Soft Tissue Sarcomas of the Extremities

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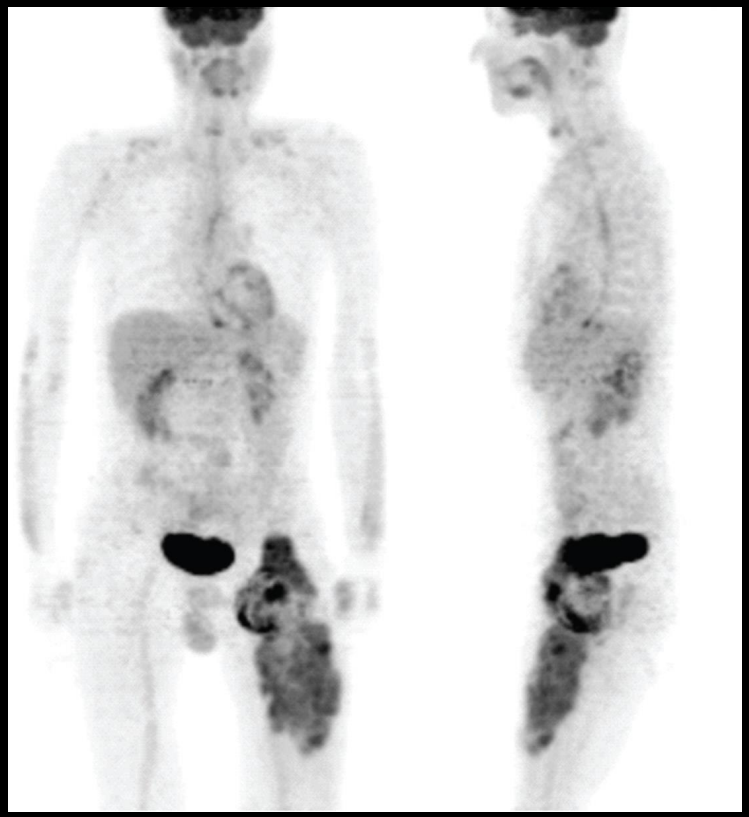
Sarcomas

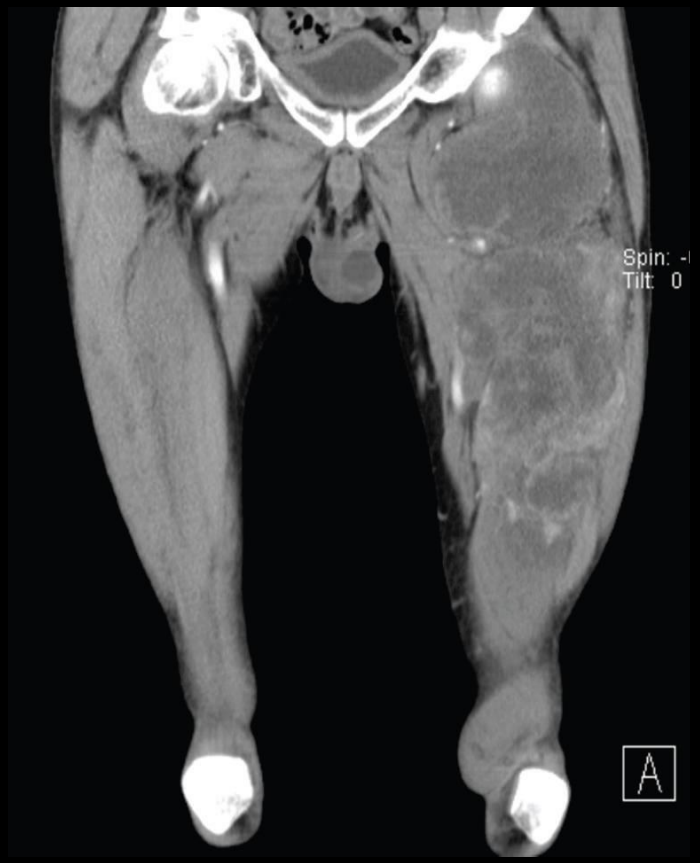
- Heterogenous group of mesenchymal malignancies that arise in soft tissue and bone
- Affect all age groups and any part of the body
- Relatively rare
  - 2% (adults), 15% (pediatric)
- STS
  - The most common



Pisters PWT, Weiss M, Maki R; 2011
Cancer management, 14th edn. Soft-Tissue Sarcomas.

Soft Tissue Sarcomas

- Can originate in any tissue of mesenchymal origin
  - Extremities: approx 50% of cases
    - Lower 39% (thigh)
    - Upper 11%
  - Chest wall, retroperitoneum, and head/neck



Cancer Facts and Figures; 2012
American Cancer Society, Atlanta,Ga, USA, 2012
Kandel et al. Curr Oncol. 2013

Soft Tissue Sarcomas

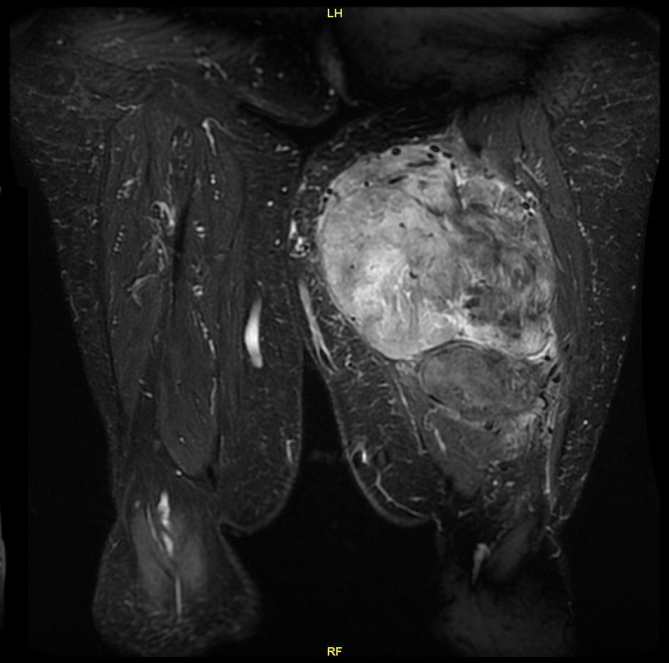
- Can occur at any age
  - >55 yrs
    - Most common age
    - Usually UPS or liposarcoma
  - <20 yrs
    - Usually rhabdomyosarcoma or synovial sarcoma

Kandel et al. Curr Oncol. 2013

Soft Tissue Sarcomas

Clinical

- Palpable mass, pain, enlargement
  - Small superficial (epithelioid, synovial)
  - Along tendon sheath (clear cell)
- Regional lymph nodes
- Often arrive late
  - Wrong operation
  - Wrong diagnosis



The principles of biopsy

- The principles are independent of the technique

Biopsy is a compromise:

To provide significant tissue

To avoid contamination

How Should Musculoskeletal Biopsies Be Performed?

Andreas F. Mavrogenis, MD; Andrea Angelini, MD; Costantino Errani, MD; Eugenio Rimondi, MD

Soft Tissue Sarcomas

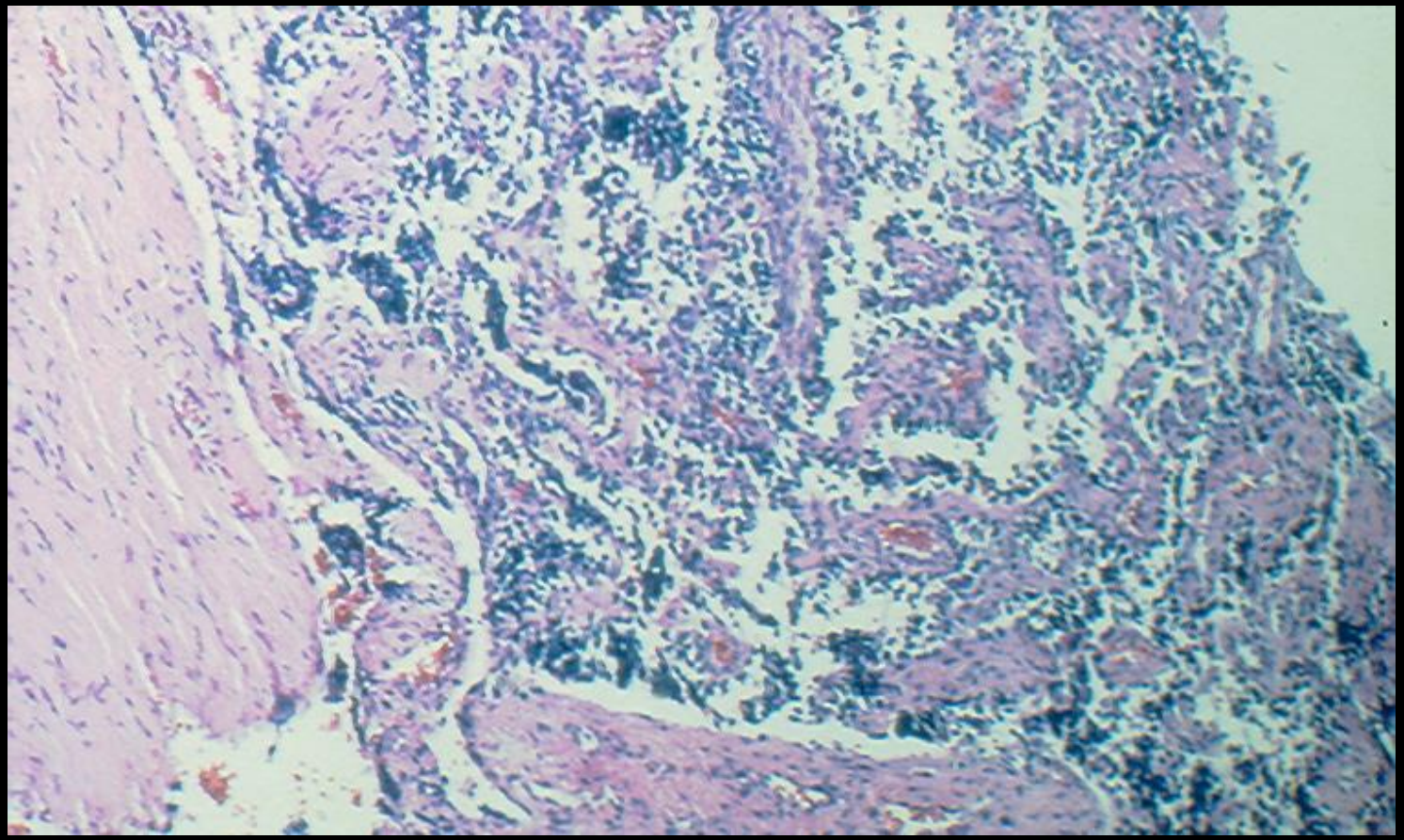
Histology

- >50 histologic types
  - Liposarc
  - UPS

Low metastatic potential	Intermediate potential	High metastatic potential
Well differentiated Liposarcoma	IMFT	Pleomorphic liposarcoma
	Haemangiopericytoma	Dedifferentiated liposarcoma
	Haemangioendothelioma	Leiomyosarcoma
	Solitary fibrous tumour	Round cell liposarcoma
		Angiosarcoma
		Synovial sarcoma
		RMS
		Ewings sarcoma
		Alveolar soft part sarcoma
		GIST

STS=Soft tissue sarcomas, IMFT=Inflammaory myofibrobalstic tumour, RMS=Rhabdomyosarcoma, GIST=GastroIntestinal stromal tumour

Many Soft Tissue Sarcomas require Immunohistochemistry and Cytogenetics



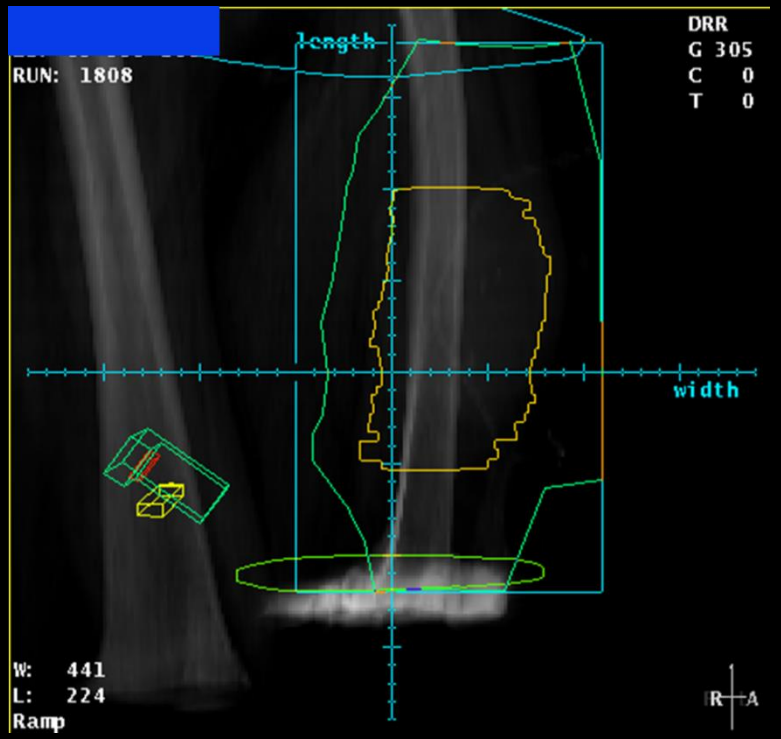
Soft Tissue Sarcomas – Genetic Analysis

NEOPLASM	TRANSLOCATION	GENES
Ewing/PNET	t(11;22)(q24;q12)	*FLY-1/,EWS*
Synovial Sarcoma	t(x;18)(p11.2;q11.2)	*SSX1 or SSX2, SYT*
Alveolar Rhabdo-myosarcoma	t(2;13)(q35;q14) t(1;13,p36;q14)	*PAX3, FHKR* *PAX7, FHKR*
Clear Cell Sarcoma	t(12;22)(q13;q12)	*ATF1, EWS*
Dermatofibrosarcoma protruberans	t(17;22)9q22;q13)	*COL1A1,* *PDGFB1*
Infantile fibrosarcoma	t(12;15)(p13;q25)	*ETV6,NTKR3*
Myxoid Chondrosarcoma	t(12;16)(q13;p11)	*CHOP,TLS*

Soft Tissue Sarcomas

Treatment

- Surgery
  - The primary treatment
  - Amputation vs. LS
- Adjuvant treatments
  - RT
    - External beam, intraop, brachytherapy
  - CMT
  - Others
    - Isolated limb perfusion
    - Chemoembolization
    - Embolization



Greto D, et al.
Radiol Med, 2013
Al Yami A, et al.
Int J Radiat Oncol Biol Phys, 2010
Kim B, et al.
Int J Radiat Oncol Biol Phys , 2010

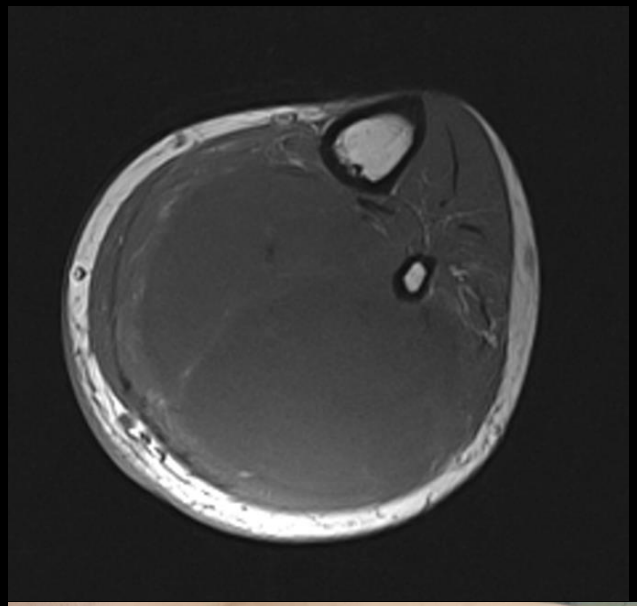
Limb salvage surgery

- Indications

  (1) ability to obtain wide margins

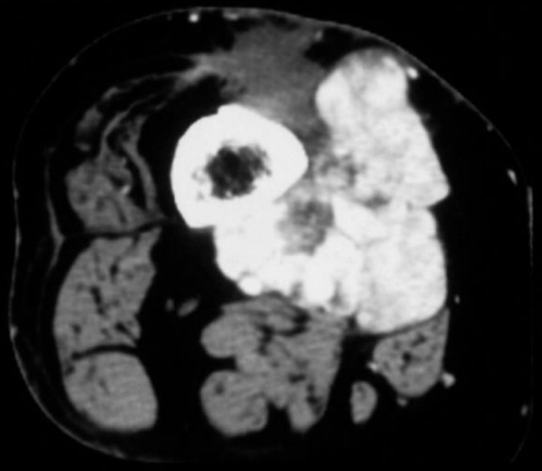
  (2) tumor sparing of the major vessels

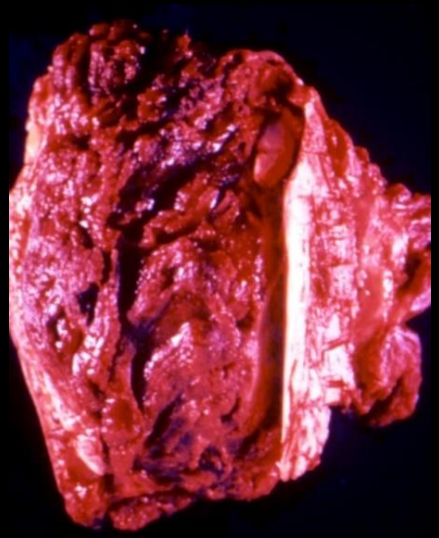
- Contraindications
  - patients who had LSS in the past but now have local recurrence
    - unless the recurrence can be definitely widely resected or amputation offers no oncological benefit

