transcription factors proliferative effects

FAP cases:

APC mutations

β-catenin stabilization

Specific APC codon mutations confer higher risk of desmoid



Desmoid Tumours

- Common sites: Extremity, intra-peritoneal, extra-peritoneal, abdominal wall & chest wall
- Asymptomatic firm mass
- Painful mass
- Bowel obstruction/ ischemia

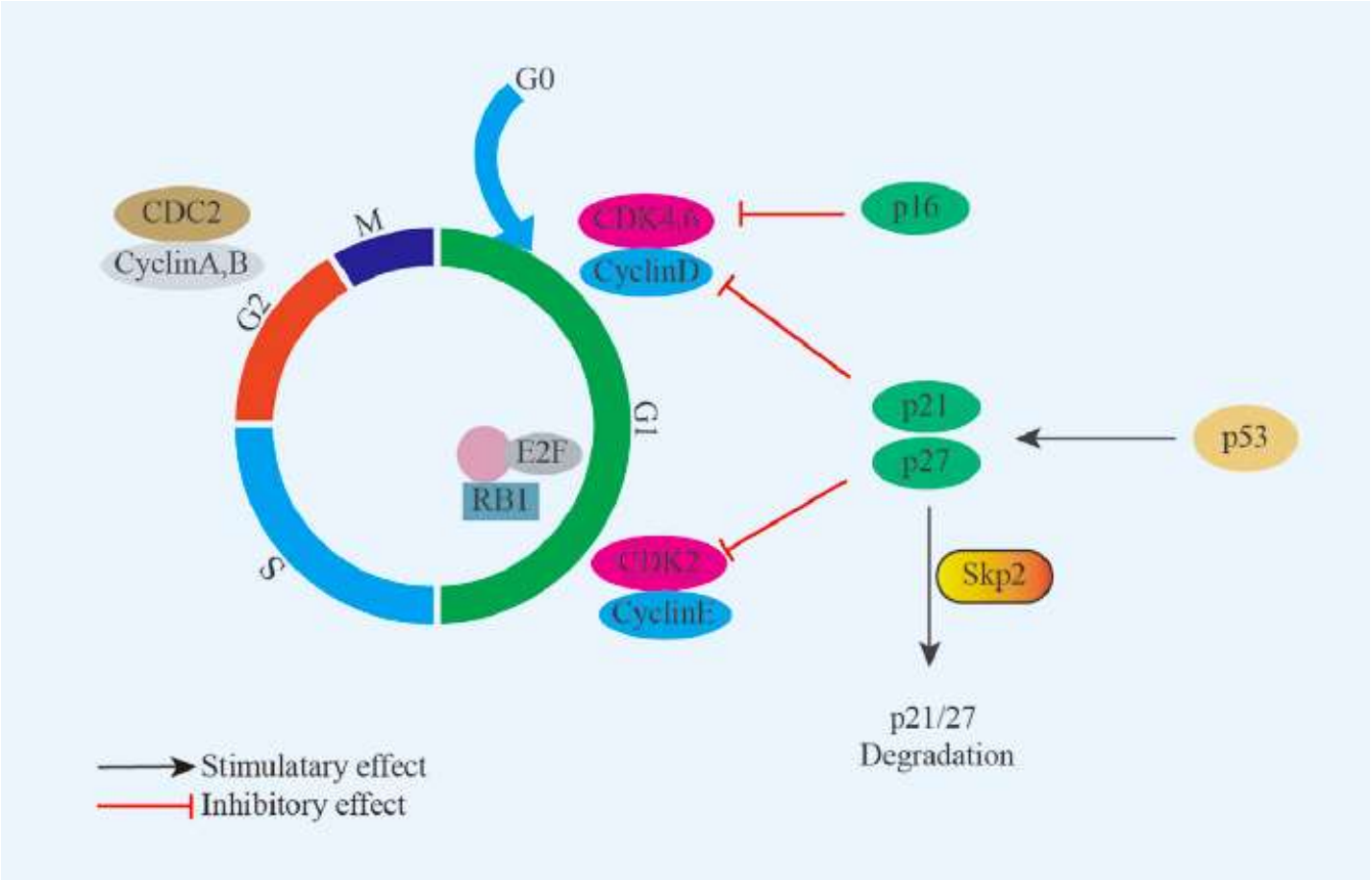
Desmoid Tumours-Treatment

- Margin negative resection
- Difficult – large/ infiltrating crucial anatomical structures
- FAP associated desmoids – high recurrence rates
- Active surveillance rather than reflexive resection
- Show very little growth after presentation
- Resection may warrant significant functional deficits

Undifferentiated Pleomorphic Sarcoma (UPS)

- Tumors previously classified as malignant fibrous histiocytoma (MFH)
- UPS commonly affects adults aged 50 -70 with a higher propensity to affect men (1:2 female: male ratio)
- Originate either from a primitive pluripotential mesenchymal cell that exhibits a range of differentiation or from high-grade neoplasms of poor differentiation

Pathogenesis

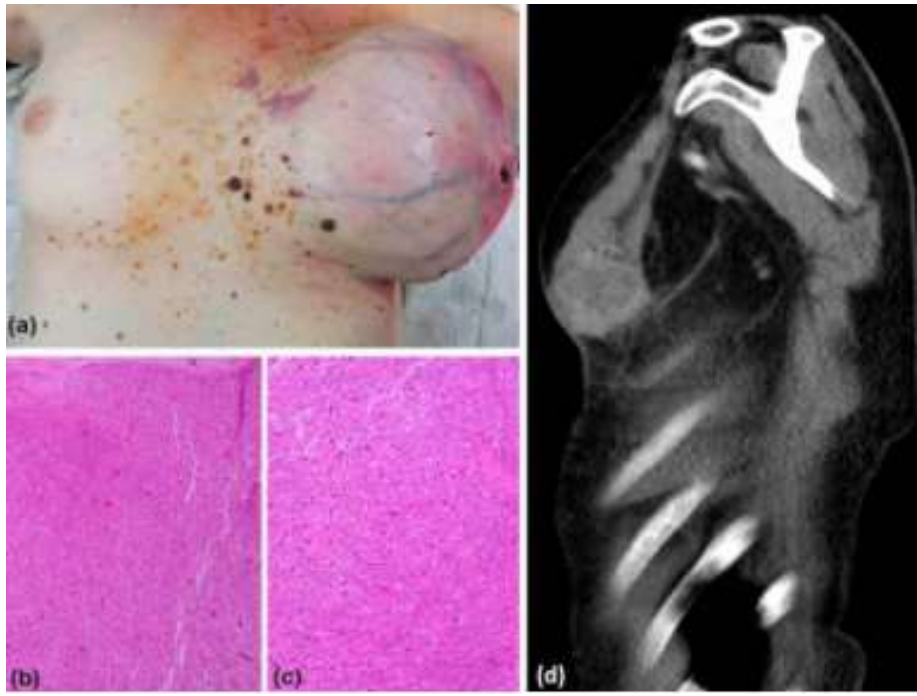


- Specific genetic alterations associated with UPS are largely unknown.
- C-MYC amplifications, gains involving regions such as 8q21.3-qter and 9q32-qter
- Losses involving multiple regions such as 13q21-q22, and 18q12-q22-reflecting the highly aggressive nature of this malignancy

TP53 deficiency renders UPS/MFS cells dependent on Skp2 which survives sarcoma cells by degrading p21 and p27

Undifferentiated Pleomorphic Sarcoma (UPS)

- UPS can arise anywhere in the body. However, the most frequent locations are in the deep soft tissue of the extremities and the retroperitoneum.
- Extremities (lower >> upper)
- Head & neck
- Previous RT site
- Site of chronic ulceration (rare)
- Elderly patients (peak @ 60-70 yrs)
- Solitary, painless, soft – firm, skin colored, deep seated mass



Undifferentiated Pleomorphic Sarcoma (UPS)

Surgery mainstay of treatment

Wide or radical excision including the infiltrative “tail” is required; otherwise, these sarcomas are prone to local recurrence and even metastasis.

Wide excision followed by radiotherapy is typically recommended for deep lesions

- Recurrence: 30-35%
- Mets: in 50% at presentation – contraindication for surgical resection
- 5 yr disease specific survival – 65%

Leiomyosarcoma (LMS)

- Arising from smooth muscles frequently affecting retroperitoneum, uterus, skin, superficial soft tissues & deep compartments of the extremities.
- Account for 10-15% of all soft tissue sarcomas
- Categorized into 3 major groups

➢Somatic soft tissue LMS

➢Cutaneous LMS

➢ Vascular LMS

- LMS are refractory tumors showing treatment resistance. Therefore, the prognosis is poor with low survival rates compared to other STSs .

