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| [Brain Mets/Palliative/Oligo/Immuno](https://bit.ly/PalliativeRoR)| [Breast](https://bit.ly/BreastRoR) | [CNS/Peds](http://bit.ly/CNSandPeds) | [Constraints](https://bit.ly/RoRConstraints) | [GI](https://bit.ly/RoRGI) | [GU](https://bit.ly/GURoR) | [Gyn](https://bit.ly/RoRGyn) | [H&N/Skin](https://bit.ly/HNRoR) | [Heme](https://bit.ly/RoRHeme) | [**Sarcoma**](https://bit.ly/RoRSarcoma)| [Thorax](https://bit.ly/RoRThorax) | [Rad Phys/Bio](https://bit.ly/RORPhysBio)  [**www.RadOncReview.org**](http://www.radoncreview.org)  For best navigation, click on the table of contents to navigate and click on a subheader or header to return to the table of contents. Otherwise, use the Document Outline feature or control-F to search for a clinical trial of interest. Best held horizontally on mobile. Type '20 to see what's new.  **This document is a collaborative resource. All comments, corrections, and additions are welcome! Editing tips [**[**here**](https://docs.google.com/document/d/163jAwVLz8Wnno7jttJnDIM-4kTxkSSmj9XLP1W5pPJs/edit)**].**  Patterns of recurrence data found in the Follow Up section for most disease sites. Ongoing Trials are found in Future Directions. |

See NCTN Trial Portfolios by Disease Site: [[Sarcoma](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Sarcoma.pdf)].

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# Sarcoma / Musculoskeletal

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| [Kaposi Sarcoma](#_zi2d03sct7dm)  [**Osteosarcoma, Chondrosarcoma, Chordoma**](#_wxxo5cfr7p83)  [Treatment](#_5t9tw7j7fq6q)  [Future Directions](#_irmg4ee3t1aq)  [**Soft Tissue Sarcoma**](#_ysnuxhlm0ojt)  [Histology](#_phiynqfeydbr)  [Angiosarcoma](#_dtum6k2adoq)  [Genomics](#_5gy427tss14w)  [Surgery](#_hmwkgk6cixyj)  [Chemotherapy](#_3trempxorlhb)  [Targeted therapy](#_x6uw1vsxxcdx)  [Metastatic STS](#_e1gbnn4g6z80)  [**STS: Extremity and trunk**](#_2i2n53rm2x1a)  [Pre-Op vs Post-op RT](#_n27i5gqwx1yg)  [Brachytherapy, IMRT and IORT](#_f510te77zpua)  [IMRT and SBRT](#_z8t5bkfr6qtm)  [Toxicity](#_39oy0omcq6ng)  [Bone fracture](#_r2ep9qu4fos)  [Treatment Planning](#_rsfg2xg9cevb)  [Follow-up](#_4kgoq929beaa)  [**STS: Retroperitoneal**](#_oejspbehx9b8)  [Toxicity](#_3lvr8tz9i1z3)  [Treatment Planning](#_i7eq8kfr5mf)  [**STS: Future Directions**](#_jjim8v26e3mg)  [**Gastrointestinal Stromal Tumors (GIST)**](#_dr59c0xaknng)  [**Desmoid Tumor (aggressive fibromatosis)**](#_jqfiocb1z710)  [Treatment planning](#_pnpn7oiiidk2)  [**Benign**](#_8l48cswry8jw)  [Heterotopic ossifications (HO)](#_822mr8dchlbg)  [Treatment Planning](#_1uzj86lbmr7d)  [Pigmented villonodular synovitis](#_ikp2mmw62le0) |

[**StatPearls: Skin, Tumors, Vascular Lesions, Face and Neck**](https://www.ncbi.nlm.nih.gov/books/NBK526003/)*Last update: 11/6/2019.*

[**StatPearls: Angiosarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK441983/) *Last update: 1/24/2019.*

[**StatPearls: Epithelioid Sarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK532911/) *Last update: 6/22/2019.*

[**StatPearls: Leiomyosarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK551667/)*Last update: 11/15/2019.*

[**StatPearls: Liposarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK538265/)*Last update: 9/10/2019.*

[**StatPearls: Sarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK519533/)*Last update: 12/2/2019.*

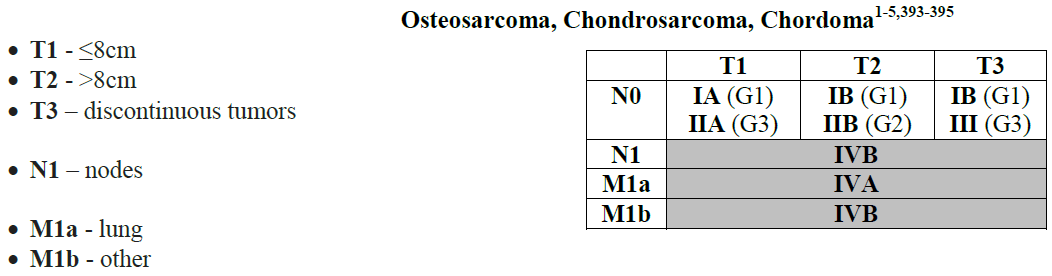
[**StatPearls: Soft Tissue Clear Cell Sarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK538426/) *Last update: 11/17/2019.*

## [Kaposi Sarcoma](#_wrgwa2aop5jm)

[**StatPearls: Kaposi Sarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK534839/)*Last update: 1/9/2019.*

* HHV-8. HAART, then 8-12/1 [[Stein IJROBP '94](https://www.redjournal.org/article/0360-3016(94)90186-4/pdf)].
  + 30/15 for the RVUs, or TSEI 4 Gy q1w x6-8c.
* Subtypes:
  + AIDS associated
  + Iatrogenic - immunosuppression
  + Endemic - sub-saharan Africa
  + Classic - elderly men with Mediterranean or eastern European heritage.

