Radiation & systemic therapy in soft tissue Sarcoma.

2. Role of Radiation in STS :

- a) Post op RT
- b) Post op Brachytherapy
- c) Intraoperative RT
- d) Pre op RT
- e) Definitive RT.

Surgery alone is sufficient in STS if ALL criteria met:

1. Superficial
2. < 5 cm
3. Low grade
4. Adequate margin ≥ 1 cm. Lesser if known barriers.
5. First presentation (Non recurrent STS)

Table 5.9 Pros and cons of preoperative radiation

	Preoperative radiation	*Postoperative radiation*
Advantage	May improve resectability	Fewer wound complications
	Radiated target volume is smaller	Immediate removal of tumor
	Improves local control for larger tumors	Histologic analysis is facilitated
	Extent of resection may be reduced	Precise assessment of tumor extent
	Decreased risk of tumor implantation	
Disadvantage	Increased postoperative complications	Radiated target volume is larger
	Diagnosis is based on limited biopsy material	Radiation is delayed
	Surgery is delayed during radiation	Amputation may be more frequent
	Tumor extent may be difficult to assess	

Source: Martin Malawer textbook of musculoskeletal cancer surgery

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* Factors that can complicate wound healing in RT
  - Previous RT
  - Baseline limb edema
  - Smoker, DM
  - PVD

a) Why RT in STS? – Trials for PORT :

① 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.

② Yang et al, PORT (EBRT) vs Sx alone:

- 10 year local Recurrence rate lower in PORT group

10YLRR	Post op RT + Chemo	No post op RT Only Chemo	p
High Grade Sa (n=91)	0%	22%	0.001
Low Grade Sa (n=50)	4%	33%	0.003

Source: DMSOG sarcoma class by Dr. Vineeta Goel on YouTube

- Updated analysis at 17 years & QOL index:
  - PORT group had - decreased limb strength, worse range of motion, limb edema.
  - But, NO significant difference in global QOL
  - OS better & PORT - 71% vs 64% (No statistical significance)

③ Pisters et al - PORT (Brachy) vs Sx alone:

in High grade STS - Brachy led LRR to 9%.
in Low grade STS - No effect on LRR.

★ Impact on OS with PORT

SEER data → Low grade - No impact.
High grade
Large >5 cm
STS
→ improved OS.

→ Trials for pre-op RT :

1) NCI Canada trial by Sullivan et al :

Pre op RT 50 Gy / 25 # fb Sx + post op boost 16-20 Gy to margin positive	(vs)	PORT only (60 – 66 Gy)
Acute wound complications	35·1·	17·1·
Late Complication	68·1·	86·1· (coz higher target volumes)
7yr Local control rate	90·1·	Similar 90·1·

Pre op RT produced higher wound complications in lower extremity compared to upper extremity.

2) National Oncology database (US study)

additionally showed survival advantage in pre op RT, especially for Synovial Sarcoma & MPNS.

* Pre-op RT not widely practised yet.
PORT should be started within 4-6 weeks of Sx.

* Modality of RT in STS :

1. **Conventional EBRT**

   - Space lymphatic corridor (a part of circumference of limb i lymphatic channels)

   Complications of EBRT :

   Edema
   Fibrosis
   Bone pathological fracture upto 7%.
   decreased range of motion.

2. * IMRT (MSKCC study) :

   - 5yr LCR - 94.1% irrespective of positive / negative margin
   - Excellent local control with low toxicity.
   - Higher LCR with IMRT when compared to Brachy therapy.

3. Brachytherapy : < True intraoperative / Perioperative

   Advantages of brachytherapy :

   - Better Radiobiology
   - Short & convinent treatment time
   - Built in SIB (Simultaneously Integrated Boost)

   Limitations

   - Large Cavity > 15 cms
   - Bone / neurovascular bundle close to catheter

   • Brachy Catheter - RT dose is 200 to 300% dose in the immediate vicinity of Catheter.

   ⊙ 5mm radius around catheter - Receives 100% of actual calculated dose.

   - Lesser wound complications
   - Less rate of bone fracture upto 1%.
   - RT starts immediately in post op needed before tumor cell repopulation.

BRT as Monotherapy- I/C

- High grade lesions with favourable surgical findings (complete surgical excision with negative margins)
- Regions that can be encompassed well with brachytherapy catheters
- Usually <10 cm
- Paediatric Sarcomas
- Previously irradiated pts.