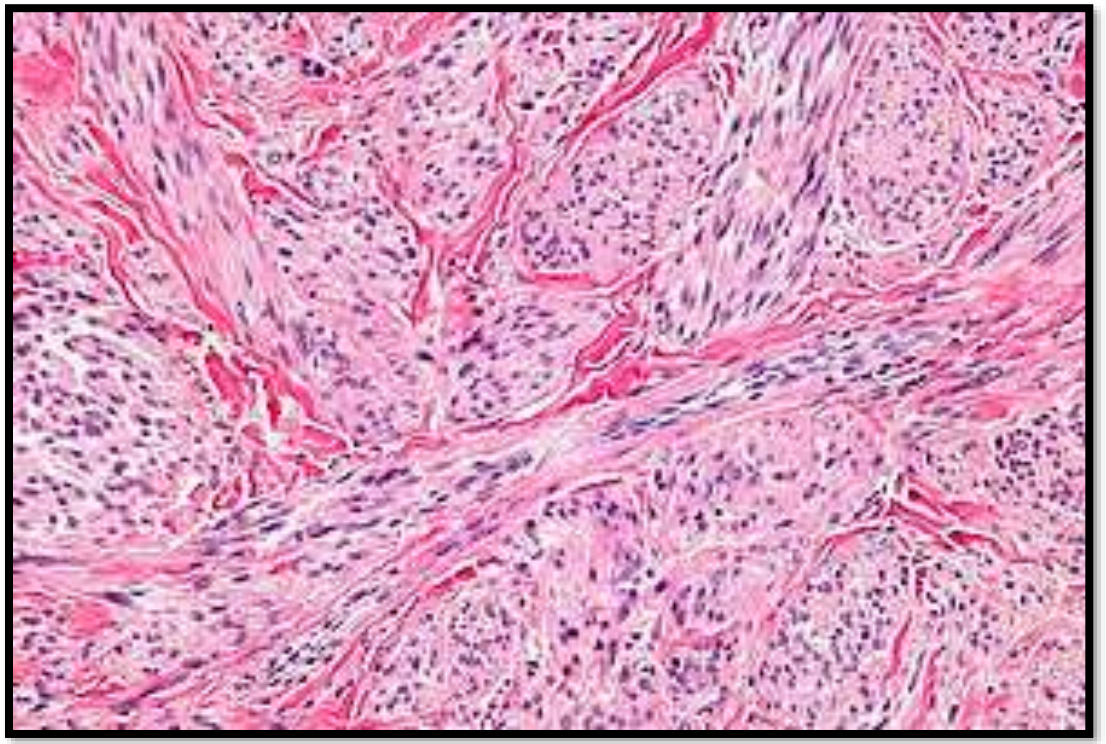
Leiomyosarcoma (LMS)

Gross- Heterogeneous, well circumscribed, Cystic/ necrotic central area

IHC - Desmin positive& Smooth muscle actin positive

Histologically-High cellularity, commonly arranged in fascicles. The malignant cells are characterized by abundant pink to deep red cytoplasm on H&E staining, with cigar-shaped, centrally located nuclei.

- Distinguishing features are lost in de-differentiated tumors



Leiomyosarcoma (LMS)

Cytogenetic changes of LMS are highly complex with many areas of deletions & amplifications of which deletion of 13q14, region harboring retinoblastoma (RB1) tumor suppressor gene, is a common event.

Deletions	*PTEN*	57–69
	RB1	27–59
Mutations	*TP53*	33–49
	ATRX	17–26
	MED12	21
Amplification	*MYOCD*	70

Leiomyosarcoma (LMS)

Malignant smooth muscle cell tumor. It is 2nd most common STS after liposarcoma

Sites

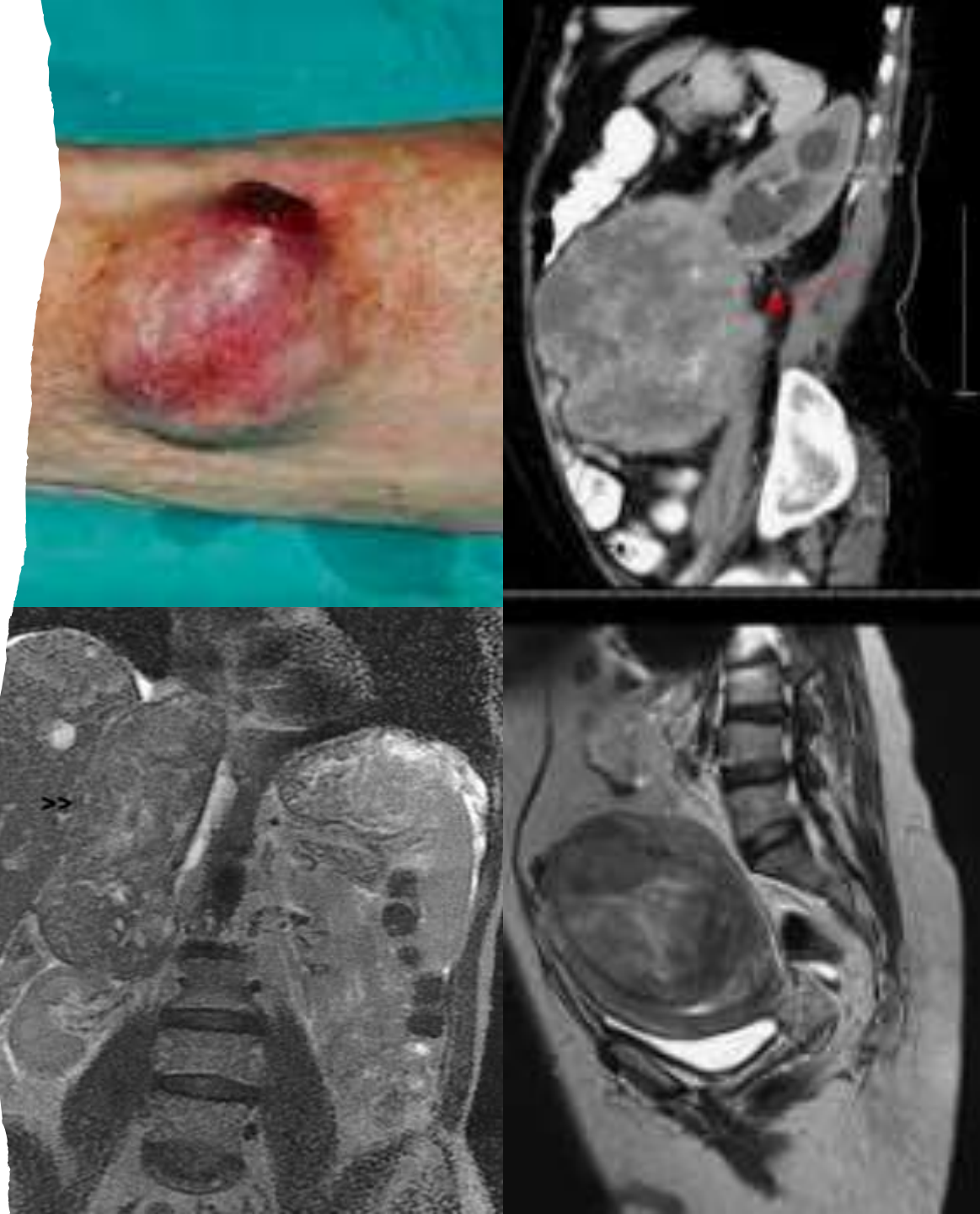
- Retroperitoneum > Peritoneal cavity (uterus)
- 25% - trunk & extremity

Predisposition

Prior radiation exposure

Immunosuppression

EBV related tumors



Leiomyosarcoma (LMS)

- Margin negative resection should be attempted
- In case of Uterine – TAH + BSO

Tumors invading/ closely abutting IVC

- Neoadjuvant RT may be useful
- Tumor resection + IVC ligation/Patching of IVC/ Interpositioning graft of IVC
- Collaterals preserved – ligation of IVC without reconstruction

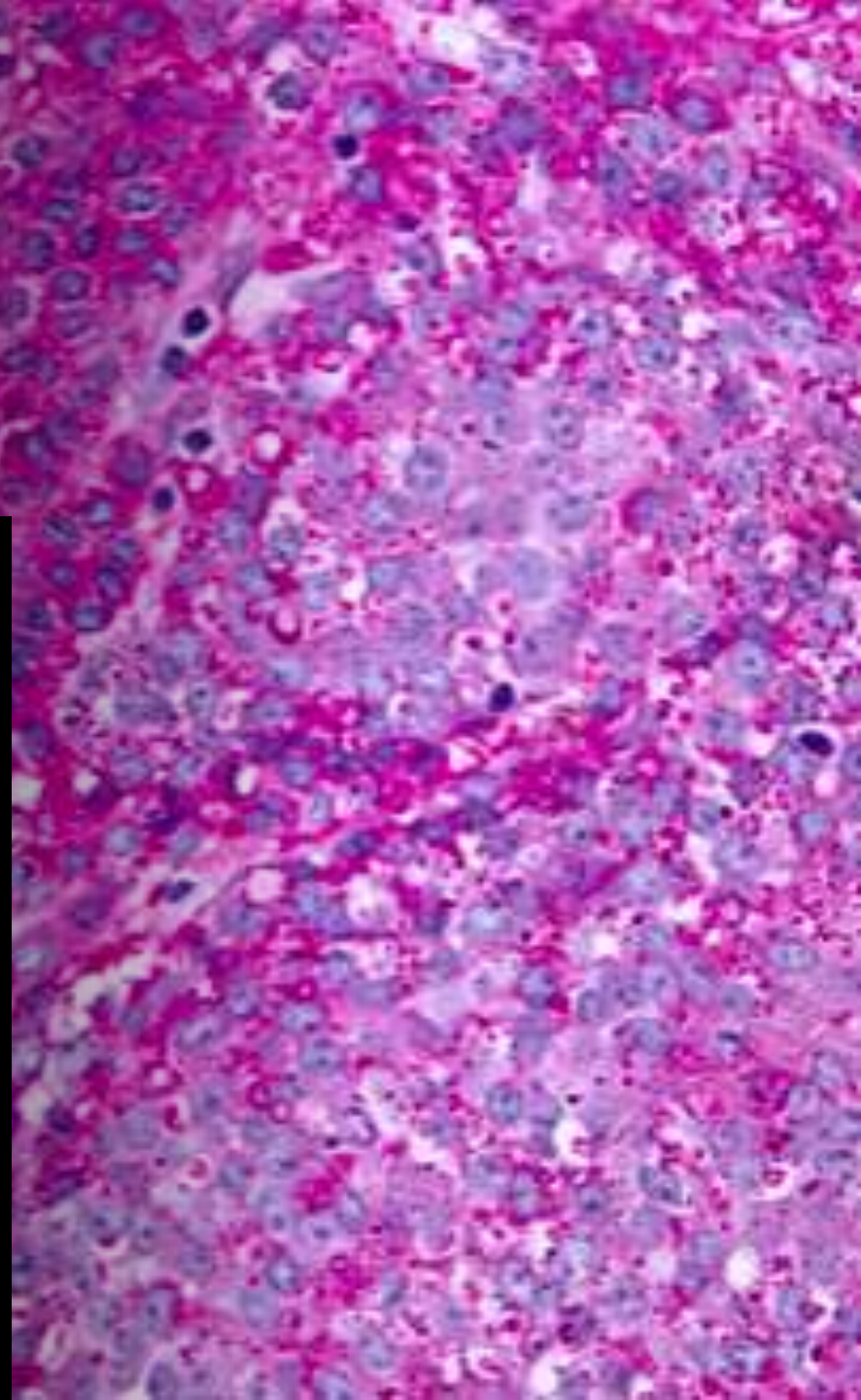
Metastasis

- Mainly haematogenous
- Lung > liver
- Poor response to chemo – doxorubicin, ifosamide, docetaxel, gemcitabine