# [Osteosarcoma, Chondrosarcoma, Chordoma](#_publg3jqpzqx)



[**StatPearls: Chondroblastoma**](https://www.ncbi.nlm.nih.gov/books/NBK536947/) *Last update: 11/12/2019.*

[**StatPearls: Chondrosarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK538132/)*Last update: 11/12/2019.*

[**StatPearls: Osteoblastoma**](https://www.ncbi.nlm.nih.gov/books/NBK536954/) *Last update: 9/23/2019.*

[**StatPearls: Osteosarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK549868/) *Last update: 11/12/2019.*

[**StatPearls: Telangiectatic Osteosarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK537309/)*Last update: 11/13/2019.*

* Primary bone tumors < 0.2% of all cancers.
* 60% occur between 10 and 20 years of age.
* 80% in long bones until epiphyseal closure, then occurs in the appendicular skeleton.
* Prevalence: Osteosarcoma > chondrosarcoma > Ewing's > UPS/MFH of bone.
* **Osteosarcoma**: Malignant osteoid is hallmark (not seen in chondrosarcoma). Most common primary bone in children and young adults (50% Osteosarcoma, ~35% Ewings, < 10% chondrosarcoma).
  + 800 cases per year. Bimodality 13-16y and >65y. Black males.
  + 75% in **metaphysis** of long bones with local pain/swelling. Blastic tumor. 85% G3-4.
    - MODE: Metaphysis = Osteo, Diaphysis = Ewings.
  + **Associations**: Li-Fraumeni and **Retinoblastoma** (second malignancy). In pts > 60y, > 50% of cases arise from other conditions (i.e. Paget's, fibrous dysplasia) and demonstrate poor chemo response.
  + **3 subtypes**: **intramedullary** (80%), **surface juxtacortical**, **extraskeletal**.
  + Most common femur > proximal tibia > humerus. DM most common in lung > bone/BM.
  + 20% have DM at presentation.
* **Chondrosarcoma**: ~25% of all primary bone cancers. Most in femur. Frequent LR, DM less common than osteosarcoma.
  + Only 33% high grade. 50% related to IDH1/IDH2 mutations.
  + Secondary and central location worse prognosis.
  + Grade I = atypical cartilaginous tumors. Almost never with mets, R0 w 10y OS 80% [[1]](https://www.ncbi.nlm.nih.gov/pubmed/890662).
  + Angelini [[JSO '12]](https://onlinelibrary.wiley.com/doi/abs/10.1002/jso.23173): 296 pts. 5y OS 92%, 10y OS 84%. G1-2 better px.
* MFH: Very aggressive locally with frequent DM. Often presents with fracture.
* Fibrosarcoma: High grade, behaves like osteosarcoma. Often presents with fracture.
* **Chordoma**: Physaliferous cell ("bubbly cell") is a histologic hallmark. S-100 and EMA positive. Associated w increased expression of brachyurh (ch6q27). Arises from notochord. Most often in the sacrococcygeal **area** (50-60%), **base of skull** (25-35%), and spine (15%).
  + Chordoma: Current concepts, management, and future directions [[Walcott Lanc Onc '12](https://www.sciencedirect.com/science/article/pii/S1470204511703370)].
  + 3 subtypes: Conventional (77%), chondroid (15%), dedifferentiated (8%).
    - However, histology is not predictive of outcome.
  + 10y OS 17→ 61% w negative margins.
* **Giant cell tumors**: Giant multinucleated osteoclast cells. Only 8-15% are malignant. Cyst formation, hemorrhage, and necrosis are important with regard to radiosensitivity. Frequent LR (45-60%).

## 

## [Treatment](#_wxxo5cfr7p83)

* **Osteosarcoma**
  + NAC and adjuvant chemo helps to prevent relapse or recurrence in pts with localized resectable primaries.
  + 5y OS for non-surgical candidates is ~60% [[Mayo](http://www.mayoclinicproceedings.org/article/S0025-6196(11)62546-9/fulltext)]. NAC→ RT (60)→ more chemo. Those who respond to chemo have 5y OS of 90%! Only 35% 5y OS if non-responders.
  + 5y OS for localized / metastatic osteosarcoma of 75→ 25% [[Kager JCO '03](https://ascopubs.org/doi/10.1200/JCO.2003.08.132)].
  + Low grade: WLE alone.
  + High grade: Chemo→ surgery→ chemo.
    - Chemo: Cisplatin and doxorubicin or MAP (MTX, adriamycin, cisplatin).
    - If no chemo, 80-90% will get mets.
    - 50% of pts w limited lung mets can be cured.
  + RT if inoperable (70 Gy) or R1/R2 resection (64-68 Gy).
* **Chordoma**
  + Maximum safe resection→ RT.
  + **≥ 70 Gy** [[Delaney IJROBP '09]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2734911/) ∴ protons and SRS attractive [[1](https://link.springer.com/article/10.1007%2Fs10143-009-0194-4),[2](https://www.sciencedirect.com/science/article/pii/S1042368013000405?via%3Dihub)], although photons are reasonable and safe [[1]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4483121/).
    - Old data: 5y LC ~30-60% for < GTR, but better in the 70 Gy era (60-80%).
  + NCCN: PORT for R1/R2 or unresectable. Dose ≥ 70 Gy. Consider adjuvant RT for R0.
  + GTR: > 50 Gy vs. Observation.
  + STR: ≥ 70 Gy.
* Spare 1.5-2 cm strip of skin in extremity XRT.
* Include surgical bed scar + 2 cm margin.

