Evaluation & Surgical principles of soft tissue Sarcoma

✱ Natural history of STS & Bone Sarcoma :

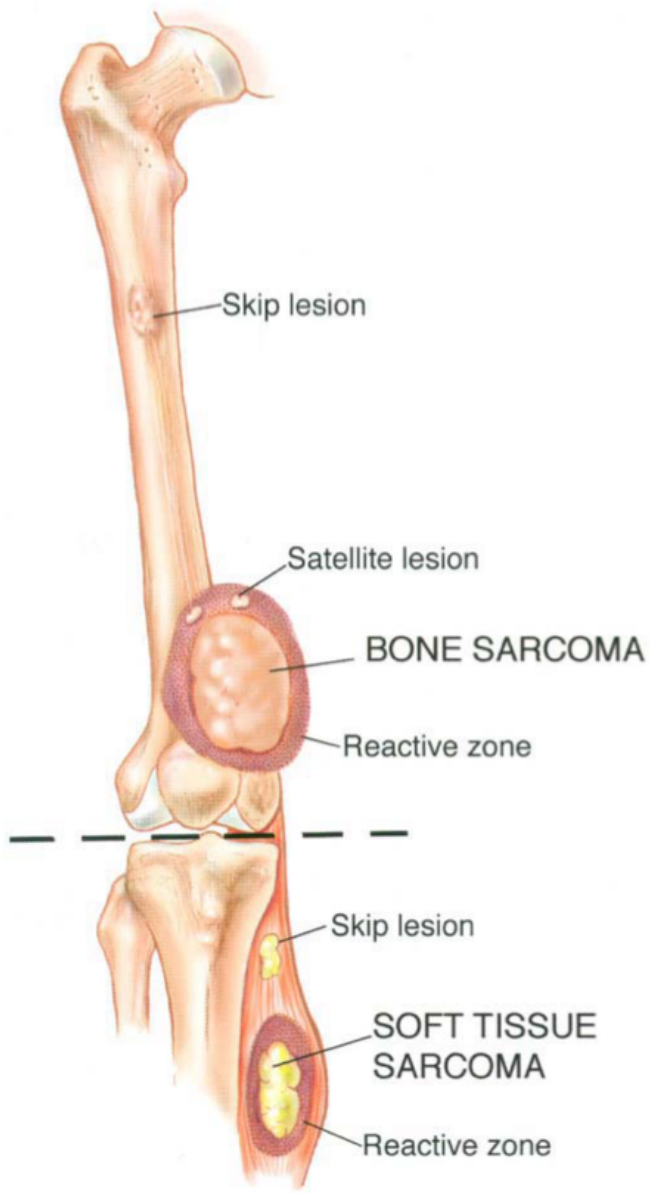

Figure 1.5 Biologic behavior of bone and soft-tissue sarcomas. Unique features are formation of reactive zone, intracompartmental growth, and, rarely, the presence of skip metastases. (Clin Orthop 1999 Nov; (368): 212–9)

Source: Martin Malawer textbook of musculoskeletal cancer surgery

- Centrifugal growth pattern – Periphery is least mature

↓

- Reactive zone / pseudocapsule – Compressed tumor cells and fibrovascular zone of reactive tissue.

Higher the grade → poorly defined pseudocapsule.

- Satellite lesion – Tumor foci within reactive zone

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- Skip metastasis – Tumor break from pseudocapsule and spread within same Anatomical Compartment – cause of local recurrence despite margin negative resection.
  - Rationale for Compartmental excision.

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- Confined to Compartment
  - Bone Sarcomas are bicompartmental at presentation
  - STS may be extra compartmental.

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- Compartment violation
  - Cortex of bone invasion
  - Aponeurosis of muscle

↓

- Distant mets

Low grade < 15-1.	- Hematogenous spread.
High grade > 15 -1.	- Extremity STS → lungs
High grade bone – 80-1. Sarcoma @ Presentation	- Abdominal / RP → liver → lung
	* Regional LN (considered M1)
	STS – 13-1.
	Bone – 7-1. @ presentation.