Source: DMSOG sarcoma class by Dr. Vineeta Goel on YouTube

EBRT + Brachy boost

- when Target volume cannot be covered by Brachy alone
- High risk of recurrence

* Safe way to dose-escalate
  66 Gy (50 + 16 Gy) vs
  60 Gy in Brachy alone

MSKCC study
5yr Local control — 100%

* Radiation associated fracture:

Risk factor:
- older age, women
- weight bearing bone
- High dose RT (PORT)
- Periosteal stripping — for
  750% circumference in
  720 cm length of bone
- Circumferential bone radiation
- Adjuvant chemotherapy.

Mechanism of RT induced fracture
- vascular fibrosis,
  Avascular necrosis
- impairment of osteoblasts and bone atrophy

Prevention → Prophylactic intramedullary nailing in high risk patients.

3. Chemotherapy in STS :

Chemosensitive	Desmoplastic small round cell tumour
	Synovial sarcoma
	Myxoid/round cell liposarcoma
	Uterine leiomyosarcoma
Moderately chemosensitive	Pleomorphic liposarcoma
	Epithelioid sarcoma
	Pleomorphic rhabdomyosarcoma
	Leiomyosarcoma
	Angiosarcoma
Relatively chemo-insensitive	Malignant peripheral nerve sheath tumour
	Myxofibrosarcoma
	Dedifferentiated liposarcoma
	Clear cell sarcoma
	Endometrial stromal sarcoma
Chemoinsensitive	Alveolar soft part sarcoma
	Extraskeletal myxoid chondrosarcoma

→ Indication for adjuvant chemo (All criteria fulfilled)

>5cm, chemosensitive, deep seated, high grade.

★ Trials for adjuvant chemotherapy in STS

OS benefit is contradicting among studies

→ SMAC meta analysis (Sarcoma Meta-Analysis Collaboration)

- Sx vs Sx + adj chemo
- 14 RCT, 1500 patients approx.
- Doxorubicin based chemo

- Chemo prolongs local & distant recurrence free survival by 15 - 20%.
- No significant advantage in OS.

→ Italian study

- High grade / Recurrent STS
- Epirubicin + Ifos vs observation

- Better DFS
- No significant OS benefit.

→ EORTC 62931

Ifos + Doxorubicin

↓

No difference in RFS,
OS

→ Another EORTC study

CYVADIC - Cyclophos + Vincristine +
Adriamycin + Dacarbazine

↓

Higher RFS, DFS
No difference in OS

Both trials combined, pooled analysis showed adjuvant CT improved RFS in subset of patients - Grade 3 & 4 years.
R1 Resection.

☆ Trials for Neoadjuvant chemotherapy in STS:

- Rationale for NACT:
  - → make Sx easier
  - → treat micromets
  - → higher Concentration of drug when vascularity is intact.

- Known benefit in
  - → Ewings
  - → Osteosarcoma
  - → Rhabdomyosarcoma
  - → Synovial Sarcoma
  - → myxoid round cell Liposarcoma.

Response assessment

- clinical examination after every cycle to s/o progression.

→ ISG-STS 0101 trial

- By Gronchi et al.
- 3# vs 5# (3 prepp + 2 post op) Epirubicin + ifosphamide
- No difference in OS.
  25.1% in 5# arm did not complete post op chemo.

→ ISG-STS 1001 trial by Gronchi et al.

- 3# Epi + ifos vs Histology tailored chemo

myxoid liposarcoma - Trabectidine
Undiff. pleomorphic sarcoma - Gem + Doce
Leiomyosarcoma - Gem + Dacarbazine
Synovial sarcoma - High dose ifos
MPNST - Etoposide + ifos

Reduced DFS for tailored chemo compared to standard chemo ←

Role for second line chemotherapy following progression of 1st line chemo is questionable in STS.

→ Isolated limb perfusion therapy

- Same as malignant melanoma.
- melphalan, TNFα

4. Combined CT/RT in STS

RTOG - 9514 trial

• High grade primary / recurrent STS ≥ 8 cm → 3 # modified MAID regime Preop (mesna + Adriamycin + Ifos + Dacarbazine)

+

Preop RT 44 Gy

↓

Sx

↓

Adjuvant 3 # MAID

• 9 pt. grade 3 toxicity @ 1 yr follow up.

• 28 pt. distant mets.

↓

Combined CT/RT feasible but with higher toxicity.

Recent studies show low toxicity with Dox - ifos - RT without Dacarbazine.