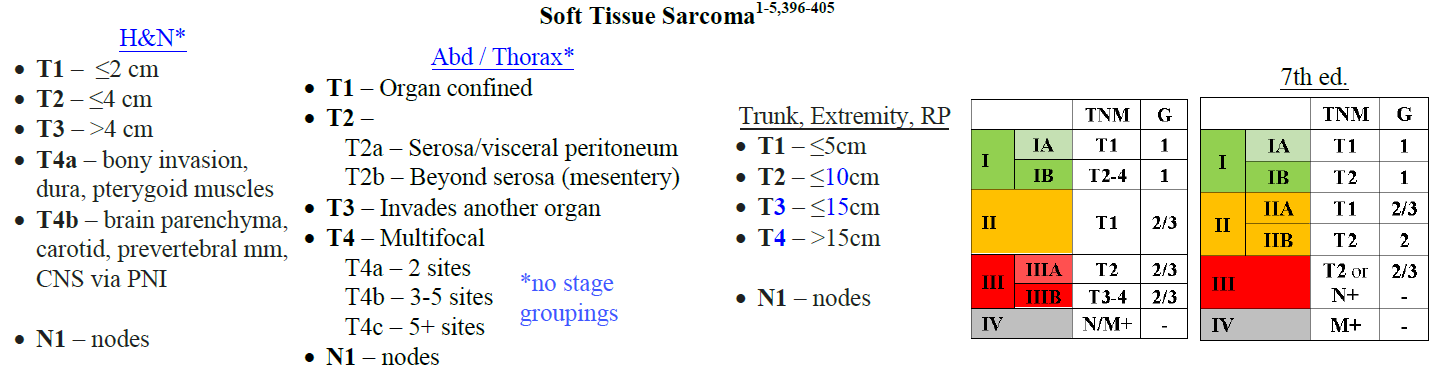
## [Future Directions](#_wxxo5cfr7p83)

See NCTN Trial Portfolios by Disease Site: [[Sarcoma](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Sarcoma.pdf)] and [[AYA](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_AYA_trials.pdf)]. See Future Directions in [[Wilms tumors](https://docs.google.com/document/d/17O0LOemBhckXGuuPBCh6u8vqBfc6lg88r46B8YctMXU/edit#heading=h.103av5145d45)] section for more.

* **ADVL 1622** [[NCT02867592](https://clinicaltrials.gov/ct2/show/NCT02867592)]: Phase II. Recurrent bone sarcoma. Cabozantinib in children and young adults with refractory sarcomas, Wilms tumor and other rare tumors.

## 

# [Soft Tissue Sarcoma](#_publg3jqpzqx)



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| [**Extremity STS**](#_2i2n53rm2x1a) | [**Retroperitoneal STS**](#_oejspbehx9b8) |

Grade II disease automatically stage II. No longer considered for staging: Superficial (not involving fascia) or deep.

T2 disease is stage IB is G1, while IIIA if G2/3.

T3-4 disease is stage IB if G1, while IIIB if G2/3.

N1 disease automatically stage IV (unless retroperitoneal).

LN+ was previously stage III disease (7th edition). Now, LN+ disease is stage IV (8th ed).

Newer NCDB evidence has pointed out that N1M0 disease behaves differently than N0-1M1 disease [[Ashamalla IJROBP '19](https://www.ncbi.nlm.nih.gov/pubmed/31201894)].

eContour: [[Lower extremity STS](http://econtour.org/cases/115)]

ARRO: [[Retroperitoneal Sarcoma](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/ARROcaseRPSarcoma.pdf)], [[Sarcoma](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/ARROCaseSarcoma.pdf)]

RTOG preop extremity STS contouring of suspicious peritumoral edema target volume agreement [[Bahig IJROBP '15](https://www.ncbi.nlm.nih.gov/pubmed/23474110)]

Consensus Panel of MSK Anatomy of LE muscle compartments [[RTOG Contouring Atlas](https://www.rtog.org/LinkClick.aspx?fileticket=jzg6pjYoy7g%3d&tabid=402), [Paper](https://www.rtog.org/LinkClick.aspx?fileticket=joD6eB80xfs%3d&tabid=402), [Boundaries](https://www.rtog.org/LinkClick.aspx?fileticket=x0REg3QGcsg%3d&tabid=402), [Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226200148969213957?s=20)]

Treatment Guidelines for Preop RT of Retroperitoneal Sarcomas [[Baldini IJROBP '15](https://www.redjournal.org/article/S0360-3016(15)00180-7/abstract), [2017 ASTRO Refresher](https://www.astro.org/uploadedFiles/_MAIN_SITE/Meetings_and_Education/ASTRO_Me%20etings/2017/Annual_Refresher_Course/Content_Pieces/Sarcomas-Baldini.pdf)]

NRG retroperitoneal sarcoma target volume and OAR agreement [[Baldini IJROBP '15](https://www.ncbi.nlm.nih.gov/pubmed/26194680)].