* Imaging :

- Always before biopsy.
- CT vs MRI - No benefit of MRI over CT (study by Radiology Diagnostic Oncology group).

- metastatic imaging :
  - CT A+P, CT chest, Bone scan.
- Role of PE-CT
  - Fails to differentiate benign from malignant.
  - SUV value correlates with grade, mitotic index of tumor, but prognostic value yet to be proven.
  - Current role in recurrent high grade STS.
  - Limited role in evaluating lung nodules < 1cm.
  - overstaging in 12.1% patients.
  - low grade sarcoma & high grade liposarcoma donot have reliable FDG uptake.

- Additional imaging specific to histology :
  - Abdomen, pelvic CT - myxoid, Round cell, Embryonal, Angiosarcoma leiomyosarcoma
  - MRI total spine - myxoid, round cell CPS
  - MRI Brain - Alveolar soft part, Angiosarcoma.

- Regional nodal staging by USG ± FNAC:

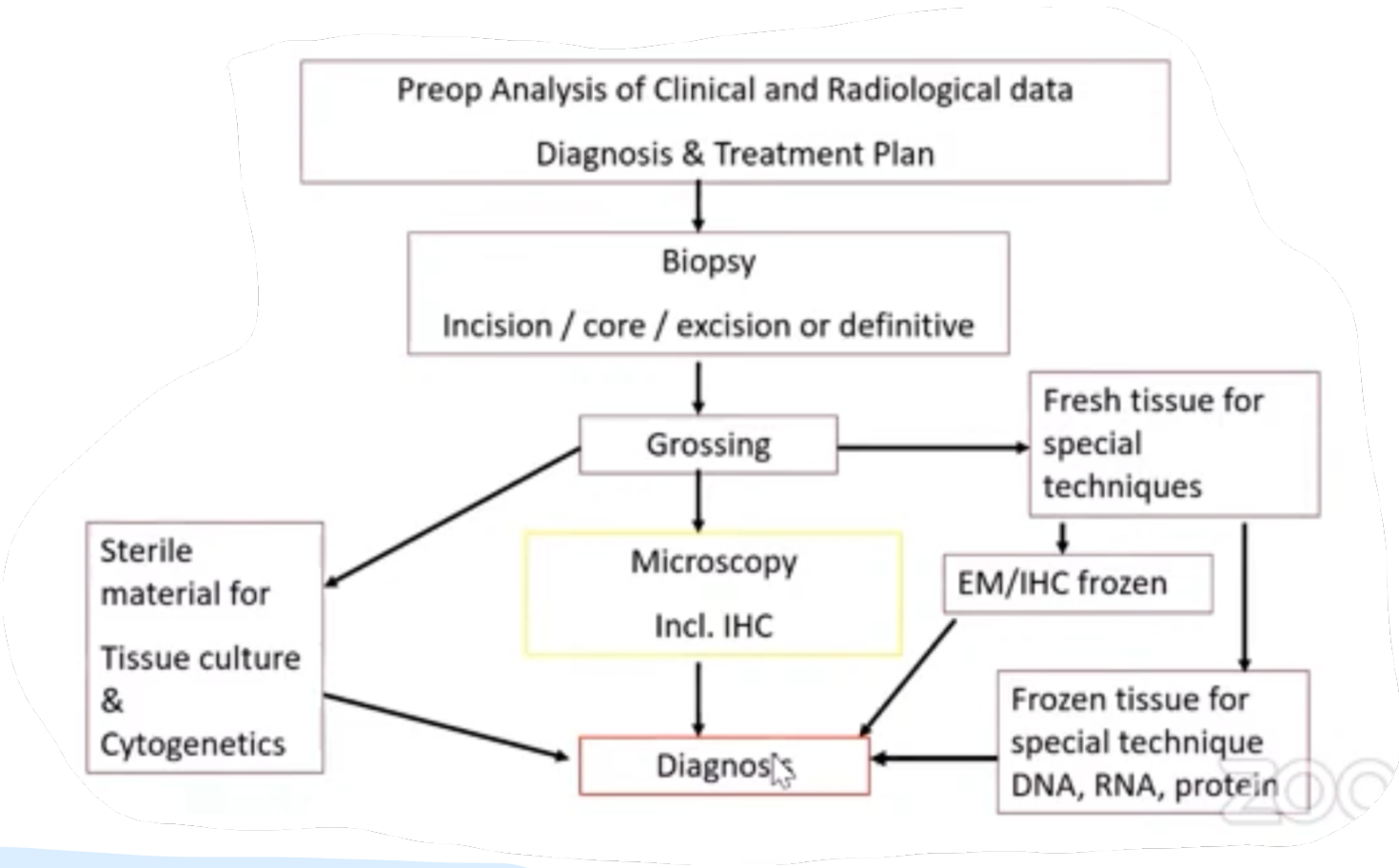
Indicated in SCARE

Synovial
Clear cell
Angiosarcoma
Rhabdomyosarcoma
Epithelioid sarcoma.

Regional Nodal basin for
- Lower limb
  - below knee
    - popliteal
    - inguinal
  - Above knee
    - inguinal
- upper limb
  - below elbow
    - epitrochlear, Cubital
    - axilla.
  - Above elbow
    - axilla

★ Biopsy : Core needle | incisional | Excisional :

- Gold std – Core needle Bx – 6 – 10 cores
  - Histopathology
  - IHC
  - cytogenetics
  - Electron microscopy
  - frozen section.
