Common Soft Tissue Sarcomas- A Brief Outline

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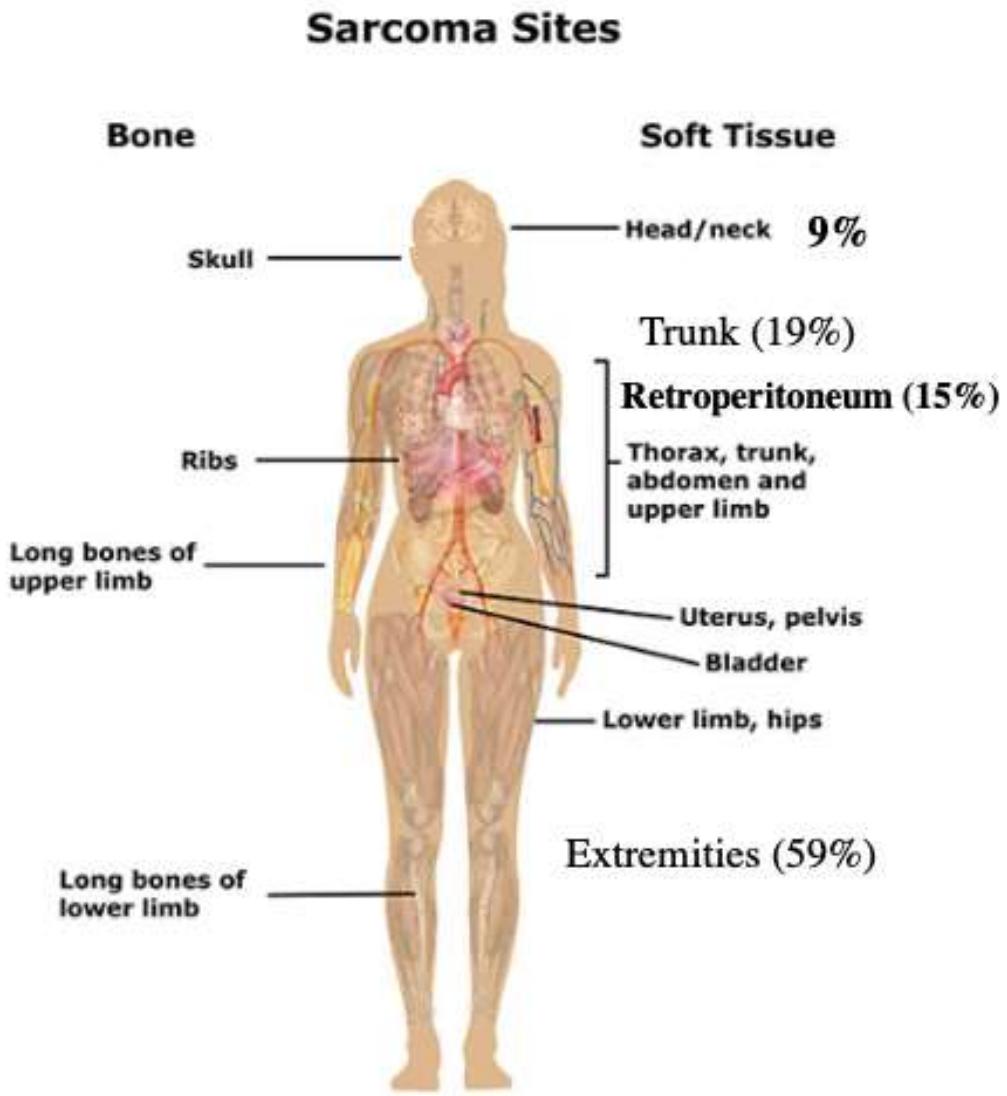
Introduction

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

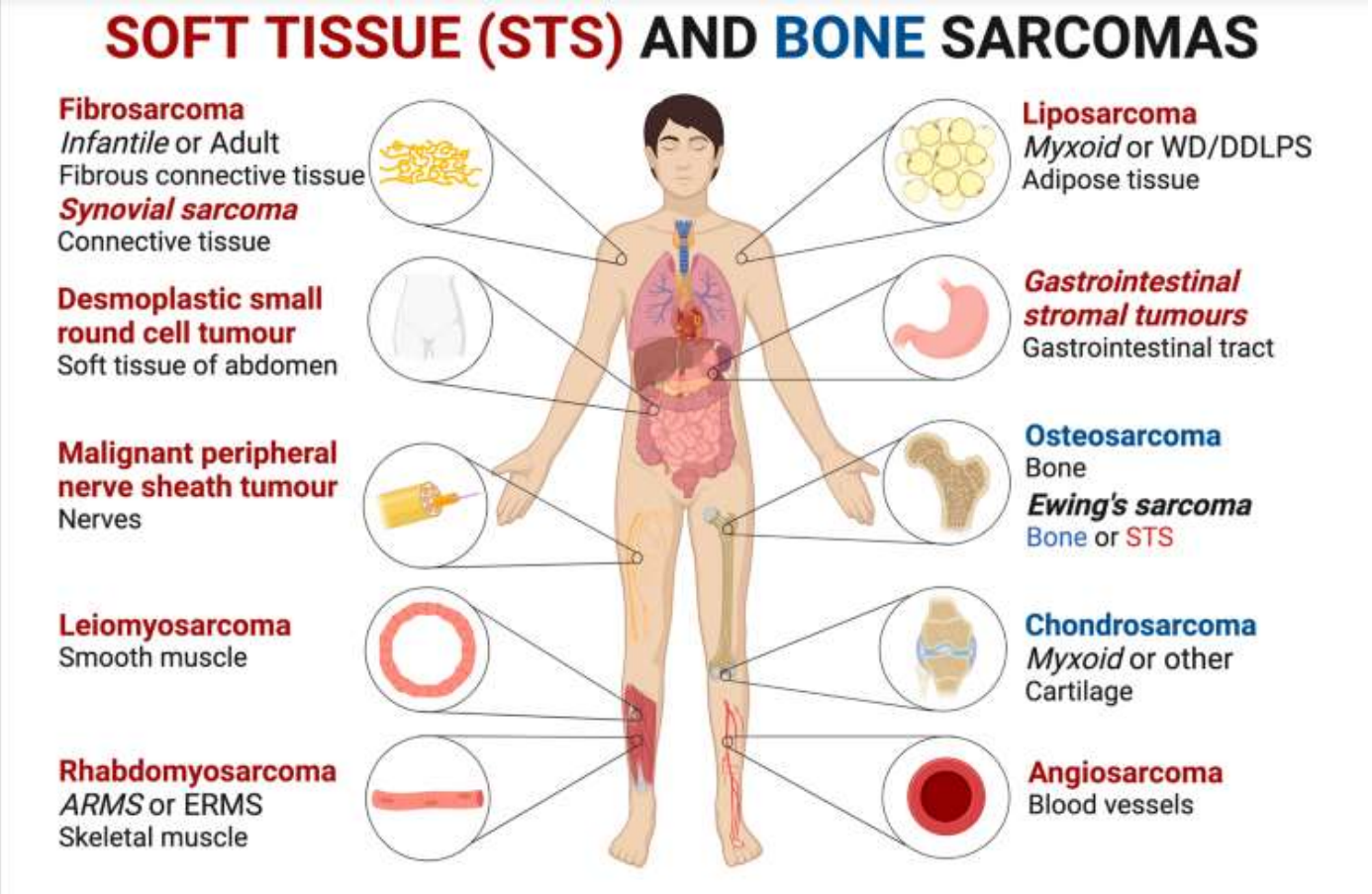
- ~11,000 new cases/yr diagnosed in US
- Occur over all age ranges, median age at diagnosis - 56–65 years

❖Account for <1% of adult malignancies

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



Soft Tissue Sarcomas



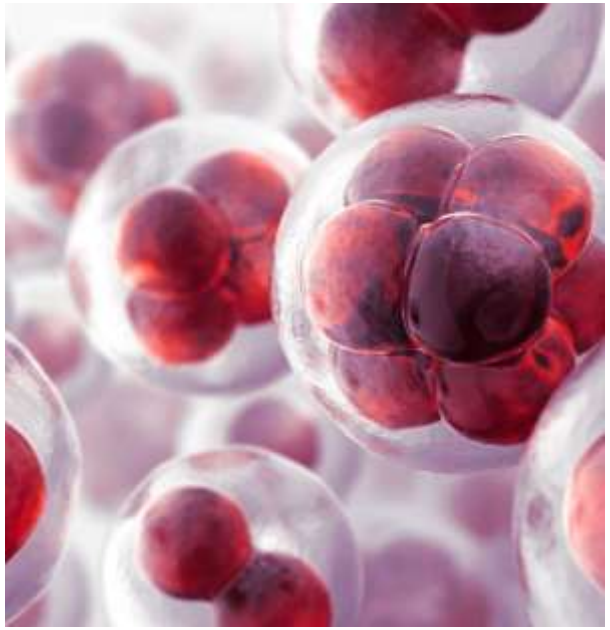
- Extra skeletal tissues -muscles, fat, blood vessels, nerves, & synovial tissues
- Typically, high grade &, if diagnosed at an advanced stage, survival rates are poor

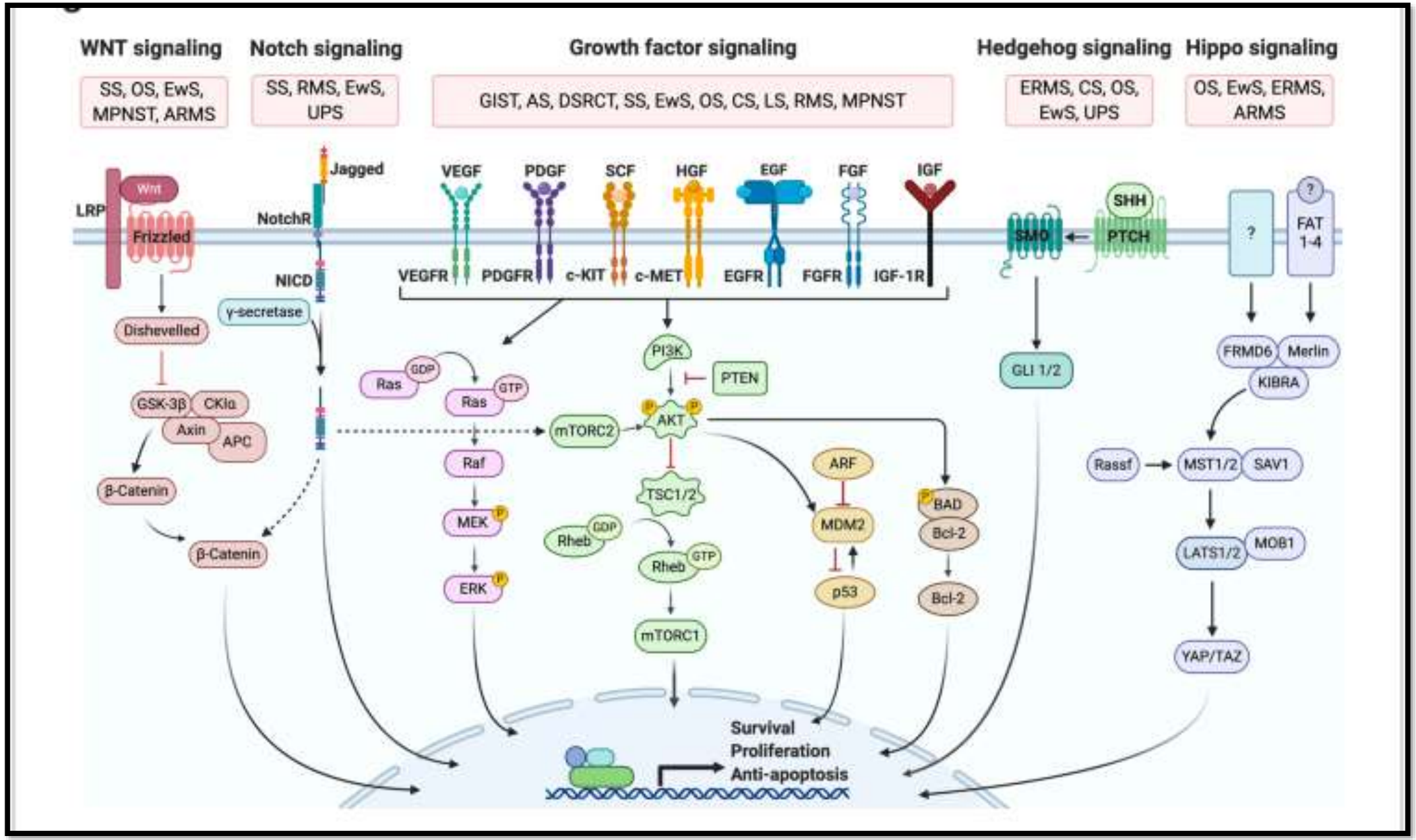
Etiology

- Etiology of most cases remains unknown/Environmental factors/ genetic predispositions

- 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 : Painless primary soft tissue mass

Retroperitoneum :Abdominal mass, Pain, grows to large size before symptoms

Viscera : Anaemia, melena, abdominal pain, wt loss, painless P/V bleed

H&N : Smaller, Mechanical problems: compression or invasion of adjacent structures.

Anatomic locations:

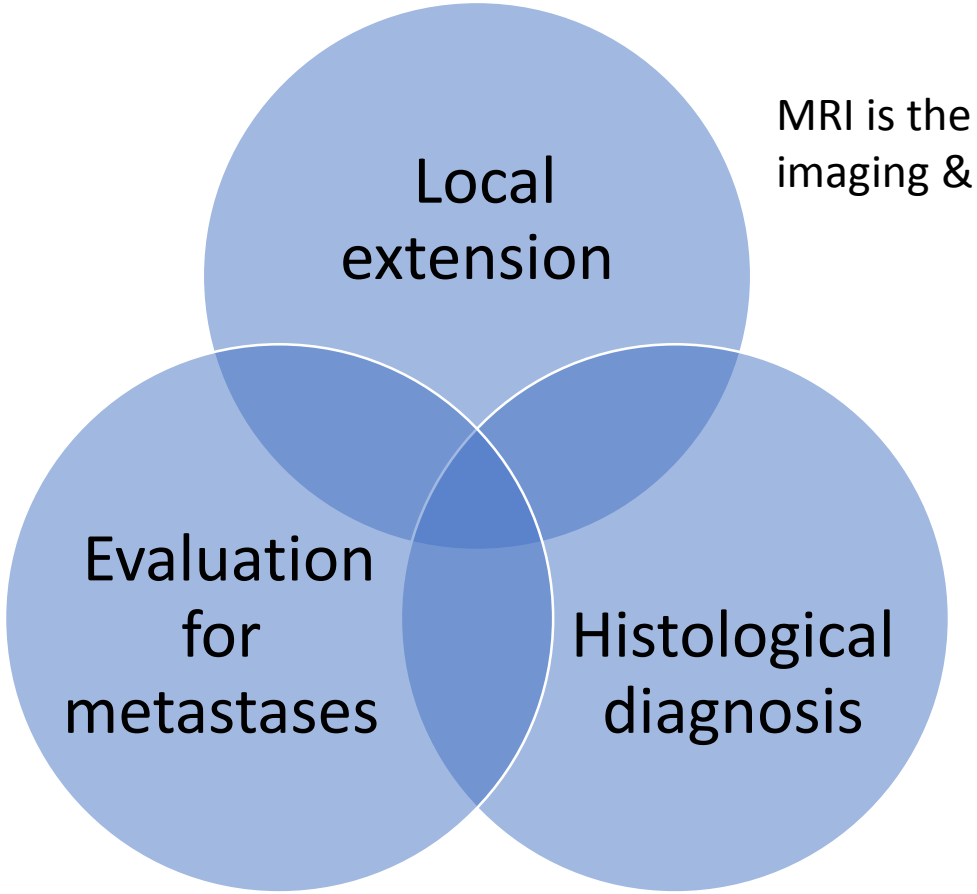
❖**Liposarcoma** is more common in **lower extremity**