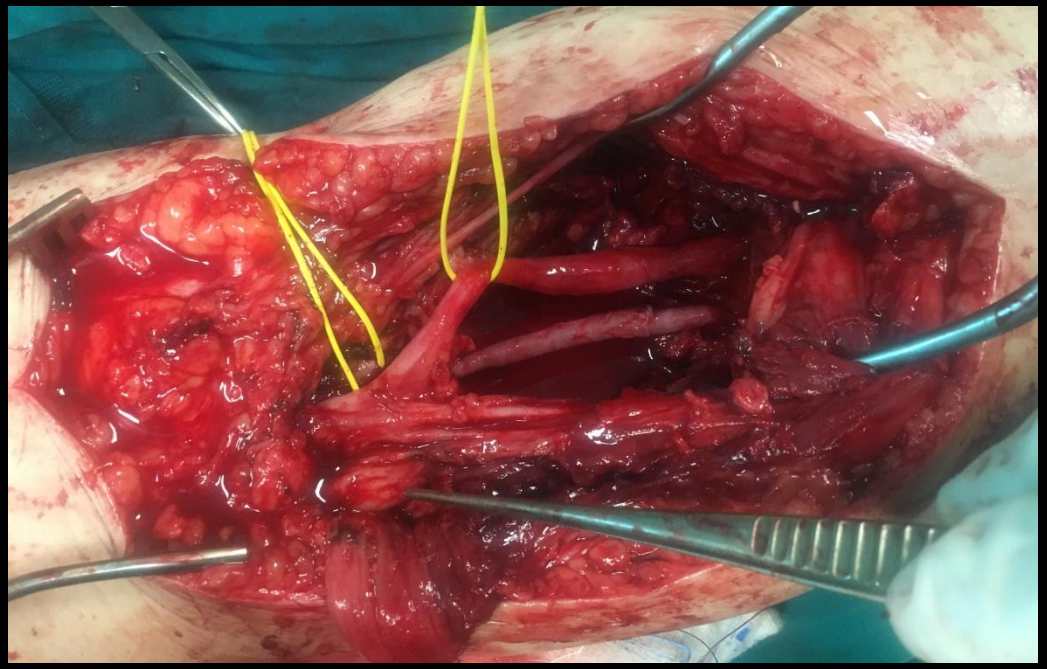


LSS

- Excision
- Excision + bone
- Excision + vessels
  - (vascular by-pass)
- Excision + joint



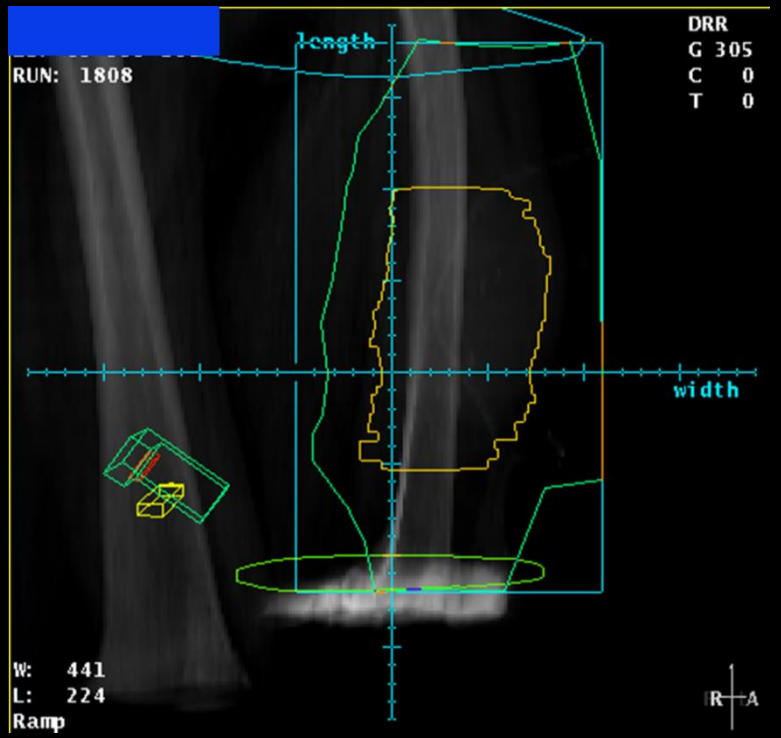




Soft Tissue Sarcomas

Adjuvant Treatments

- RT
- CMT
- Isolated limb perfusion
- Chemoembolization
- Embolization



Greto D, et al.
Radiol Med, 2013
Al Yami A, et al.
Int J Radiat Oncol Biol Phys, 2010
Kim B, et al.
Int J Radiat Oncol Biol Phys , 2010

Embolization

Palliative treatments for advanced osteosarcoma.

Mavrogenis AF, Rossi G, Palmerini E, Errani C, Rimondi E, Ruggieri P, Soucacos PN, Papagelopoulos PJ.
J BUON. 2012 Jul-Sep;17(3):436-45. Review.
PMID: 23033278 [PubMed - indexed for MEDLINE]
Related citations

Palliative embolisation for advanced bone sarcomas.

Mavrogenis AF, Rossi G, Altimari G, Calabrò T, Angelini A, Palmerini E, Rimondi E, Ruggieri P.
Radiol Med. 2012 Aug 8. [Epub ahead of print]
PMID: 22872460 [PubMed - as supplied by publisher]
Related citations

Chemoembolization

CardioVascular and Interventional Radiology

October 2016, Volume 39, Issue 10, pp 1420–1428

Treatment Outcome Following Transarterial Chemoembolization in Advanced Bone and Soft Tissue Sarcomas

Authors | Authors and affiliations

Chunyu Jiang, Jianbo Wang ✉, Yonggang Wang, Jungong Zhao, Yueqi Zhu, Xu Ma, Jia Zhou, Xuebing Yan

Isolated Limb Perfusion

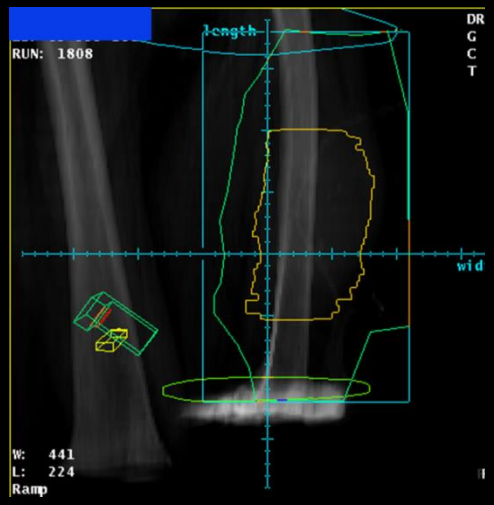
- Isolated limb perfusion with melphalan and TNF-α has been employed for unresectable intermediate/high-grade soft tissue sarcomas of the extremities with the aim of limb salvage

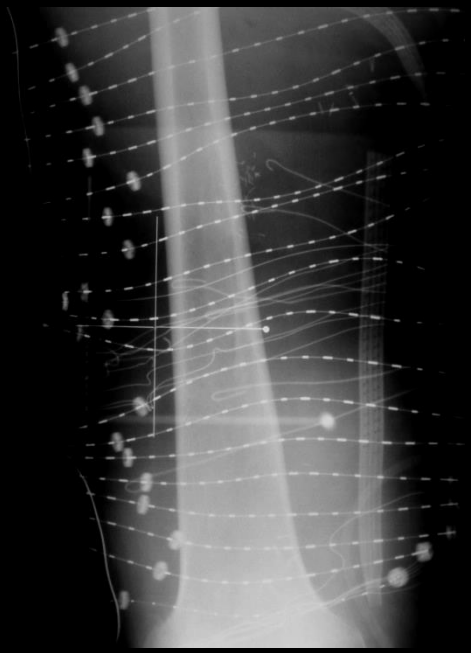
Wong J, et al. Ann Surg Oncol. 2013
Bhangu A, et al. Eur J Surg Oncol. 2013
Vohra NA, et al. Int J Hyperthermia. 2013

Soft Tissue Sarcomas

RT

- Clear adjuvant to surgery
  - LR reduced from 30% to 10%
- Types
  - External Beam
  - Brachytherapy
  - Intraoperative electron
  - Combination

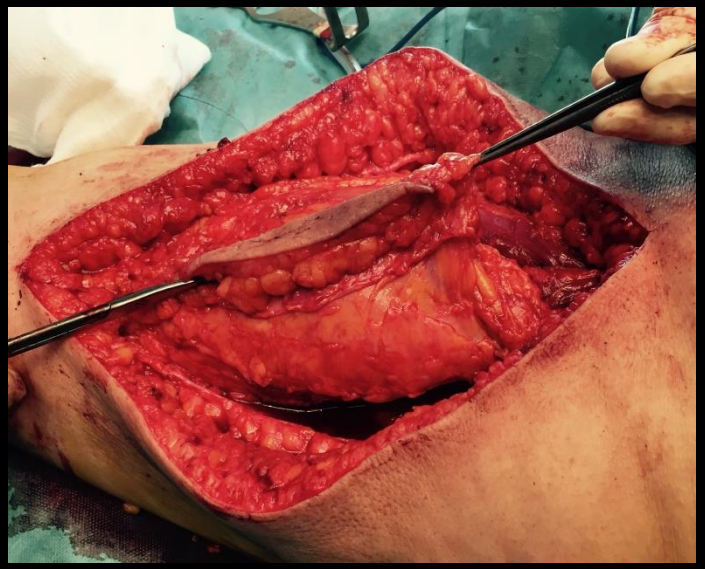




Soft Tissue Sarcomas

Preoperative RT – Indications

- tumors located in critical areas and close to bundles
- to improve the chance of limb salvage and local control

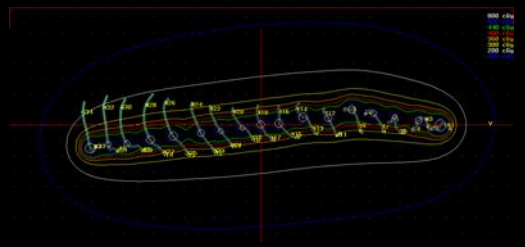


NCCN, www.nccn.org. Accessed 04 Dec 2019

Soft Tissue Sarcomas

Preoperative RT

- Advantages
  - smaller treatment volume (dose and field)
  - early radiotherapy
  - capsular fibrosis
  - tumor shrinkage

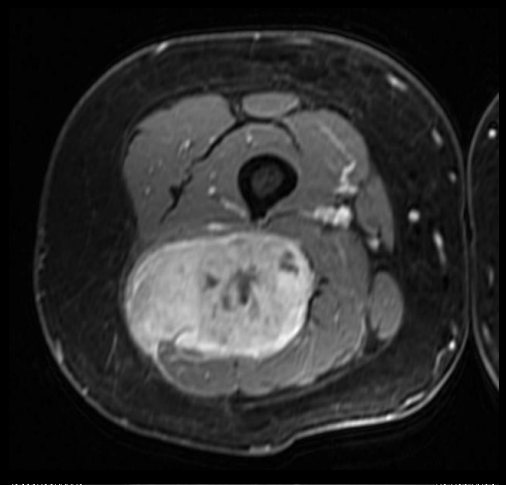


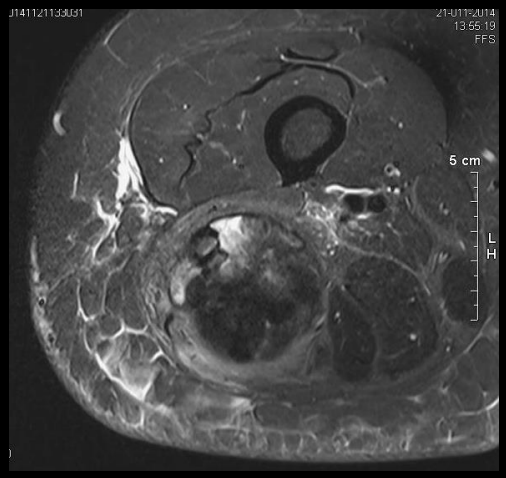
O'Sullivan B, et al. Lancet, 2002
Clarkson P, Ferguson PC,
Curr Treat Options Oncol, 2004

Soft Tissue Sarcomas

Preoperative RT

- Disadvantages
  - necrotic tumor material for pathology
  - wound complications (35% vs 17%)





O'Sullivan B, et al. Lancet, 2002
Clarkson P, Ferguson PC , Curr Treat Options Oncol, 2004
Mavrogenis AF, et al. J Long Term Eff Med Implants, 2011
Mavrogenis AF, et al. J Surg Oncol, 2012
Mavrogenis AF, et al. Int J Immunopathol Pharmacol, 2011

Soft Tissue Sarcomas

Postoperative RT – Indications

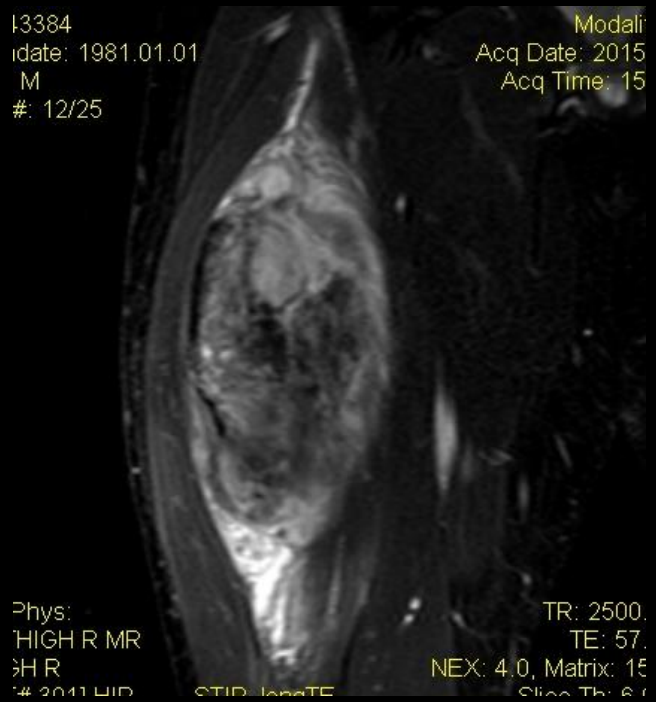
TABLE II Comparison of guideline criteria for giving radiotherapy and for irradiated margins

Reference	*Recommended clear surgical margin*	*Criteria for giving radiation*	*Margin irradiated*
Association of Directors of Anatomic and Surgical Pathology guideline, 1999 [9]	Should be 2 cm or more if possible	Surgical margins of less than 1.5–2 cm predispose to an increase in local recurrence and further surgery or radiation should be undertaken; if the surgical margin is bounded by an unbreached layer of fascia or periosteum, this risk probably does not apply	Not reported
Dutch Association of Comprehensive Cancer Centres, 2004 [10]	Not reported	Radiation is recommended for tumours with margins that are <2 cm fresh or <1 cm fixed	5–10 cm depending on the type of sarcoma 2 cm for boost
National Comprehensive Cancer Network, 2010 [7]	Negative margins should be obtained, but close margins may be necessary to preserve critical uninvolved neurovascular structures	<1 cm or microscopically positive on bone or major blood vessel or major nerve	Not reported
European Society for Medical Oncology, 2010 [8]	1 cm (but in some areas with anatomic barriers, the margins may be minimal)	Radiation is standard for tumours >5 cm	Not reported

NCCN, www.nccn.org. Accessed 04 Dec 2013

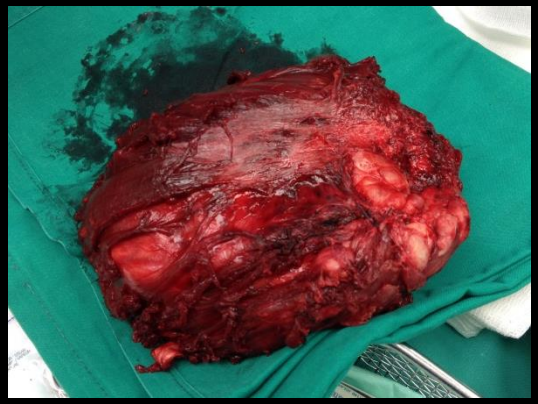
Kandel et al. Curr Oncol 2013

Soft Tissue Sarcomas



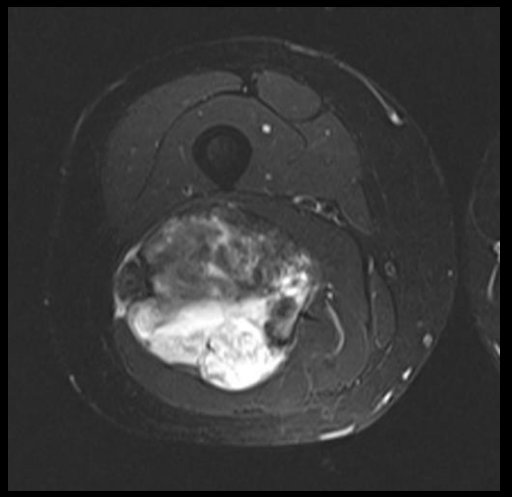
Postoperative RT

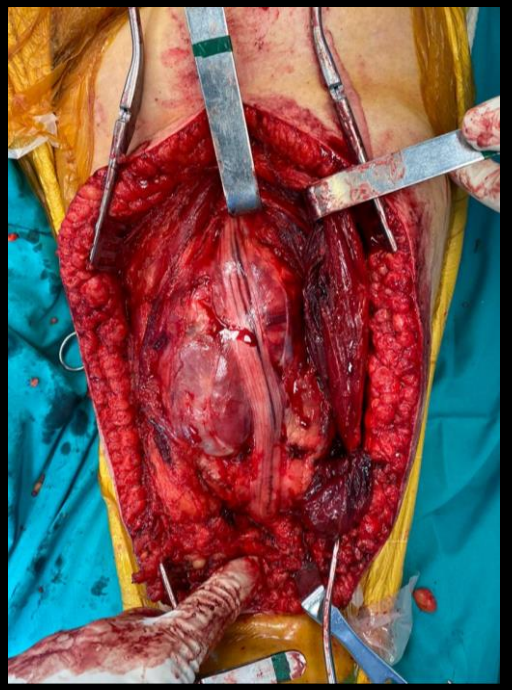
- Advantages
  - early surgery
  - viable tumor for pathology
  - minimal wound complications
- Disadvantages
  - extended treatment volume



NCCN, www.nccn.org. Accessed 04 Dec 2013

Soft Tissue Sarcomas





CMT

- Continues to be <u>controversial</u>
  - Localized STS, resected with clear margins (R0)
  - Poor response (4-12% survival benefit)
  - Neo- vs. adjuvant CMT
- <u>Except for</u>
  - Rhabdomyosarcoma, extraskeletal Ewing/osteosarcoma, synovial sarcoma

Albritton KH, Randall RL, J Pediatr Hematol/Oncol, 2005

NCCN Guidelines

National Comprehensive Cancer Network

www.nccn.org

AJCC

https://cancerstaging.org

Primary tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Tumor 5.0 cm or less in greatest dimension
  - T1a: superficial tumor
  - T1b: deep tumor
- T2: Tumor more than 5.0 cm in greatest dimension
  - T2a: superficial tumor
  - T2b: deep tumor

Regional Lymph Nodes (N)

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

Distant metastasis (M)

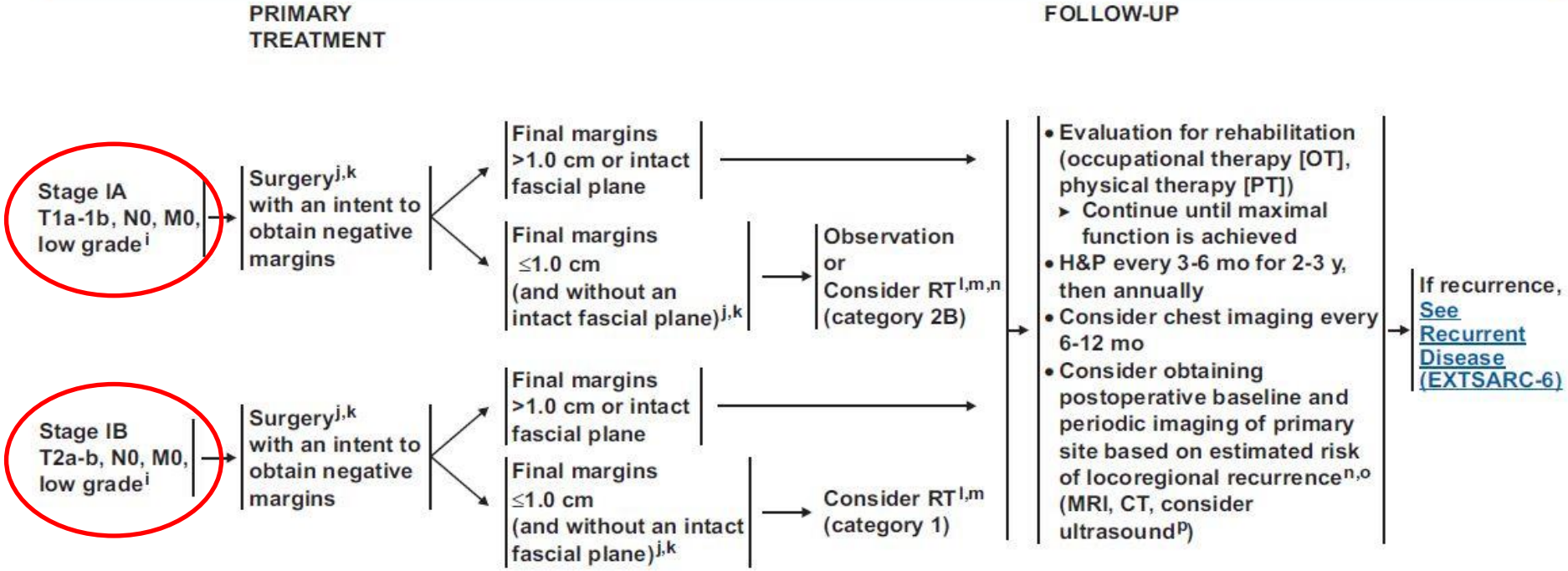
- MX: Presence of distant metastasis cannot be accessed
- M0: No distant metastasis
- M1: Distant metastasis

Histopathologic Grade (G)

- GX: Grade cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- G4: Undifferentiated

Stage IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
Stage IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
Stage IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
Stage IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
Stage III	T2a, T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

[a]*Reprinted with permission from AJCC: Soft tissue sarcoma. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 291-8.*



[i] See American Joint Committee on Cancer (AJCC) Staging, 7th Edition (ST-1).