- Excision biopsy – avoided in lesions > 3 cms.



★ Grading in sarcoma :

includes
- mitotic index — most important
- Necrosis — most important
- Cellularity
- pleomorphism
- histologic subtype

Grading systems →	2 grades	3 grades	4 grades
	MSK	NCI	Broders
	– high | low – excellent clinical correlation – avoids confusion of intermediate grade	FNCLCC ↓ most widely accepted.	

Table 7. FNCLCC Histologic Grading System

Tumor Differentiation	
Score 1	Sarcoma closely resembling normal adult mesenchymal tissue (e.g., well-differentiated liposarcoma)
Score 2	Sarcomas for which histologic typing is certain (e.g., myxoid liposarcoma)
Score 3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, and synovial sarcomas
Mitotic Count	
Score 1	0–9 mitoses per 10 HPF
Score 2	10–19 mitoses per 10 HPF
Score 3	≥20 mitoses per 10 HPF
Tumor Necrosis	
Score 0	No necrosis
Score 1	<50% tumor necrosis
Score 2	≥50% tumor necrosis

FNCLCC = Fédération Nationale des Centres de Lutte Contre Le Cancer; HPF = high-power field.

Sarcomas not graded in the FNCLCC system: embryonal and alveolar rhabdomyosarcoma, angiosarcoma, extraskeletal myxoid chondrosarcoma, alveolar soft part sarcoma, clear cell sarcoma and epithelioid sarcoma

↓

FNCLCC grade

G_X - Grade cannot be assessed.

G_1 - score 2/3

G_2 - score 4/5

G_3 - score 6, 7, 8

→ Cytogenetics & molecular Analysis in STS :