❖ **Synovial sarcoma, epithelioid sarcoma & fibrosarcoma** -more often in **upper extremity**

❖Rarely (<5%) metastasize to lymph nodes (SS, RMS, epithelioid sarcoma, clear cell sarcoma & angiosarcoma)

Evaluation of a Soft-Tissue Sarcoma

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



MRI is the gold standard- cross sectional imaging & relation to NV Bundle

At initial presentation
- chest computed tomography (CT)-scan/PETCT

Staging of STSs

Summary - Soft Tissue Sarcoma

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

TABLE 4: AJCC Staging for Soft-Tissue Sarcoma in the Trunk, Extremity, and Retroperitoneum

Disease Stage	Characteristics
IA	T1N0M0G1, T1N0M0GX
IB	T2N0M0G1, T2N0M0GX, T3N0M0G1, T3N0M0GX, T4N0M0G1, T4N0M0GX
II	T1N0M0G2, T1N0M0G3
IIIA	T2N0M0G2, T2N0M0G3
IIIB	T3N0M0G2, T3N0M0G3, T4N0M0G2, T4N0M0G3
IV, extremity only	Any T with N1, M0, and any G
IV, extremity and retroperitoneum	Any T with any N, M1, and any G

Note—T1 = tumor 5 cm or less in greatest dimension; N0 = no regional lymph node metastasis; M0 = no distant metastasis; G1 = total differentiation, mitotic rate, and necrosis score of 2 or 3; GX = grade cannot be assessed; T2 = tumor greater than 5 cm but less than or equal to 10 cm in greatest dimension; T3 = tumor greater than 10 cm but less than or equal to 15 cm in greatest dimension; T4 = tumor greater than 15 cm in greatest dimension; G2 = total differentiation, mitotic rate, and necrosis score of 4 or 5; G3 = total differentiation, mitotic rate, and necrosis score of 6–8; N1 = regional lymph node metastasis; M1 = distant metastasis; T0 = no evidence of primary tumor. A full description of this staging system is set out in [1].

Treatment

Goals of treatment -- functional extremity without local tumor relapse

- Involves a **multidisciplinary team decision** - surgical resection with or without adjuvant radiation for successful limb salvage.
- Chemotherapy reserved for management of metastatic disease/ facilitate local tumor down-staging for very extensive lesions

Surveillance

- High-risk pts -follow-up every 3 mos for first 2 years for clinical examination & a chest x-ray or CT-scan
- High-risk patients every 6 months until five years & annually till 10 yrs
- MRI- if there is clinical concern for local or regional recurrence

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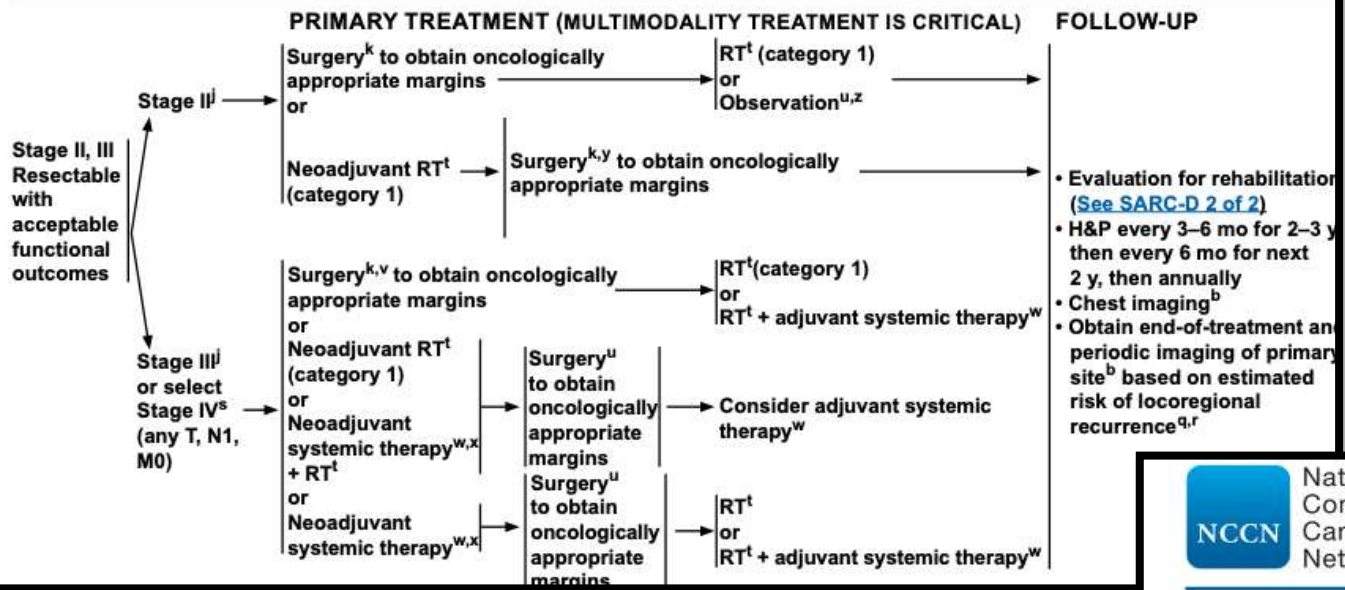

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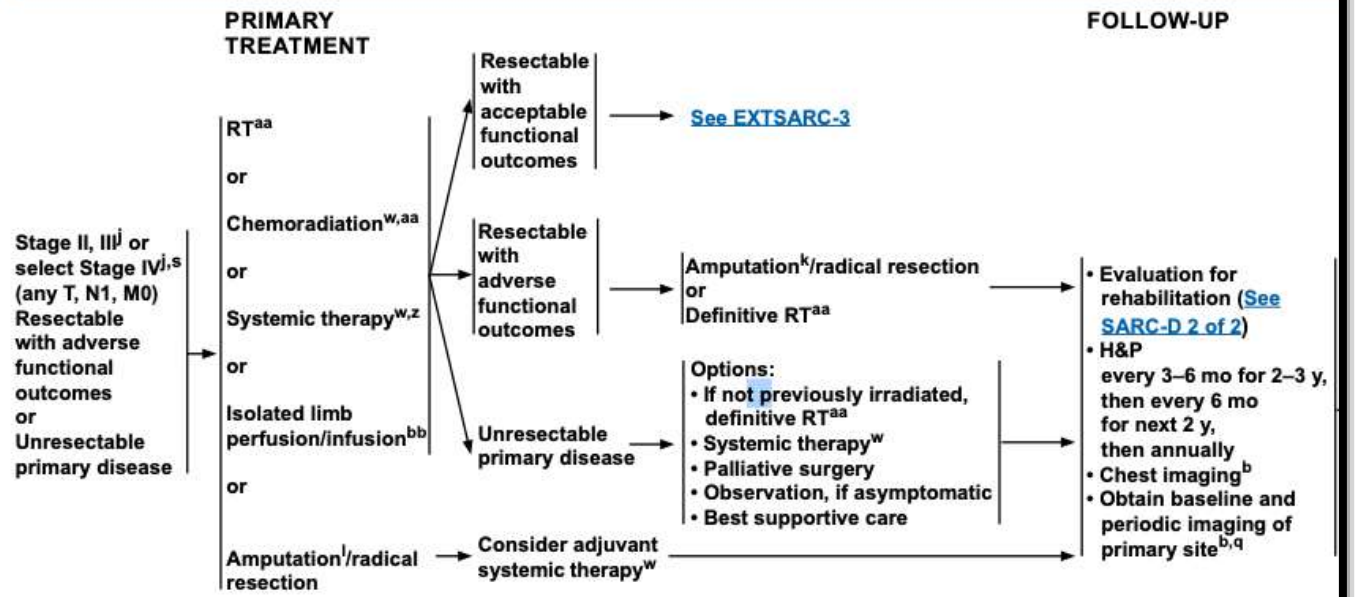

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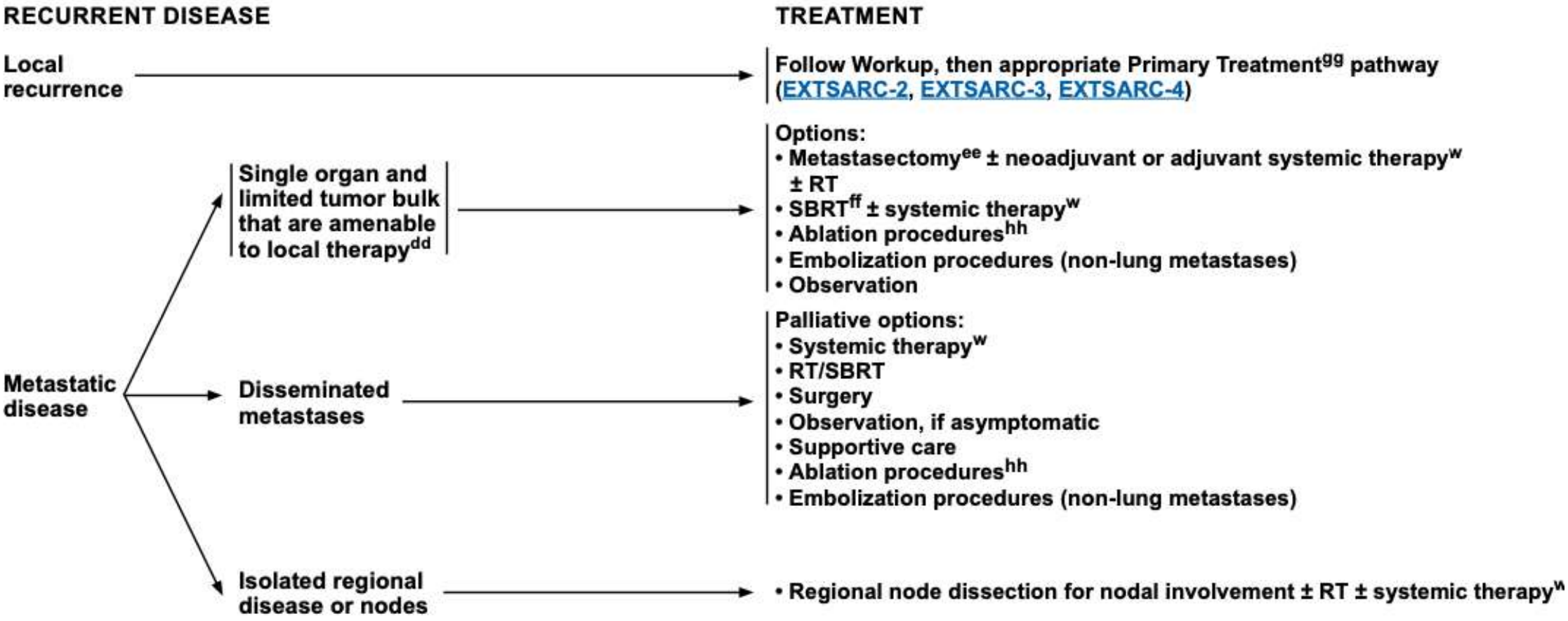

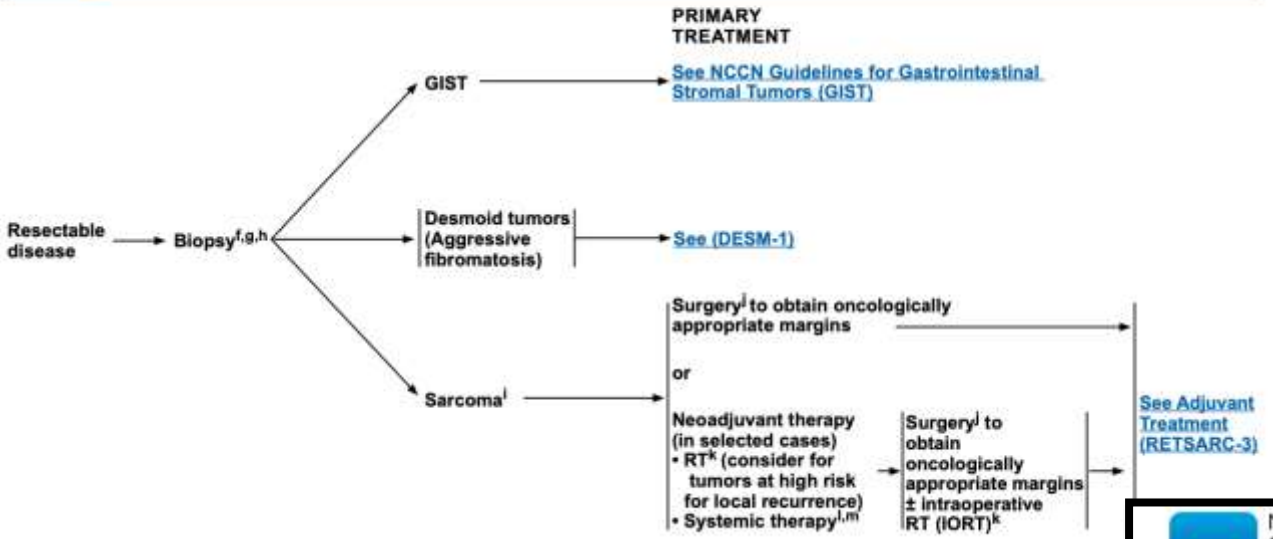

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Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial

Sylvie Bonvalot, PhD • Alessandro Gronchi, MD • Cécile Le Péchoux, MD • Prof Carol J Swallow, MD • Dirk Strauss, MD • Pierre Meeus, MD • et al. Show all authors

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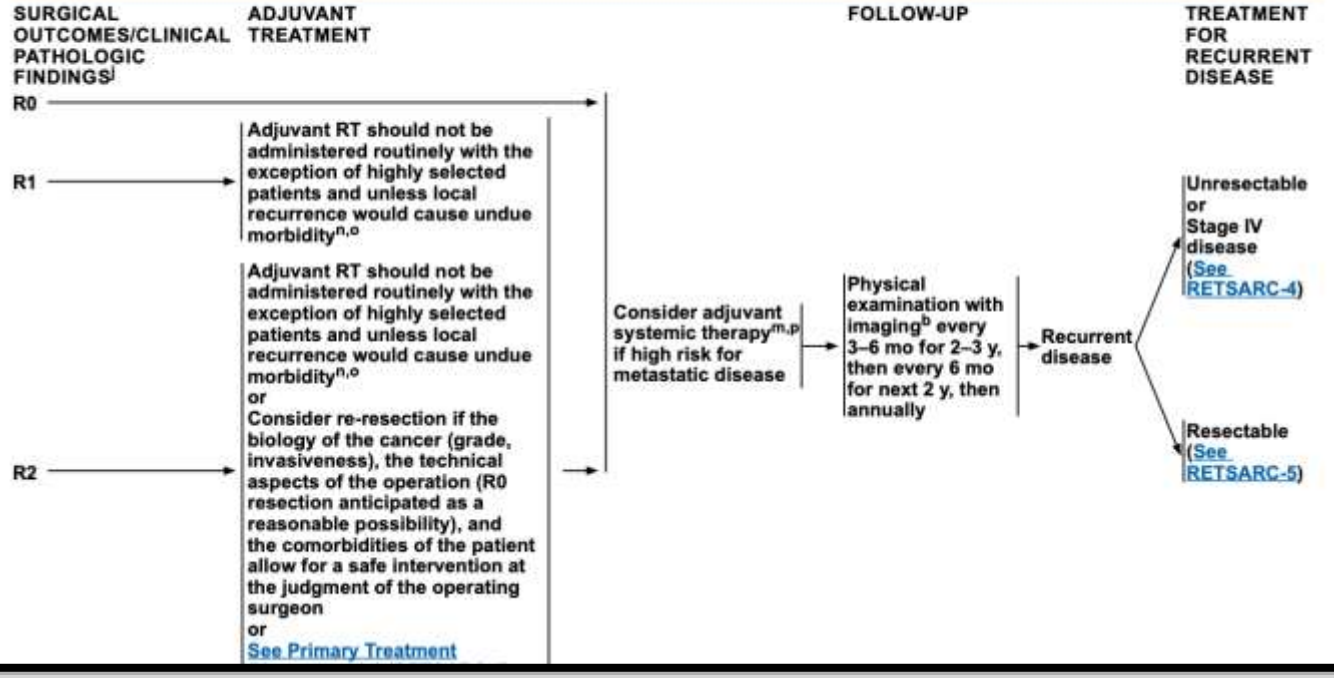
Discussion