Extraosseous Ewing Sarcoma (EES)

- Rare, small, round, blue cell tumor of mesenchymal origin with same histologic appearance & pathogenesis as ES of bone.
- Seen in 2nd or 3rd decade of life with a 1:2 female:male ratio.
- Most commonly affected sites include lower extremity, head & neck, paravertebral region & pelvis
- **About 10% of cases arise in extra skeletal soft tissues**
- Extraskeletal location can be present as an extension from a primary bone tumor (parosteal or periosteal location)

Histological Features



- Diffuse & monotonous proliferation of small round cells fluctuating between undifferentiated patterns (conventional Ewing's sarcoma) to histology deserving neuroectodermal differentiation with Homer-Wright pseudo-rosettes
- Presence of atypical variants is mainly based upon cell size. Small, round, discohesive cells with round to oval nuclei, inconspicuous nucleoli, and scant, eosinophilic, or clear cytoplasm. Also called "small round blue cell tumor" because of the intense, dark nuclear
- H&E staining in tumor cells, intermixed with round cells showing fine chromatin. Stroma can be scant and fibrotic or can show sclerosis and a lace-like appearance. Rich neoangiogenesis & hemorrhagic lacunae (hemangio-endothelial ESFT)

ESFT IHC & cytogenetics

- CD99-negative ESFT nearly always express CAV-1.
- Fli-1, HNK-1 & ERG are frequently expressed in ESFT
- Epithelial differentiation (CK-AE1/AE3) - in 20–30% of ESFT.
- Etiologic gene fusions of EWS to different members of the ETS transcription factor family.
- Expression of these chimeric EWS ETS fusion proteins is pathognomonic

Extraosseous Ewing Sarcoma (EES)

- Prognostic factors & treatment Strategy -similar to osseous Ewings S
- Systemic chemotherapy is combined with surgery &/or radiotherapy, depending on the location &size of neoplasm.
- Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE) - chemotherapy regimens
- Targeted therapeutics -clinical responses for IGF-1R inhibitors have been documented.
- Immunotherapies are emerging as a possible option in advanced sarcomas, including ESFT.

Gastrointestinal Stromal Tumor (GIST)

- Most common mesenchymal-derived tumor arising from digestive tract—
- Accounts for ~3% of all gastrointestinal malignancies
- Affects adults 40 -70 years old, and lacks gender predilection
- **Origin – interstitial cells of Cajal within myenteric plexus.(function as pacemakers in viscera, mediating contractions)**

Sites – Stomach, small bowel, rectum.

- Majority – Sporadic
- Syndromic association- NF1

○ Germ line SDH mutations

○ Carney-Stratakis syndrome, VHL disease

Classically a spindle cell neoplasm of smooth muscle origin

GIST

Markers: CD 34, CD 117 (KIT gene), DOG 1 expression
KIT gene (CD 117) (Chr 4)

↓

c-kit (TK transmembrane receptor)

A proto-oncogene (PDGFR superfamily)

↓

Natural c-kit ligand (a stem cell factor) binds with c-kit receptor

↓

Activates multiple pathways

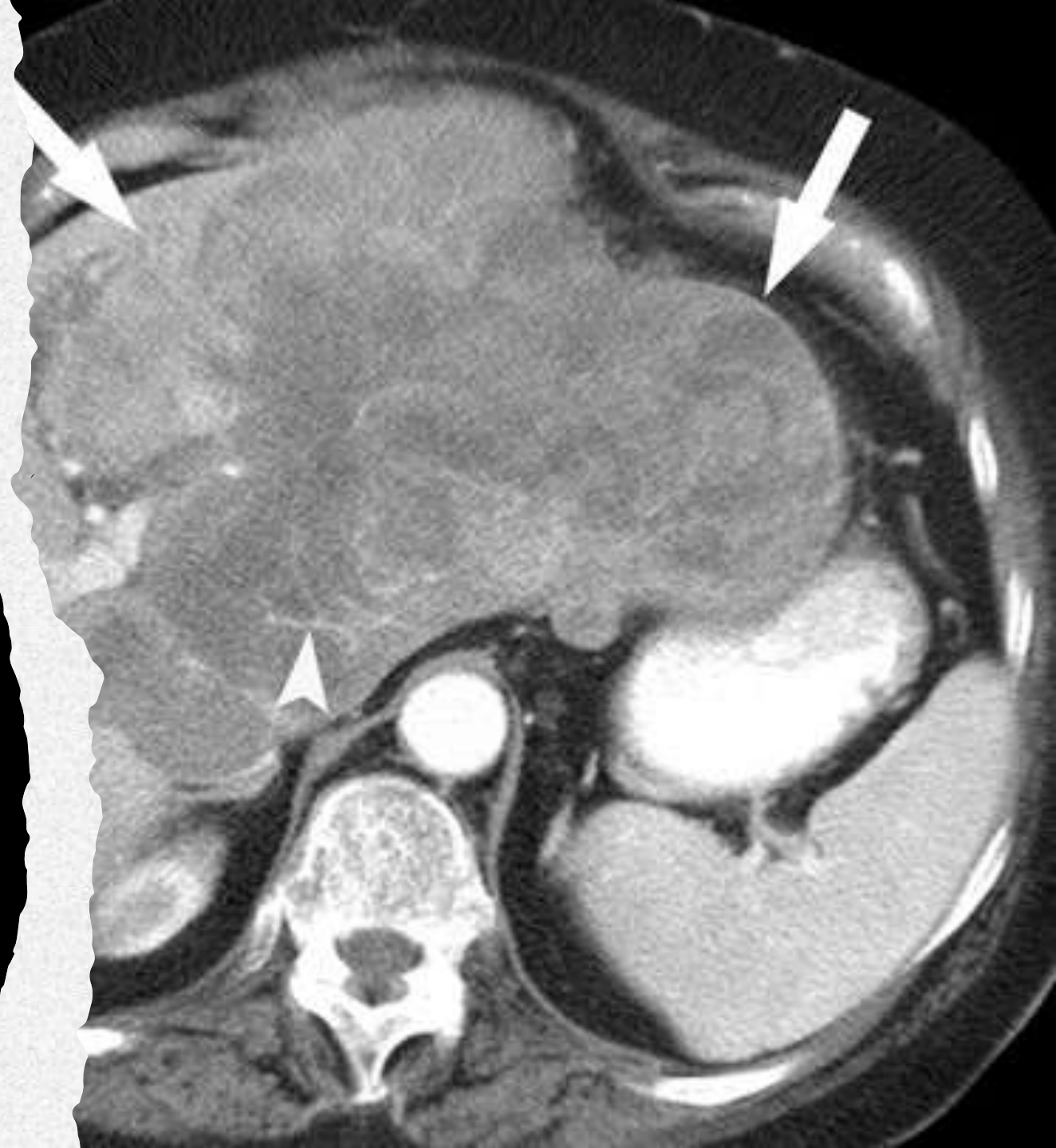
(RAS, RAF, MAPK, AKT, STAT3)

c-kit receptor mutation constitutive activation cellular proliferation

70% GIST – KIT gene mutations
07% GIST – PDGFRA mutations
15% GIST – Wild type KIT & PDGFRA genotypes
Other mutations – SDH (Carney- Stratakis syndrome), BRAF, KRAS and NF1 (NFtype 1)

GIST

- Asymptomatic (incidental)
- Pain, Nausea, vomitingGI blood loss (rare)
- Associated syndromic features
- **Endoscopic**: smooth submucosal tumor, extrinsically impinging on visceral lumen
- Serosally pedunculated tumor – no obstruction
- **CT findings**
- Well encapsulated with heterogeneous contrast enhancement
- Endoscopic US guided needle biopsy – spindle cell neoplasm
- Double balloon enteroscopy/ capsule endoscopy
- Pre-op staging: CECT chest, abdomen, pelvis



Treatment GIST

- Prognosis for localized GIST is favorable, -complete surgical excision
- High recurrence rate and up to 40 90% of pts show hepatic or mesenteric implants , possibly due to tumor rupture .
- Surgery: margin negative excision with wide surgical margins
- Lymphadenectomy not mandatory
- **Ideal pathology report should mention- Tumor site and organ of origin,Tumor focallity, mitotic rate*, CD 117 status (IHC), Total count of mitoses per 5 mm2 (tumor grade) & integrity of capsule**