[j] See Principles of Surgery (SARC-C).

[k] In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended. Reresection, if feasible, may be necessary to render margins >1.0 cm.

[l] See Guidelines for Radiation Therapy (SARC-D).

[m] Randomized clinical trial data support the use of radiation therapy as an adjunct to surgery in appropriately selected patients based on an improvement in disease-free survival (although not overall survival). (Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1998;16:197-203).

[n] In situations where the area is easily followed by physical examination, imaging may not be required.

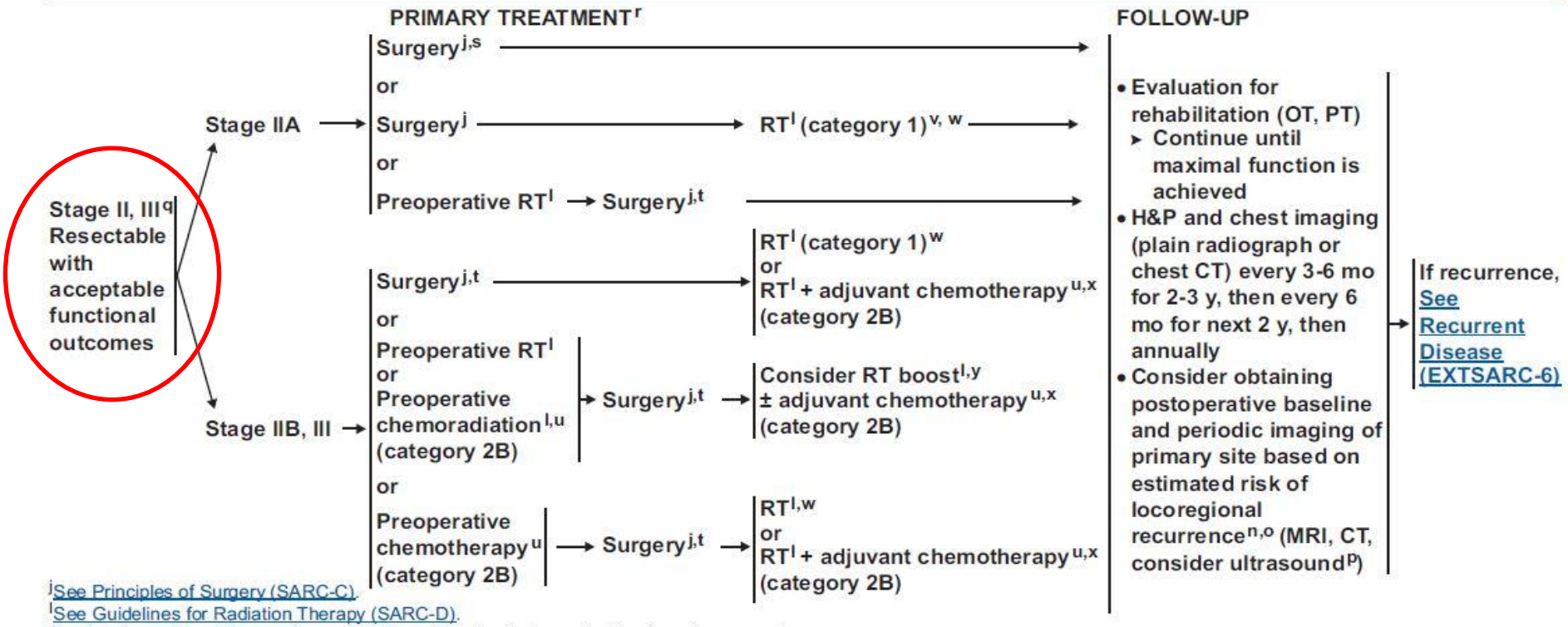
[o] After 10 y, the likelihood of developing a recurrence is small and follow-up should be individualized.

[p] Consider ultrasound for smaller lesions that are superficial. Ultrasound should be done by an ultrasonagrapher experienced in musculoskeletal disease. (Choi H, Varma DGK, Fornage BD, Kim EE, et al. Soft-Tissue Sarcoma: MR Imaging vs Sonography for Detection of Local Recurrence After Surgery. AJR 1991;157:353-358.)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 1.2013
Extremity/Trunk, Head/Neck

NCCN Guidelines Index
Soft Tissue Sarcoma, Table of Contents
Discussion



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[q] Patients with stage III tumors with lymph node involvement should undergo regional lymph node dissection at the time of primary tumor resection ± RT.

[r] Treatment options for stage II and III should be made by a multidisciplinary team and involve consideration of the following: performance status, comorbid factors (including age), site of disease, histologic subtype, and institutional experience.

[s] Surgery alone may be an option for small tumors resected with wide margins.

[t] Consider re-imaging to assess primary tumor and to rule out metastatic disease.

[u] See Systemic Therapy Agents and Regimens With Activity in Soft Tissue Sarcoma (SARC-E).

[v] RT may be used in select circumstances such as close or positive margins where re-excision is not feasible or for functional considerations.

[w] Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1998;16:197-203.

[x] There are limited and conflicting data regarding the potential benefits of adjuvant chemotherapy in stage II or stage III patients.

[y] For residual gross disease or microscopically positive margins.

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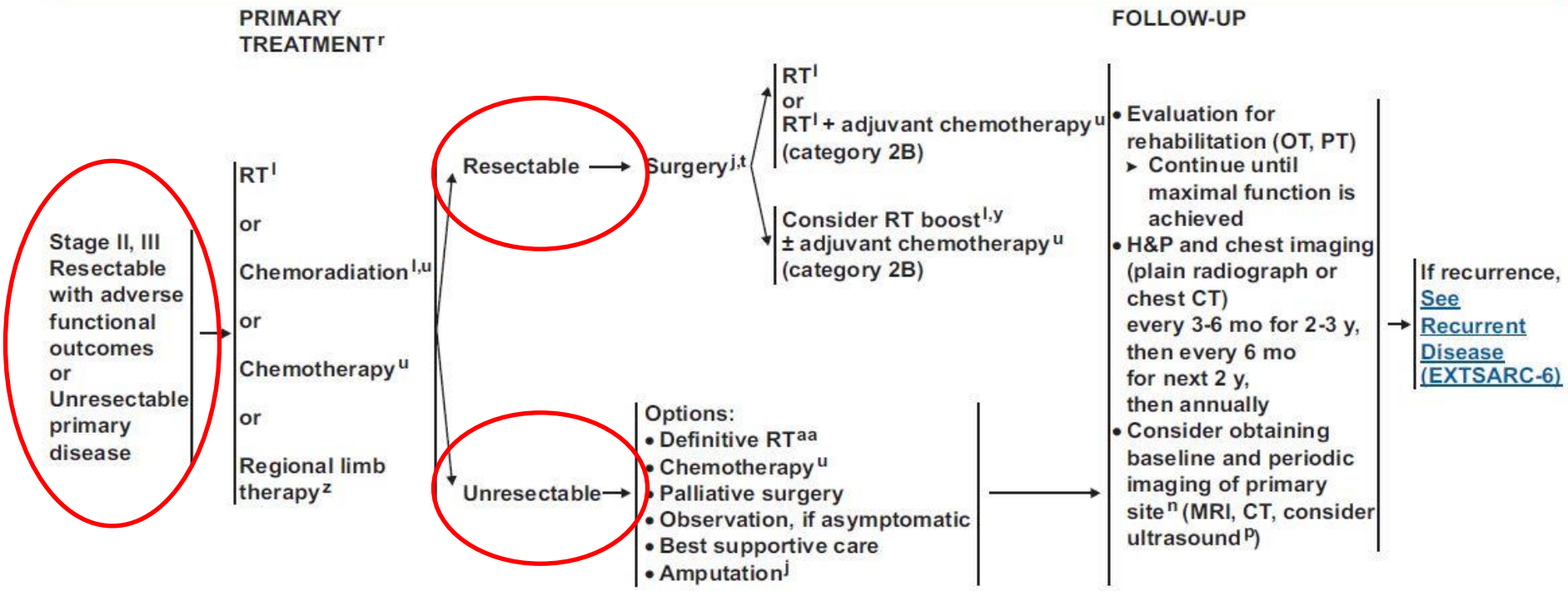

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[t] Consider re-imaging to assess primary tumor and to rule out metastatic disease.
[u] See Systemic Therapy Agents and Regimens With Activity in Soft Tissue Sarcoma (SARC-E).
[y] For residual gross disease or microscopically positive margins.
[z] Should only be done at institutions with experience in regional limb therapy.
[aa] Definitive RT entails delivering the maximal local dose compatible with known normal tissue tolerance, typically in the range of 7000-8000 cGy with sophisticated treatment planning techniques being a necessity in this setting.

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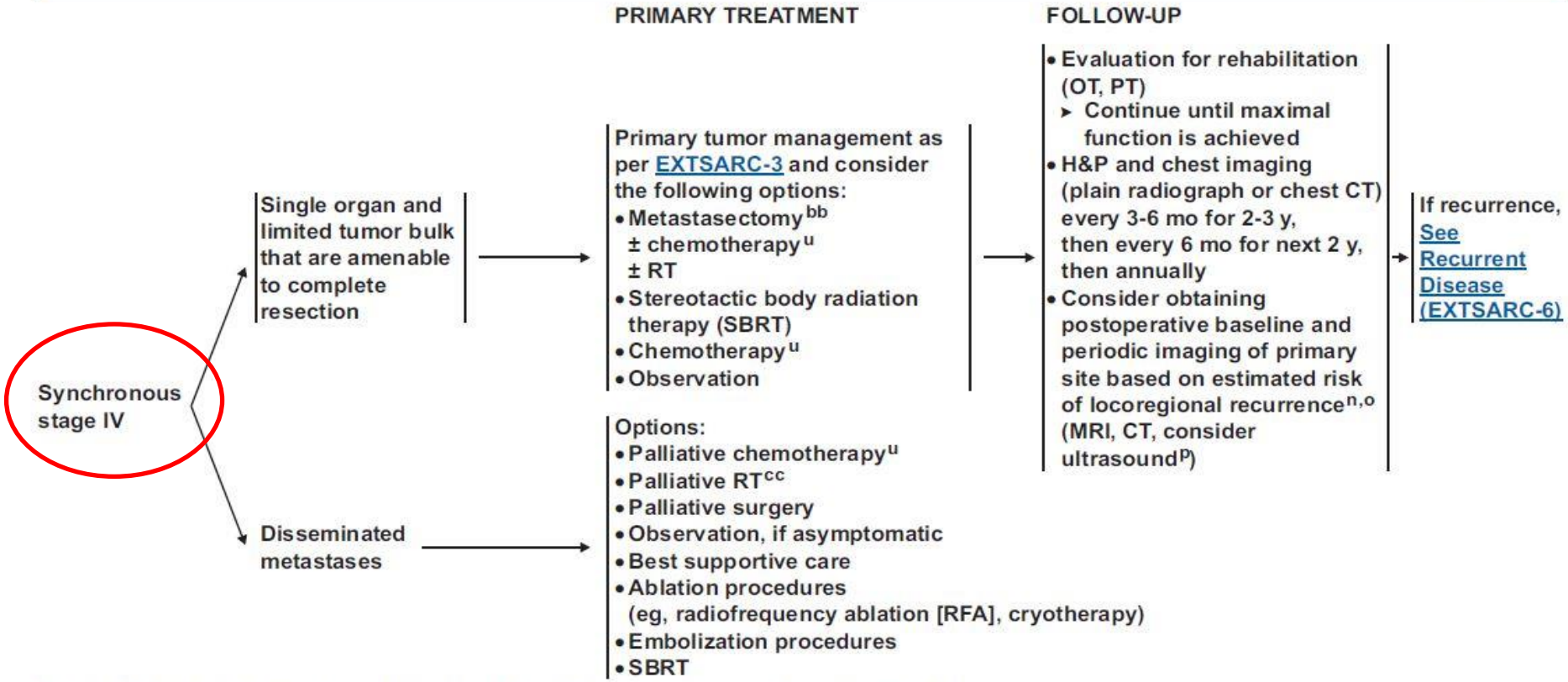

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[uu] See Systemic Therapy Agents and Regimens With Activity in Soft Tissue Sarcoma (SARC-E).

[bb] Thoracotomy and video-assisted thoracic surgery (VATS) should be available and used selectively depending on the clinical presentation of metastatic disease.

[cc] Palliative RT requires balancing expedient treatment with sufficient dose expected to halt the growth of, or cause tumor regression. Numerous clinical issues regarding rapidity of growth, the status of systemic disease, and the use of chemotherapy must be considered.

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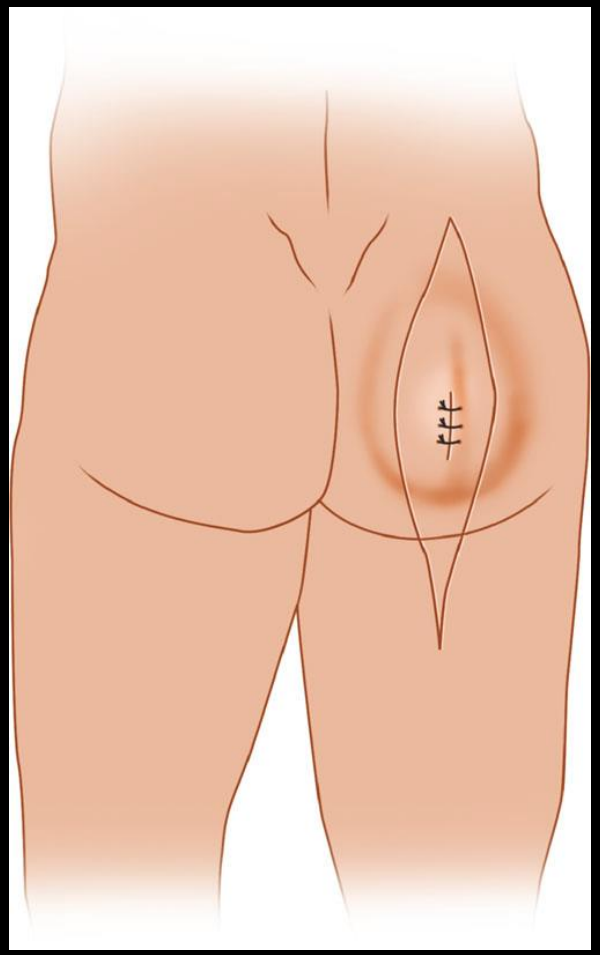
STS SURGICAL TREATMENT

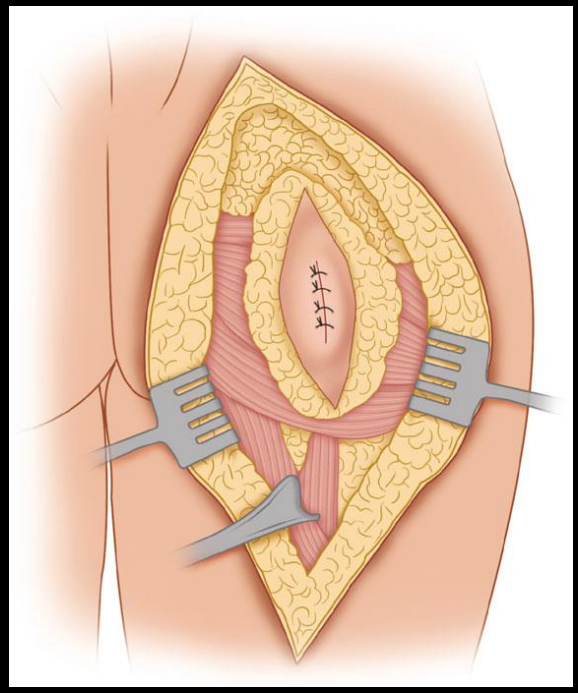
Lower extremity

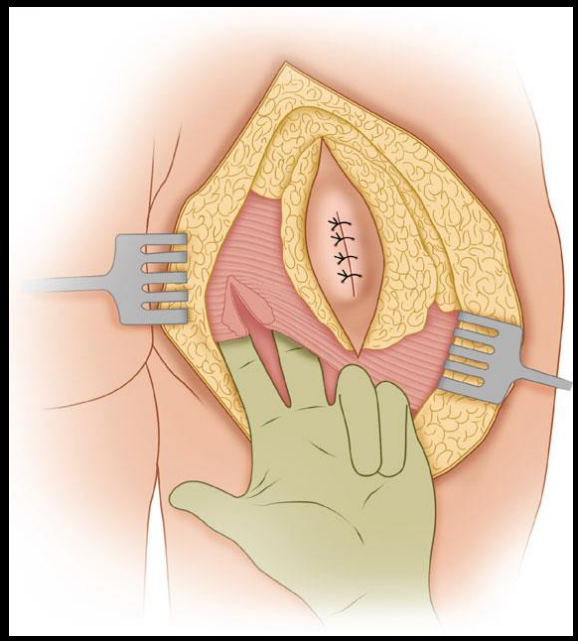
STS in the Buttock Area

- Buttockectomy
- The gluteus maximus is more often involved by sarcoma than the other glutei