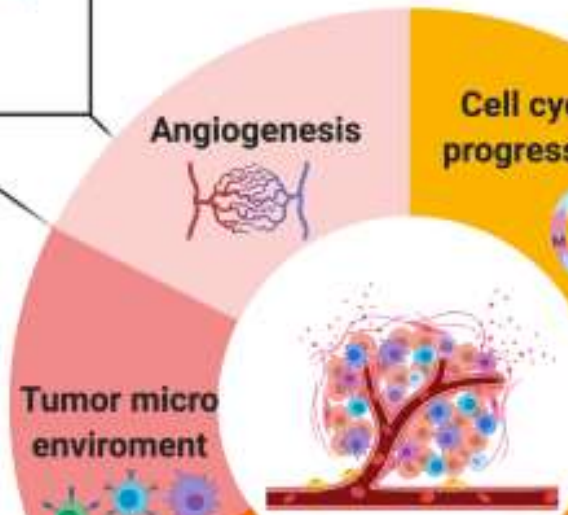
Preop RT indications

- If tumour adjacent to or involving critical structures.
- Likely difficult resection
- Tumour initially inoperable at diagnosis

Adjuvant RT Indications

- High Grade STS.
- Low-Int Grade STS with close or positive margins.
- Tumour recurrence
- Tumor size of >5 cm
- Lesions deep to or invading superficial fascia

Current Targeted Therapies for Sarcomas



Angiogenesis

- Pazopanib (VEGFR/PDGFR/KIT)
- Sunitinib (VEGFR/PDGFR/KIT)
- Sorafenib (VEGFR/PDGFR)
- Regorafenib (VEGFR)
- Apatinib (VEGFR)
- Bevacizumab (VEGFR)

Cell cycle progression

- Flavopiridol (Pan-CDKs)
- Dinaciclib (CDK1/2/5/9)
- Palbociclib (CDK4/6)
- Ribociclib (CDK4/6)
- Abemaciclib (CDK4/6)
- Nutlin-3 (MDM2)
- RG112 & RG7388 (MDM2)

Tumor micro enviroment

- Nivolumab (anti-PD1)
- Durvalumab (anti-PD1)
- Ipilimumab (anti-PD1)
- Pembrolizumab (anti-PD1)
- Tremelimumab (anti-CTLA4)
- CB-1158 (Arginase)
- GM-CSF (Macrophages)
- L-MTP-PE (Macrophages)
- Zoledronic Acid (Macrophages)
- Anti-GD2/3
- Anti-CD47
- Anti-RANKL antibodies
- CAR-T cell therapy

Sustained proliferative signaling

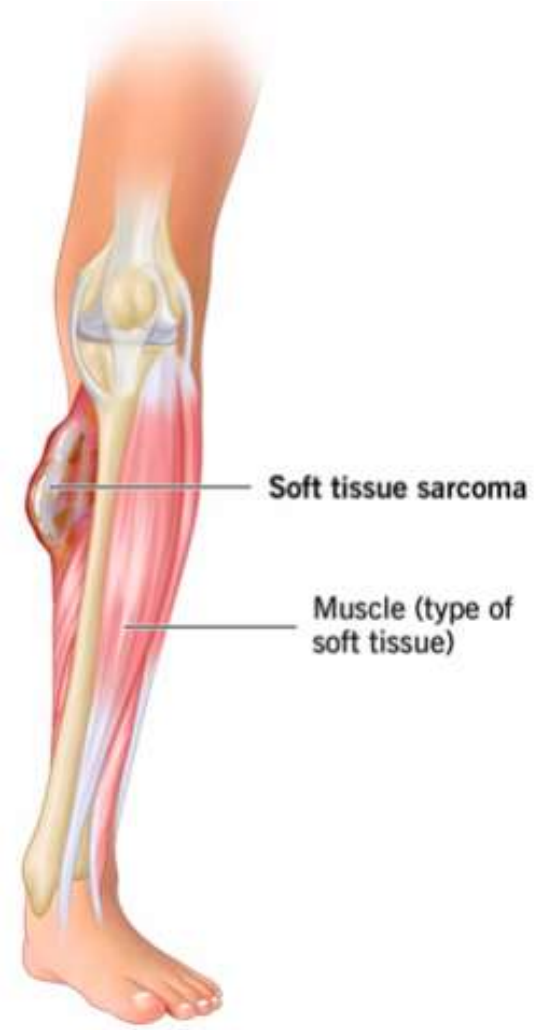
- Imatinib (PDGFR/KIT)
- Olaratumab (PDGFR/KIT)
- Crizotinib (MET)
- Dasitinib (Src/KIT/PDGFR)
- Alisertib (AURKA)
- ENMD-2076 (AURKA)
- IMC-A12 (IGFR1)
- R1507 (IGFR1)
- Ridaforolimus (mTOR)
- Temsirolimus (mTOR)
- Everolimus (mTOR)
- Sirolimus (mTOR)
- STAT3 inhibitors

Epigenetics

- Panobinostat (HDAC)
- Entinostat (HDAC)
- Belinostat (HDAC)
- Tazemetostat (EZH2)
- Guadecitabine (DNA methyltransferase)

DNA repair

- Olaparib (PARP)
- Rucaparib (PARP)
- Niraparib (PARP)
- Talazoparib (PARP)
- Veliparib (PARP)



Common Soft Tissue Sarcomas

Malignant peripheral Nerve Sheath Tumours

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

❖Malignant form of benign schwannoma

❖Sporadic or as part of NF1

❖Age: 20 to 50 years

- Often painless but aggressive in nature
- 20 % local recurrence risk

Prognostic factors include--

- Tumor size at presentation
- Tumor grade

Treatment : Margin negative resection is cornerstone of success

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

Angiosarcoma

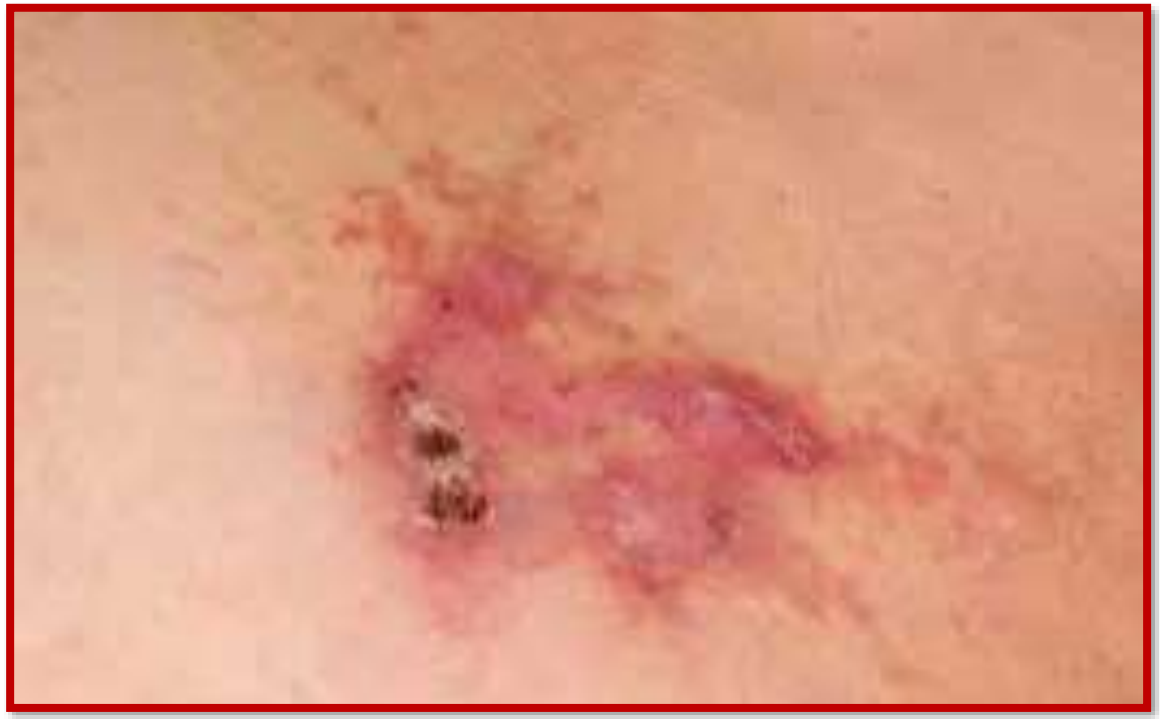
Origin – Endothelial lining of blood vessels

Sites –Trunk, H & N (Scalp),Viscera

- Common age 7th – 8th decade
- High regional node involvement

Causative factors-

- ❖ Maximum cases sporadic
- ❖ 40% are radiation associated
- ❖ Other association - lymphedema



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

Angiosarcoma

Metastasis- 20% at presentation

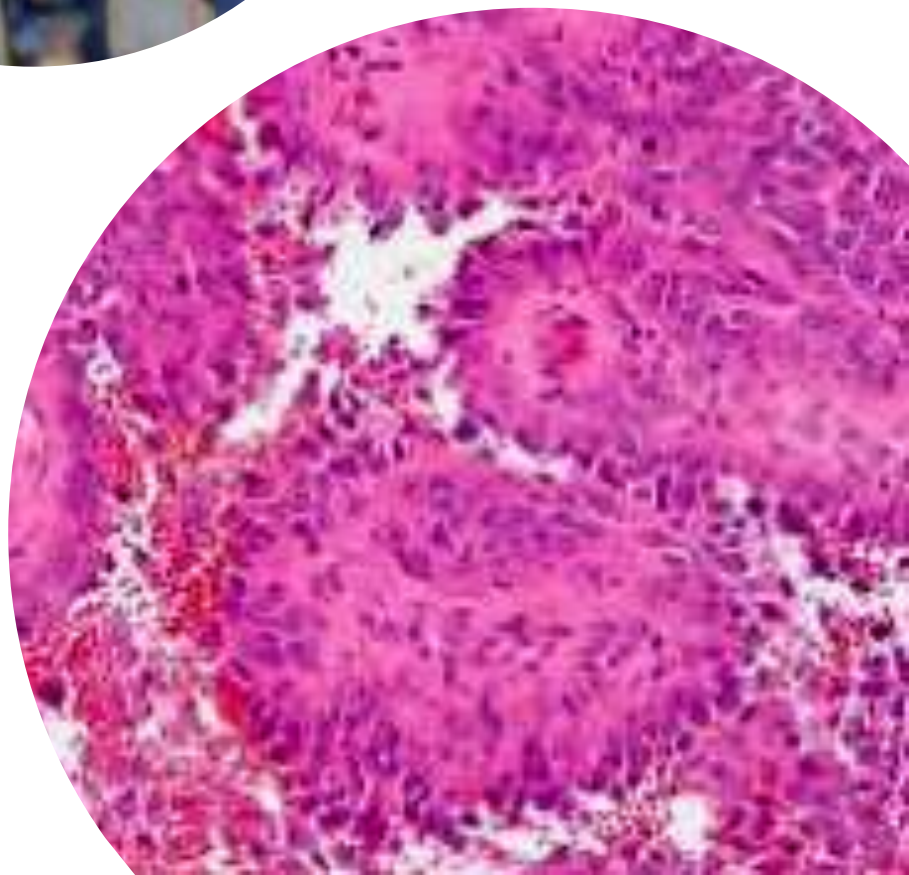
- Commonest – lung
- Liver In breast angiosarcoma

Histology

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

Poor prognostic factors

- Tumor > 5 cm
- Epithelioid component on histology



Angiosarcoma-Treatment

Localized angiosarcoma- Surgery followed by radiotherapy(Margin negative resection whenever possible)

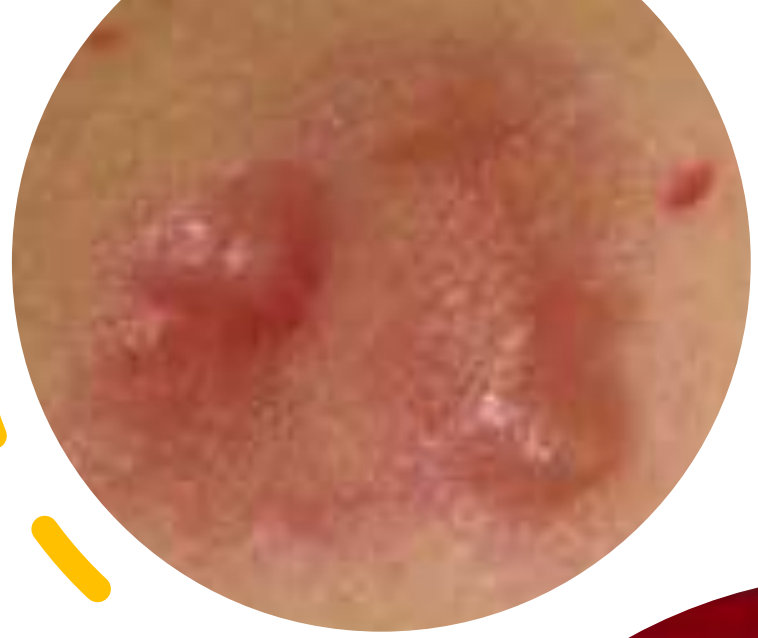
- Poor outcome – 5 yr DFS- 53% & Distant failure common
- Chemo & radio-responsive

Unresectable/ metastatic disease

- Paclitaxel + doxorubicin → RT(except when RT is the etiological factor)
- Second-line - pazopanib, eribulin mesylate, and trabectedin.
- Propranolol may be a promising alternative.
- TKIs; Angiogenesis inhibitors + cytotoxic agents &Immunotherapy may be active