[**StatPearls: Angiosarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK441983/) *Last update: 1/24/2019.*

[**StatPearls: Leiomyosarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK551667/)*Last update: 11/15/2019.*

[**StatPearls: Liposarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK538265/)*Last update: 9/10/2019.*

[**StatPearls: Sarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK519533/)*Last update: 12/2/2019.*

* 12k annual in the US, 4k deaths. < 1% of all cancers. 1% of all adult malignancies, 15% of peds.
  + The incidence of GISTs is at least 5000 new cases per year.
    - True incidence is underestimated w GISTs not having been included in the tumor registry before 2001.
  + 2.7 cases of retroperitoneal STS per 1 million people.
  + Most have no clear etiology > 95%.
  + **Stewart-Treves syndrome**: Chronic lymphedema or upper extremity→ **lymphangiosarcoma**.
  + **Genetics**: Li-Fraumeni, FAP, [[Gardner syndrome](https://www.ncbi.nlm.nih.gov/books/NBK482342/)], Carney-Stratakis, RB1, NF-1.
    - c-Kit - response to Gleevec (GIST).
    - **2:13 or 1:13** translocation: Usually **alveolar**, response to doxorubicin-based chemotherapy.
  + **Distant metastasis in 20**% at dx: Extremity→ lung (most common), bone, soft tissue, retroperitoneum, liver.
  + **LN involvement is rare! ~5%**.

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| **Lymph node involvement = Rare in sarcomas**  Exceptions: “CARE” (15-20%) [[Behranwala ASO '04]](https://link.springer.com/article/10.1245%2FASO.2004.04.027).  Synovial sarcoma is no longer thought to be high risk for LN involvement [[Andrew Clinical Ortho '18]](https://journals.lww.com/clinorthop/fulltext/2018/03000/Synovial_Sarcoma_Is_Not_Associated_With_a_Higher.28.aspx).   * **Clear cell sarcoma** - 10% * **cutaneous Angiosarcoma** - < 15% (more than triple that if scalp angiosarcoma). [RoR](#xmbfpd74ql3w) * **Rhabdomyosarcoma** - 20% * **Epithelioid sarcoma** - 20% * Estimated 5y OS of 57% for patients who had resection of involved lymph nodes [[Riad Clinical Ortho '04]](https://insights.ovid.com/pubmed?pmid=15346063).   + Isolated nodal vs. nodal + systemic 4y OS of 71→ 21%.   + Patients with nodal disease and lung disease fare very poorly versus nodes alone. |

[**Workup**](#_ysnuxhlm0ojt)

* Evaluation of primary: MR (extremity/superficial trunk), CT (retroperitoneum). Obtain PRIOR to biopsy.
  + If myxoid liposarcoma, include CT A/P due to frequent mets to peritoneum. Consider MRI spine.
  + MRI brain for alveolar type.
* **Core needle** preferred initially due to the low incidence of complications and high dx accuracy [[Heslin ASO '97](https://www.ncbi.nlm.nih.gov/pubmed/9259971)].
  + True Cut core biopsy with inner and outer sheath, decreases seeding along tract [[YouTube](https://www.youtube.com/watch?v=Kl-NoRjoeMI&feature=youtu.be)].
  + **Incisional biopsy** generally accepted if done by your friendly ortho onc.
  + Mass < 3 cm: excisional biopsy with incision parallel to the long axis of underlying muscle.
  + Avoid FNA (unless specialty center).
* Only able to make ddx 25% of the time based on MRI.
  + Lipoma. Homogeneous.
  + If CT reveals homogeneous fat-density retro mass suggestive of WD-LS, no bx needed [[Lahat Cancer '09](https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.24045)].

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| **Histology and recurrence patterns**  Myxofibrosarcoma has finger-like projections which increases the rate of OOF and repetitive local recurrence [[MSKCC](#ynmu76q89xa6)].  Leiomyosarcomas and Dedifferentiated liposarcomas most commonly recur distantly [[MSKCC](#ynmu76q89xa6), [Gronchi](#kix.qnrsvadwmnzq)].  Retroperitoneal WD-LS are typically quite large, but appear to be radiosensitive [[Gronchi](#kix.qnrsvadwmnzq), [STRASS](#kix.g4gie4g850us)].  Myxoid liposarcoma is exquisitely radiosensitive, and will reduce in size the most during RT [[PMH](#y5xmk8ufux76)].   * **Fibrosarcoma**: Relatively rare. * **Liposarcoma**: By far the most common [[retroperitoneal](#_oejspbehx9b8)] histology. Also found in lower extremities.   + WD-LS/ALT: They are the same morphologically and biologically. Locally aggressive.   + DD-LS: MDM2 amplification is common. Usually non-lipogenic. Rarely, the high-grade component may be lipogenic. G1-G2 DD-LS liposarcoma are most common in the retroperitoneum and usually fail locally.   + Pleomorphic liposarcoma.   + Myxoid (inclusive of round cell) liposarcoma. Myxoid liposarcoma is exquisitely radiosensitive [[PMH](#y5xmk8ufux76)]. * **Leiomyosarcoma** (**LMS**): Most commonly visceral, and the second most common retroperitoneal histology.   + Commonly found in retroperitoneum. May arise in blood vessels, most commonly the IVC. * **MPNST**: Relatively rare overall. * **UPS**: "Garbage bag" diagnosis is becoming less common. Commonly lower extremities. Previously MFH. * **Myxofibrosarcoma**: Essentially non-existent in the retroperitoneum and viscerally. * **Synovial sarcoma**: Typically lower extremity. * **GIST**: Visceral. See the [[GIST](#_dr59c0xaknng)] section for more. * **Rhabdomyosarcoma**: The most common STS in children. |

[**StatPearls: Angiosarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK441983/) ***Last update: 1/24/2019.***

[**StatPearls: Leiomyosarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK551667/) ***Last update: 11/15/2019.***

[**StatPearls: Liposarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK538265/) ***Last update: 9/10/2019.***

[**StatPearls: Sarcoma**](https://www.ncbi.nlm.nih.gov/books/NBK519533/) ***Last update: 12/2/2019.***

## [Histology](#_ysnuxhlm0ojt)

See Histology and recurrence patterns Summary Box above.