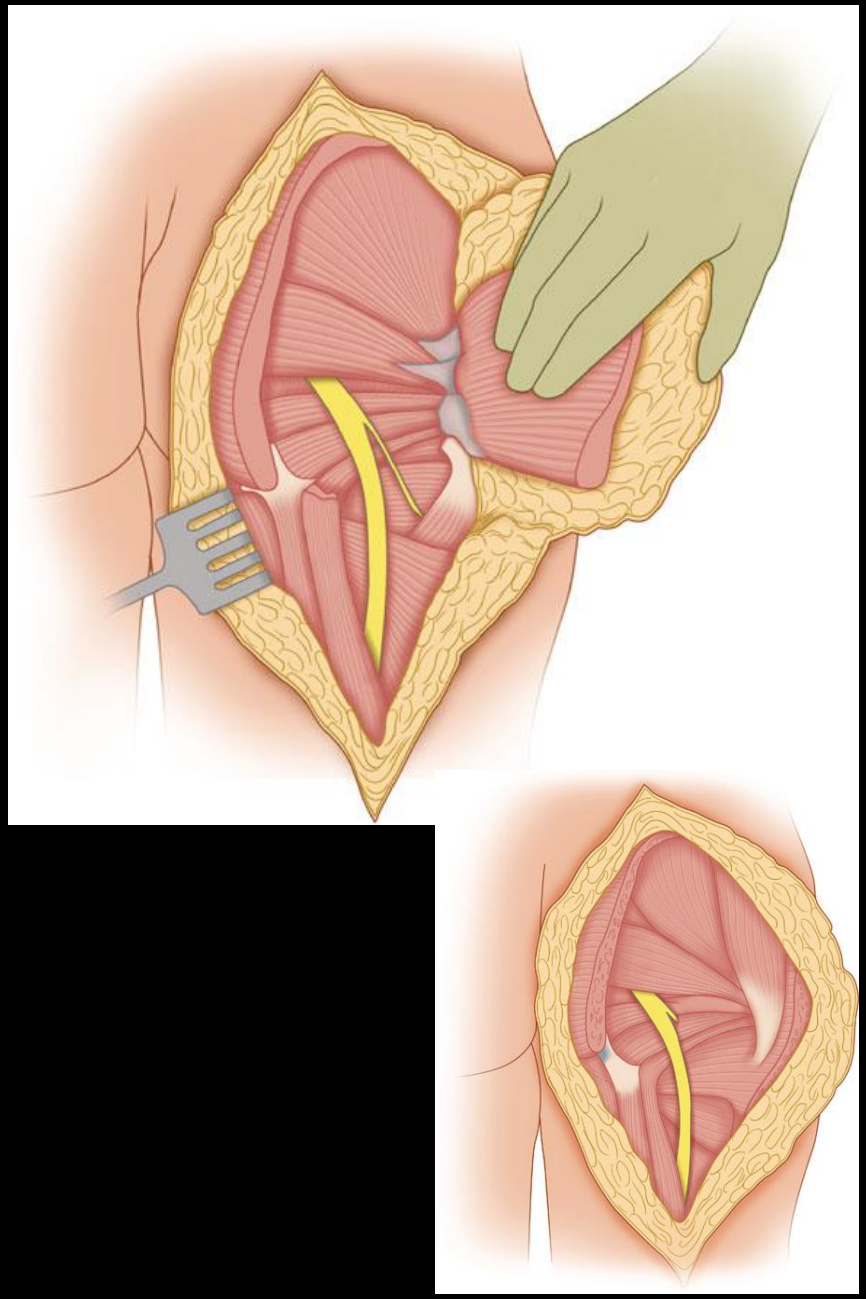


- Lateral or a prone position
- Vertical or elliptical incision
  - Gluteus max fibers
- The incision is deepened between the ischial tuberosity and the GT and below the edge of the gluteus maximus



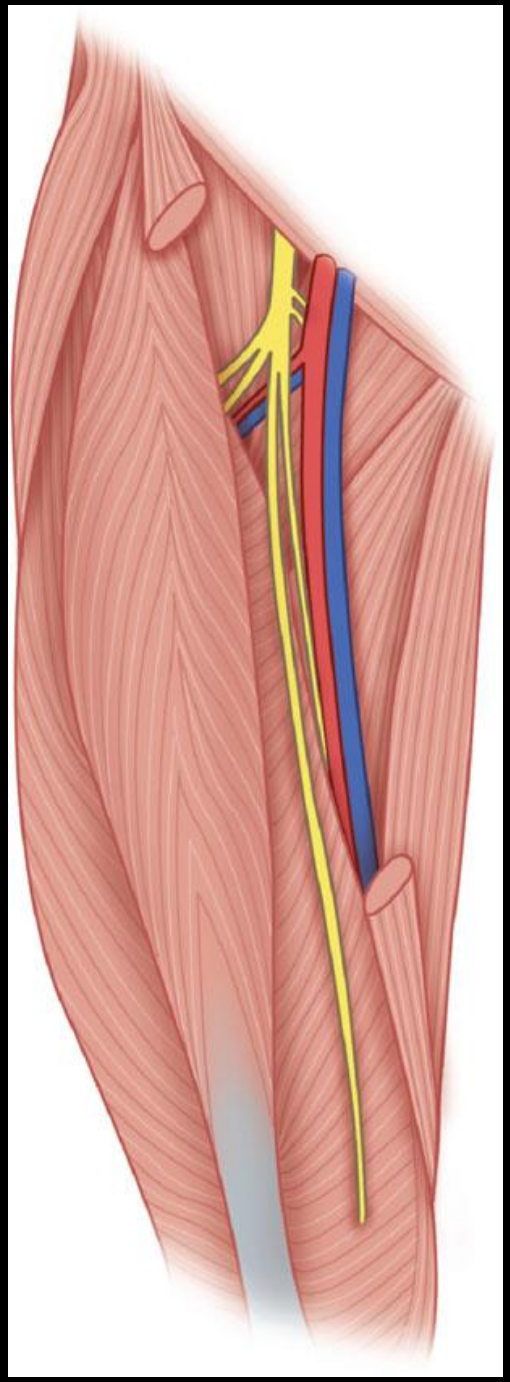


- Below the lower edge of the gluteus maximus, the sheath of the sciatic nerve is about to be incised to expose the nerve



STS in the anterior thigh

- The muscles of the thigh
- Anterior compartment
  - quadriceps and sartorius (femoral n.)
- Medial compartment
  - adductors (obturator n.)
- Posterior compartment
  - hamstrings

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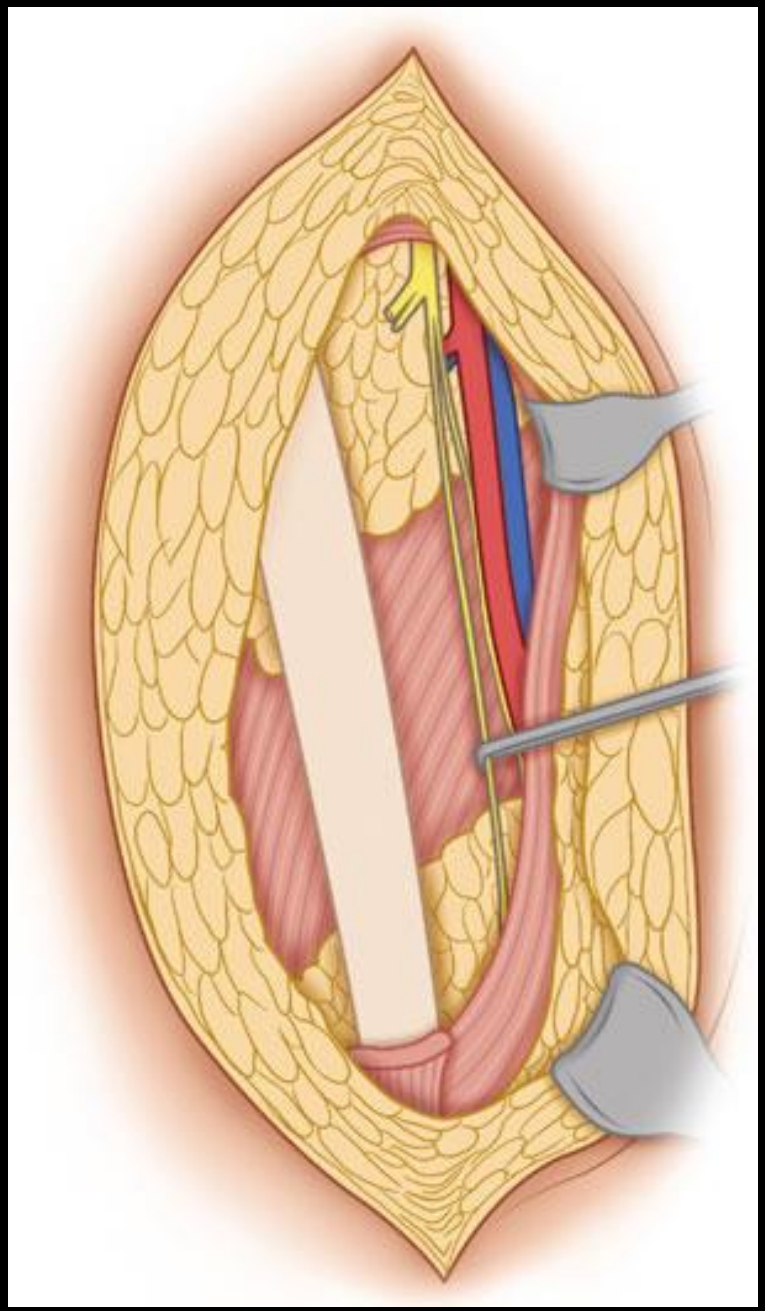
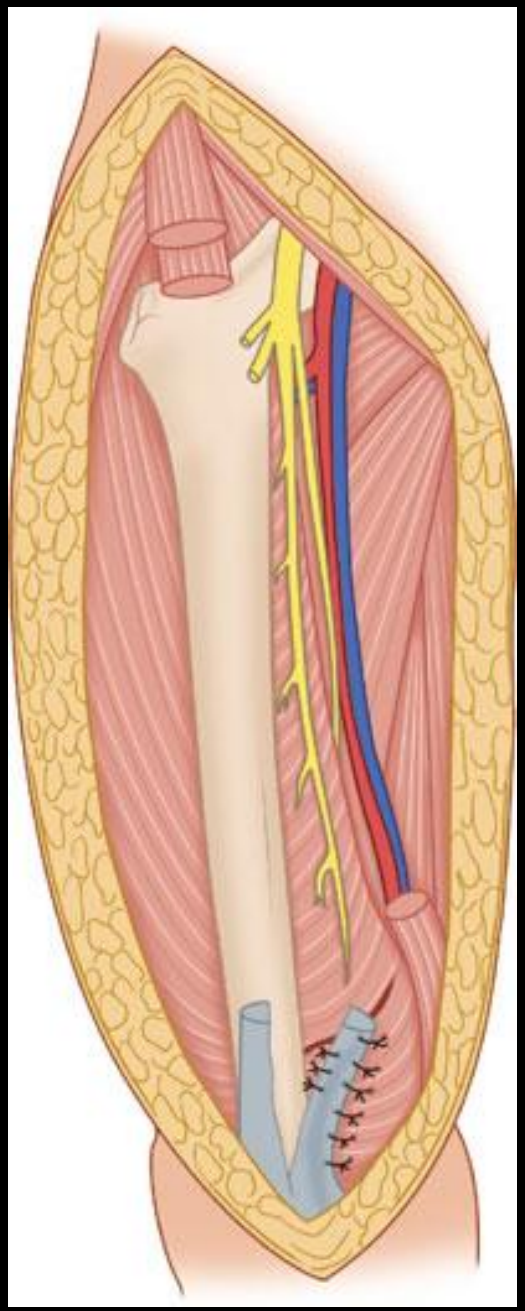
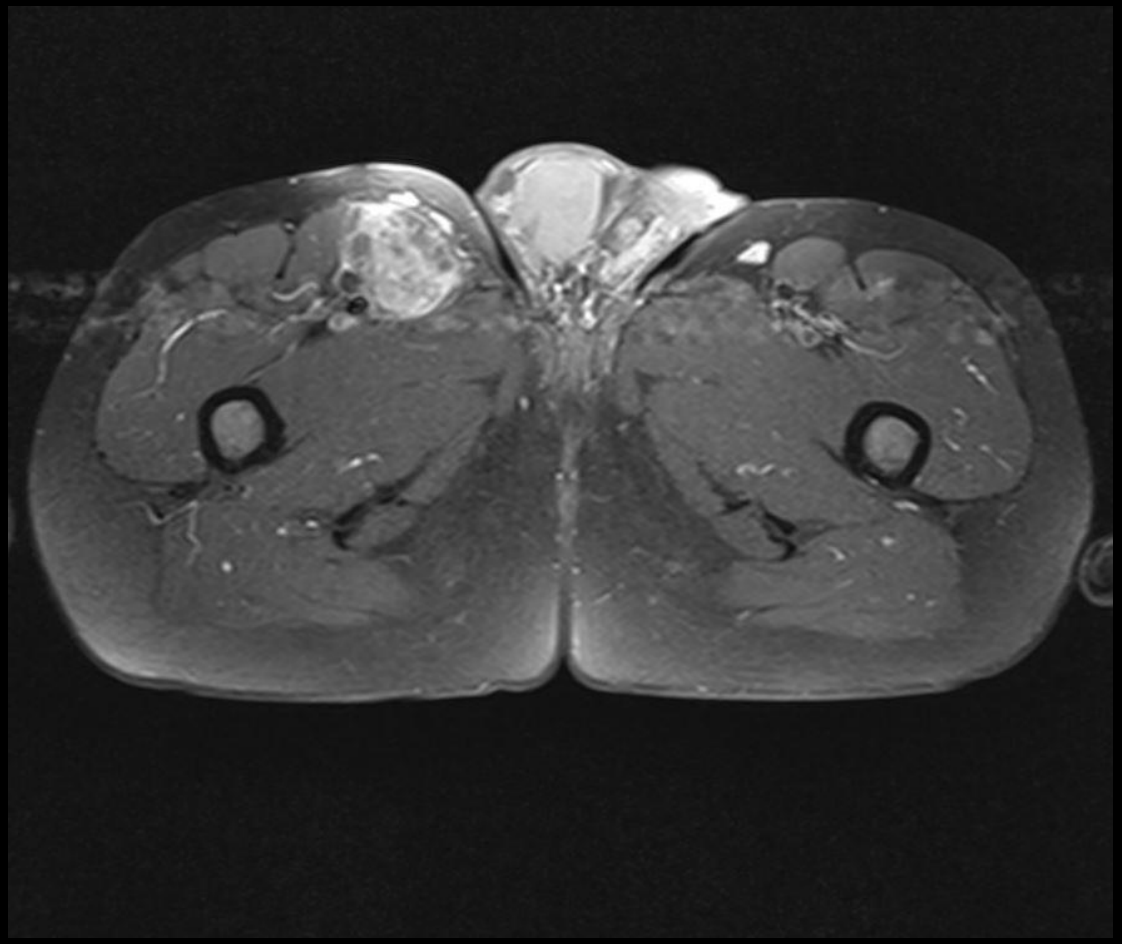
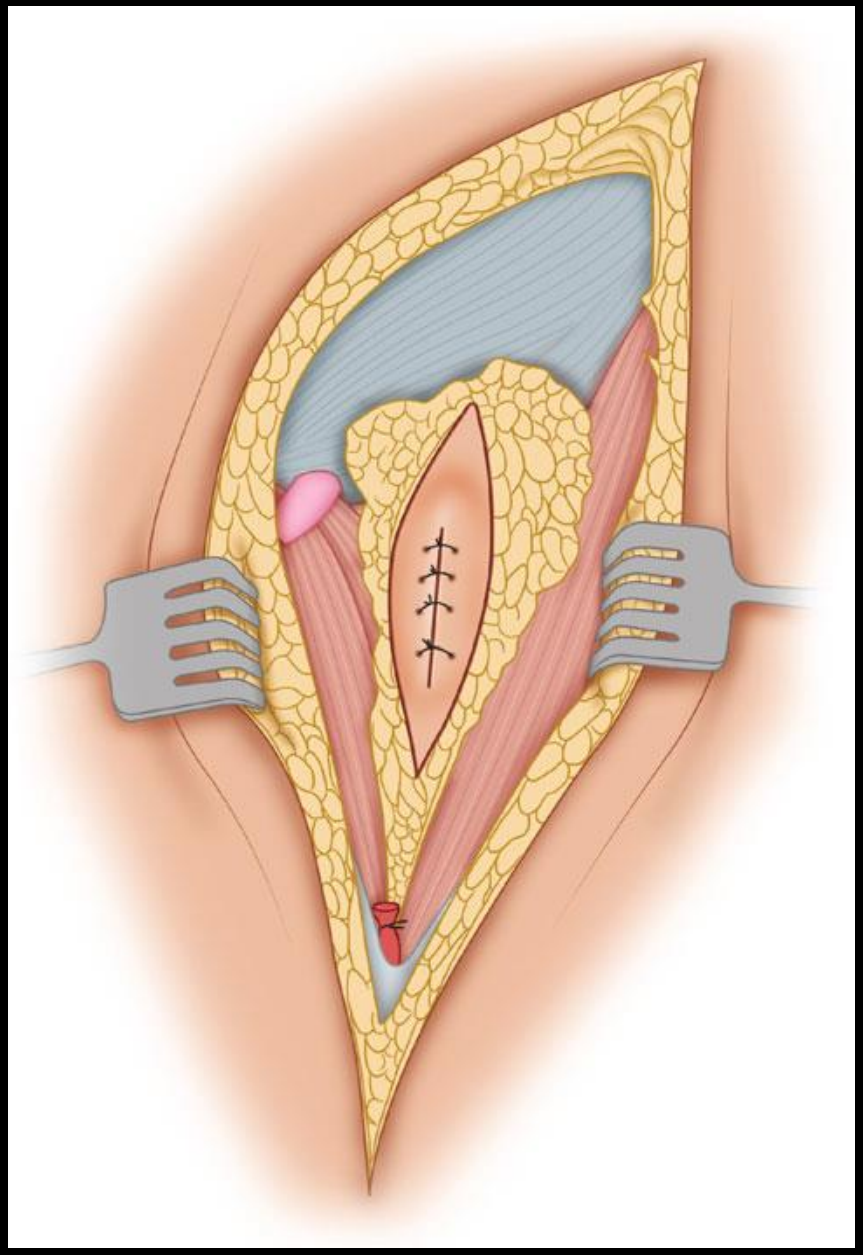
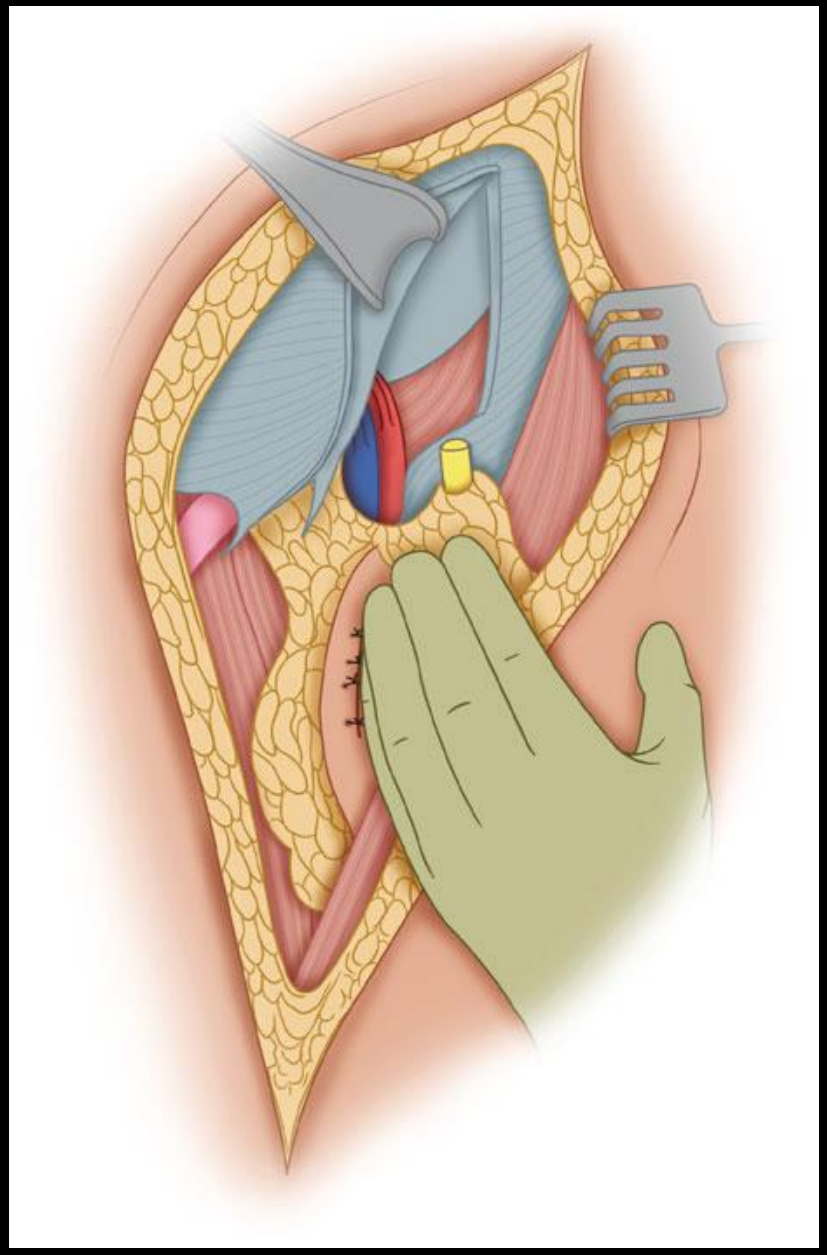