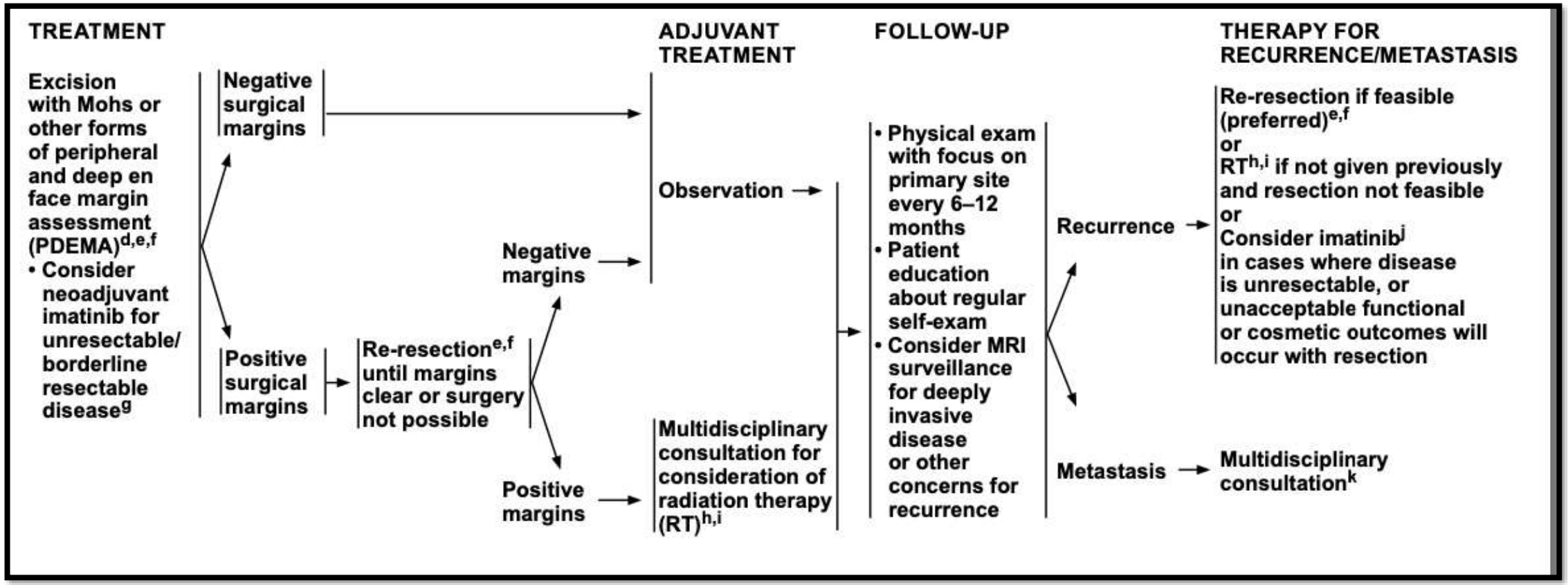
Dermatofibrosarcoma Pertubrans

- Uncommon, No gender prediliction
- Accounts for 1%- 6% of all STSs & 18% of all cutaneous STS
- African Americans afflicted more than whites
- Commonest age affected- 4th – 7th decade
- Translocation t(17;22)(q22;q13) & PDGFB overexpression
- Majority occur on trunk (50%), extremities (35%) & head and neck (15%).



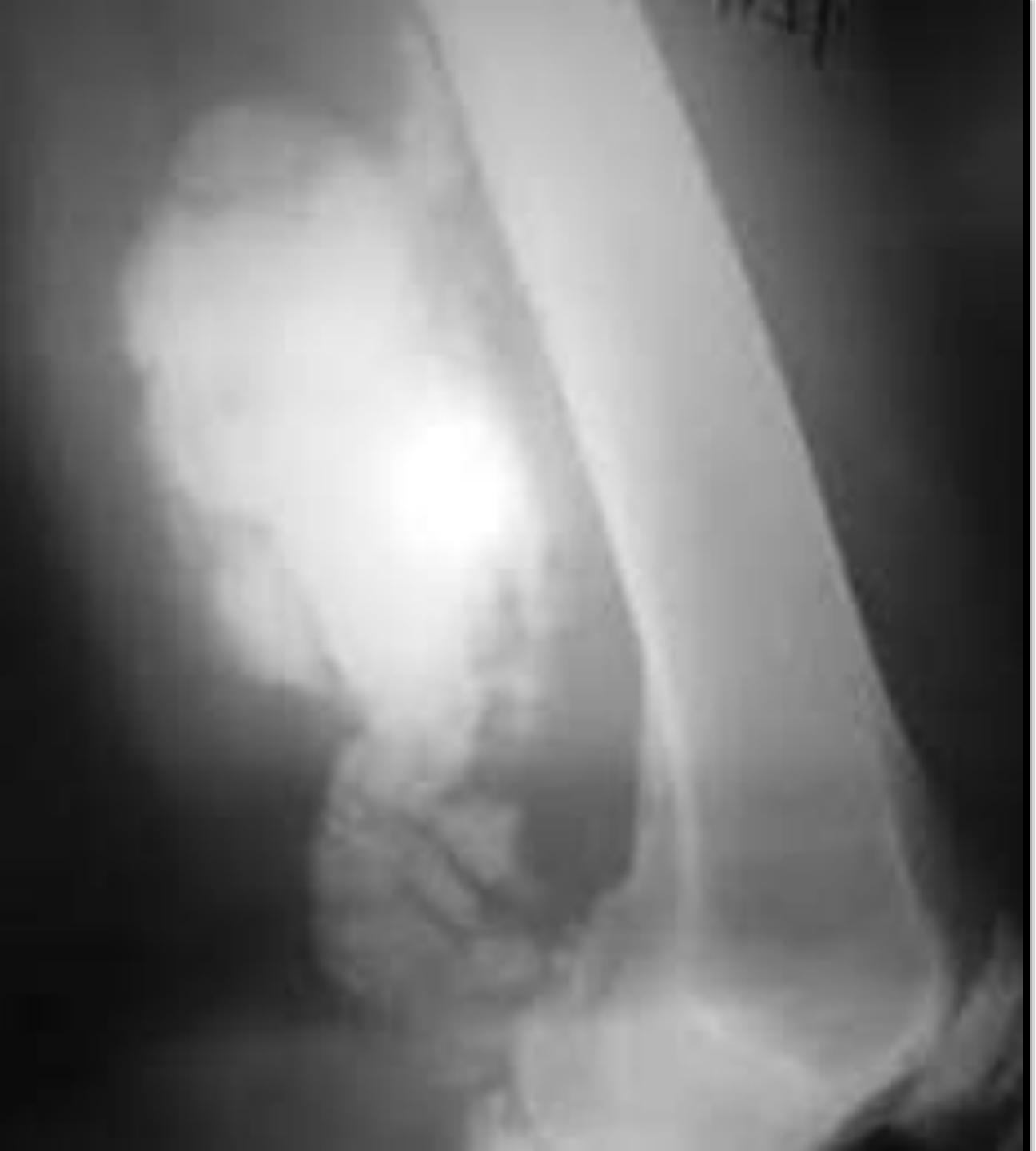
Reddish/ brown, firm, indurated nodules
Usually painless – can be large at presentation
May be mistaken for keloid/ hypertrophic scar

Dermatofibrosarcoma Pertubrans



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

Metastasis- Rare & Implies degeneration to fibrosarcoma



Extraosseous Osteosarcoma

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

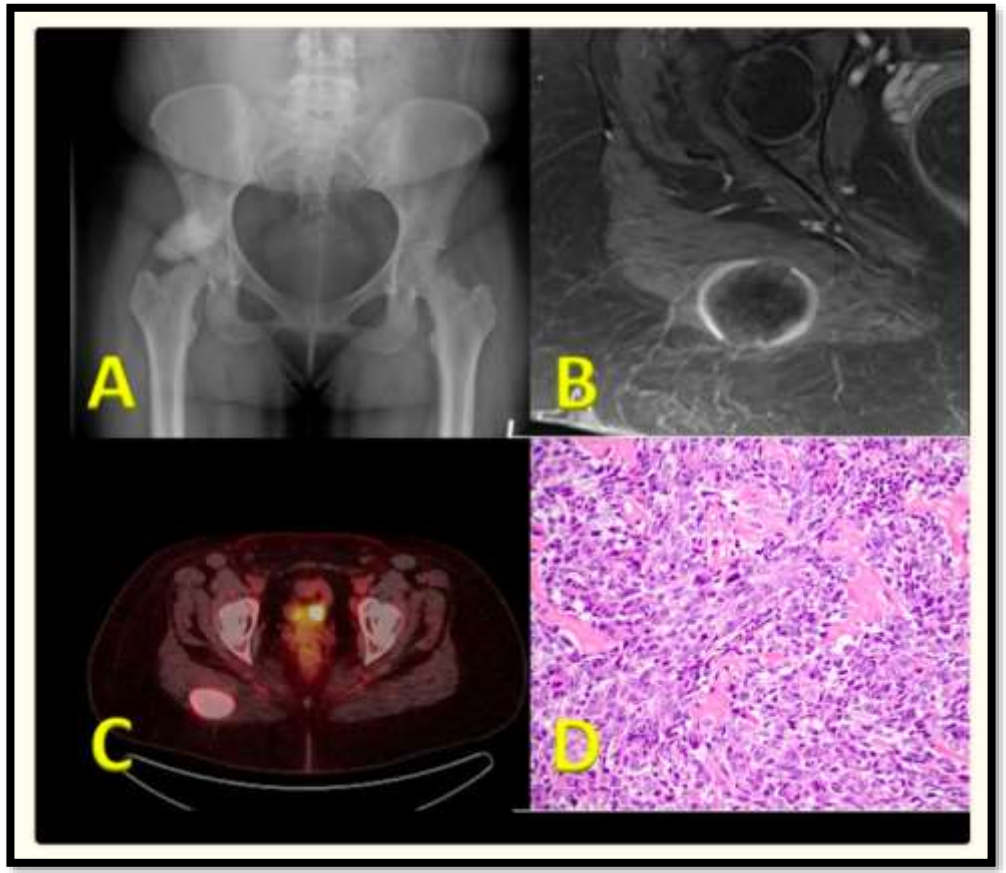
Variants:

- Osteoblastic
- Chondroblastic
- Fibroblastic

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

Extraosseous Osteosarcoma

Histopathologic diagnosis -Presence of osteoid a homogeneous, pink, structureless extracellular material .Tumour cells- pleiotropic, containing small & round, clear, multinucleated, spindled, epithelioid, plasmacytoid, and/or fusiform cells



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

Extraosseous Osteosarcoma -Etiology

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

Up to 60% of high-grade EOS show TP53 mutations, compared with 1% of low grade OS

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.
- Multidisciplinary approach, long-term survival has increased to 70%.
- Recurrent disease or metastatic lesions (in lungs) at diagnosis have a lower survival rate of 20%

Liposarcoma (LPS)

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.

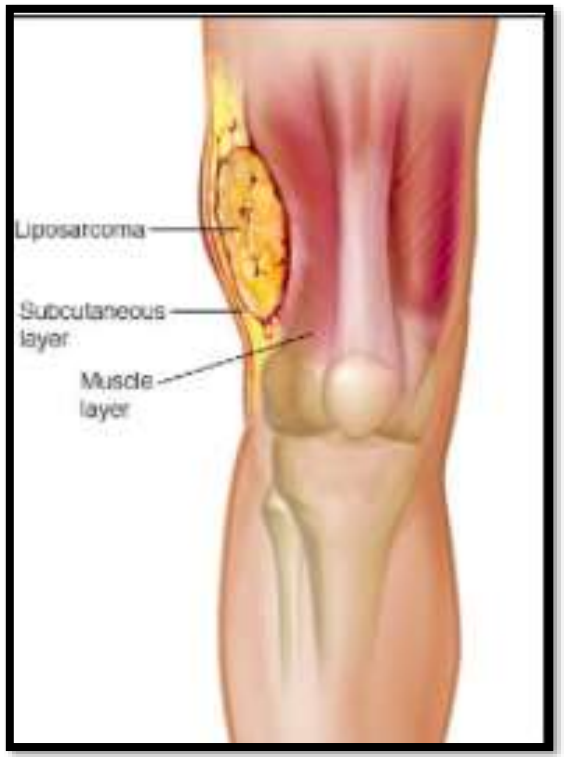
MLPS

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

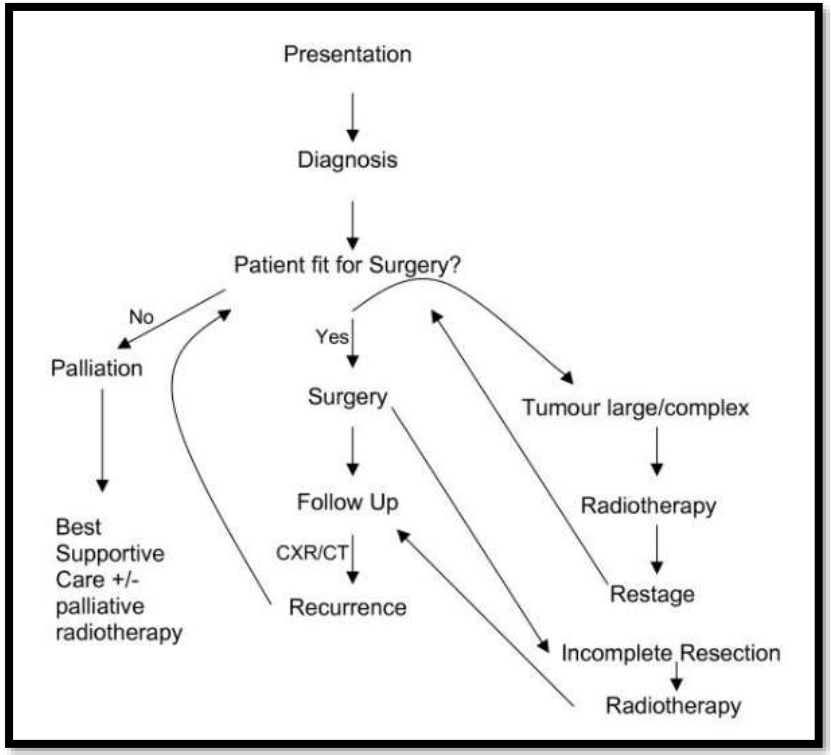
- Most frequent STS subtypes in adults
- Arise from primitive mesenchymal cells
- Account for 14 -18% of all STS
- Commonly arising in deep soft tissues – thigh/ retroperitoneum
- Prognosis depends on histologic features, site, and size



Liposarcoma

Morphological diversity correlated with their biologic behaviour

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



Desmoid Tumours

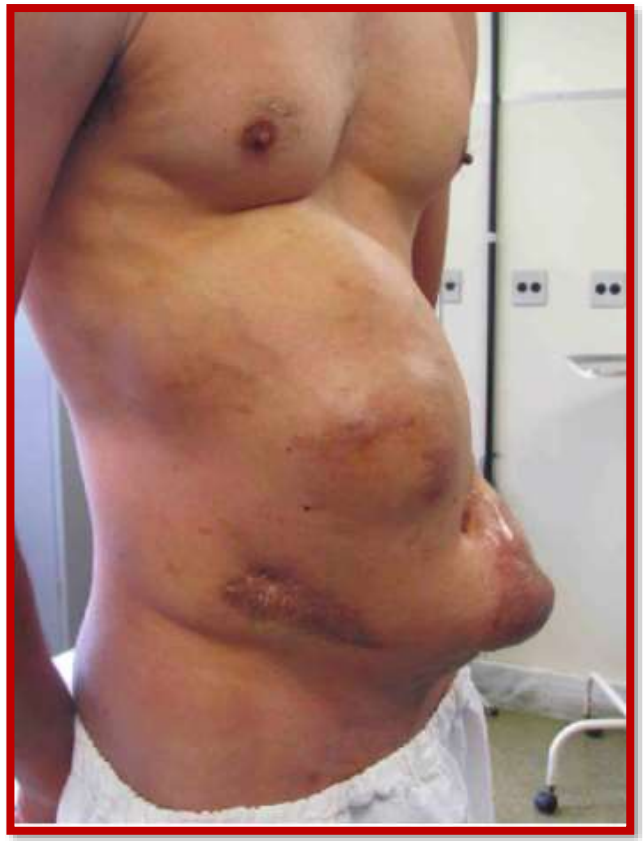
- Aggressive fibromatosis
- Majority Sporadic (75-85%)
- Age: 30-40 yrs
- Recent pregnancy& Antecedent trauma
- Others – related to FAP
- Seen in 20% pts with FAP
- Preceded by colonic polyposis
- Occur at prior colectomy scar