Gradeis the most important prognostic factor for survival and distant metastases [[Coindre Cancer '01](https://onlinelibrary.wiley.com/doi/full/10.1002/1097-0142%2820010515%2991%3A10%3C1914%3A%3AAID-CNCR1214%3E3.0.CO%3B2-3)].

* Two most widely used: **French Federation of Cancer Centers Sarcoma Group** (**FNCLCC**) and NCI.
  + FNCLCC (preferred): "MiND" Mitosis, Necrosis, Differentiation
  + NCI: Histology, location, necrosis.
* 25 major categories, ~60 different types with >300 synonyms.
  + Change in diagnosis 30-70% of the time, disagreement among specialists 25-40% of the time.
  + Ddx: other malignancies, desmoids, benign lesions e.g. lipoma, lymphangioma, leiomyoma, neuroma.
* Most common: MFH/UPS, GISTs, liposarcoma, leiomyosarcoma, synovial sarcoma, MPNST, clear cell.
  + Malignant fibrous histiocytoma (MFH) is now called pleomorphic undifferentiated sarcoma (UPS).
* **Location**: **75% extremities** (LE > UE), trunk = retroperitoneal 15%, H&N < 10% [[Lawrence AS '87]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1492738/).
  + Extremity: Liposarcoma, MFH/UPS, synovial sarcoma, myxofibrosarcoma (upper medial thigh), LMS, MPNST, fibrosarcoma.
  + Retroperitoneal: Liposarcoma (fewer diabetes) > leiomyosarcoma (increased diabetes). Never myxoid.
  + H&N: MFH, usually high grade (except myxoid MFH, which is an intermediate grade).
* **Radiation induced STS**: G3 UPS / Angio / Leiomyo / fibrosarcoma 26→ 21→ 12→ 12% [[Gladdy JCO '10]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3651600/).

### [Angiosarcoma](#_phiynqfeydbr)

* Usually associated with "field cancerization". Most are superficial and in H&N area. Presents as a spreading bruise that is blue to red in color. Nodules may develop over time and ulcerate. Clinical exam underestimates imaging.
* A margin of at least 3 cm is desired, but some centers deem 0.5 cm acceptable.
* Affects endothelial cells of blood vessels.
* Accounts for < 2% of all STS and < 1% of H&N cancer cases.
* Can arise anywhere, including scalp, breast, and extremities.
* Scalp angiosarcomas account for > 60% of all cases.
* The most common site of metastasis is the lung, followed by bone and liver.
* **MDACC Angiosarcoma** [[Guadagnolo H&N '10]](https://onlinelibrary.wiley.com/doi/abs/10.1002/hed.21513): Retro. Surgery ± RT.

Tumor size > 5 cm and satellitosis were prognostic for inferior OS and DSS.

* + 70 pts with nonmetastatic angiosarcoma. MFU 2y.
  + 5y OS 32→ 68%, 5y DSS 33→ 76%, 5y LC 24→ 84%.

* **Regional Lymph Node Mets of Scalp Angiosarcoma** [[Kang ASO '20](https://pubmed.ncbi.nlm.nih.gov/32458324/)]: Retro.

It appears reasonable to include prophylactic evaluation of regional lymph nodes for localized disease.

* + 40 patients. Adjuvant RT in 22 patients, definitive/palliative RT in 9 patients. Median size 5 cm. 1999-2018.
    - RT: 46-50 Gy to entire scalp, with boost of 10-14 Gy to primary site + 2 cm margin. Typically given with concurrent taxane-based chemotherapy.
  + 2y OS 36%. 2y DMFS 27%.
  + Regional lymph node mets in 53% of patients.
  + Direct spread to direct organs in 28%.
  + Regional LN mets predicts manifestation of systemic disease within 3-6 mo.
  + Occurrence of LN mets seemed to be correlated with high mitotic rate of the primary, but not grade or dimension.
  + The first echelon were peri-parotid, post-auricular, and level II lymph nodes (Fig 6).

## [Genomics](#_ysnuxhlm0ojt)

* Two main divisions of genetic groups:
  + Specific genetic alterations (chromosomal translocations or point mutations), simple karyotypes.
    - **Synovial sarcoma t(X;18)**. SS18-SSX [[Cell '18](https://www.ncbi.nlm.nih.gov/pubmed/29100075)].
    - DSRCT t(11;22). EWS-WT1.
    - Alveolar RMS t(2;13). PAX-FOX01 (PAX7 is more favorable than PAX3).
    - **Myxoid liposarcoma t(12;16)**. TLS-CHOP. *Repetitive LR, fingerlike projections.*
    - Myxoid chondrosarcoma t(9;22). EWS-CHN.
    - Clear cell t(12;22). EWSR1-ATF1
    - **WD/DD-LS**: **12q amplification** in > 80% involving MDM2 and CDK4 genes [[Cell '18](https://www.ncbi.nlm.nih.gov/pubmed/29100075)].
* Advances in sarcoma genomics and new therapeutic targets [[Taylor Nat Rev Cancer '11](https://www.ncbi.nlm.nih.gov/pubmed/21753790)]
  + Focuses on emerging genomic and functional genetic approaches that, coupled with novel therapeutic strategies, have the potential to transform the care of patients with sarcoma.
* Genomics [[Cell '18](https://www.ncbi.nlm.nih.gov/pubmed/29100075)]:

Along with novel insights into the biology of individual sarcoma types, we report three overarching findings: 1) unlike most epithelial malignancies, these sarcomas (excepting synovial sarcoma) are characterized predominantly by copy number changes, with low mutational loads and only a few genes (TP53, ATRX, RB1) highly recurrently mutated across sarcoma types, 2) within sarcoma types, genomic and regulomic diversity of driver pathways defines molecular subtypes associated with patient outcome, and 3) the immune microenvironment, inferred from DNA methylation and mRNA profiles, associates with outcome and may inform clinical trials of immune checkpoint inhibitors.