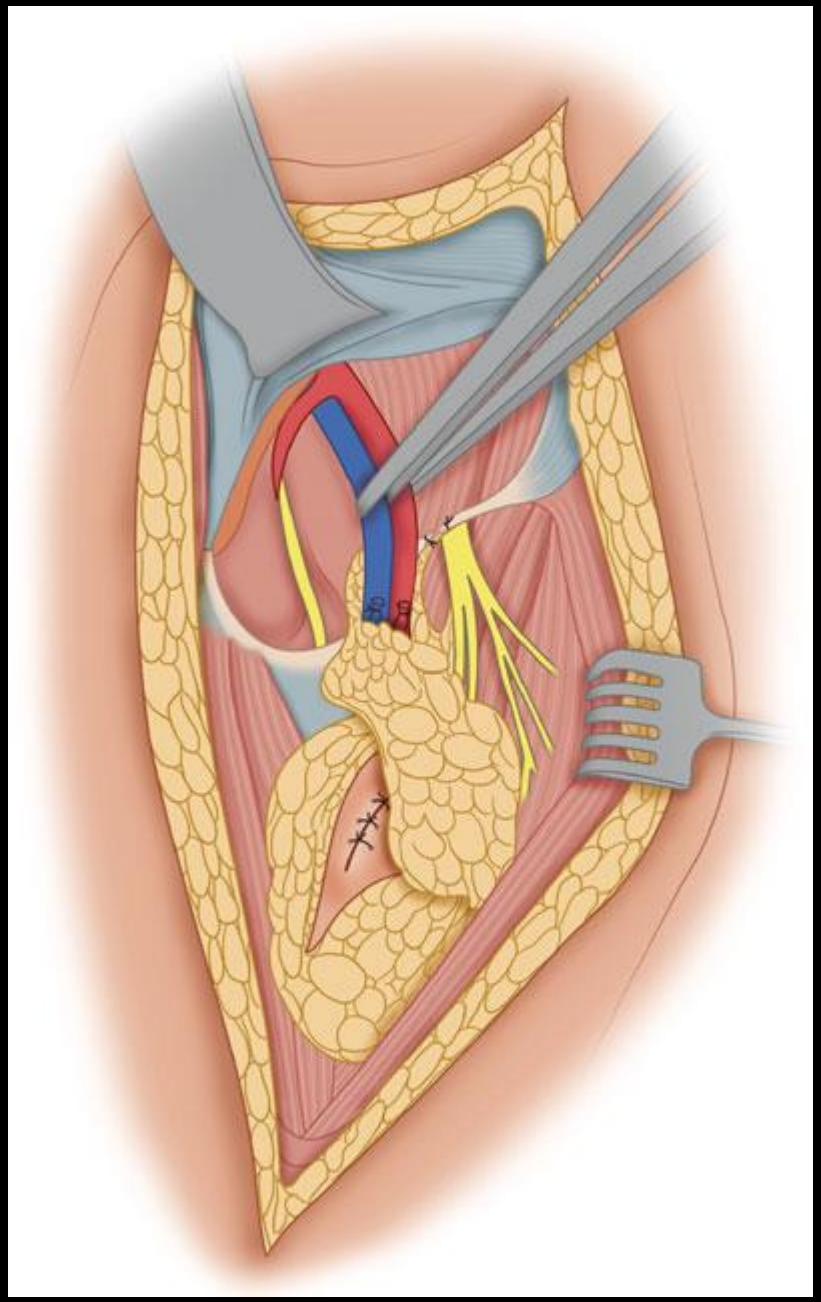


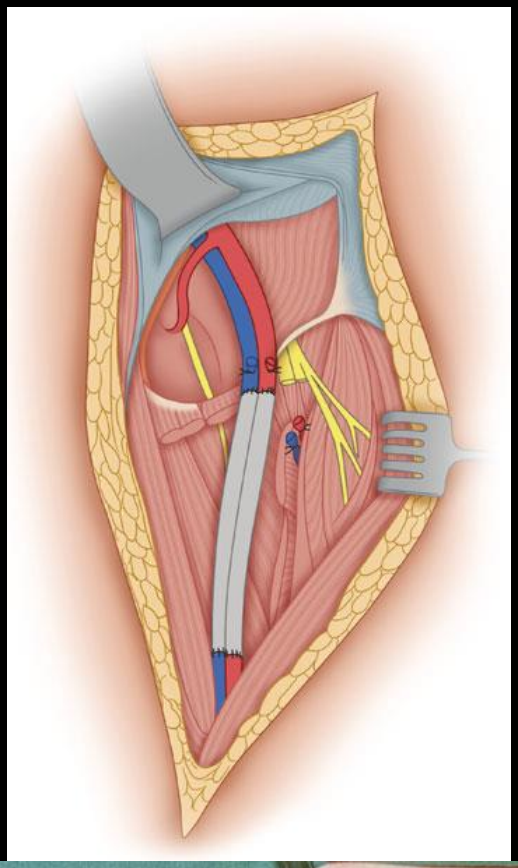
STS along the femoral vessels

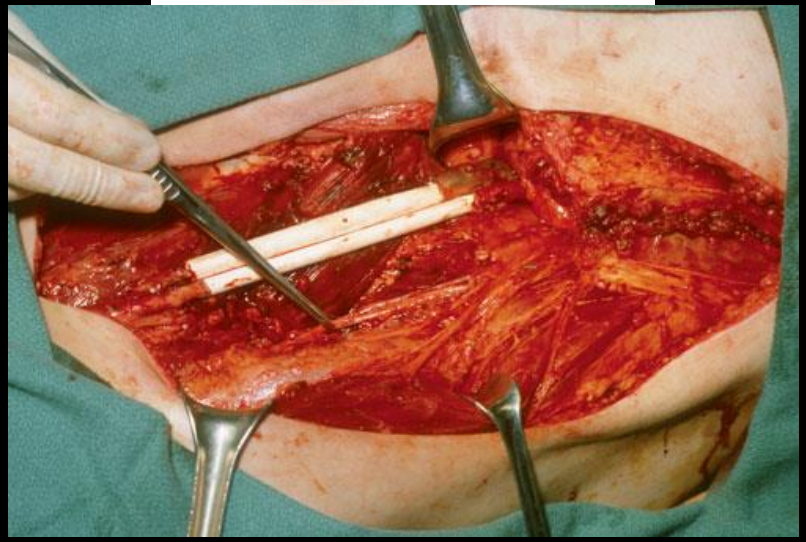






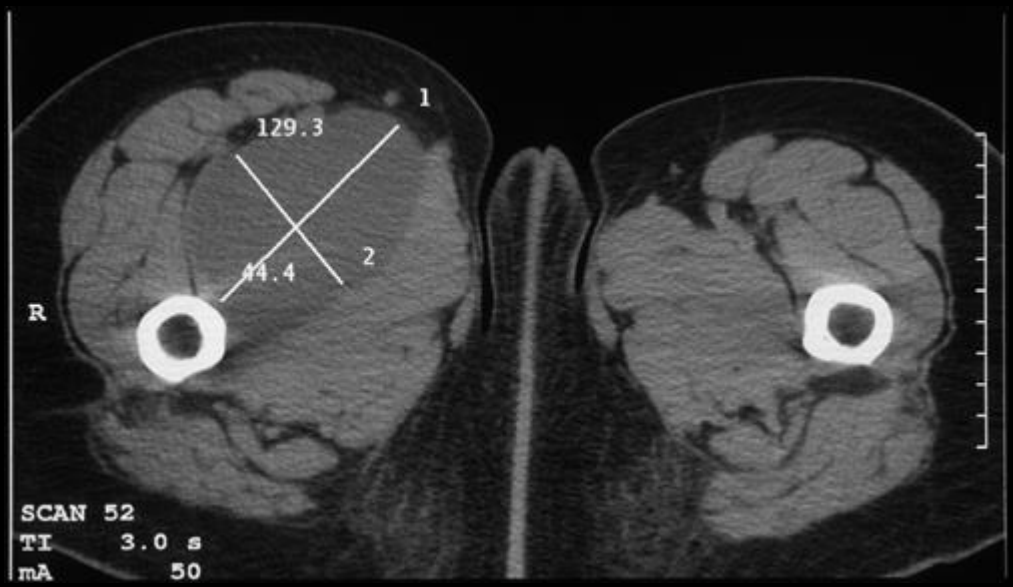




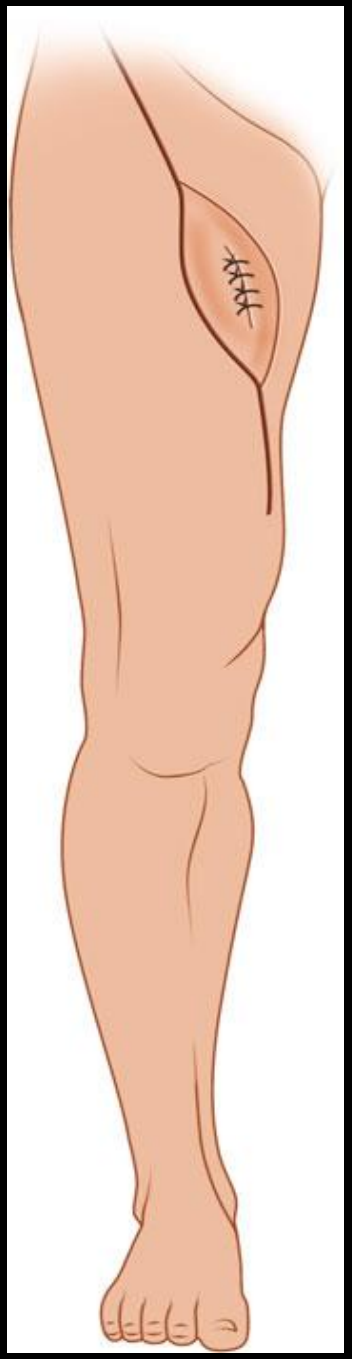


STS in the medial thigh

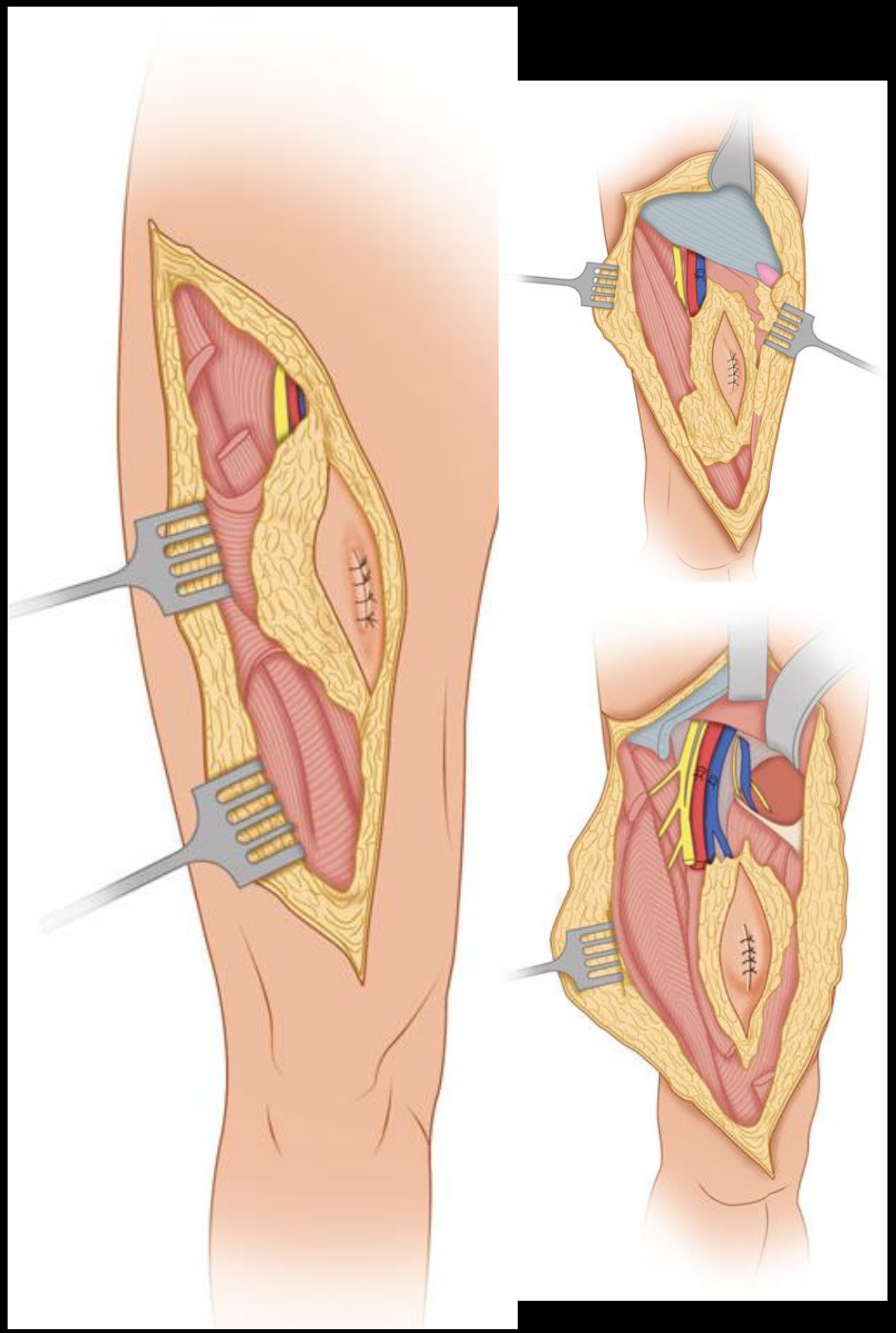
- Supine position and the affected leg prepped and draped free in flexion and external rotation