Treatment GIST

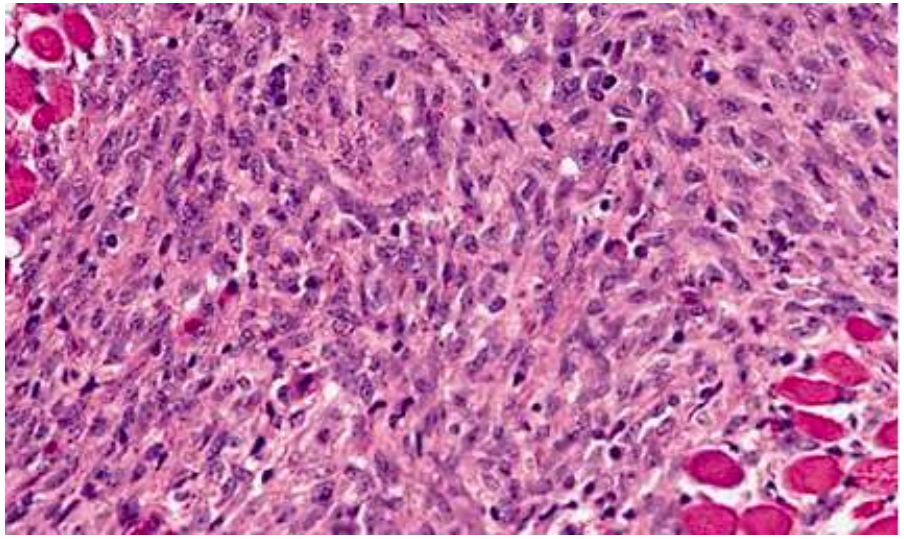
- Systemic therapy indicated as adjuvant therapy in resected GIST
- Neoadjuvant therapy of metastatic/ unresectable/ locally advanced GIST

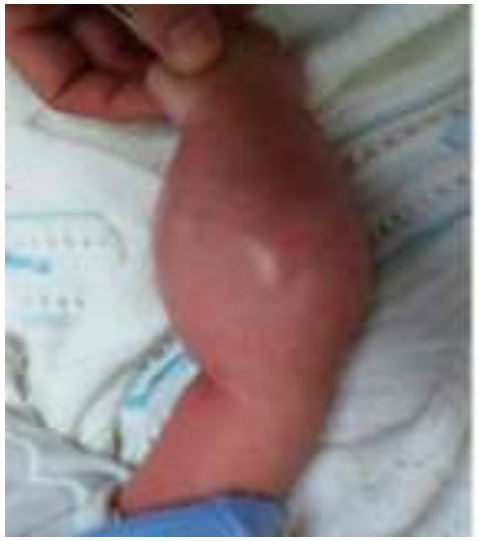
Agents

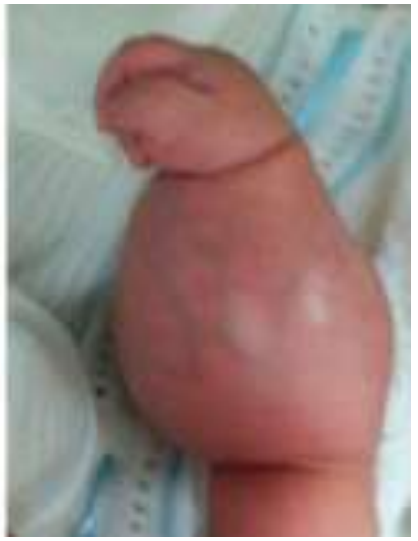
- 1st line – Imatinib (oral TKI inhibitor of c-KIT); Others – Sunitinib, regorafenib
- TKI imatinib mesylate binds to ATP-binding pocket crucial for phosphorylation/activation of the growth factor receptor--nhibiting tumor growth.
- TKIs are used preoperatively for patients with unresectable or borderline resectable tumors, or patients at high risk of recurrence after surgical removal of primary GIST tumor.

Congenital Fibrosarcoma (CFS)

- Congenital (or infantile) fibrosarcoma (CFS) is a malignant neoplasm of fibroblasts that occurs in patients aged 2 years or younger.
- Excellent prognosis and a very low metastatic rate.
- Comprised of sheets of malignant spindle cells forming interlacing cords with focal collections of inflammatory cells.
- Areas of haemorrhage, necrosis, and calcifications are frequently seen Mitoses can often be readily identified







Congenital Fibrosarcoma (CFS)

Genes
ETV6-NTRK3
EML4-NTRK3
TPM3-NTRK1
LMNA-NTRK1
MIR584F1-NTRK1
SQSTM1-NTRK1
TPR-NTRK1
STRN-NTRK2
NTRK1 rearrangement, not otherwise specified
ETV6 rearrangement, not otherwise specified
RET-MYH10
RET-K1AA1217
RET-CLIP2
BRAF point mutations
FOXN3- BRAF and TRIPP1-BRAF
EPB41L2-BRAF
KIAA1549-BRAF
OSBP-BRAF
DAAM1-BRAF
SEP7-BRAF
CUX1-BRAF
BRAF rearrangement, not otherwise specified
BRAF intragenic deletion
BRAF intragenic deletion and ETV6-NTRK3
BMPR1A-RAF1

Congenital Fibrosarcoma (CFS)

- Limited number of IFS can regress spontaneously without treatment
- Surgical extirpation - curable treatment approach
- Conservative surgery so as to avoid functional damage
- About 48%–62% of primary tumors are unresectable & require a multidisciplinary strategy
- Preop chemotherapy can be used in inoperable pts,& delayed conservative surgery or complete resection may be performed when tumor shrinkage is achieved
- Postop chemotherapy has been recommended as first-line treatment for pts with macroscopic residual disease to decrease the local recurrence
- Radiotherapy application is limited

Synovial Sarcoma (SS)

- Aggressive STS subtype, commonly arising from synovial tissue lining joint cavities of extremities, which often affects adolescents and young adults rather than older individuals
- Accounts for approximately 8% of all soft tissue sarcomas
- The history of trauma some days or weeks before diagnosis is considered a coincidence, as the trauma draws attention to an already existing mass

Synovial Sarcoma (SS) Location

- Deep soft tissue of extremities, with a predilection for lower extremities. Close to a large joint, especially around the knee. Tendon sheaths, ligaments, aponeuroses.
- Rarely in joint cavities and bursae.
- Head & neck area is the second most common site, in the retropharyngeal and parapharyngeal region.
- Less frequent in the trunk.
- Any anatomic site can be affected, including unusual locations such as skin, lung, prostate, bone, kidney, and CNS.

Synovial Sarcoma (SS)

- Expansile, multilobular mass - circumscribed by a pseudocapsule but may infiltrate neighboring structures such as tendons & aponeuroses.
- Averages 3–10 cm in diameter.
- Consistency is soft to firm, and the cut surface is compact and gray-white to yellow.
- Secondary changes can be present as necrosis, cyst formation, hemorrhage, myxoid areas, and calcification.

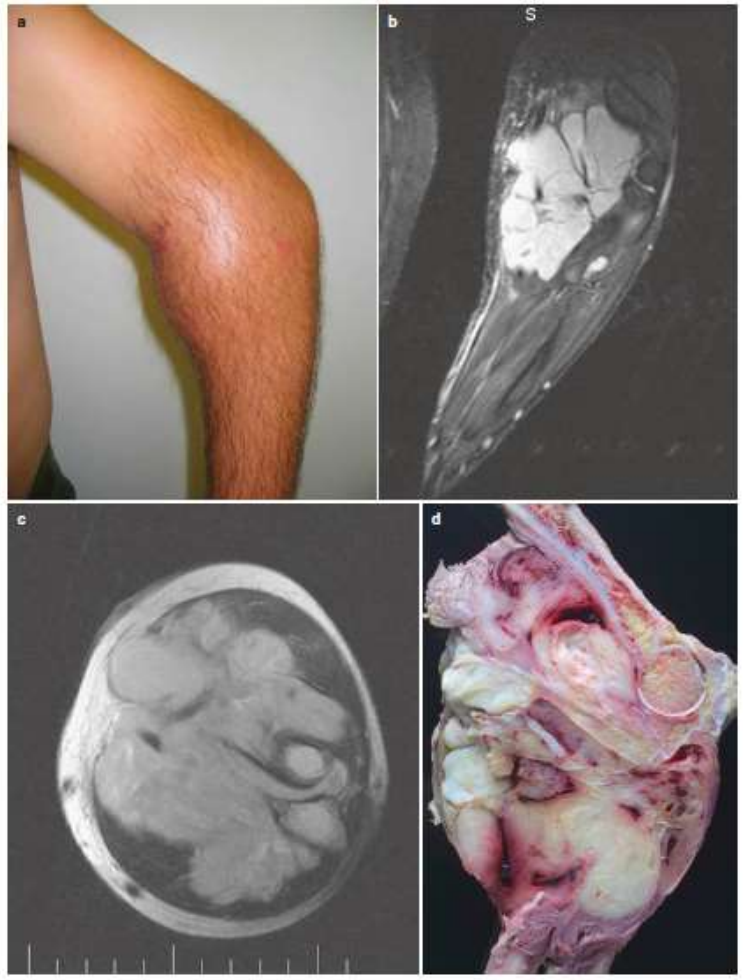
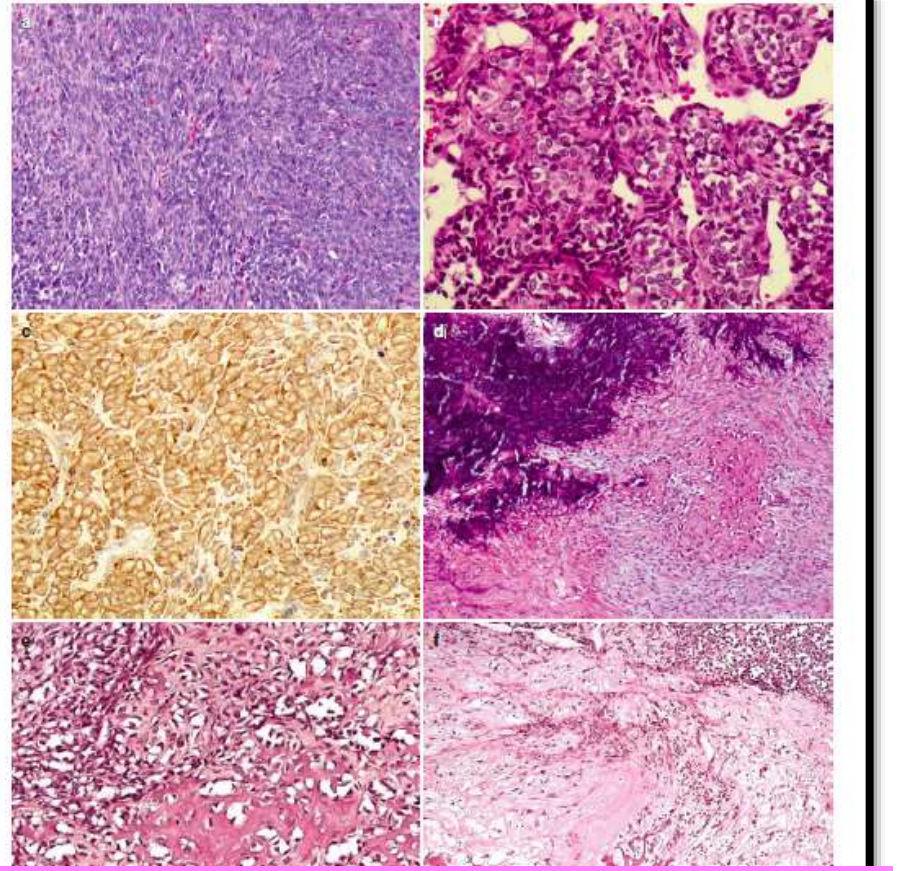
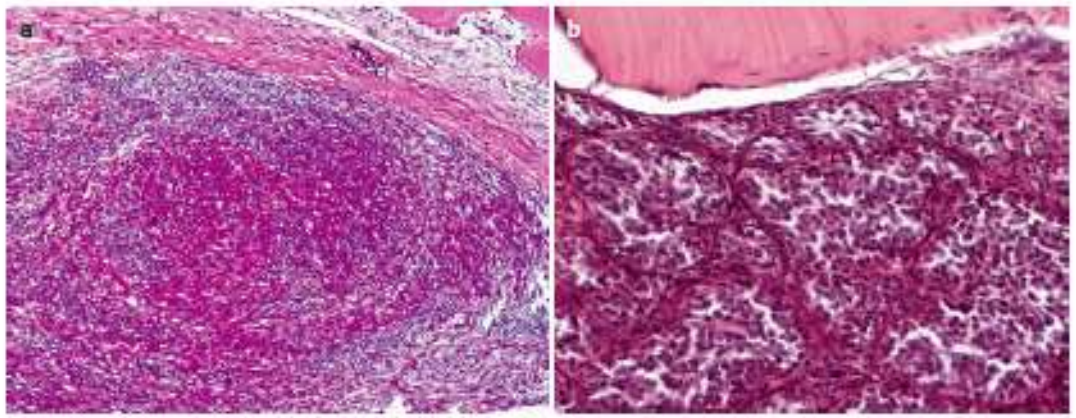