TABLE 60.2

Cytogenetic and Molecular Abnormalities in Soft Tissue Sarcomas

Disease	Diagnostic Morphology or Immunohistochemistry	Cytogenetic Event	Molecular Abnormality	Molecular Diagnostic[a]
Myxoid/round cell liposarcoma	Lipoblasts, plexiform vasculature, myxoid matrix	t(12;16)(q13;p11) t(12;22)(q13;q12)	*FUS-DDIT3* (>90%) *EWSR1-DDIT3* (<5%)	*DDIT3* (FISH, RNA-seq)[37,38]
Ewing sarcoma family tumor	Small, blue, round cells; CD99 and FLI1 expression; lack of lymphoid biomarker expression	t(11;22)(q24;q12) t(21;22)(q22;q12) Alternative events: fusions of 22q12 with 7p22, 17q22, 2q33; inv 22q12; t(16;21)(p11;q22) t(4;19)(q35;q13) or t(10;19)(q26;q13) t(X;4)(p11.4;q31.1)	*EWSR1-FLI1* (>80%) *EWSR1-ERG* (10% to 15%) Other ETS family partners: *ETV1, ETV4, FEV, PATZ1* (~5%) *FUS-ERG* (<1%) *CIC-DUX4* *BCOR-MAML3*	*EWSR1* (FISH,[39] RT-PCR, RNA-seq)
Desmoplastic small round cell tumor	Small, blue, round cell nests in desmoplastic stroma; positive for keratin, desmin, vimentin, and WT1	t(11;22)(p13;q12)	*EWSR1-WT1* (>75%)	*EWSR1* (FISH, RNA-seq)[39]
Synovial sarcoma	Biphasic histology, positive for TLE1[40]	t(X;18)(p11;q11) (>90%)	*SYT-SSX1* (66%), *SYT-SSX2* (33%), *SYT-SSX4* (<1%)	*SYT* (FISH, RNA-seq)[41]
Alveolar rhabdomyosarcoma	Small, blue cells expressing desmin, myogenin, myoD1	t(2;13)(q35;q14) t(1;13)(p36;q14)	*PAX3-FOXO1* (~80%) *PAX7-FOXO1* (~20%) *PAX3-NCOA1* (<1%) *PAX3-NCOA2* (<1%)	*PAX3/7* type-specific (FISH, RT-PCR, RNA-seq[42])
Alveolar soft-part sarcoma	Nested polygonal cells in vascular network; positive for TFE3[43]	t(X;17)(p11;q25)	*ASPSCR1-TFE3* (>90%)	*ASPSCR1-TFE3* (RT-PCR, RNA-seq)[44] or *TFE3* (FISH)[45]
Dermatofibrosarcoma protuberans	Bland spindle cells, storiform growth in dermis and subcutis, positive for CD34	Rings derived from t(17;22) (>75%) t(17;22)(q22; q13.1) (10%)[46–48]	*COL1A1-PDGFB*	*PDGFB* (FISH)
Gastrointestinal stromal tumor	Spindle (70%), epithelioid (20%) or mixed (10%) morphology, positive for CD117 (KIT), DOG1, and CD34	Monosomies 14 and 22 (>75%) Deletion of 1p (>25)	*KIT* or *PDGFRA* mutation (>90%)[53,54]	PCR mutation analysis
Desmoid fibromatosis	Bland myofibroblastic-type cells, fascicular growth, nuclear positivity for β-catenin	Trisomies 8 and 20 (30%)	*APC* inactivation by mutation/deletion (10%) *CTNNB1* (β-catenin) mutations (85%)	β-catenin mutation (PCR)
Well-differentiated/ dedifferentiated liposarcoma	Atypical multinucleated stromal cells, lipoblasts, positive for MDM2, CDK4	12q13-15 rings and giant markers	*MDM2* and *CDK4* amplification (>85%)	*MDM2* amplification (FISH)

Source: DeVita 12th Edition

✯ Sarcoma staging:

changes from AJCC 7th edition:

1. different staging based on anatomic subsite
   - Head & neck.
   - Trunk & extremity
   - Retroperitoneal.
   - visceral.
2. Smaller primary T size staging for head & neck. (<2, 2-4, >4 cm)
3. T_3, T_4 newly added.
4. N_1 restaged from stage III to stage 4. (N_1 was stage 4 in 6th AJCC, 3 in 7th AJCC, 4 in 8th AJCC)
5. Guidance for unique histologic types.