Detailed family history to r/o unappreciated FAP (Gardners Syndrome)

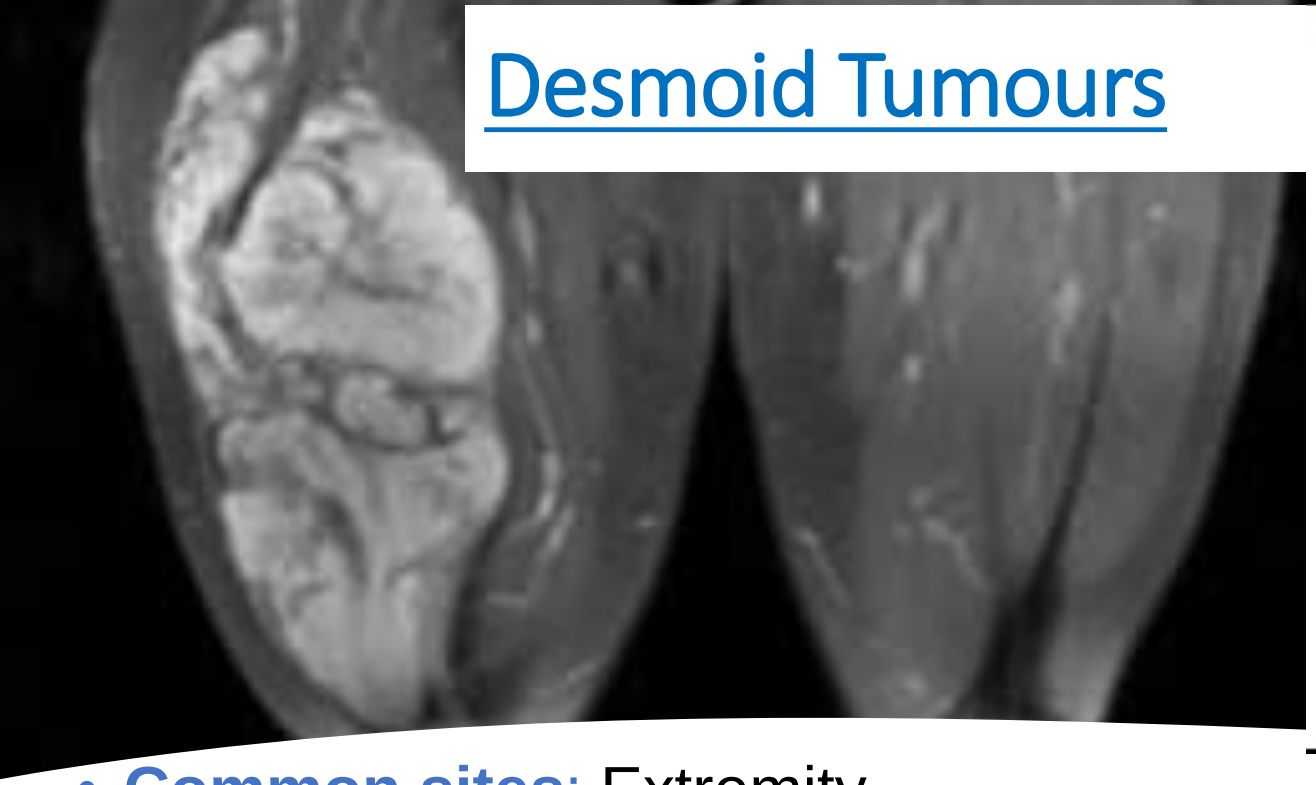
Consider screening colonoscopy

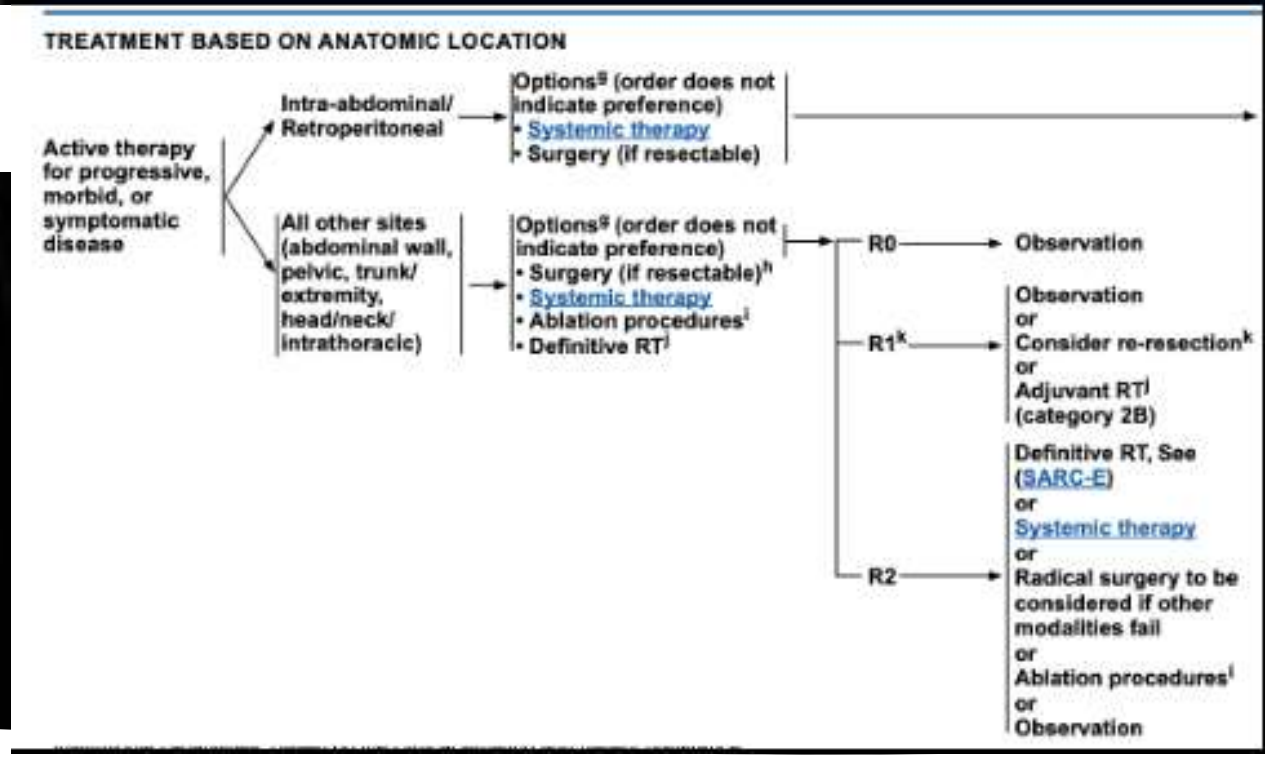
- **Related to WNT signaling pathway**
- Sporadic cases
- CTNNB1 mutation
- Stabilized form of β-catenin
- Accumulates & transported to nucleus
- Activated transcription factors proliferative effects

FAP cases:
APC mutations
β-catenin stabilization
Specific APC codon mutations confer higher risk of desmoid



Desmoid Tumours



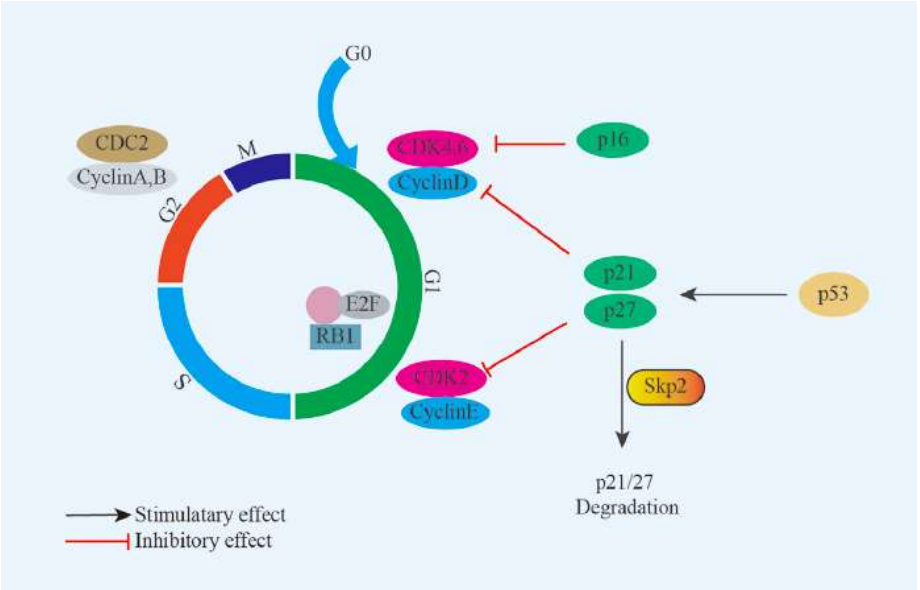


- **Common sites**: Extremity, intra-peritoneal, extra-peritoneal, abdominal wall & chest wall
- Asymptomatic firm mass
- Painful mass
- Bowel obstruction/ ischemia

- 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

Undifferentiated Pleomorphic Sarcoma (UPS)

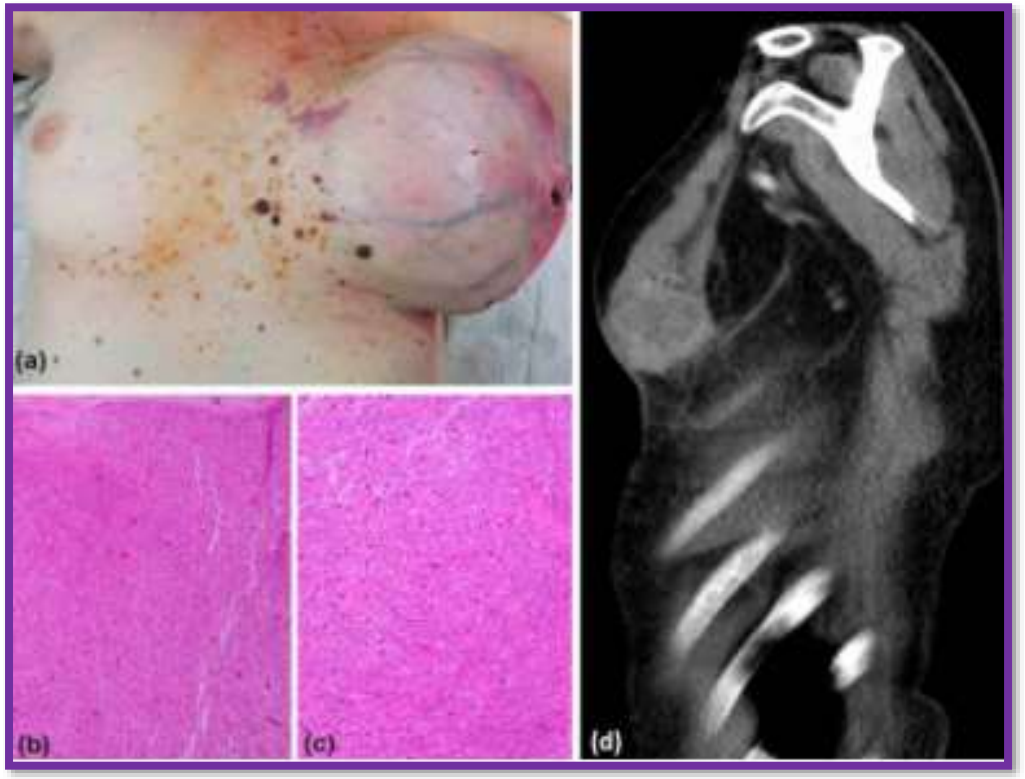
- Previously classified as malignant fibrous histiocytoma (MFH)
- Commonly affects adults aged 50 -70
- 1:2 female: male ratio
- Originate from a primitive pluripotential mesenchymal cell or from high-grade neoplasms of poor differentiation



- 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
- 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 body
- Most frequent locations are in deep soft tissue of extremities & retroperitoneum.
- Extremities (lower >> upper), Head & neck
- Previous RT site
- Site of chronic ulceration (rare)
- Elderly pts (peak- 60-70 yrs)
- Solitary, painless, soft – firm, skin colored, deep seated mass



Undifferentiated Pleomorphic Sarcoma (UPS)

Surgery mainstay of treatment

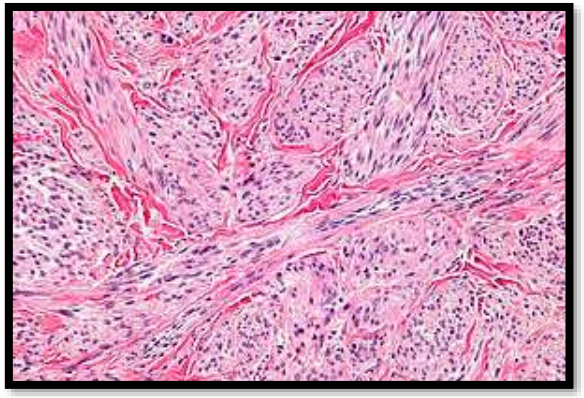
Wide or radical excision including **infiltrative "tail"** is required; prone to local recurrence & metastasis.

Wide excision followed by radiotherapy recommended for deep lesions

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

Leiomyosarcoma (LMS)

Deletions	*PTEN*
	RB1
Mutations	*TP53*
	ATRX
	MED12
Amplification	*MYOCD*



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

- Arising from smooth muscles -affecting retroperitoneum, uterus, skin, superficial soft tissues & deep compartments of extremities.
- Account for 10-15% of all STS
- Categorized into 3 major groups
  - ➢ Somatic soft tissue LMS
  - ➢ Cutaneous LMS
  - ➢ Vascular LMS
- LMS are refractory tumors showing treatment resistance.
- Prognosis is poor with low survival rates compared to other STSs .

Leiomyosarcoma (LMS)

Malignant smooth muscle cell tumor.