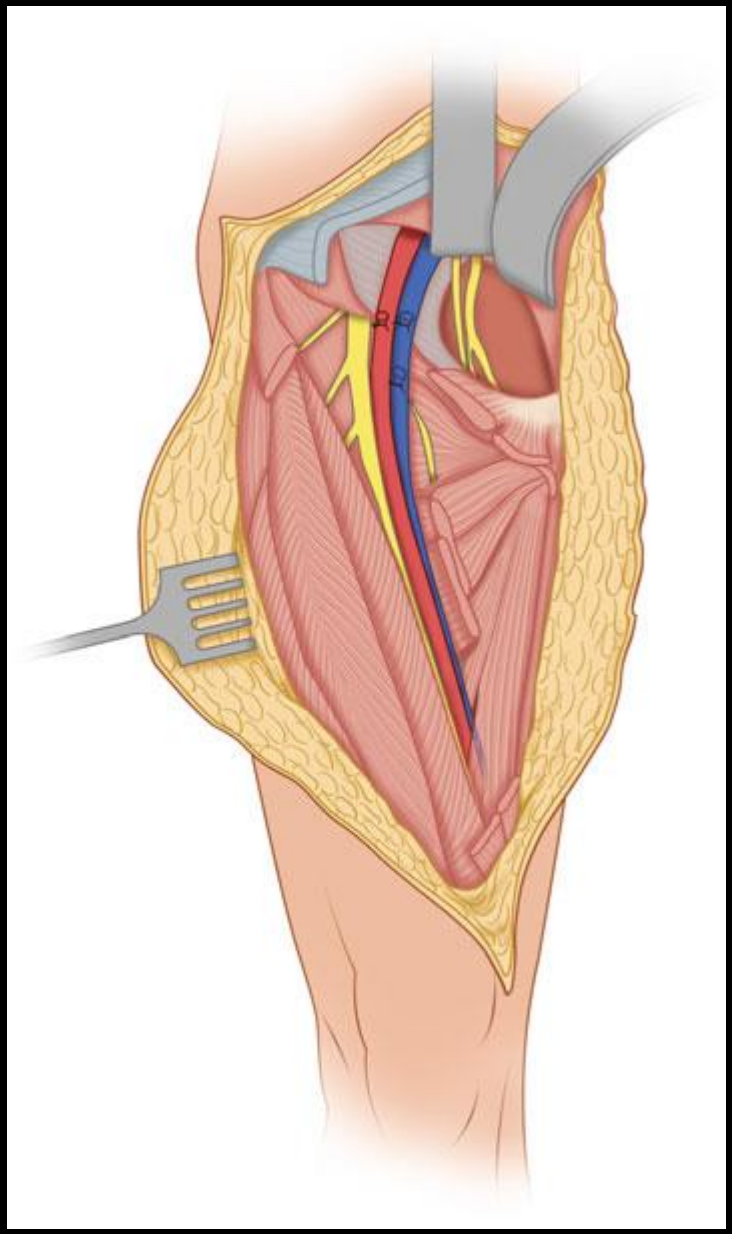
- Incision is made in the medial aspect of the thigh along the course of the gracilis muscle from the pubic bone to the medial femoral condyle



- The femoral vessels are exposed proximally
- It is best to avoid unnecessary skeletonization of the vessels, because skeletonization involves division of a significant number of lymphatics coursing along the vessels and may increase the chance of postoperative lymphedema

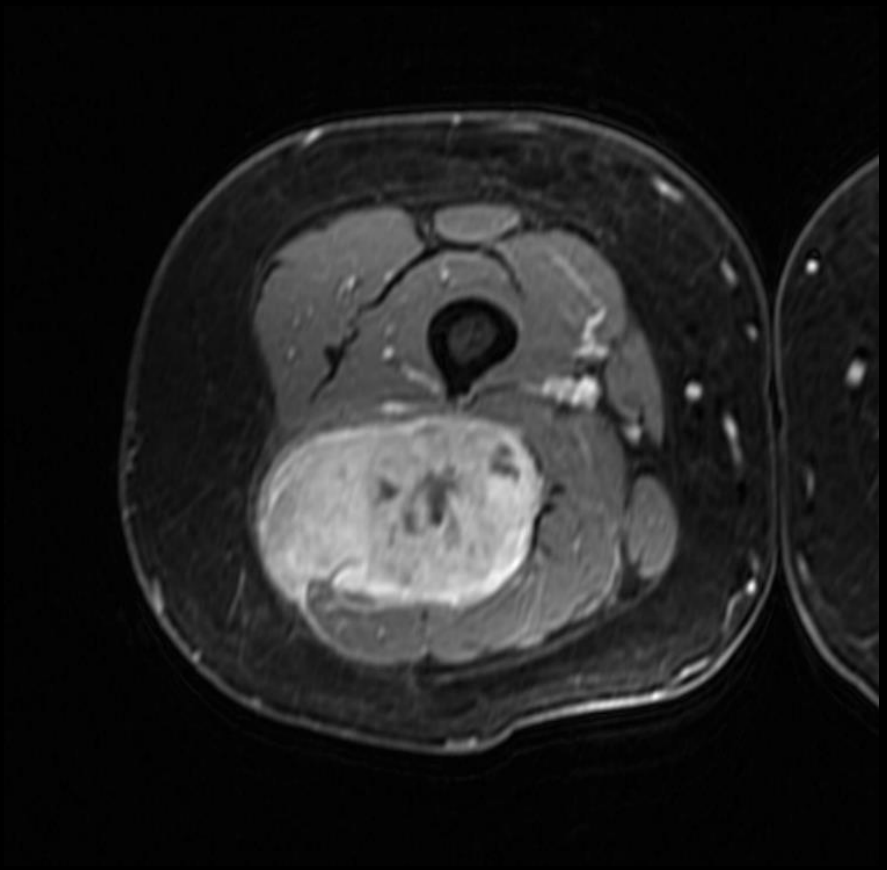


- Proximal exposure of the external iliac vessels, when the tumor nears the inguinal ligament, may be obtained by extending the incision along the iliac crest



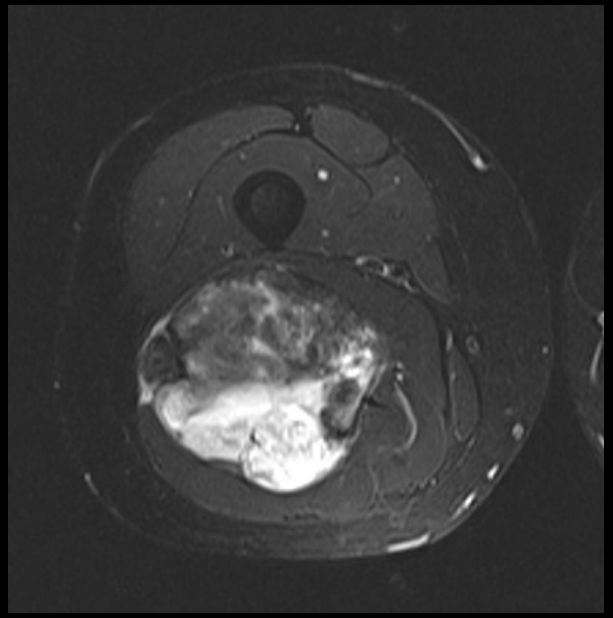
STS in the posterior thigh

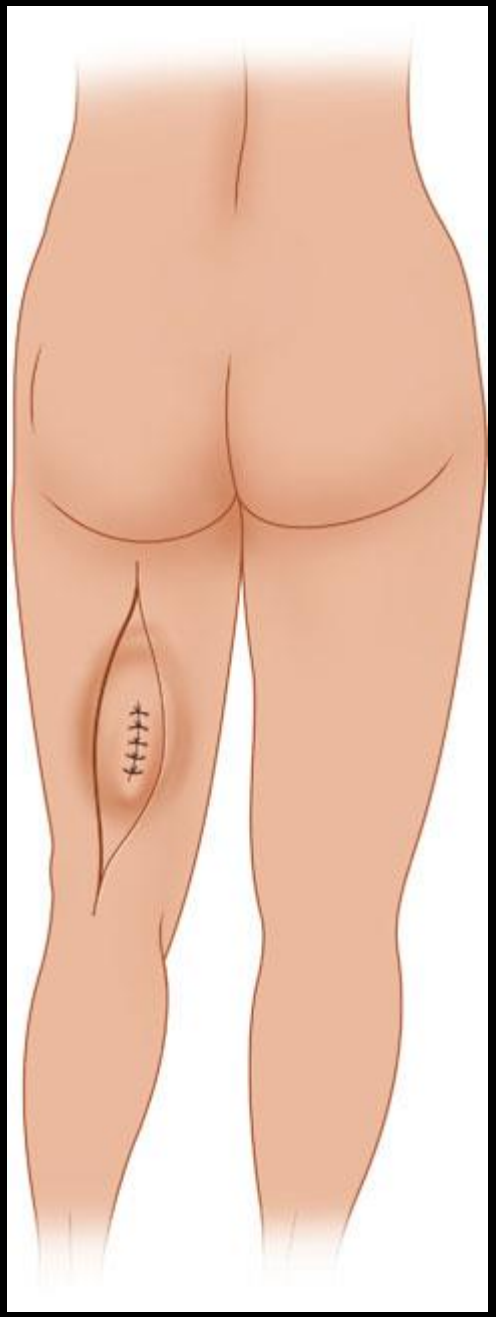
- Prone position



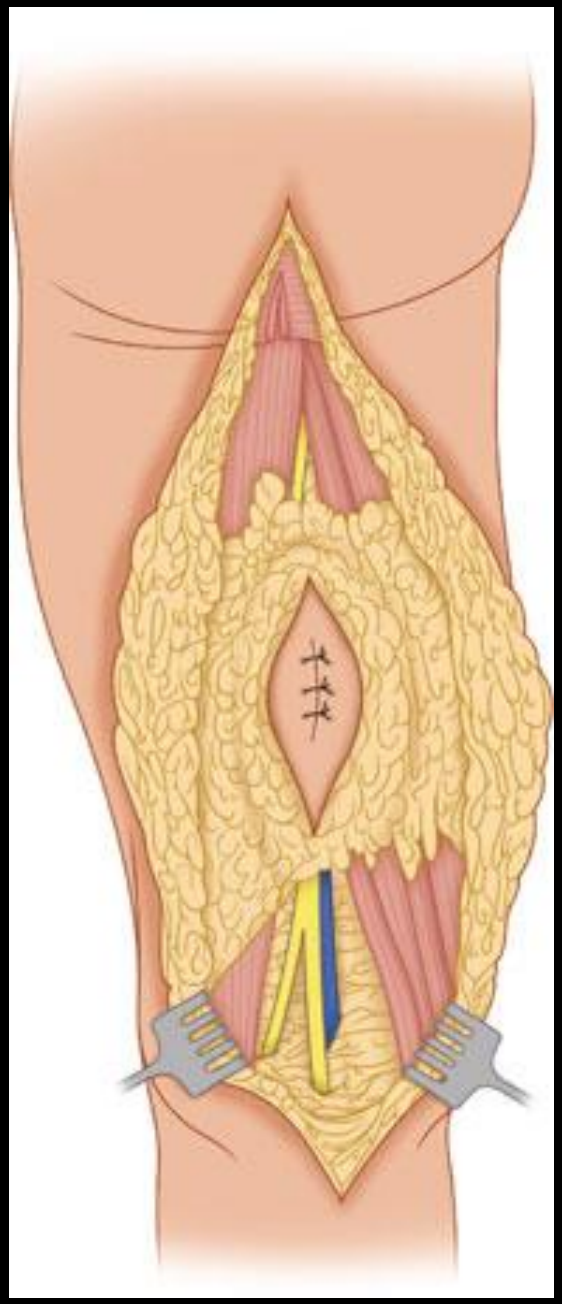
STS in the posterior thigh

- Vertical longitudinal incision from the gluteal crease to the popliteal fossa

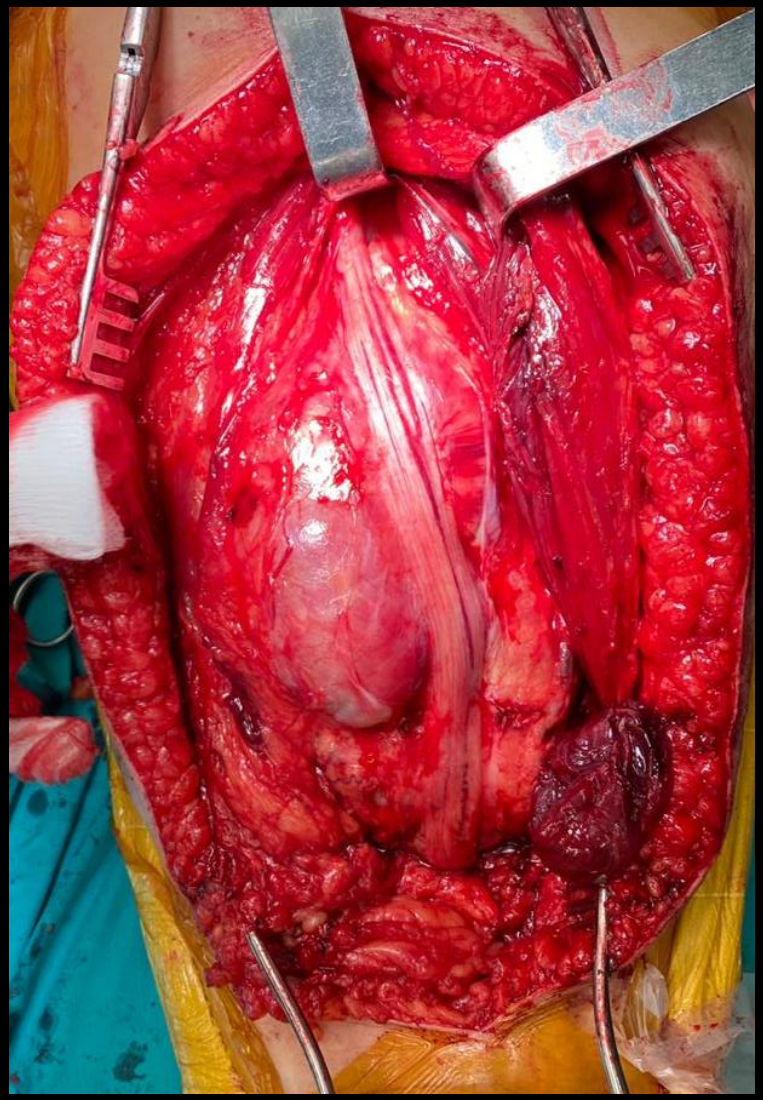




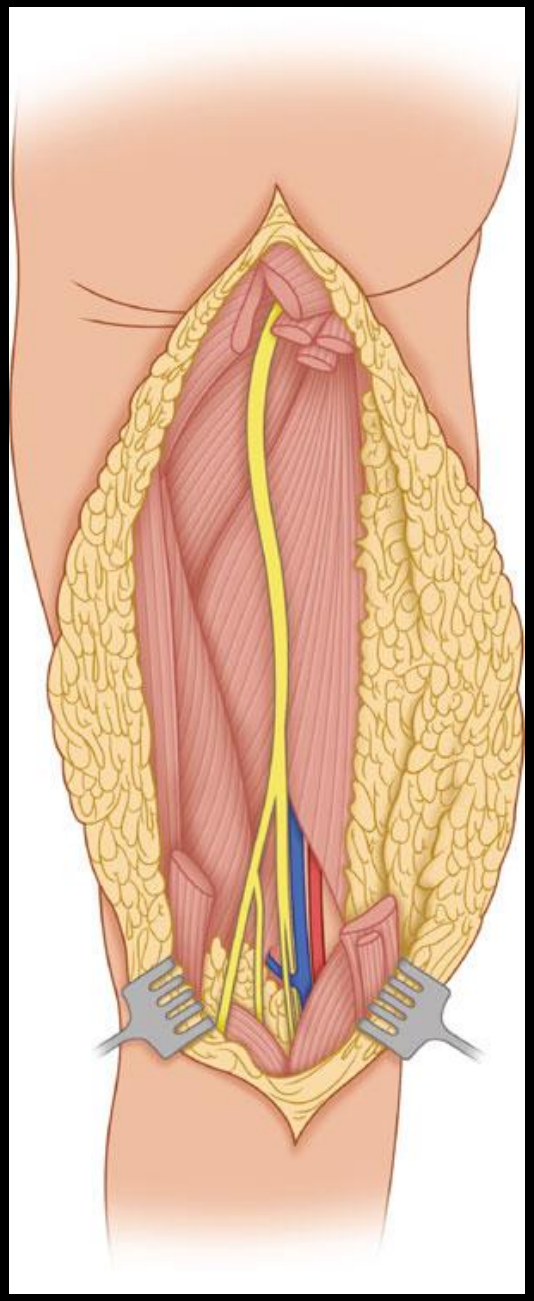
- Superiorly, below the edge of the gluteus maximus, the sciatic n. may be exposed between the origin of the hamstring muscles from the ischial tuberosity and the greater trochanter
- If the tumor comes close to the gluteal crease, one may need to incise the edge of the gluteus maximus in a superior direction to provide exposure for the identification of the sciatic nerve proximal to the tumor



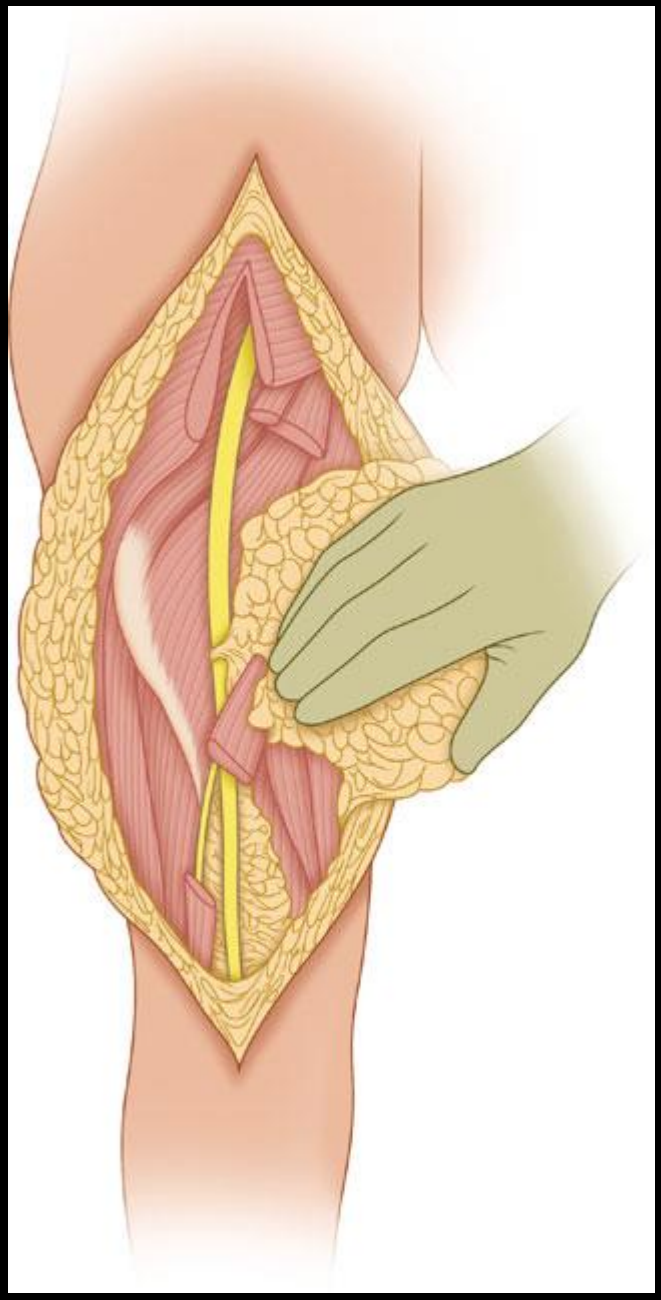
- The sheath of the sciatic nerve is entered on the side opposite to the tumor and incised along the length of the nerve, leaving the sheath attached to the tumor to be removed en bloc with the tumor



- Removal of all hamstring muscles is tolerated well
  - ability to flex the knee, apparently through the use of the sartorius muscle, the gracilis, and the gastrocnemius muscle with its two heads