Fig. 86.1 Synovial sarcoma (SS) near the left elbow of a patient. (a) Large swelling in the upper extremity. (b) Coronal T2-weighted MRI showing a mass with homogeneously high-intensity signal. (c) Axial T1-weighted MRI of the same patient; signal is slightly hyperintense. (d) Gross picture of the same lesion



Monophasic fibrous SS

- Sheets of spindle cell proliferation. “School of fish” is a characteristic growth pattern of this type
- Densely packed cells.
- Distinct fascicles with shoal pattern and less frequent nuclear palisading.



Biphasic SS (BSS)

- Biphasic SS presents all the features described for monophasic fibrous SS, with the addition of characteristics of the epithelial component in varying proportions
- The epithelial cells are large and cuboidal to cylindrical, with abundant eosinophilic cytoplasm, sometimes containing mucin— The nuclei are round to oval.

Synovial Sarcoma (SS) Genetics

- t(X;18)(p11;q11) chromosomal translocation in over 95%
- FISH & RT-PCR demonstrate SS18-SSX1 gene fusion in about 70%, mostly biphasic cases.
- Other related fusions are SS18-SSX2 and SS18-SSX4.

Synovial Sarcoma (SS)

- Prognosis is poor with 50 70% of cases developing metastases.
- Management strategy - wide resection followed by polychemotherapy with or without irradiation
- Multiple chemotherapy for advanced disease.
- Targeted, immune, and metabolic therapies are in testing.

Rhabdomyosarcoma (RMS)

- Most common STS in childhood populations-----50% of STSs in children
- Two thirds cases occur before the age of 6 years, a second peak occurring during mid-adolescence
- Arising in limbs, central axis, or head and neck areas

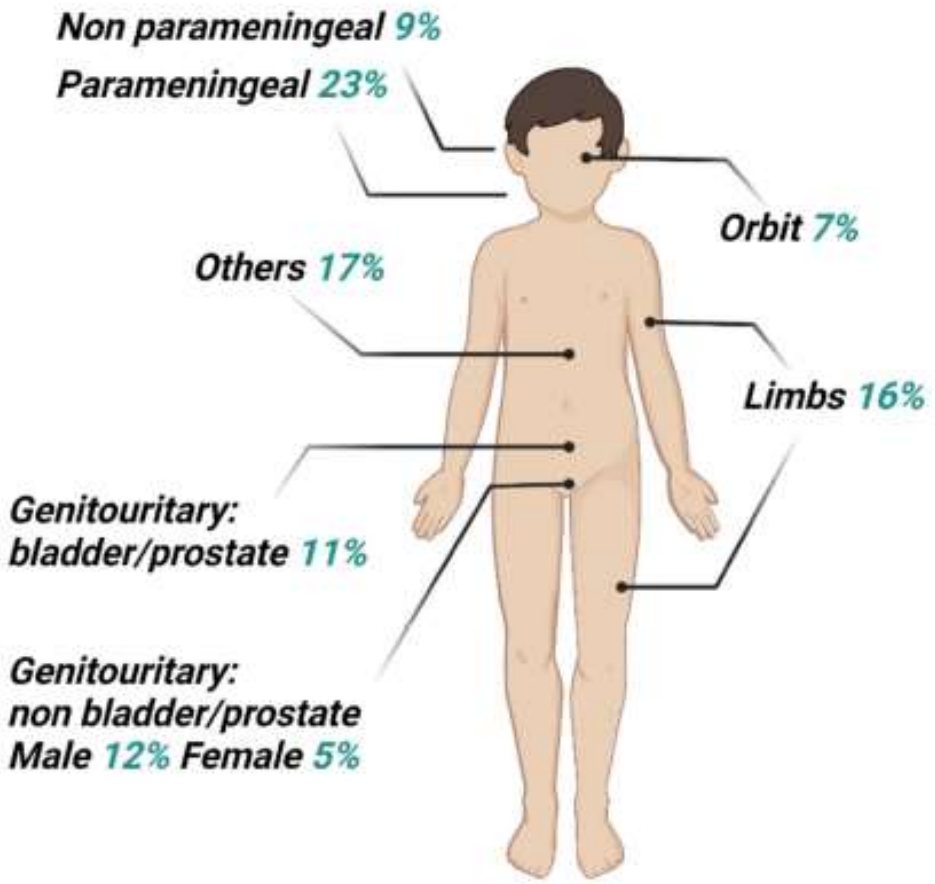
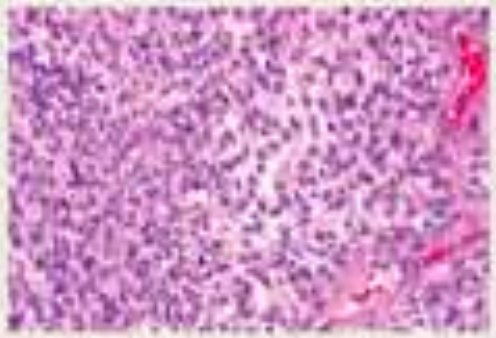
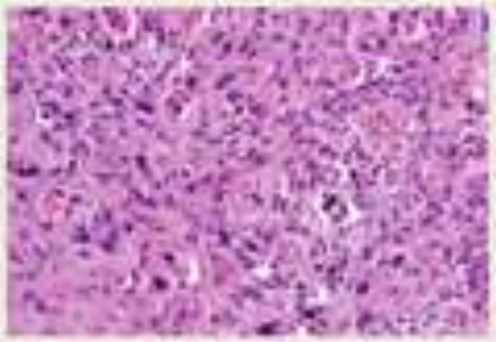
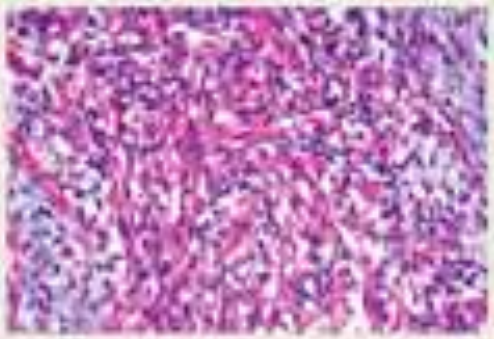
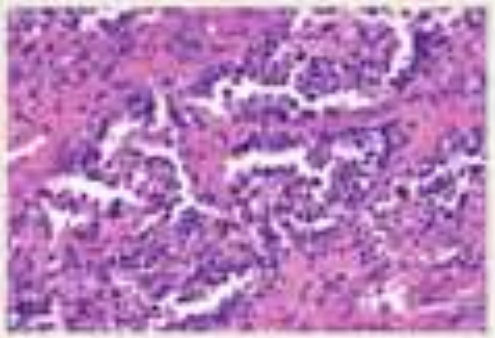


Table 1 | **RMS subtypes based on histological morphology**

Subtype	Embryonal	Pleomorphic	Spindle cell	Alveolar
Histology				
	Small, round-to-elongated cells with interspersed loose myxoid stroma	Large anaplastic cells with enlarged, hyperchromatic nuclei, multipolar mitotic figures	Relatively differentiated spindle cells with features reminiscent of smooth muscle neoplasms	Discohesive primitive round cells within interwoven fibrous septa
Location	Genitourinary tract, head and neck, urinary bladder, prostate, biliary tract, abdomen, pelvis, retroperitoneum	Extremities, chest and abdomen	Paratesticular, and head and neck in children; head and neck in adults	Extremities, head and neck, chest, genital organs, abdomen, and anal area
Age (years)	<10	60–80	<10 >40	10–25
~% of all RMS cases	60%	10%	10%	20%
Prognosis*	Favourable	Unfavourable	Favourable (children) Unfavourable (adults)	Unfavourable

Subclass	Variant	Distinguishing Histologic Features	Age	Locations
Embryonal		Cells exhibit different stages of development from myoblast to myotubular, in a mucinous stroma	Juvenile/adult	Face, skull, masticatory muscle, oropharynx, trachea, axilla, scapula, perirenal, tongue, flank, leg, mammary gland, hard palate
	Myotubular	Myotube forms predominate		
	Rhabdomyoblastic	Large myoblast cells with abundant cytoplasm		
	Spindle cell	Streams of plump spindle cells		Skull
Botryoid		Characteristic submucosal location and gross appearance; mixed round and myotubular cells in mucinous stroma	Juvenile	Urinary bladder, uterus
Alveolar			Juvenile	Hip, maxilla, greater omentum, uterus
	Classic	Fibrous bands divide small round cells into clusters, loose aggregates		
	Solid	Closely packed cells, ± thin fibrous septa		
Pleomorphic		Haphazardly arranged plump spindle cells with marked anisocytosis and anisokaryosis and bizarre mitotic figures	Adult	Skeletal muscle

Histologic variants

Embryonal and alveolar subtypes - most common

Botryoid and pleomorphic subtypes - less frequent.