2nd most common STS after liposarcoma

Sites

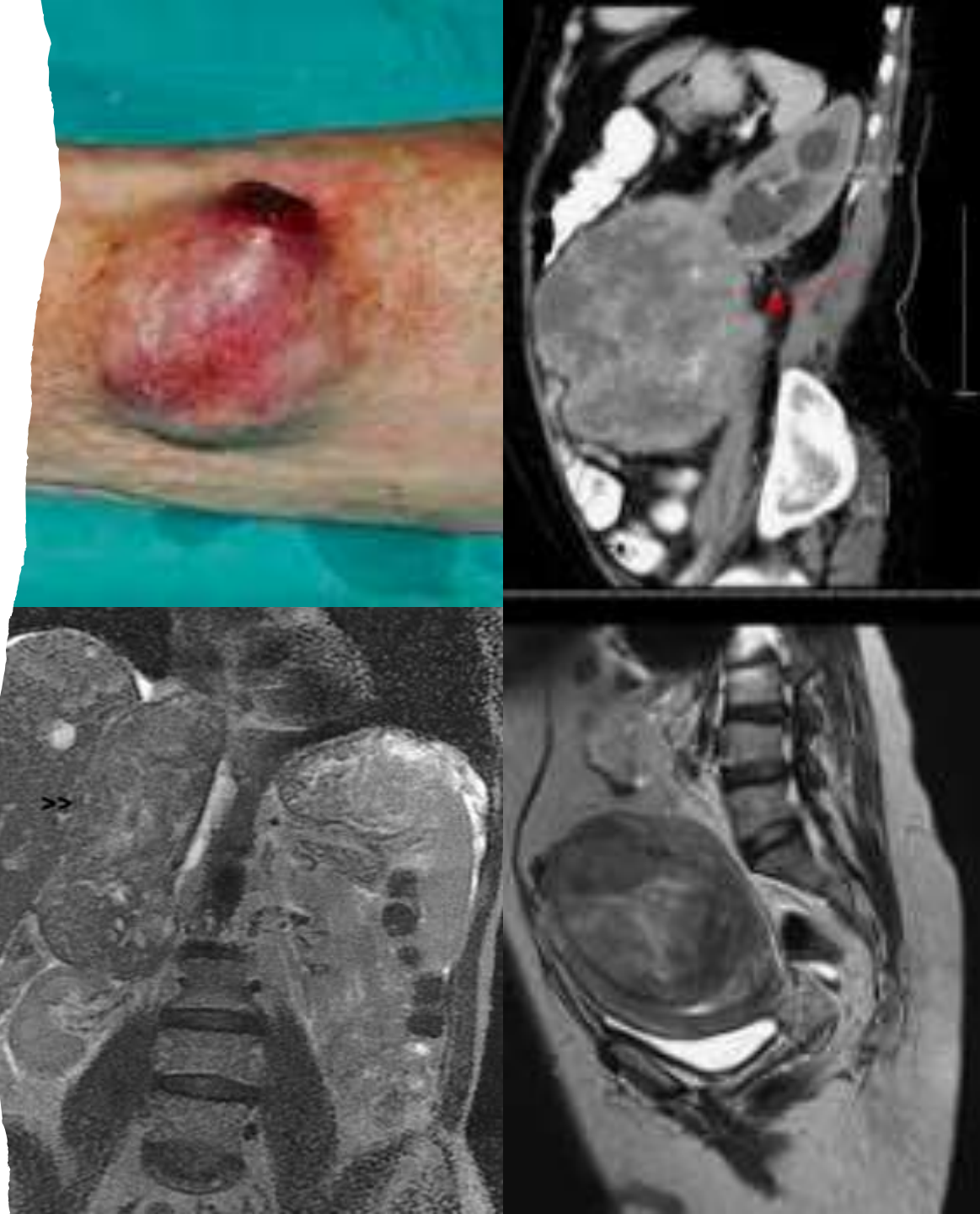
- Retroperitoneum > Peritoneal cavity (uterus)
- 25% - trunk & extremity

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/ Inter-positioning graft of IVC
- Collaterals preserved – ligation of IVC without reconstruction

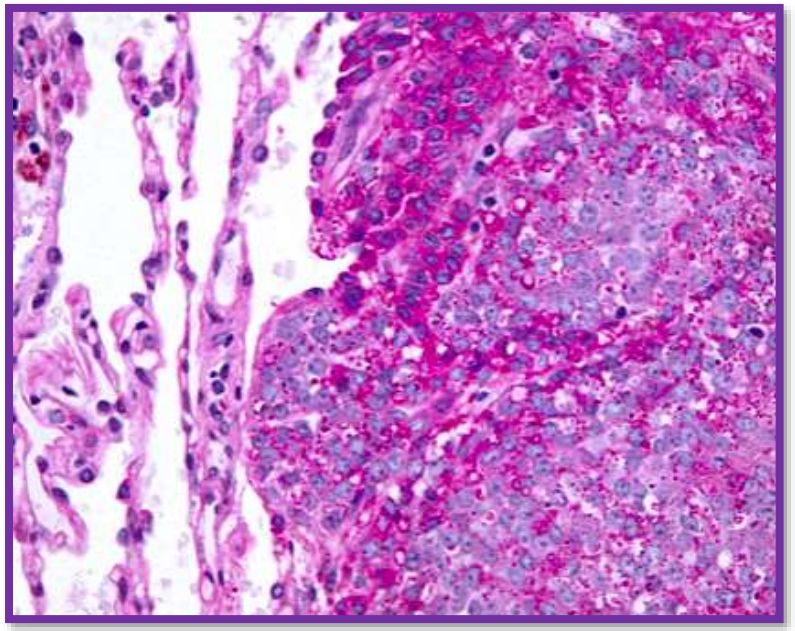
Metastasis

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

Extraosseous Ewing Sarcoma (EES)

- Rare, small, round, blue cell tumor of with same histology & pathogenesis as ES of bone.
- Seen in 2nd or 3rd decade of life, 1:2 female:male ratio.
- Commonly sites - 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)

- CD99-negative ESFT express CAV-1.
- Fli-1, HNK-1 & ERG expressed in ESFT
- Epithelial differentiation (CK-AE1/AE3) - in 20–30% of ESFT



Tumor cells, intermixed with round cells showing fine chromatin. Stroma can be scant & fibrotic or can show sclerosis & lace-like appearance.

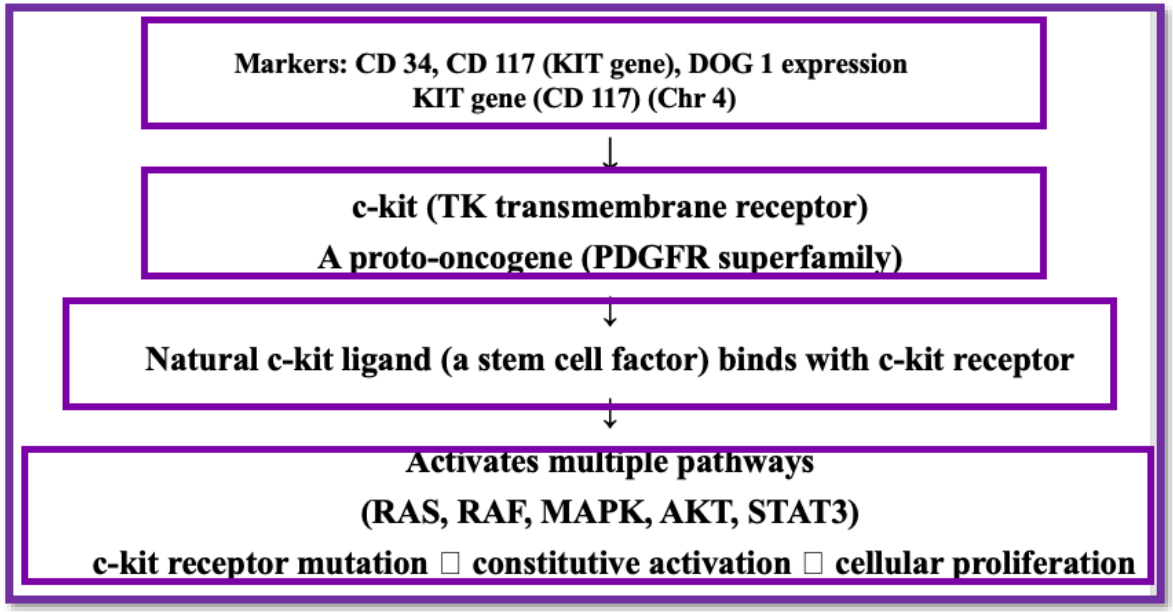
Extraosseous Ewing Sarcoma (EES)

- Prognosis & management -osseous Ewings Sarcoma
- **Systemic chemotherapy is combined with surgery &/or radiotherapy, depending on location &size of neoplasm.**
- Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide & etoposide (VDC/IE) - chemotherapy regimens
- Targeted therapeutics -clinical responses for IGF-1R inhibitors
- Immunotherapies are emerging option in advanced EES

Gastrointestinal Stromal Tumor (GIST)

- Mesenchymal-derived tumor arising from digestive tract—spindle cell neoplasm of smooth muscle origin
- Accounts for ~3% of all GI malignancies
- Affects adults 40 -70 years & No gender predilection
- **Origin – I**nterstitial cells of Cajal within myenteric plexus.(function as pacemakers in viscera)

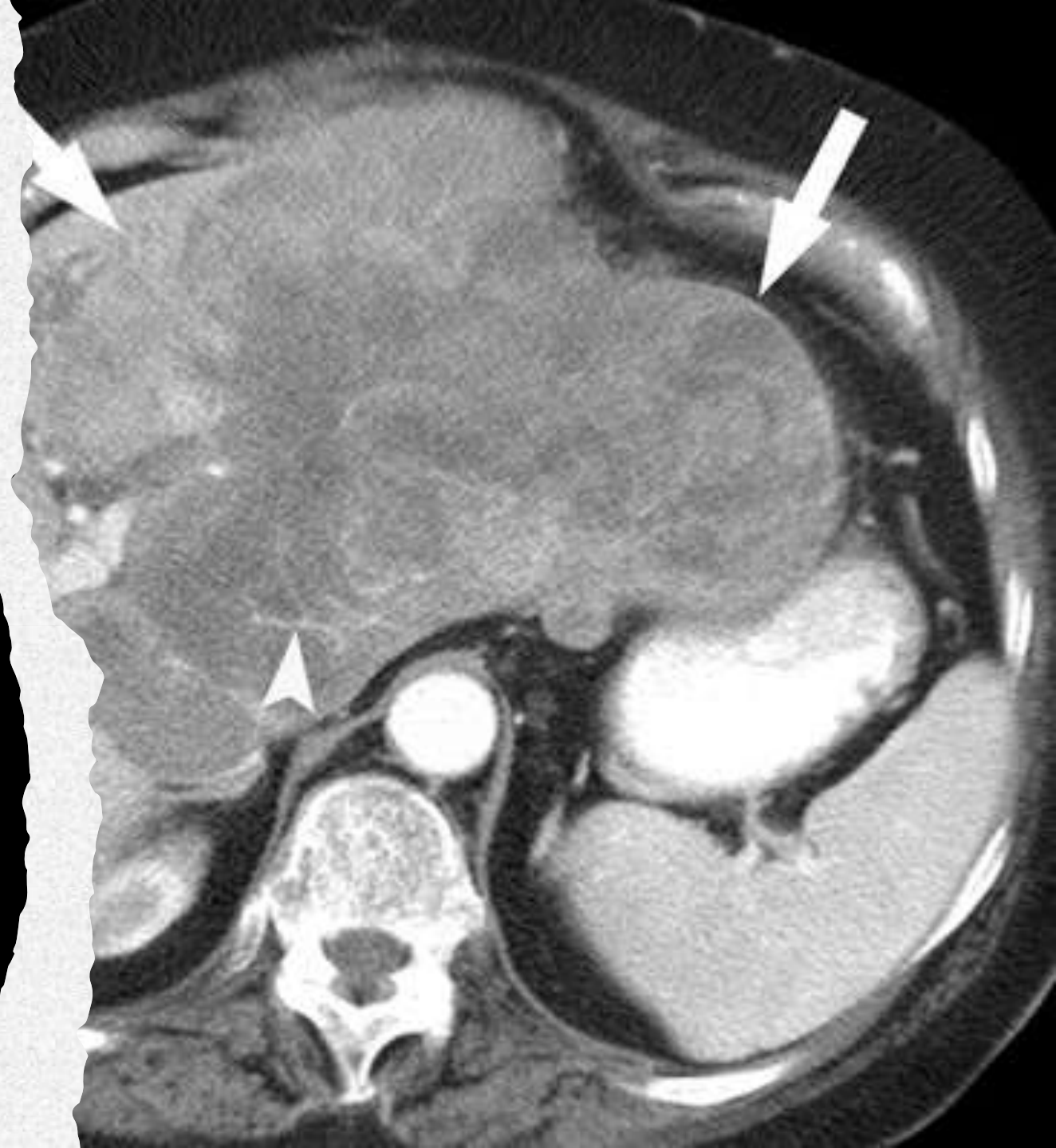
Sites – Stomach, small bowel, rectum.

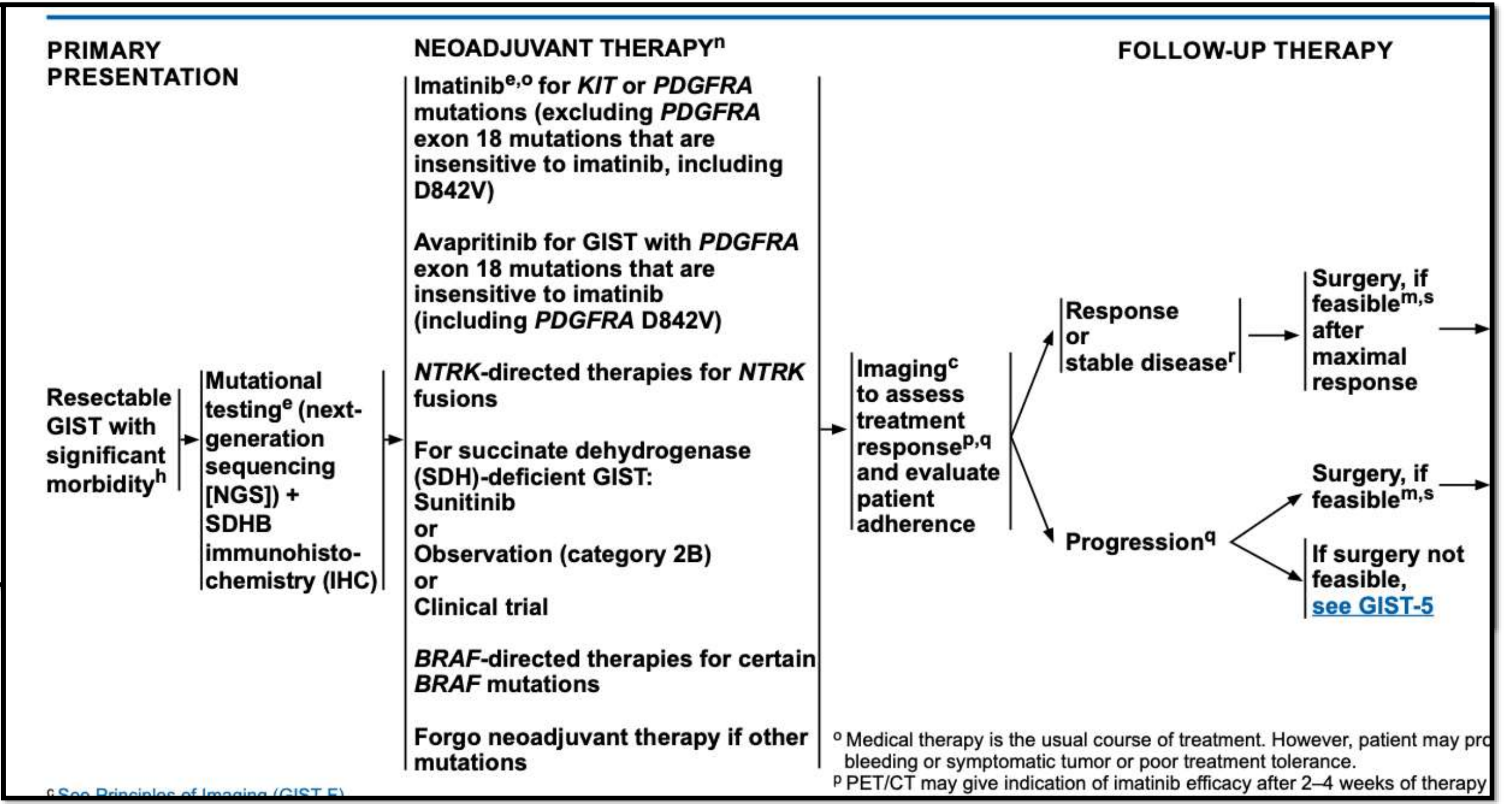


70% GIST – KIT gene mutations
07% GIST – PDGFRA mutations
15% GIST – Wild type KIT & PDGFRA genotypes
Other mutations – SDH (Carney- Stratakis syndrome), BRAF, KRAS and NF1 (NFtype 1)

GIST

- Asymptomatic (incidental)
- Pain, Nausea, vomiting, GI blood loss (rare
- Associated syndromic features
- **CT findings**
- Well encapsulated with heterogeneous contrast enhancement
- Endoscopic US guided needle biopsy – spindle cell neoplasm
- Pre-op staging: CECT chest, abdomen, pelvis





[c] See Principles of Imaging (GIST-F)

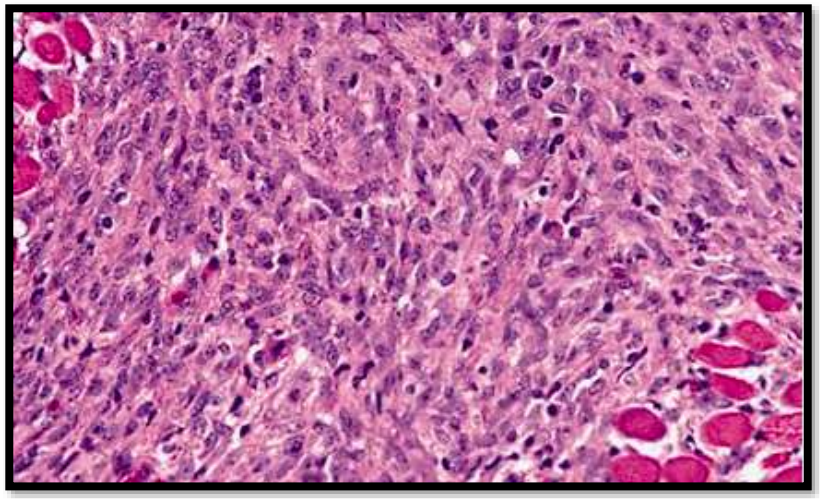
[o] Medical therapy is the usual course of treatment. However, patient may pro bleeding or symptomatic tumor or poor treatment tolerance.