Indication

- Borderline Resectable
- Rhabdomyosarcoma.
-

Source: DeVita 12th Edition

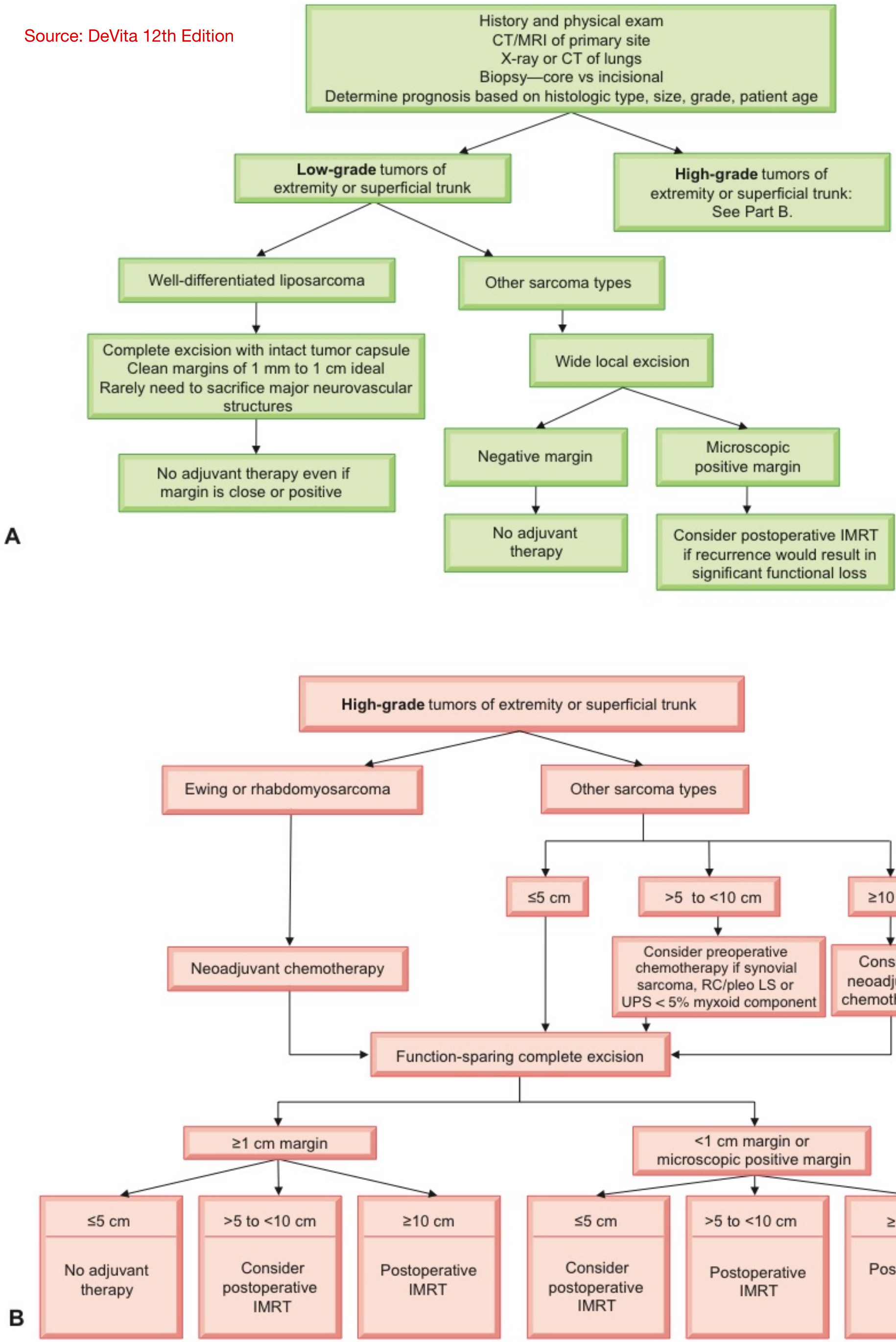

Figure 60.7 Management algorithm for extremity and superficial truncal soft tissue sarcoma. **A:** Low-grade sarcomas. **B:** High-grade sarcomas. Note that although postoperative intensity-modulated radiation therapy (IMRT) is mentioned in the algorithm, preoperative IMRT could be used in the same types of patients, particularly when lesions are localized close to a joint or in smaller compartments such as the forearm or calf where significant injury to nearby normal tissue would be expected. Preoperative IMRT may also be of value prior to rare resections that may require in situ transection of the sarcoma. BRT, brachytherapy; CT, computed tomography; MRI, magnetic resonance imaging; Rhabdo, rhabdomyosarcoma; RC, round cell; Pleo, pleomorphic; LS, liposarcoma;