Embryonal RMS (ERMS) subtype (B70% of RMS cases) tends to affect infants & toddlers

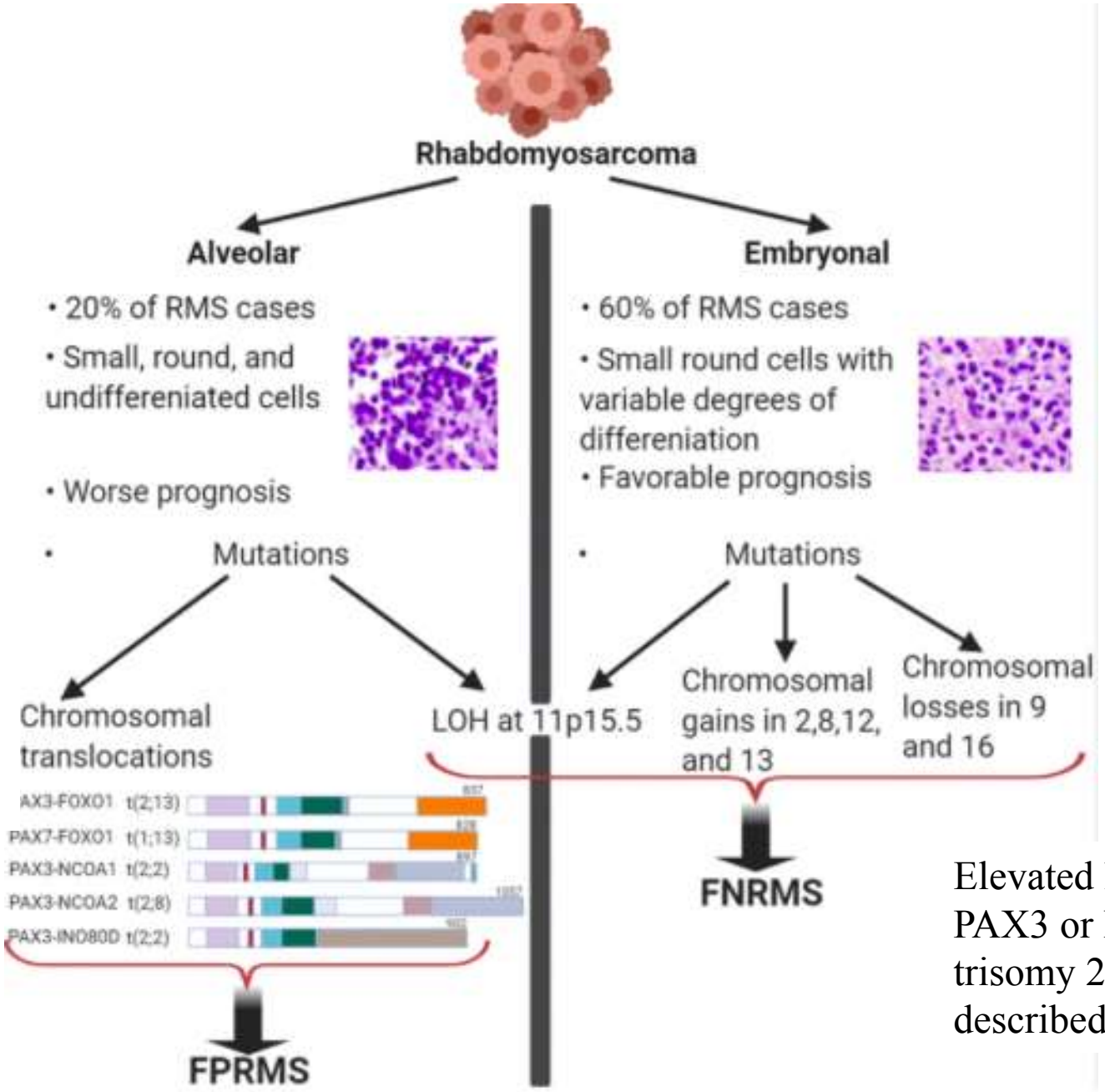
ARMS (B20% of RMS cases) affects all age groups.

Botryoid & pleomorphic subtypes (B10% of RMS cases) commonly affect adults

ARMS & ERMS most commonly occur as a mass & presenting signs & symptoms are related to anatomic site of primary tumor

Most common locations of primary disease are head & neck region, genitourinary tract, & extremities survival is poor for pts with distant tumor spread

Other amplification events in ARMS include 2p24, 12q13-q14, & 13q31 chromosomal regions, of which target genes include MYCN, CDK4 & MIR17HG



Elevated levels of wild-type PAX3 or PAX7 expression & trisomy 2 have also been described in ERMS

Rhabdomyosarcoma (RMS) Risk Groups

Treatment strategies designed are based on both pre-treatment clinical & radiographic data, as well as surgical & pathological findings

Risk Group	Subgroup	Fusion Status	IRS Group	Site	Node Stage	Size or Age
Low Risk	***A***	Negative	I	Any	N0	Both Favourable
Standard Risk	***B***	Negative	I	Any	N0	One or both Unfavourable
	C	Negative	II, III	Favourable	N0	Any
High Risk	***D***	Negative	II, III	Unfavourable	N0	Any
	E	Negative	II, III	Any	N1	Any
	F	Positive	I, II, III	Any	N0	Any
Very High Risk	***G***	Positive	II, III	Any	N1	Any
	H	Any	IV	Any	Any	Any

Rhabdomyosarcoma (RMS)

- Involves local control measures including surgical resection & radiotherapy in conjunction with systemic chemotherapy because of high metastatic potential
- Management strategies for adults with RMS are similar to those for children
- International Society of Pediatric Oncology Malignant Mesenchymal Tumor (MMT) Group prefers use of chemotherapy as a front-line approach with its aim at avoiding, if possible, major surgical procedures & long-term effects of radiotherapy
- Soft Tissue Sarcoma (STS) Committee of the Children's Oncology Group (COG) (COG-STS) apply local control measures for non-metastatic cases soon after initial operation or biopsy

Low Risk Group (A)

Localized non alveolar RMS, microscopically completely resected (IRS Group I), at all sites,
and
nodes negative
and
tumour size < 5 cm
and
age < 10 years

Primary re-excision is justified here if it can be done without important functional or cosmetic sequelae, and if there is a realistic prospect of achieving complete microscopic resection (R0).

If the primary re- excision confirms clear margins, whether or not there is residual tumour in the resected specimen, the patient will be classified in the Low Risk Group and treated accordingly.

	V	V	V	V			V	V	V	V			V	V	V	V			V	V	V	V
	A			A			A			A			A			A			A			A
Weeks	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*
Cycle no.	1			2			3			4			5			6			7			8

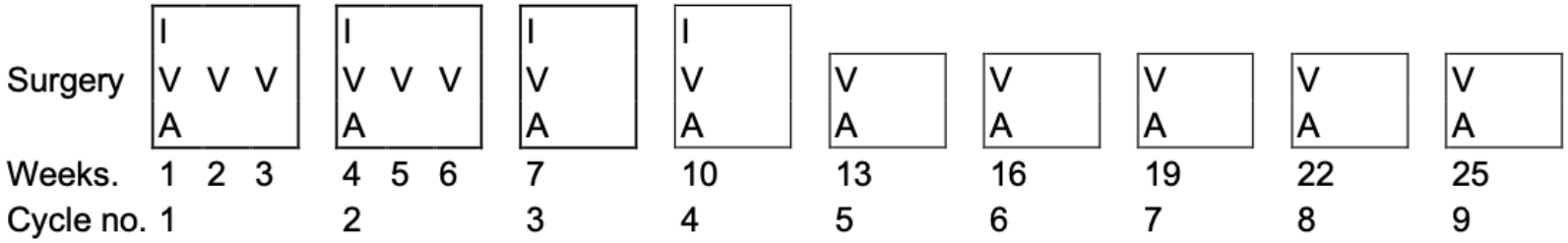
V = Vincristine 1.5 mg/m^2 (maximum single dose 2 mg) as a single intravenous injection.

A = Actinomycin D 1.5 mg/m^2 (maximum single dose 2 mg) as a single intravenous injection.

Subgroup B Treatment

Localised non alveolar RMS, microscopically completely resected (IRS Group I), at all sites,
and
nodes negative
and
tumour size > 5 cm or age > 10 years

The treatment comprises of 4 cycles of Ifosfamide, Vincristine and Actinomycin D (IVA) followed by 5 courses of Vincristine and Actinomycin D (VA). The total duration of chemotherapy is 25 weeks.