[p] PET/CT may give indication of imatinib efficacy after 2–4 weeks of therapy

Congenital Fibrosarcoma (CFS)

- Congenital (or infantile) fibrosarcoma (CFS) - malignant neoplasm of fibroblasts that occurs in pts aged 2 years or younger.
- Excellent prognosis & a very low metastatic rate.

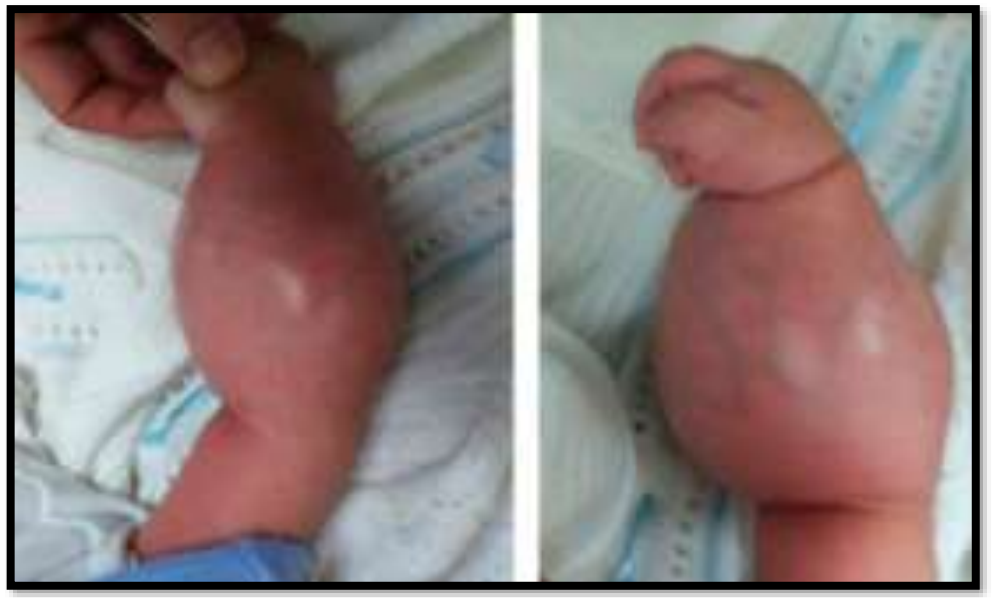
Genes
ETV6-NTRK3
EML4-NTRK3
TPM3-NTRK1
LMNA-NTRK1
MIR584F1-NTRK1
SQSTM1-NTRK1
TPR-NTRK1
STRN-NTRK2
NTRK1 rearrangement, not otherwise specified
ETV6 rearrangement, not otherwise specified
RET-MYH10
RET-K1AA1217
RET-CLIP2
BRAF point mutations
FOXN3- BRAF and TRIPP1-BRAF
EPB41L2-BRAF
KIAA1549-BRAF
OSBP-BRAF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



- Sheets of malignant spindle cells forming interlacing cords with focal collections of inflammatory cells.
- Areas of haemorrhage, necrosis, & calcifications
- Mitoses can often be identified

Congenital Fibrosarcoma (CFS)

- Limited number of IFS can regress spontaneously
- 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



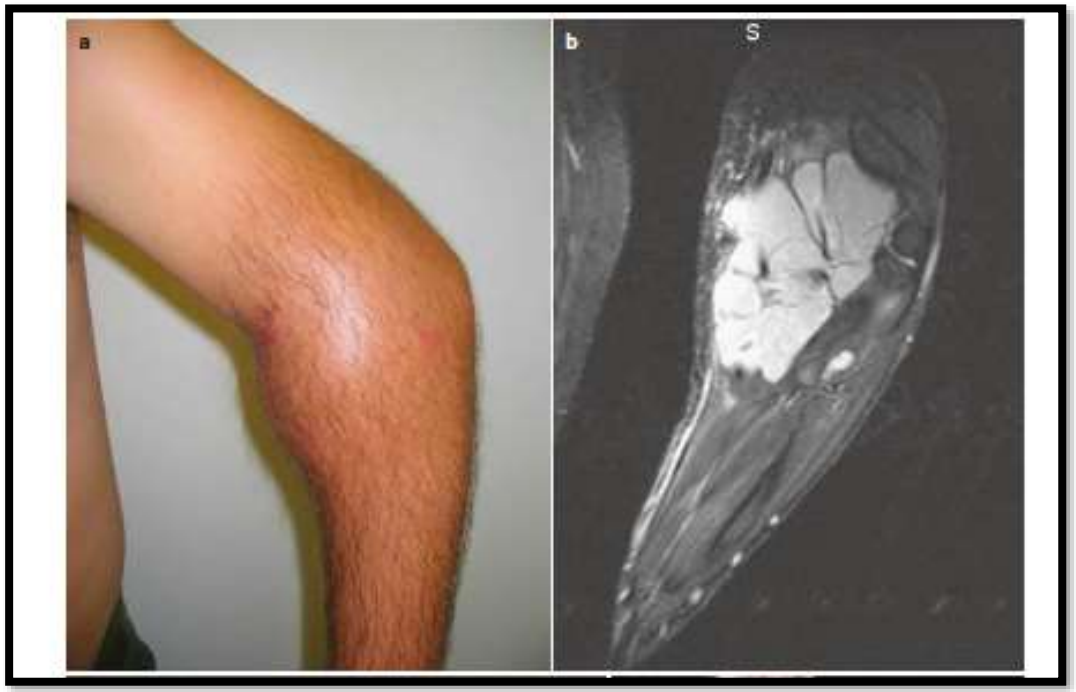
- **Preop chemotherapy** used in inoperable pts → delayed conservative surgery or complete resection when tumor shrinkage is achieved
- **Postop chemotherapy** recommended as first-line treatment for pts with macroscopic residual disease to decrease local recurrence
- **Radiotherapy application is limited**

Synovial Sarcoma (SS)

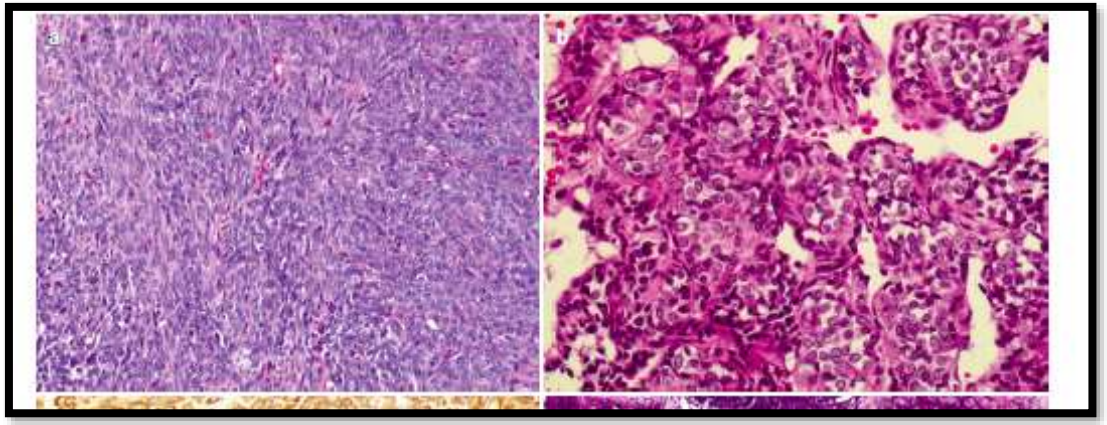
- Aggressive subtype-arising from synovial tissue lining joint cavities of extremities,
- Often affects adolescents and young adults
- Accounts for ~ 8% of all STS
- Trauma can draws attention to an already existing mass
- Deep soft tissue of extremities & predilection for lower extremities..
- Head & neck area is 2nd most common site- retropharyngeal & parapharyngeal
- Less frequent in trunk.
- Unusual locations such as skin, lung, prostate, bone, kidney, and CNS.

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.

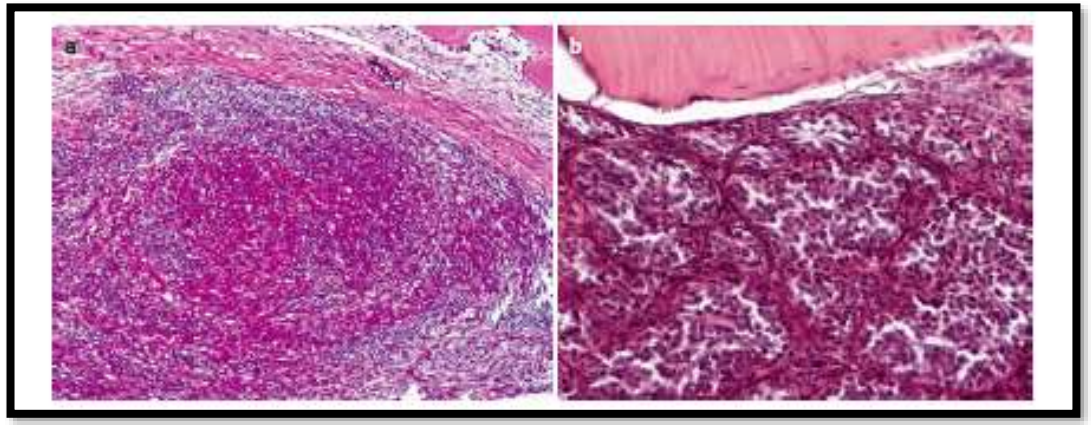
Synovial Sarcoma (SS)



- Expansile, multilobular mass - circumscribed by a pseudocapsule (Averages 3–10 cm in dia.)
- Secondary changes can be present as necrosis, cyst formation, hemorrhage, myxoid areas & calcification.



Sheets of spindle cell proliferation. "School of fish" is a characteristic growth pattern of this type



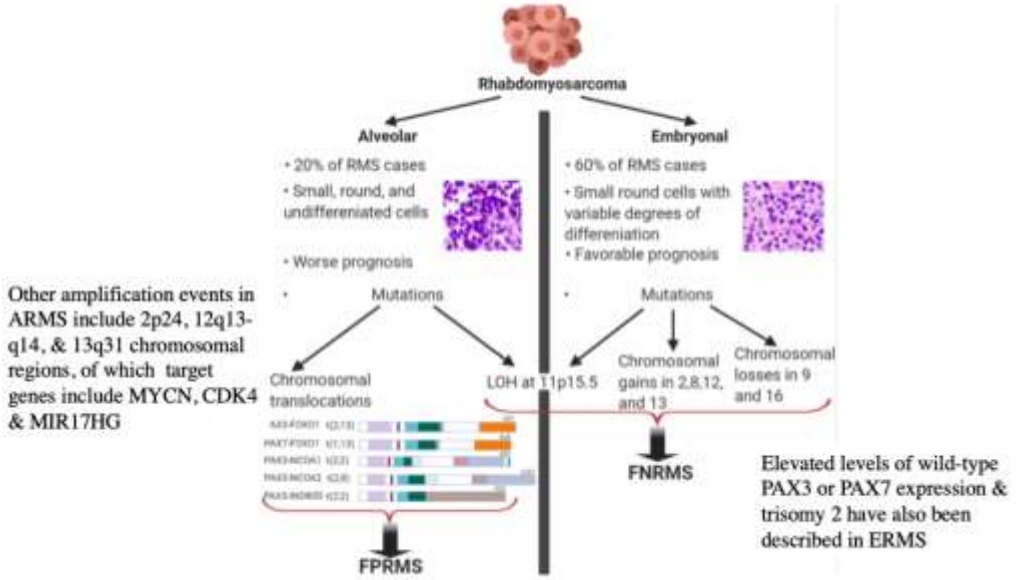
Biphasic SS have the addition of characteristics of the epithelial component in varying proportions

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 age of 6 years, a second peak during mid-adolescence
- Arising in limbs, central axis, or head and neck areas



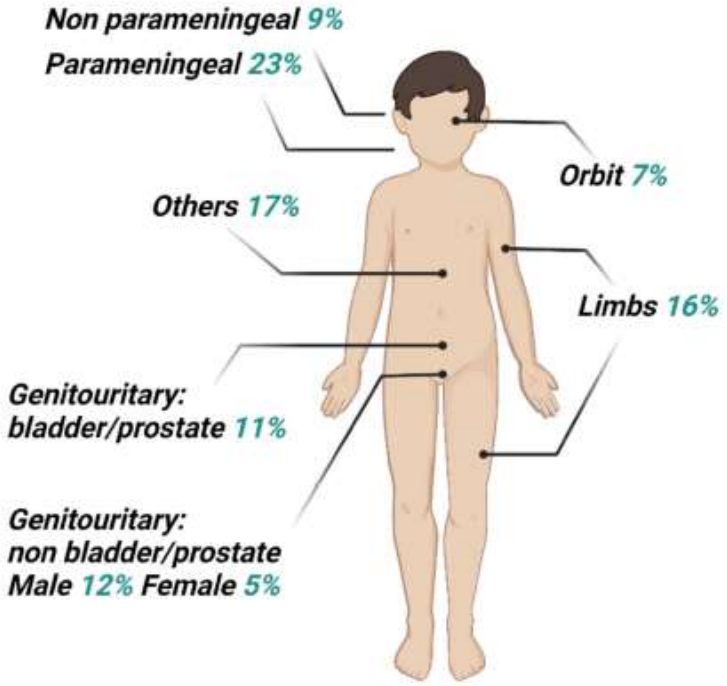
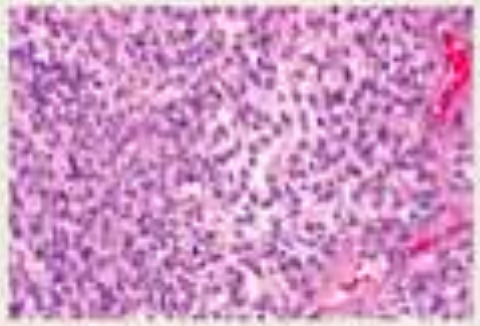
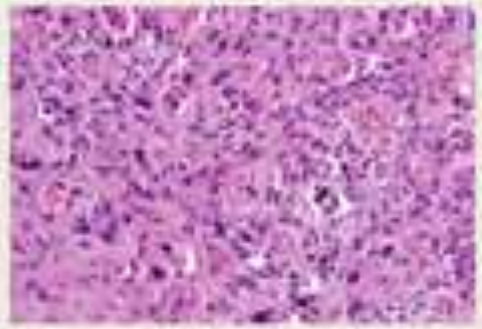
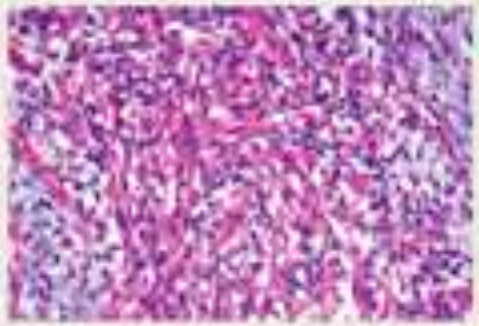
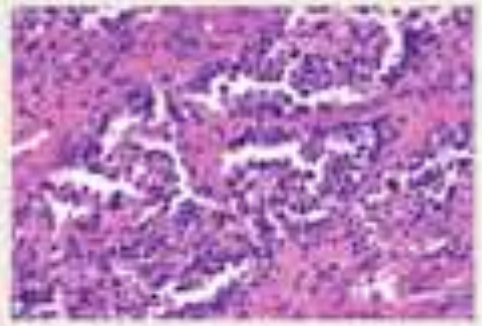