* + TP53 mutation is relatively infrequent in STS compared with other types of human malignancy. Attenuation of p53 function occurs as a consequence of MDM2 amplification or overexpression in STS containing wild-type p53 (e.g., liposarcoma). See Figure 1 from [[Trino Front Pharmacol '16](https://www.frontiersin.org/articles/10.3389/fphar.2016.00491/full)] for more on MDM2 inhibition.
  + UPS and MFS are almost genetically identical.
  + Myxofibrosarcoma and UPS may have immunogenic signals.
* **Sarcoma Immune Class and Response to Pembro** [[Petitprez Nature '20](https://www.nature.com/articles/s41586-019-1906-8)]
  + Sarcomas can be divided into five different groups based on their immune class.
  + SIC group E (Figure 1) is enriched at the gene expression level for genes for T and B cells.
  + SIC group E has pronounced response to Pembrolizumab (Figure 4). *Data from SARC028.*

* **NRG-DT001** [[Welliver Protocol](https://www.nrgoncology.org/Clinical-Trials/Protocol/nrg-dt001?filter=nrg-dt001)]: Phase Ib. **Neoadjuvant AMG-232 (MDMi) + NART in P53wt STS** (typically liposarcoma).

See NCTN Trial Portfolios by Disease Site: [[Sarcoma](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Sarcoma.pdf)] and [[Future Directions](#_jjim8v26e3mg)] section for more information.

See Figure 1 from [[Trino Front Pharmacol '16](https://www.frontiersin.org/articles/10.3389/fphar.2016.00491/full)] for more on MDM2 inhibition.

* + STS, G2-3, ≥ 5 cm. Biopsy sent for TP53 NGS. Patients with wild type p53 continue on study.
  + Two cohorts based on tumor location: Retroperitoneal/abdomen/pelvis vs. extremity/body wall.
* **SU2c-SARC032** [[Kirsch NCT03092323](https://clinicaltrials.gov/ct2/show/NCT03092323)]: Phase II. **NART ± Concurrent and adjuvant Pembro**.
  + High risk, localized STS of the extremity. G2-3. ≥ 5 cm. UPS and dedifferentiated / pleomorphic sarcoma based on phase II SARC028 study [[Tawbi Lanc Onc '17](https://www.ncbi.nlm.nih.gov/pubmed/28988646)]. There were no responders in the LMS subgroup.
* **MDACC** [[Roland ASCO '20](https://meetinglibrary.asco.org/record/185571/abstract)]: Phase II. Neo **Nivo ± Ipi for surgically resectable RP-DDLPS or extremity/trunk UPS**.

UPS appears exquisitely sensitive to ICI! Too bad we have to wait until 2025 for results of SU2C-SARC032 (Neo Pembro+RT), but it's amazing to see progress in the realm of sarcomas and systemic therapy.

* + 24 patients.
  + Median path response in the UPS cohort was 95%, while 22.5% in the DDLPS cohort.
  + 8 patients with path response ≥ 85%, including 1 PR, 5 SD and 2 PD by RECIST criteria.

[**Risk factors**](#_ysnuxhlm0ojt)

Gradeis the most important prognostic factor for survival and distant metastases [[Coindre Cancer '01](https://onlinelibrary.wiley.com/doi/full/10.1002/1097-0142%2820010515%2991%3A10%3C1914%3A%3AAID-CNCR1214%3E3.0.CO%3B2-3)].

* **MSKCC RF for LR and DM in localized extremity STS** [[Pisters JCO '96]](http://ascopubs.org/doi/abs/10.1200/JCO.1996.14.5.1679): 1,041 pts. Prospective from 1982 to 1994.
  + **RF for LR**: Fibrosarcoma including desmoid (RR 2.5), locally recurrent disease (RR 2.0), Micro SM+ (RR 1.8), MPNST (RR 1.8), > 50y (RR 1.6).
  + **RF for DM**: G3 (RR 4.3), Deep (RR 2.5), >5 cm (RR 1.9), local recurrence (RR 1.5), LMS (RR 1.7), LS (RR 0.64).
    - Another paper [[1]](https://www.ncbi.nlm.nih.gov/pubmed/11346874) suggests **grade** as an independent predictor of DM, though not for MPNST and RMS.
  + **RF for DSS**: G3 (RR 4.0), Deep (RR 2.8), > 10 cm (RR 2.1), LMS (RR 1.9), MPNST (RR 1.9), Micro SM+ (RR 1.7), proximal LE (RR 1.6), local recurrence (RR 1.5).

* **MSKCC RF for LR after LSS** [[Cahlon Ann Surg '12]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5016830/): Prospective. **WLE alone**. No adjuvant chemo or RT.   
  Nomogram developed to predict local recurrence.

Risk factors from most to least impactful: non-ALT or WDLS, close/SM+, G3, advancing age, and larger size.

* + 684 pts. Primary non-metastatic extremity sarcoma, nonmetastatic. MFU nearly 5y.
  + Overall LR at 3 / 5 / 10y of 11→ 13→ 19%.
  + LR HR for Non-ALT or WDLS / Close or SM+ / G3 / > 50y / > 5cm of 2.86→ 2.37→ 2.02→ 1.72→ 1.59

* **MSKCC** [[Mutter Cancer '11](https://onlinelibrary.wiley.com/doi/abs/10.1002/cncr.26296)]: LSS for **Myxofibrosarcoma vs. leiomyosarcoma**. 70% received adjuvant RT.