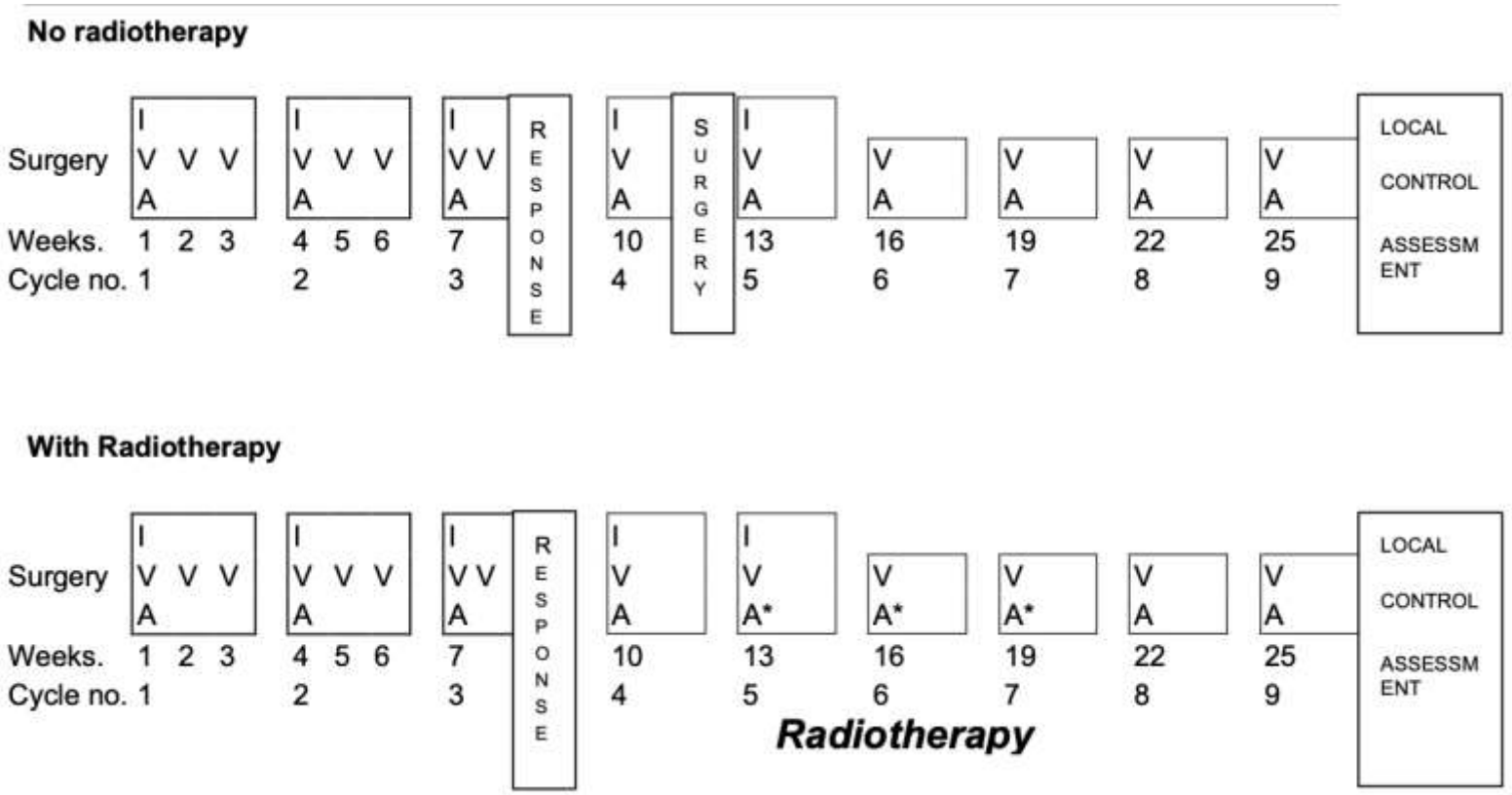
I — Ifosfamide 3 g/m^2 is given as a 3 hour intravenous infusion daily, with Mesna (3 g/m^2) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m^2).

V — Vincristine 1.5 mg/m^2 (maximum single dose 2 mg) is given as a single intravenous injection on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.

A — Actinomycin D 1.5 mg/ m^2 (maximum single dose 2 mg) as a single intravenous injection on day 1 of each course of treatment.

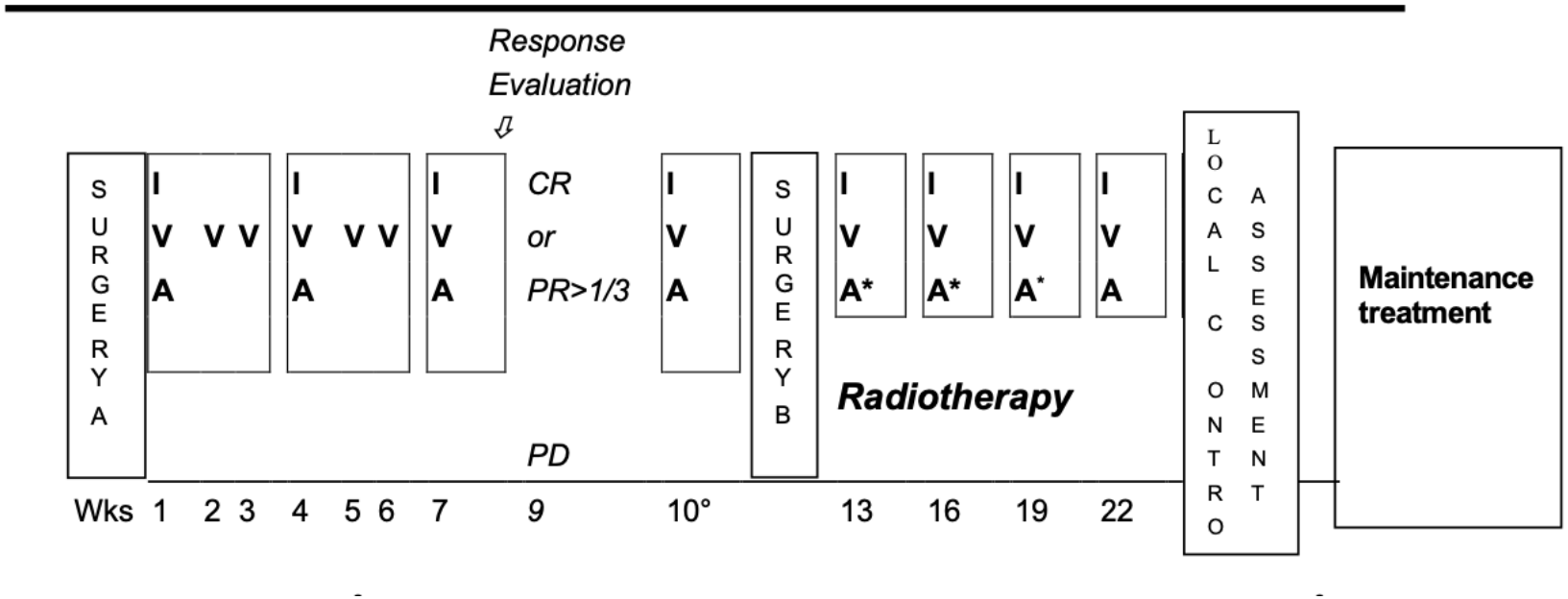
Subgroup C treatment (ARM SR-C)

Non alveolar RMS, IRS Group II or III,
localised in orbit, head and neck non PM or GU including bladder-prostate, and
nodes negative
and
any size or age



- Ifosfamide 3 g/m$_2$ with Mesna (3 g/m$_2$) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m$_2$).
- Vincristine 1.5 mg/m$_2$ (max. single dose 2 mg) day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.
- Actinomycin D 1.5 mg/m$_2$ (maximum single dose 2 mg) on day 1

High risk patients (groups D, E and F)



- Ifosfamide 3 g/m$_2$ with Mesna (3 g/m$_2$), on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m$_2$).
- Vincristine 1.5 mg/m$_2$ (maximum single dose 2 mg) is given as a on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.
- Actinomycin D 1.5 mg/m$_2$ (maximum single dose 2 mg) on day 1

Subgroup D

non alveolar, fusion negative RMS, IRS Group II or III, localised in parameningeal, extremities, or "other sites"
and
nodes negative
and
any tumour size or age

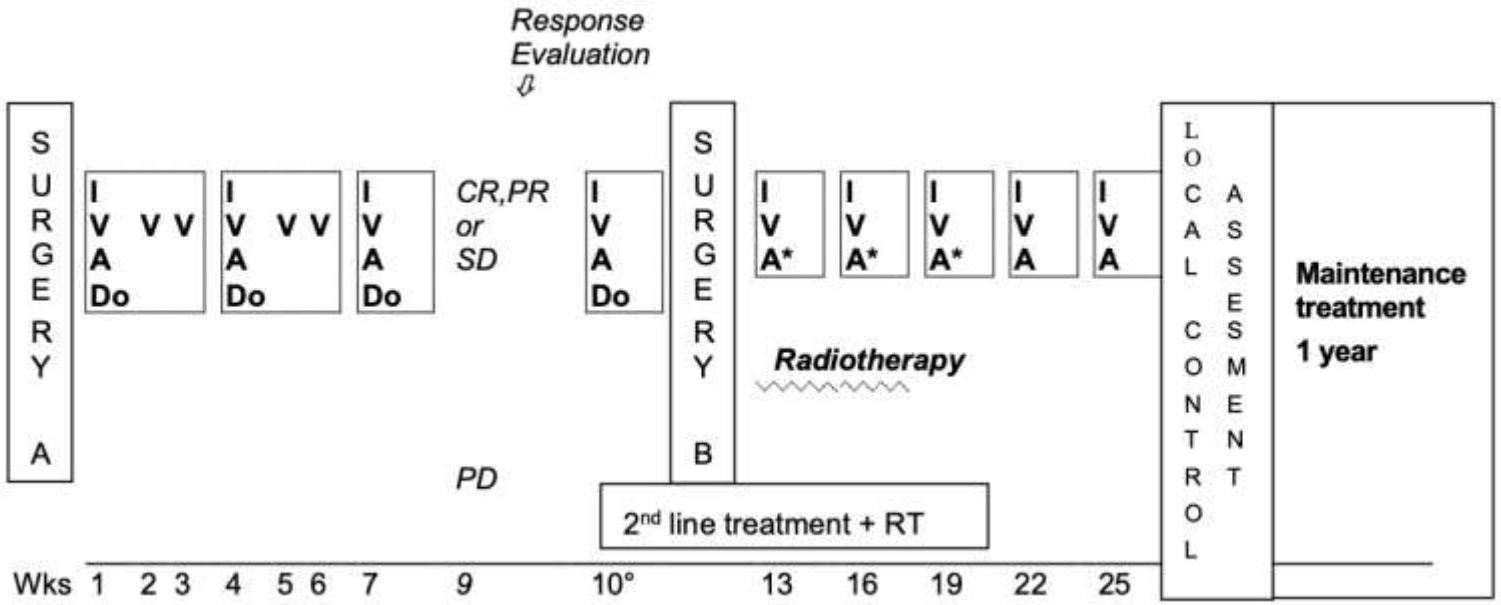
Subgroup E

non alveolar, fusion negative RMS, IRS Group II or III, any site
and
nodes positive
and
any tumour size or age