Table 1 | **RMS subtypes based on histological morphology**

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

Rhabdomyosarcoma (RMS)

- 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 Paediatric Oncology Malignant Mesenchymal Tumor (MMT) Group prefers use of chemotherapy as a front-line approach with its aim at avoiding, 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

Small molecule inhibitors include

- Targeting of IGF-1 receptor
- Anti-angiogenic drugs
- Kinase Inhibitors-Sorafenib (Nexavar)
- mTOR inhibitors such astemsirolimus (Torisel) & everolimus (Afinitor)
- Additional therapeutic focus - immune mediated destruction of PAX FOXO1 fusion oncoprotein by vaccination or by kinase inhibitors

Low Risk Group (A)

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

Subgroup B Treatment

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

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

Subgroup D

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

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

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 & nodes negative & any tumour size or age

Subgroup G

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

Subggroup H

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

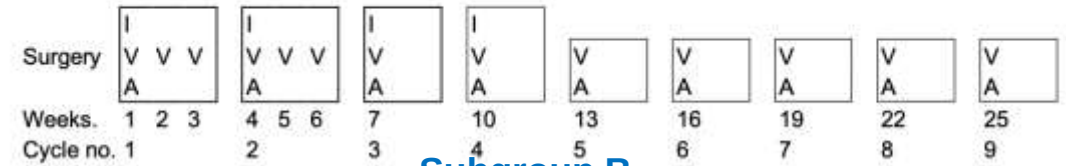
	V	V	V	V			V	V	V	V			V	V	V	V			V	V	V	V
	A			A			A			A			A			A			A			A
Weeks	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*
Cycle no.	1			2			3			4			5			6			7			8

Low Risk Group (A)

V = Vincristine 1.5 mg/m² (maximum single dose 2 mg) as a single intravenous injection.

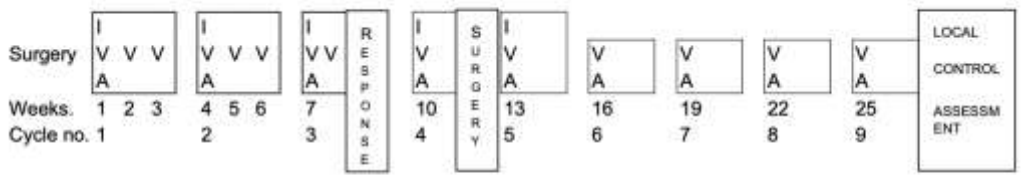
A = Actinomycin D 1.5 mg/m² (maximum single dose 2 mg) as a single intravenous injection.

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.



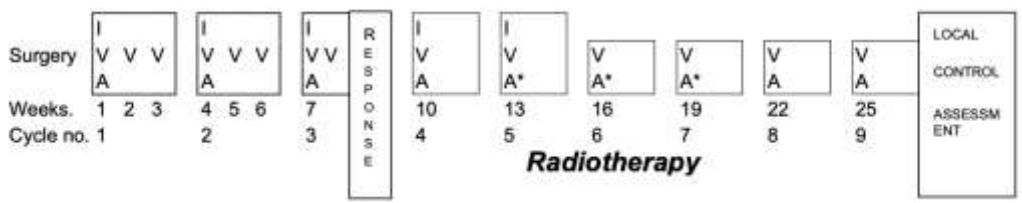
Subgroup B

No radiotherapy

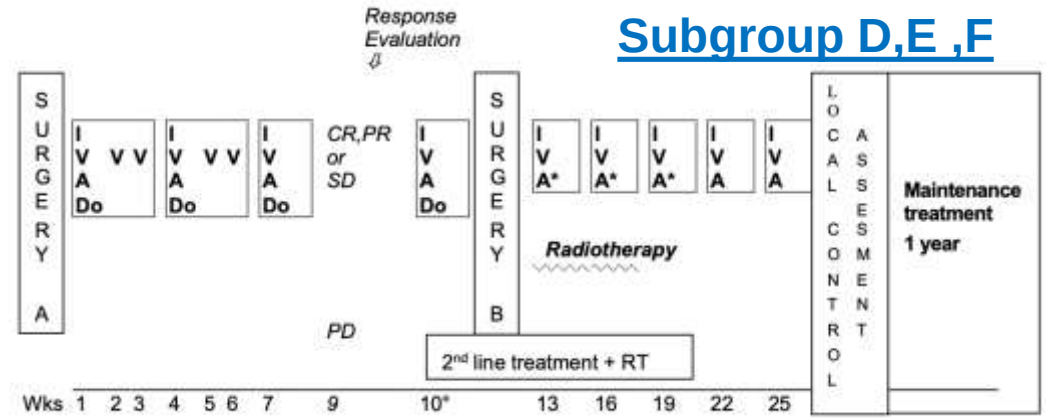


Subgroup C

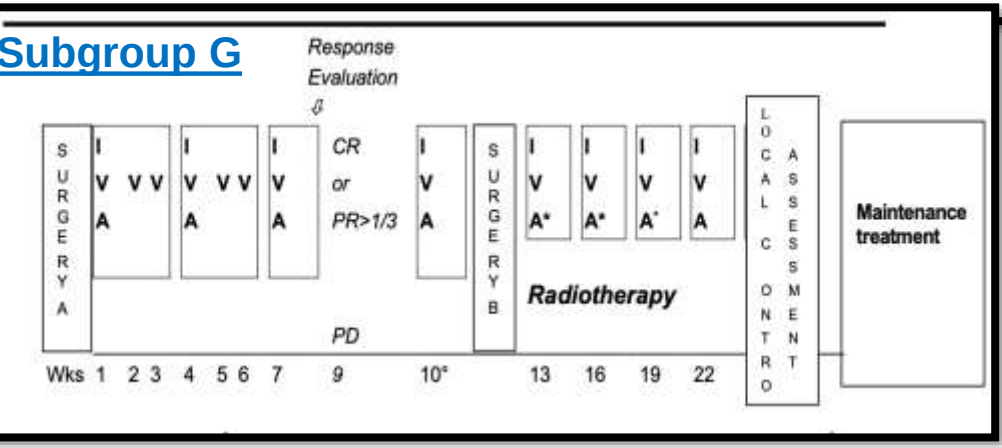
With Radiotherapy



Subgroup D,E ,F

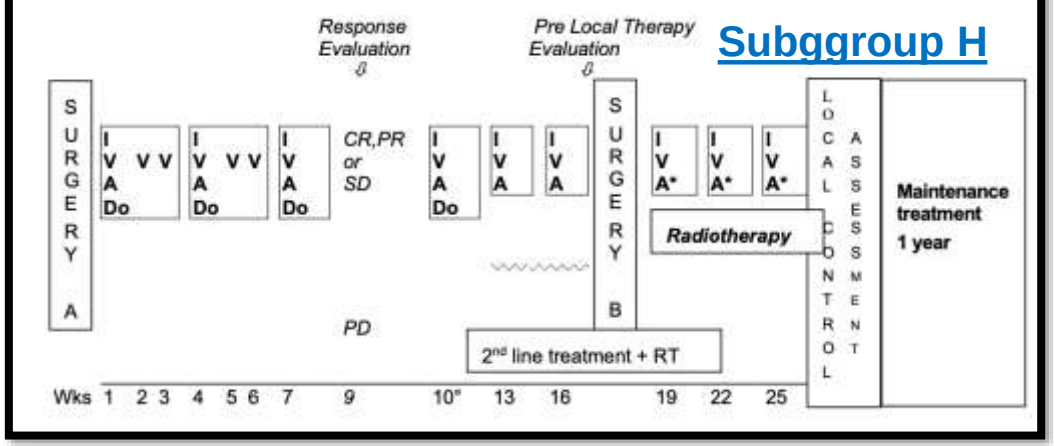


Subgroup G



SIOPE
SIOP Europe
the European Society for Paediatric Oncology

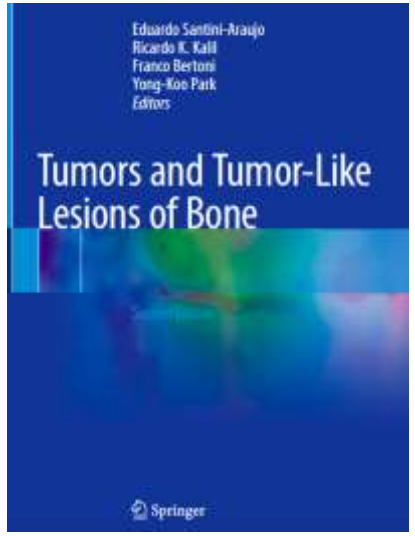
Subggroup H

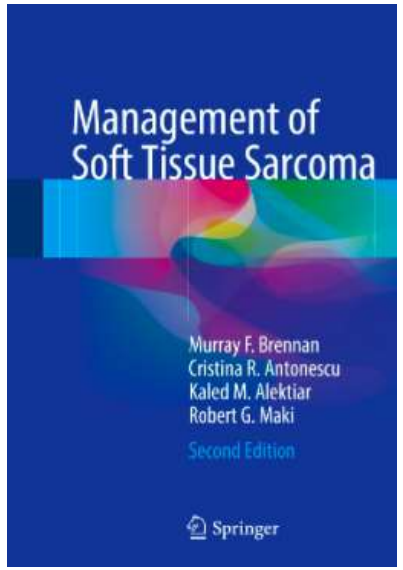


Summary

- Rare heterogeneous group of cancers of mesenchymal origin
- More common in paediatric age groups
- 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





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Review Article

Liposarcoma: Molecular Genetics and Therapeutics

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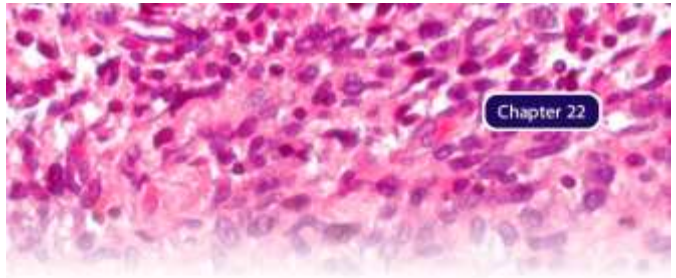

Cancer Genomics

Soft Tissue Sarcomas

Amal M. El-Naggar
Gabriel Lepriver
Poul H. Sorensen

Contents

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Current research and management of undifferentiated pleomorphic sarcoma/ myofibrosarcoma

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

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REVIEW ARTICLE OPEN ACCESS

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

Eyal M. Ramu[1,2,3], Matthew T. Houdek[1,2,3,*], Christian E. Isaac[1,2,3], Colleen I. Dickie[4], Peter C. Ferguson[1,2,3], and Jay S. Wunder[1,2,3]

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Review

Synovial Sarcoma: A Clinical Review

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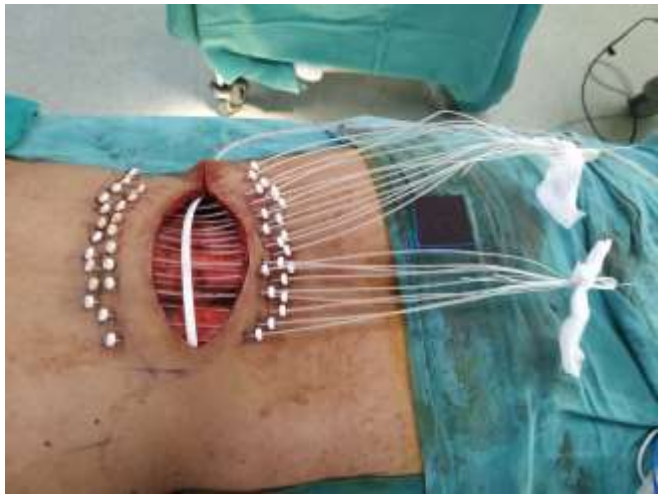
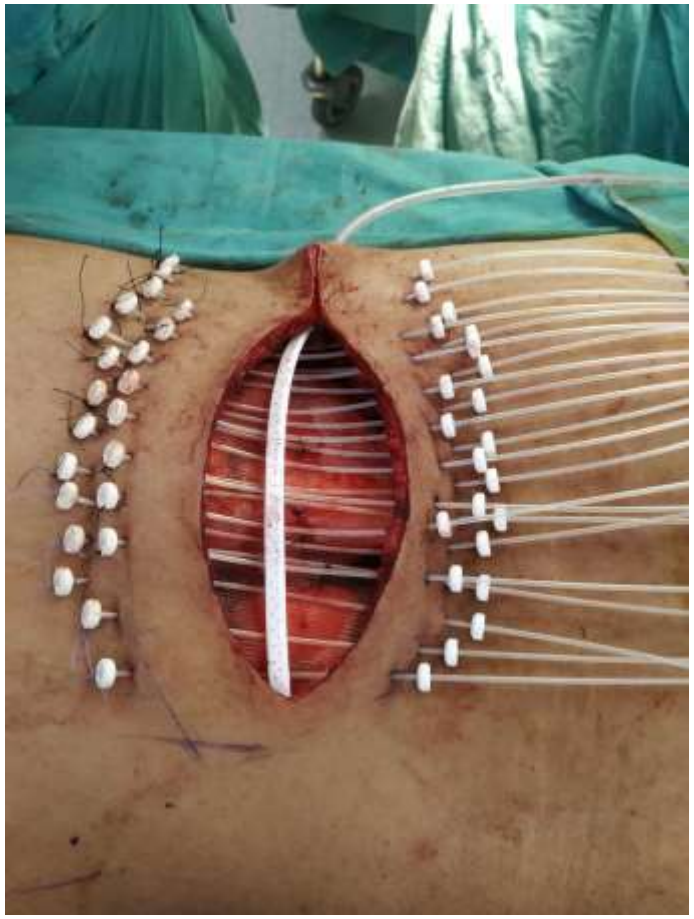
CLINICAL PRACTICE GUIDELINES FOR PATIENTS WITH RHABDOMYOSARCOMA





Thank You