**Myxofibrosarcoma have finger-like projections** which increases the rate of out of field and repetitive local recurrence.

**Leiomyosarcoma most commonly recur distantly**, which is a little surprising because myxoid had worse features.

* + 222 patients. All primary high grades. 1991-2006. MFU 4y.
  + Myxofibrosarcoma were commonly larger, deep, upper extremity. Rate of SM+ and RT were higher.
  + 5y LR of ~14%.
  + OOF LR 47→8%. Repetitive LR 0→ 35%.
  + DM 54→ 24%.
* **MSKCC Tumor histology and LC** [[Yang IJROBP '18](https://www.redjournal.org/article/S0360-3016(18)32574-4/fulltext)]: **LSS→ IMRT**. Median IMRT dose 63 Gy.   
  The high propensity of LR for UPS or myxofibrosarcoma warrants further investigation on a genomic level.
  + 317 patients. 2002 - 2015. LE 70%. SM < 1mm 50%. Chemo 25%. Pre-op in 30%. MFU nearly 5y.
  + 5y LR 6.2%. Double that LR if UPS, no LR if myxoid liposarcoma or pleomorphic liposarcoma.
  + MTTLR 19.5 mo.
* **Princess Margaret** [[Chung Cancer '09](https://www.ncbi.nlm.nih.gov/pubmed/19472403)]: **LSS + RT for Other histology vs. Myxoid liposarcoma**.

**Myxoid liposarcoma is exquisitely radiosensitive**.

* + 691 patients with extremity STS. 88 myxoid liposarcoma. 1989-2004. All received RT pre or post-op. MFU ~7y.
  + 5y LC 90→ 98%.
  + G3 in 7→ 59%.
  + 5y OS 76→ 94.
  + 5y DMFS 66→ 89%. Metastasis to lung in 78→ 42%.
* French Sarcoma Group database [[Toulmonde Cancer '14]](https://onlinelibrary.wiley.com/doi/abs/10.1002/cncr.28836): 719 pts.
  + 9y **late** **LR** 9%. MVA for LR significant for **internal trunk location** (25% late LR) and **> 10 cm** (14% late LR).
  + 9y **late** **DM** 6%. MVA for DM significant for grade >1 (HR 4.7).
* NCDB RF for poor prognosis [[Mahmoud RTO '17]](https://www.sciencedirect.com/science/article/pii/S0167814017324805?via%3Dihub): Age > 50y, tumor size > 11 cm, and trunk/pelvis location.
* Summary: Grade is the most consistent predictor for DM. Deep/internal trunk location, SM location predictor for LR.
* **DOREMY Study** [[NCT02106312](https://clinicaltrials.gov/ct2/show/NCT02106312)]: Phase II. **Dose de-escalation from 50/25 to 36/18**.

DOse REduction of pre op radiotherapy in MYxoid liposarcomas.

* + 80 patients target accrual. Primary endpoint: pCR.

## Surgery

* Prefer wide en bloc resection with ≥ 2 cm margin throughout.
* Radical resection includes the entire anatomic compartment and neurovascular structures.
* Wide excision removes the cuff of normal tissue.
* Excisional biopsy is a shellout of the pseudocapsule.
* Intralesional biopsy inside pseudocapsule.
* **RT for control of STS resected with positive margins** [[Delaney IJROBP '07]](https://www.sciencedirect.com/science/article/pii/S0360301606034997?via%3Dihub): Retro. **≥ R1 ± 64 Gy RT**.
* Doses > 64 Gy, superficial location, and extremity site are associated with improved local control.
  + 154 pts with tumor on ink.
  + 5y LC for positive margins of 66→ 86%
  + CTV\_SM+\_>64 Gy due to association with improved LC

### 

|  |
| --- |
| **Chemotherapy Sensitivities**  See the [[STRASS II](#2q3ev9lsxq0i)] trial for more information on the role of chemotherapy in retroperitoneal sarcomas.   1. Very Sensitive: Rhabdomyosarcoma, Synovial sarcoma, angiosarcoma, myxoid liposarcoma. 2. Average sensitivity: Leiomyosarcoma, high grade undifferentiated sarcoma, DD-LS, DSRCT. 3. Low sensitivity: Extra skeletal myxoid chondrosarcoma, fibrosarcoma, epithelioid sarcoma, MPNST, [[hemangiopericytoma](https://docs.google.com/document/d/17O0LOemBhckXGuuPBCh6u8vqBfc6lg88r46B8YctMXU/edit#heading=h.y9t81j3bsfo8)]/solitary fibrous tumor. 4. Resistant: GIST, Alveolar soft part sarcoma, clear cell sarcoma. |

### 

## [Chemotherapy](#_ysnuxhlm0ojt)

See Chemotherapy sensitivities Summary Box above.

NCCN Category 2B for Chemo in Extremity STS.