TABLE 60.3

Prognostic Stage Groups According to American Joint Committee on Cancer Staging System (8th Edition, 2017)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor <5 cm in greatest dimension
T2	Tumor 5 cm to 10 cm in greatest dimension
T3	Tumor >10 cm to 15 cm in greatest dimension
T4	Tumor > 15 cm in greatest dimension

Stage	Grade	Tumor	Nodes	Metastasis
IA	G1, GX	T1	N0	M0
IB	G1, GX	T2, T3, T4	N0	M0
II	G2, G3	T1	N0	M0
IIIA	G2, G3	T2	N0	M0
IIIB	G2, G3	T3, T4	N0	M0
IV	G any	T any	N1	M0
IV	G any	T any	N any	M1

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2020).

Source: DeVita 12th Edition

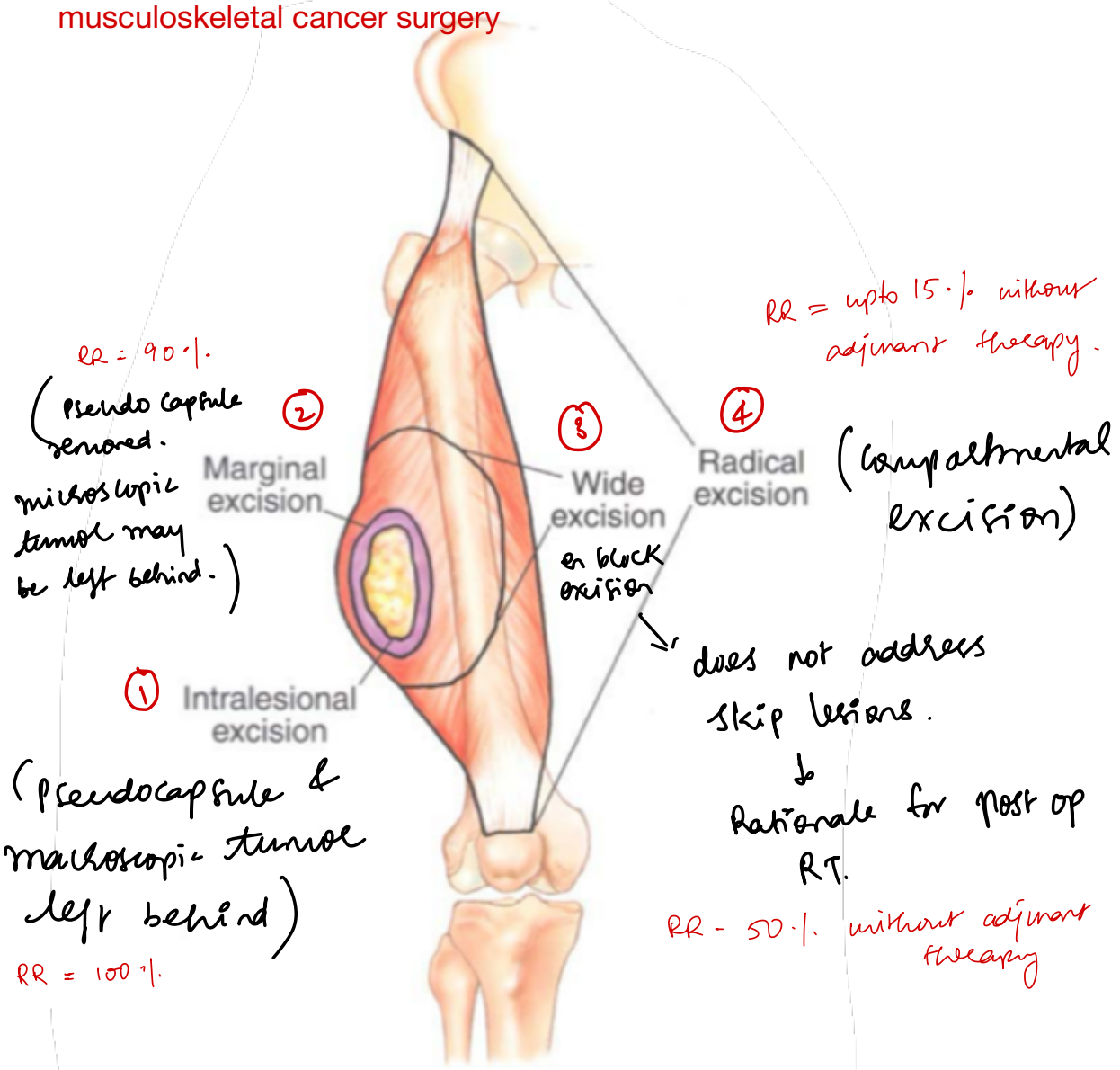
✯ Prognostic factors

1. site of disease
   - Trunk & extremity better than visceral/RP.
2. Histologic subtype
   - MPSNT
3. Initial size
4. Grade
5. Recurrent presentation
6. margin
7. Bone & neurovascular invasion.

✱ Management of extremity / Truncal sarcoma

1. Role of Surgery:

Source: Martin Malawer textbook of musculoskeletal cancer surgery



RR = 90%. (pseudo capsule removed. microscopic tumor may be left behind.)

RR = upto 15% without adjuvant therapy.

(compartmental excision)

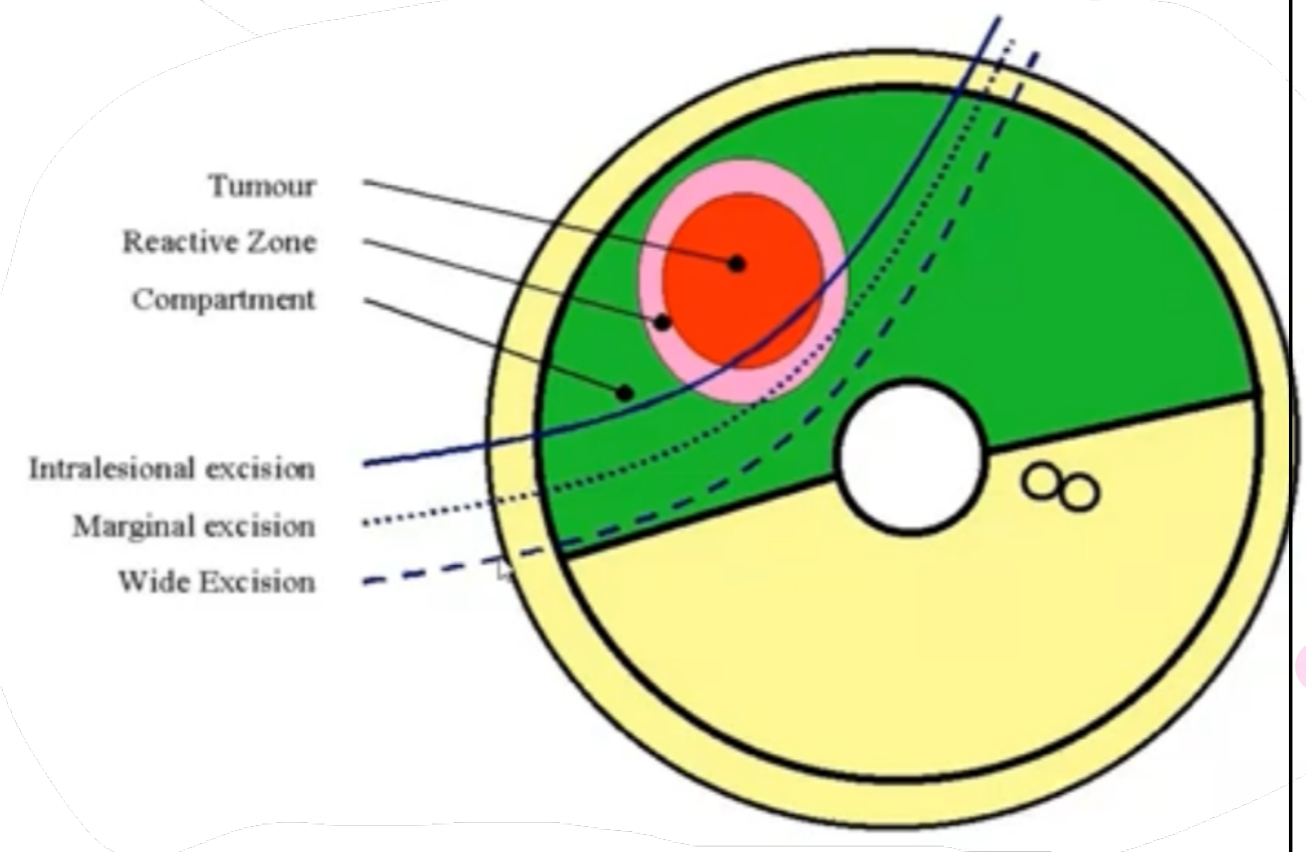
does not address skip lesions.
↓
Rationale for post op RT.