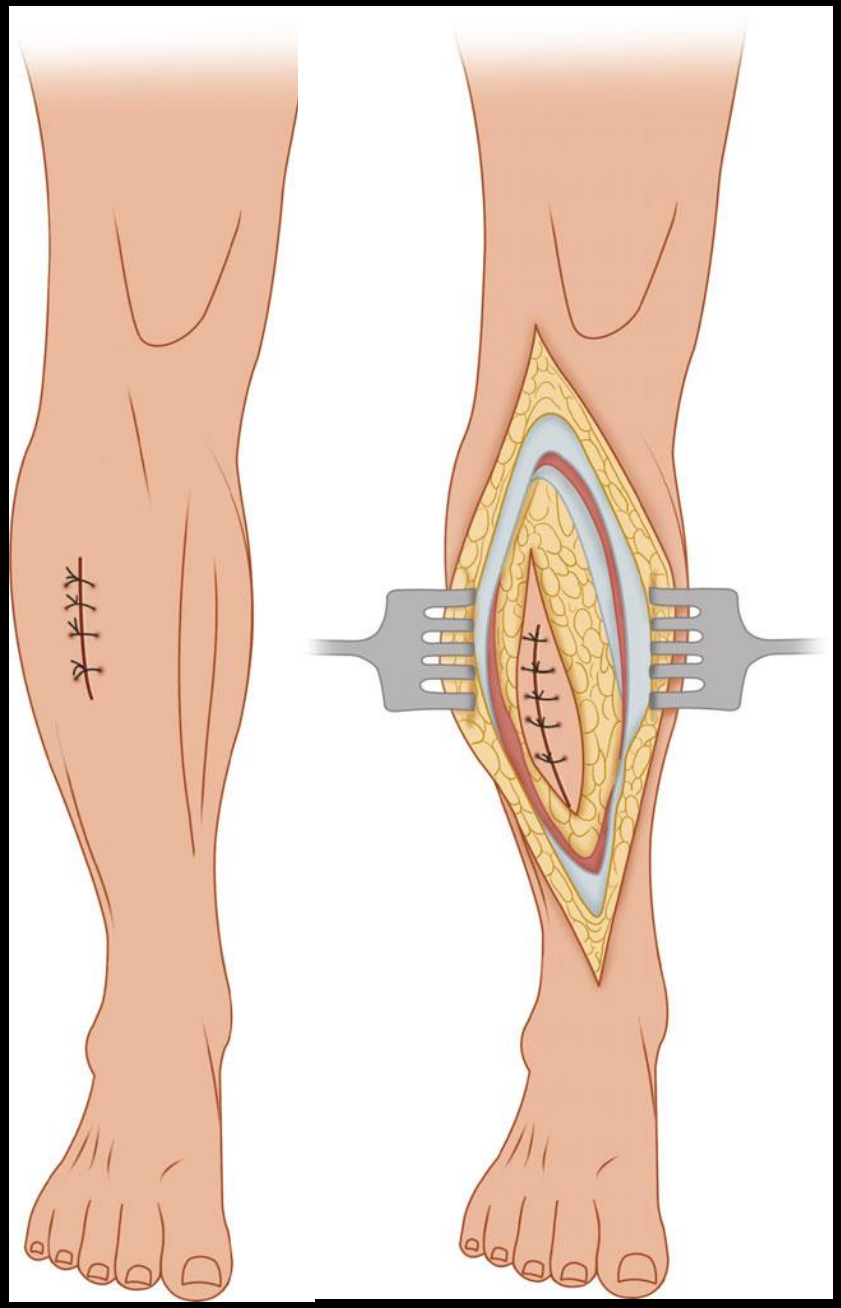
- High resection of the sciatic nerve
  - no sensation in the back of the leg or foot
  - the anterior aspect of the leg all the way to the ankle is supplied by the saphenous branch of the femoral nerve
  - able to flex the knee by using the sartorius and gracilis muscles
  - unable to move the ankle (foot drop)



STS in the leg

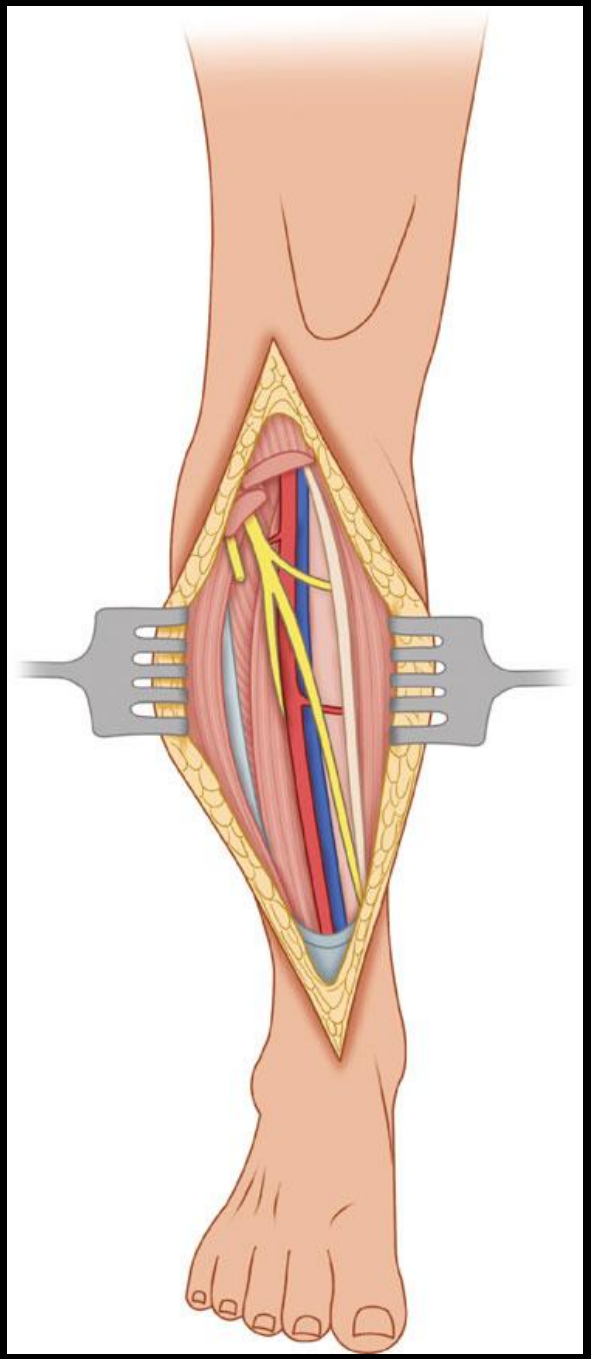
Anterior compartment

- Dorsiflexion of the foot (tibialis anterior and peroneus tertius muscles), of the great toe (extensor hallucis longus), and of the other four toes (extensor digitorum longus)



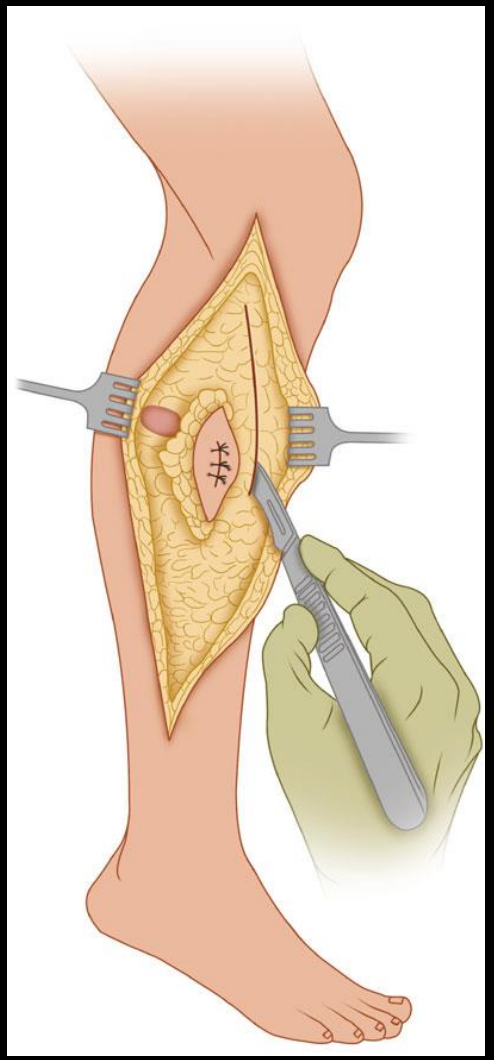
STS in the leg

- In surgery for anterior compartment sarcomas, the aim is to preserve at least one of the four muscles in the anterior compartment with intact nerve supply so as to avoid foot drop

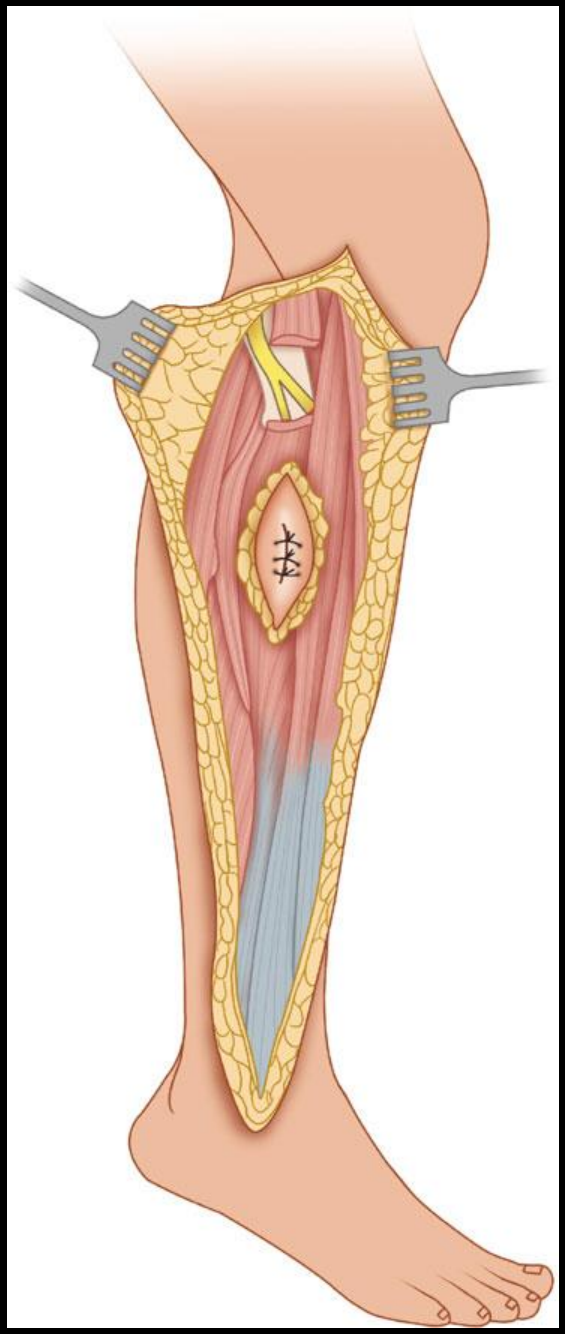


Lateral compartment

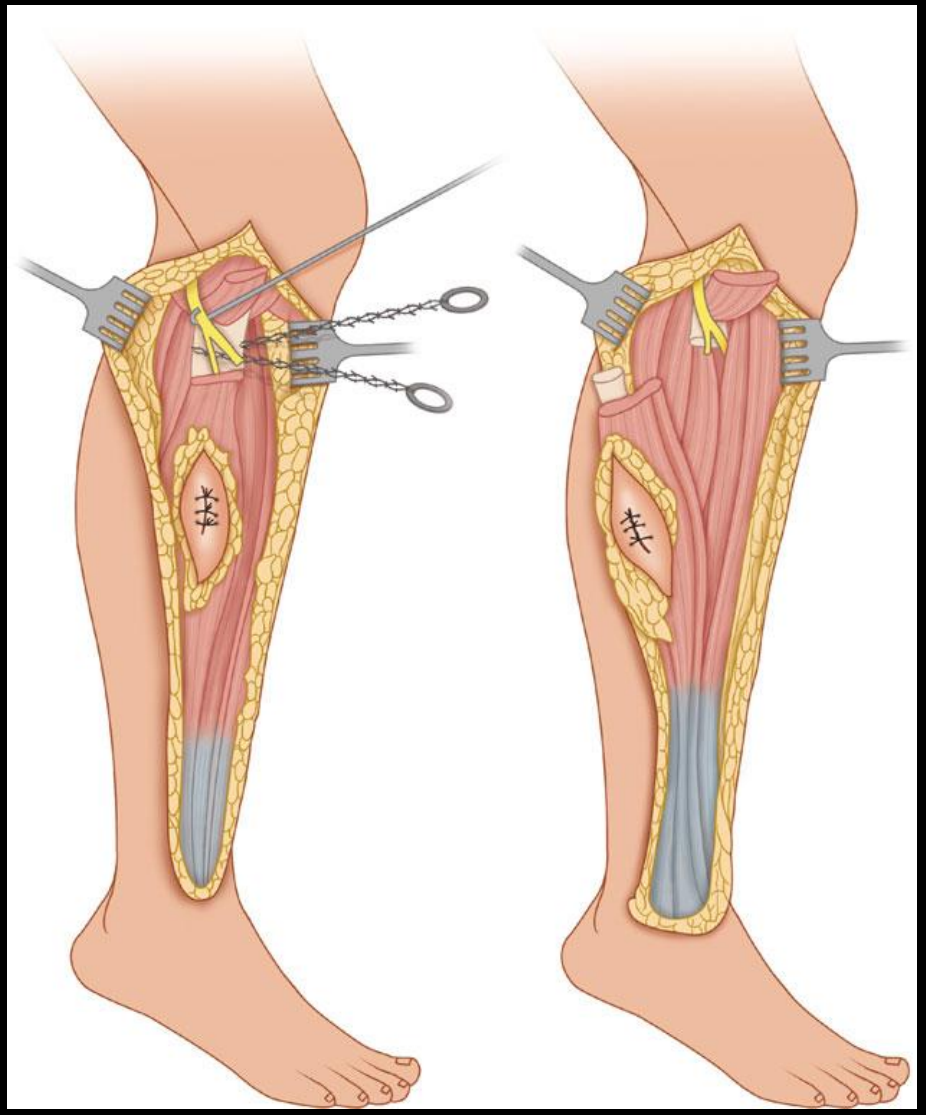
- Peroneus longus (arising from the upper two thirds of the dorsal surface of the fibula), the head of the fibula, the adjacent lateral condyle of the tibia, and the peroneus brevis (arising from the lower two thirds of the lateral surface of the fibula)



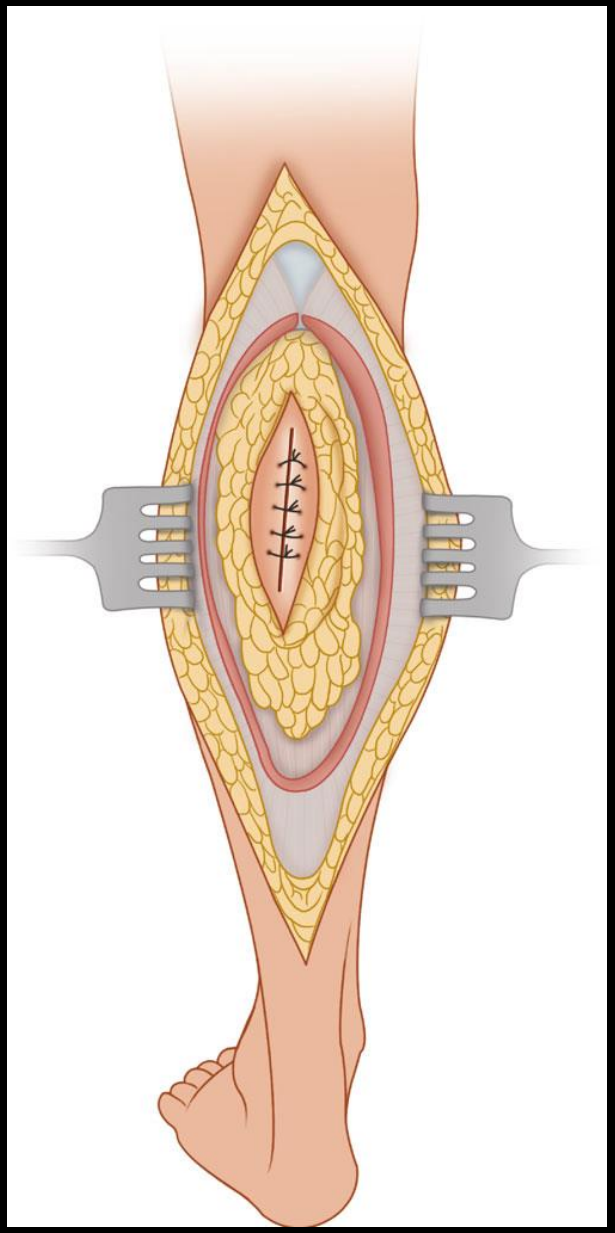
- Superiorly, the peroneus longus may be divided below its origin from the head of the fibula
- The common peroneal nerve courses beneath this muscle, crossing over the neck of the fibula between the peroneus longus and the neck of the fibula and splitting at that level into the deep peroneal nerve (anterior tibial), which enters the anterior compartment, and the superficial peroneal nerve (musculocutaneous), which runs deep in the peroneus longus and peroneus brevis, supplying both these muscles with motor fibers; it emerges in the distal third of the lateral leg as a sensory nerve supplying the lateral aspect of the lower leg and the dorsolateral aspect of the foot