Subgroup F

Alveolar, fusion positive RMS, IRS Group I or II or III, and any site and
nodes negative
and
any tumour size or age

Very High Risk Fusion positive AND node positive patients (Subgroup G)

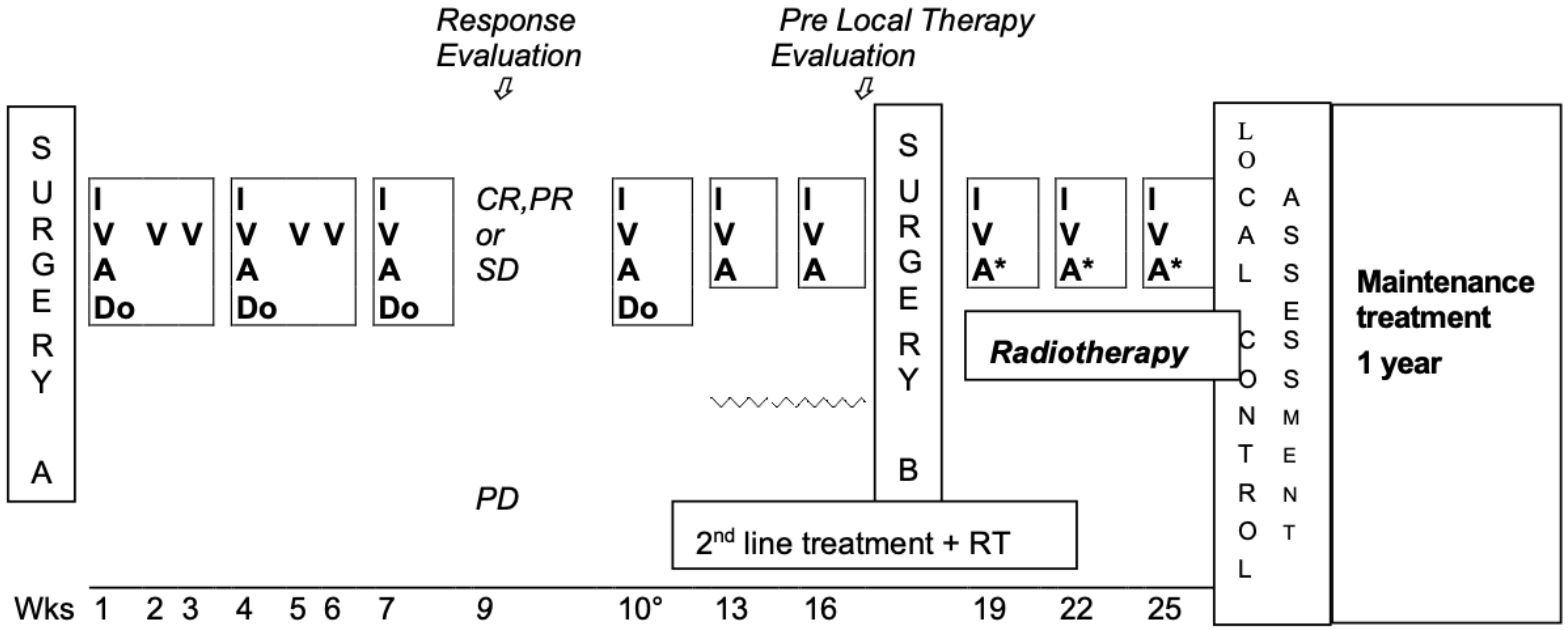


Subgroup G
Alveolar, fusion positive
RMS, IRS Group II or III, and
any site and
nodes positive
and
any tumour size or age

- Ifosfamide 3 g/m$_2$ with Mesna (3 g/m$_2$) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m$_2$).
- Vincristine 1.5 mg/m$_2$ (maximum single dose 2 mg) on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.
- Actinomycin D 1.5 mg/m$_2$ (maximum single dose 2 mg) on day 1 of each course of treatment.
- Doxorubicin 30 mg/m$_2$ given as a 4-hour intravenous infusion daily on days 1 & 2 for courses 1- 4 of treatment (total dose per course = 60 mg/m$_2$).

Very high risk: Metastatic patients (Subgroup H)

Alveolar/non-alveolar fusion positive/negative RMS, IRS Group IV, and any site and **nodes any**
and
any tumour size or age



- Ifosfamide 3 g/m$_2$ with Mesna (3 g/m$_2$) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m$_2$).
- Vincristine 1.5 mg/m$_2$ (maximum single dose 2 mg) is given on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7. Actinomycin D 1.5 mg/m$_2$ (maximum single dose 2 mg) on day 1
- Doxorubicin 30 mg/m$_2$ given as a 4-hour intravenous infusion daily on days 1 & 2 for courses 1- 4 of treatment (total dose per course = 60 mg/m$_2$).

Targetted therapy Rhabdomyosarcoma (RMS)

Small molecule inhibitors include -

- Targeting tyrosine kinases such as IGF-1 receptor inhibitor
- Anti-angiogenic drugs such as bevacizumab (Avastin)
- Kinase Inhibitors-Sorafenib (Nexavar)
- mTOR inhibitors such astemsirolimus (Torisel) and everolimus (Afinitor)
- Many of these agents are in clinical trials and showed potential benefits when used alone or in combination with other anticancer regimens, providing encouraging approaches for RMS treatment.
- Additional therapeutic focus of research is immunemediated destruction of the PAX FOXO1 fusion oncoprotein by vaccination or by kinase inhibitors

Surveillance

- Majority of local recurrences as well as lung metastases will become evident within first two years following treatment.
- High-risk patients are seen in follow-up every three months for the first two years for clinical examination and a chest x-ray or CT-scan.
- MRI of the surgical site or lymph nodes as part of regular follow-up if there is clinical concern for local or regional recurrence, based on physical examination in the clinic or changes noted by the patient.
- After first two years high-risk patients are reviewed every six months until five years and then annually until 10 years.

Summary

- Rare heterogeneous group of cancers of mesenchymal origin
- More common in paediatric age groups
- Histological subtypes of STSs share common features
- Many STSs are highly aggressive tumors with a strong propensity for local recurrence and metastasis
- Metastatic spread represents the single-most powerful predictor of poor outcome in high-risk STSs
- Genetic and non-genetic factors play a role in sarcomagenesis
- Multimodality treatment is desirable with margin negative surgery the curative procedure followed by risk adapted adjuvant treatment.

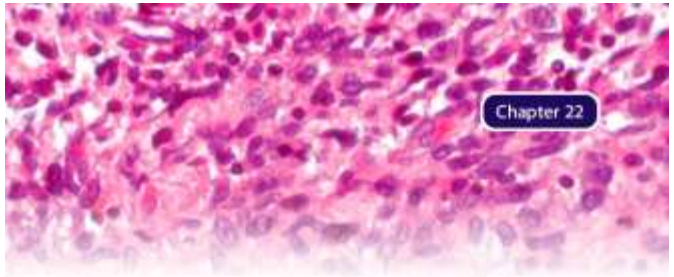
Suggested readings

Eduardo Santini-Araujo
Ricardo K. Kalil
Franco Bertoni
Yong-Koo Park
Editors

Tumors and Tumor-Like Lesions of Bone

Second Edition

Springer



Cancer Genomics

Soft Tissue Sarcomas

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THE TREATMENT AND OUTCOMES OF EXTRASKELETAL OSTEOSARCOMA: INSTITUTIONAL EXPERIENCE AND REVIEW OF THE LITERATURE

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SICOT J 2017, 3, 20
© The Authors, published by EDP Sciences, 2017
DOI: 10.1051/sicotj/2017010

SICOT-J

Available online at:
www.sicot-j.org

Special Issue: "Musculoskeletal tumors: Current approaches and controversies"
Guest Editor: A. Kulidjian

REVIEW ARTICLE OPEN ACCESS

Management of soft-tissue sarcomas; treatment strategies, staging, and outcomes

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Received 1 November 2016, Accepted 3 January 2017, Published online 10 March 2017

Hindawi Publishing Corporation
Sarcoma
Volume 2011, Article ID 483154, 15 pages
doi:10.1155/2011/483154

Review Article

Liposarcoma: Molecular Genetics and Therapeutics

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Received 16 September 2010; Accepted 29 October 2010

frontiers | Frontiers in Genetics

TYPE Review
PUBLISHED 16 February 2023
DOI 10.3389/fgene.2023.1109486

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Current research and management of undifferentiated pleomorphic sarcoma/ myofibrosarcoma

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Review

Synovial Sarcoma: A Clinical Review

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