RR - 50% without adjuvant therapy

(pseudocapsule & macroscopic tumor left behind)

RR = 100%.

Figure 1.18 Various excision types for soft-tissue sarcoma. ← 4 types



✱ Frozen section for margin assessment

✱ Specimen Orientation

✱ Place vascular clips to direct PORT.

✱ Principles of margins in STS

Kawaguchi & Matsumoto et al.

Quantitative vs Qualitative margin

↓ measured margins

↓ protective margins provided by anatomical tough structures

↓

- Periosteum children, fascia lata, joint capsule – equivalent to 3 cm margin
- Periosteum adult, epineurium, perimysium, vessel sheath – 2 cm
- joint Cartilage – 5 cm margin

NCCN
- Low grade STS → 1 mm – 1 cm margin
- High grade STS → ≥ 1 cm margin

✱ Planned positive margin

- when tumor is close to vital structures
- close resection - microscopic tumor ⊕
- marked by clips → RT boost given.
- Rate of LR less in planned positive margin than unplanned positive margin.

✱ Handling bone in STS abutting bone

- periosteum stripping.
↓
increases risk of radiation related pathologic fracture
↓
✱ Pre op RT preferred
✱ Prophylactic bone fixation recommended if ~ 50% circumference periosteum is stripped for entire length of bone.

✱ Handling nerve in STS

- major nerve resection in MPSNT
- Nerve grafts, tendon transfer → upper limb
- Ankle foot orthosis → Lower limb after complete excision of sciatic nerve.

✱ Handling vessels:

- major arteries excised to achieve negative margin, reconstruction with vein graft / prosthesis graft
- vein resection — if vein thrombosed preop → good collateral flow
  ↓
  Reconstruction not needed.

✱ "In-situ Preparation"

- For STS close to neurovascular structure.
- By Kawaguchi & Matsumoto

Procedure — Tumor & neurovascular structure lifted en-bloc from surgical bed and separated from field by vinyl sheets.

↓

margin between tumor & neurovascular bundle done

↓

In situ preparation ⊂ pasteurisation / alcohol soaking / distilled water soaking to provide safe margin

✱ Salvage after "unplanned excision"

Series by Giuliano et al — Tumor resection without pre-op diagnosis and without the intent to achieve negative margins.

Local recurrence rate — 30–40%.

All should be re-resected — Residual tumor on re-resection — > 50%.

Determining adequate surgical resection is complicated

- margin difficult to determine on imaging since reactive changes from prior surgery do not correspond with actual tumor extent
- scar tissue
- loss of normal anatomical planes
- lack of a palpable mass that provides a visual and tactile guide to judge resection extent
- Need for soft tissue coverage

Source: DMSOG sarcoma class by Dr. Anand Raja on YouTube

→ Limb salvage vs Amputation in STS :

NCI study - prospective RCT : by Rosenberg et al.

LSS + PORT vs Amputation (2:1 Randomisation)

Local Recurrence 15% vs 0%

No significant difference in 5 yr. DFS / OS.