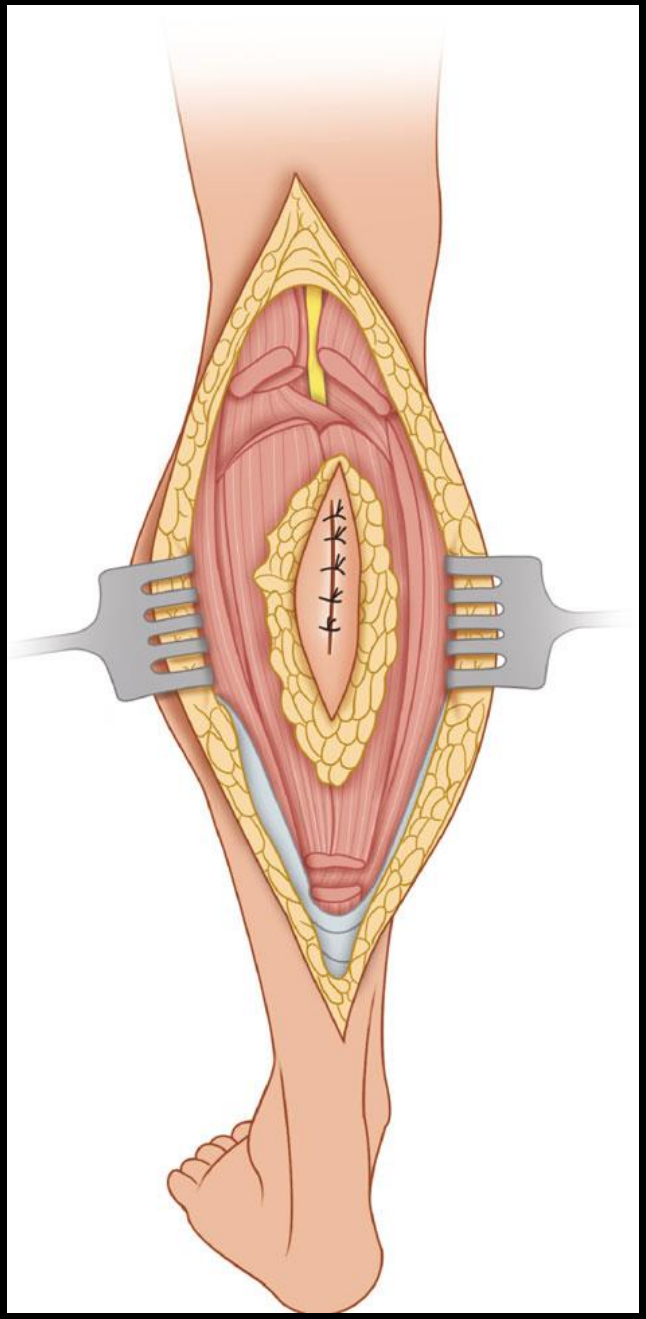
- For larger tumors of the lateral compartment, the neck of the fibula is divided with a Gigli saw after dissection and protection of the common peroneal and the deep peroneal nerves



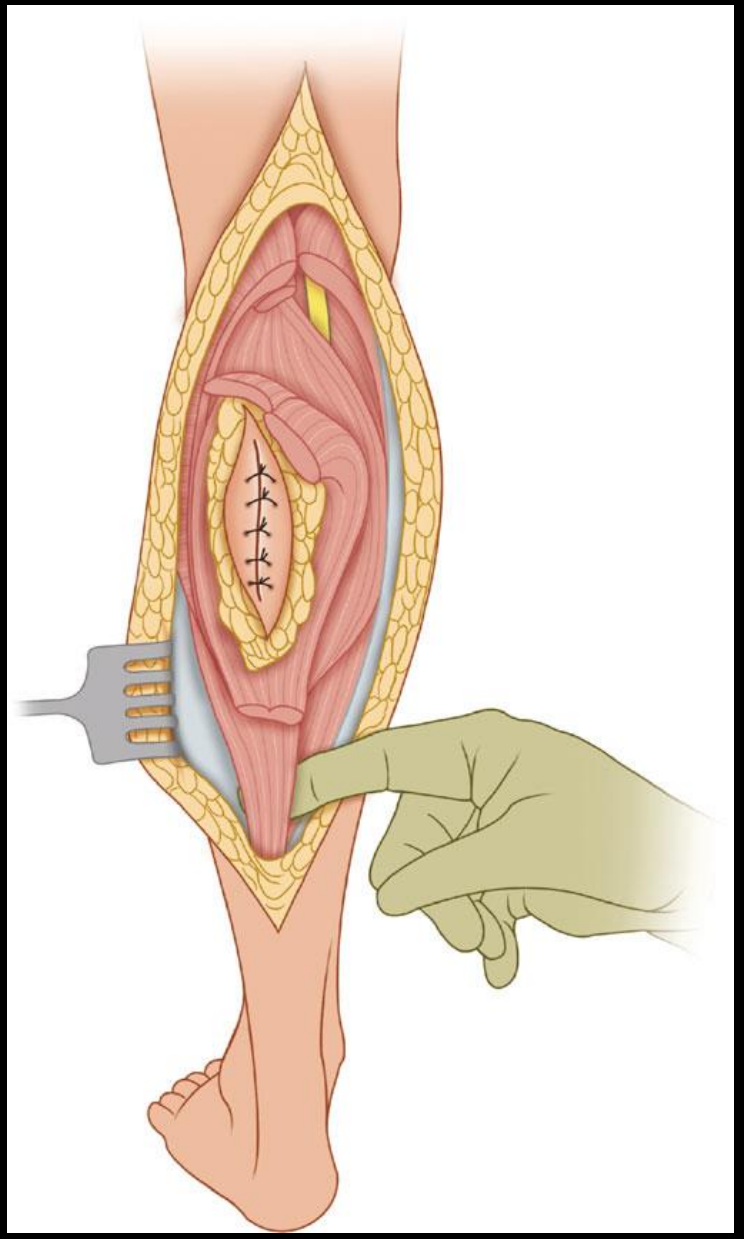
Posterior compartment



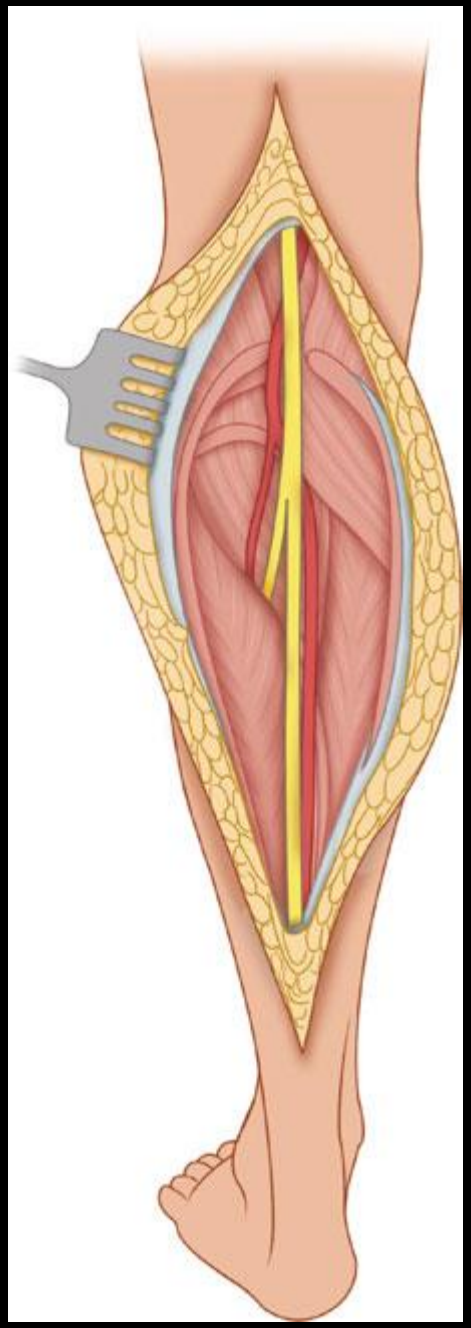
- Tumors confined in the gastrocnemius muscle may be resected by removing one or both heads of the gastrocnemius



- Sarcomas located in the soleus muscle, the incision is carried out through the gastrocnemius, removing also the central part of the gastrocnemius
- The soleus muscle is resected in its entirety or widely enough around the tumor mass



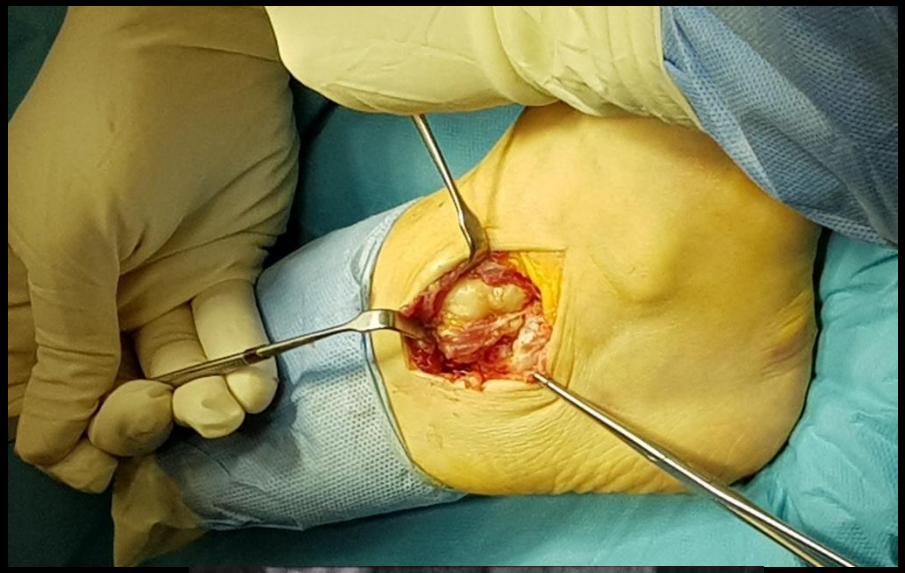
- Beneath the tendinous arch of the soleus, the tibial n. and posterior tibial vessels, covered by a tendinous intermuscular septum, course on the tibialis posterior



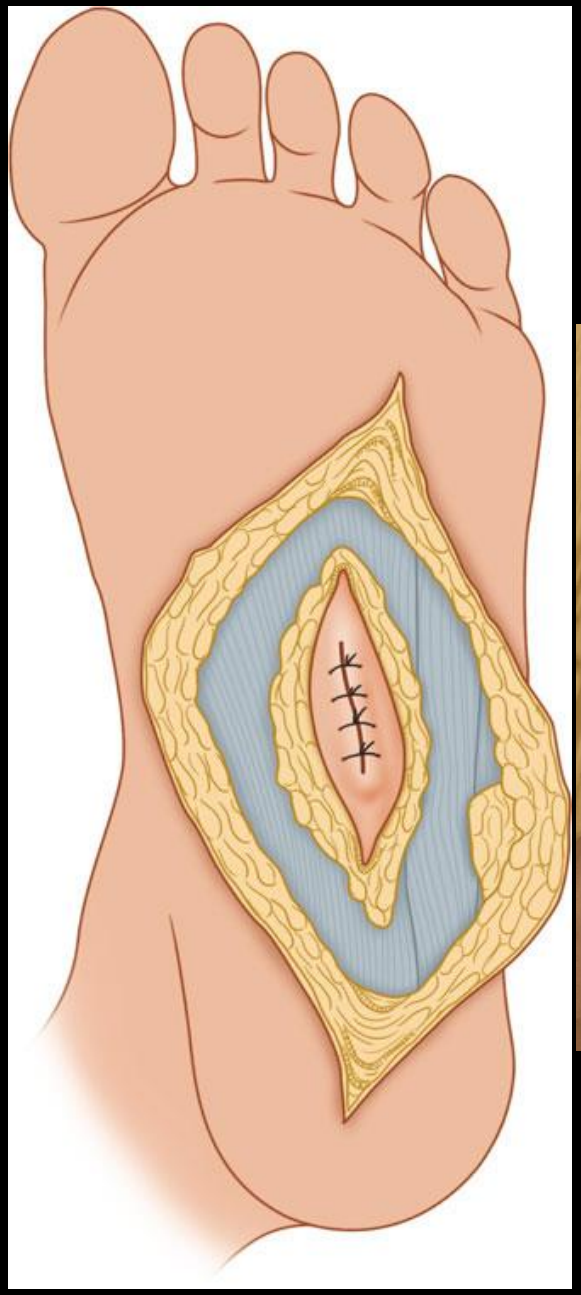
- Due to the bulk of the gastrocnemius and soleus, in most instances, it should be possible to preserve part of the gastrocnemius or soleus and its continuation to the tendo calcaneus after an adequate resection

STS in the foot

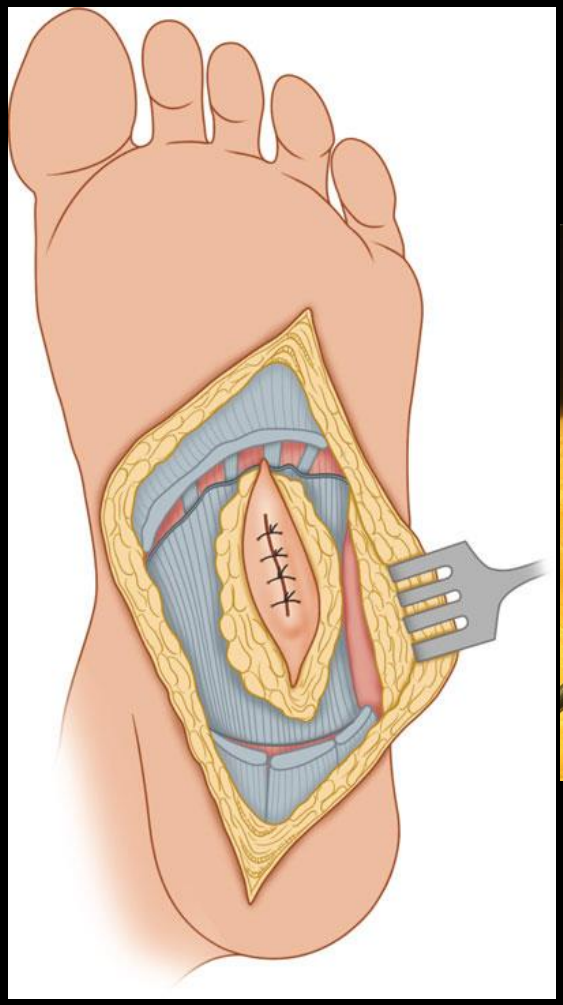
- Tumors occurring in the dorsal aspect of the foot preclude the possibility of limb-preserving resection unless they are small
- Tumors occurring in the plantar surface of the foot are more common

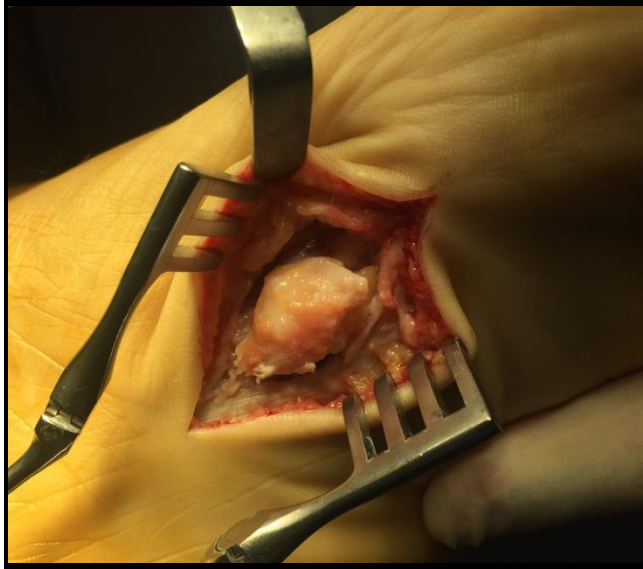


- Sole of foot
  - the superficial muscle layer consists of the abductor hallucis, flexor digitorum brevis, and abductor digiti minimi
  - these muscles can be removed without any obvious functional difficulty for the patient

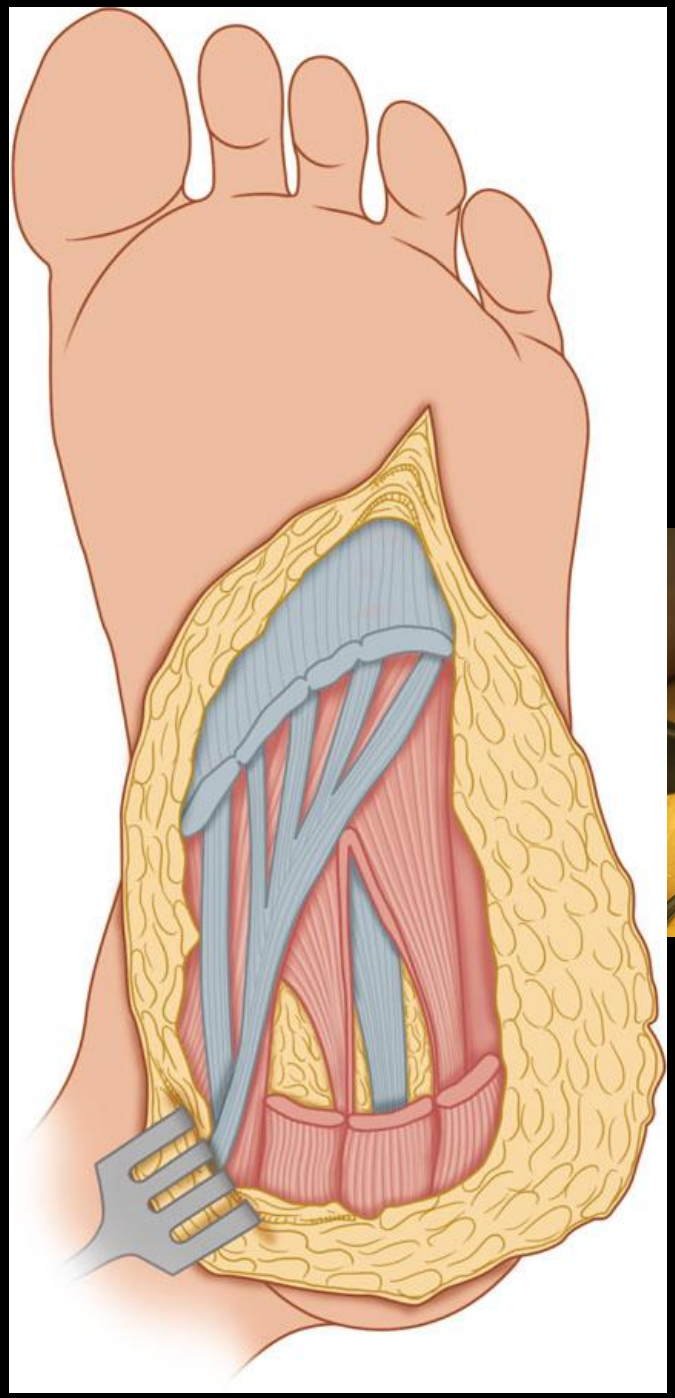


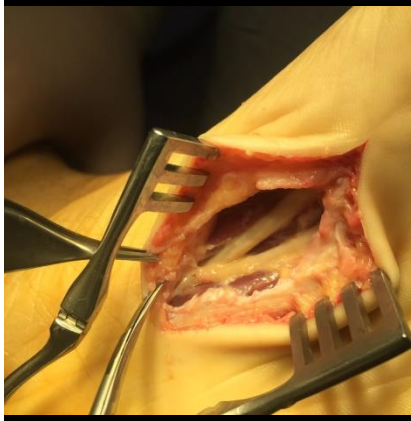
- The plantar aponeurosis is incised exposing the tendons of the flexor digitorum brevis





- The plantar aponeurosis and the underlying abductor hallucis, flexor digitorum brevis, and abductor digiti minimi have been removed en bloc with the tumor, exposing the second layer of muscles of the plantar aspect of the foot





- Many patients with tumors in the foot will have inadequate margins and will need postoperative radiation
- In the plantar aspect of the foot extra caution should be exercised in making this decision or the dose of radiation be somewhat reduced
  - A dose of 60 Gy in a weight-bearing area may result in chronic, disabling pain
  - Simple excision and split-thickness skin graft in weight-bearing area is recommended