* Chemo may be of benefit for high-grade lesions >10cm. Consider for large deep high-grade tumors since ~50% develop DM.
* **~50% of patients with high-grade tumors will die of DM despite LC of the primary**.
  + LN mets have a much greater 5y OS (59% vs. 8% for pulmonary mets).
* Most active single agent = anthracycline, ifosfamide (15-30% response).
* Meta-Analysis [[Pervaiz Cancer '08](https://onlinelibrary.wiley.com/doi/abs/10.1002/cncr.23592)]: **OS advantage with multi-agent doxorubicin + ifosfamide** (OR 0.56).
  + **No clear OS benefit for doxorubicin alone**: OR 0.84 (95% CI, 0.68‐1.03; P = .09).
* **Preop**: MAID regimen may be of benefit (mesna, doxorubicin, ifosfamide, dacarbazine) per single institution, RTOG 9514.
  + Consider regional hyperthermia to increase the benefit of preop chemo in pts with localized high risk STS.
  + Synovial: usually always chemo with doxorubicin and ifosfamide.
  + **EORTC 62012** [[Judson Lancet Oncology '14](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)70063-4/fulltext)]: First line **Doxorubicin ± ifosfamide**.  
    The vast majority of patients will progress if treated with chemotherapy alone.

Combined doxorubicin + ifosfamide is not supported unless the specific goal is tumor shrinkage (synovial).

* **Neoadjuvant chemo** [[Gronchi JCO '12](https://ascopubs.org/doi/full/10.1200/JCO.2011.37.7218)]: 3c of epirubicin+ifosfamide→ Surgery with or without RT→ **± 2c adjuvant chemo**

Gives a hint what to expect with neoadjuvant chemotherapy. No difference in distant metastases.

* + 328 patients. High-risk extremity/trunk.
  + 5y distant mets **33%**.
* **Postop**: may improve RFS but data involving OS conflicting [SMAC vs. Italian]; may be of more benefit in G3 and R1. SMAC - doxorubicin/ifosfamide, Italian - epirubicin/ifosfamide.
* Advanced dz: Gemcitabine + docetaxel/vinorelbine/dacarbazine. Single agents: Temozolomide, doxorubicin, vinorelbine.
  + Trabectedin: DNA binding agent shows promise.
  + Eribulin: microtubule inhibiting agent, approved for liposarcomas only.
* **EORTC 62931** [[Woll Lancet '12](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(12)70346-7/fulltext)]: R0/R1 with or without PORT **± Adjuvant chemo**.  
  Around 1/3 of sarcomas will develop distant metastasis, regardless of adjuvant chemotherapy.
  + 351 patients. Resected STS. Chemo: 5c adriamycin and ifosfamide with growth factor support.
  + No difference in overall survival or 5y distant relapse (**33%**).
* **Unresectable**: 70-80 Gy; Regional limb therapy (isolated limb perfusion [ILP] and isolated limb infusion [ILI]) with TNF-α with melphalan or doxorubicin (TNF-α not legal in the US).
* **NAC + RT→ LSS**Data exists for NAC in STS, but it is not standard.
  + UCLA retro [[Pennington IJROBP '16]](https://www.redjournal.org/article/S0360-3016(16)30397-2/abstract): 122 HR extremity STS. **Ifosfamide x2c S/CCRT→ LSS** (95%).
    - RT 28/8 (3.5 Gy).
    - 6y LC, DMFS and OS 83, 63, 68%.
  + MGH [[DeLaney IJROBP '03]](https://www.sciencedirect.com/science/article/pii/S036030160300186X?via%3Dihub): MAID x3 **CCRT 44 Gy→ LSS** w 16 Gy given post-op for SM+
    - 48 HR G3 extremity STS ≥ 8 cm pts.
    - 5y LC 86→ 92% [p=0.12] compared to historical controls.
    - 5y DMFS 44→ 75%, 5y DFS 42→ 70%, 5y OS 58→ 87% compared to historical controls.
    - There was a 29% rate of wound complications.
* **ARST 0332** [[Spunt Lanc Onc '19](https://www.ncbi.nlm.nih.gov/pubmed/31786124)]: Prospective. **RT/Ifosfamide/Doxorubicin**. Non-RMS STS in patients < 30y.  
  Most low risk patients can be cured without adjuvant therapy. Novel treatments are needed for IR and HR tumors.

Treatment groups: Surgery alone, RT to 55.8 Gy, CCRT to 55.8 Gy, or NACCRT to 45 Gy with boost based on margins and continued chemotherapy.

* + 550 pts. 2007-2012. New dx of intermediate (rarely metastasizing) or malignant STS. MFU 6.5y.
    - Chemo: Ifosfamide and doxorubicin.
  + MPNST, non-metastatic and grossly resected dermatofibrosarcoma protuberans, undifferentiated embryonal sarcoma of the liver, or unclassified malignant STS.
  + LR: non-metastatic R0 or R1 low grade, or ≤ 5 cm R1 high-grade.
  + IR: non-metastatic R0 or R1 > 5 cm high-grade, or unresected tumor of and size and grade
  + HR: metastatic tumor.
  + 5y EFS / OS for LR group of 89→ 96%.
  + 5y EFS / OS for IR group of 65→ 79%.
  + 5y EFS / OS for HR group of 21→ 36%.

## 

## [Targeted therapy](#_ysnuxhlm0ojt)

* **Pazopanib**: Multitarget. Works in **non-adipocytic**: Try for non-lipogenic STS who have failed at least one anthracycline. Improves PFS with a trend towards OS.
* **Regorafenib**: VEGFR2-TIE2 inhibitor for non-adipocytic patients treated previously treated with both chemotherapy and pazopanib appears to double overall survival [[Penel EJC '20](https://www.ncbi.nlm.nih.gov/pubmed/31918233)].
* Imatinib, sunitinib: advanced/metastatic GIST, SFTs; also sorafenib (e.g. leiomyosarcoma, desmoid tumors).
  + Crizotinib: ALK inhibitor was active in inflammatory myofibroblastic tumor (IMT) with ALK translocation.
  + Ceritinib is also a next-gen ALK inhibitor that has been successful in treating NSCLC.
  + Olaratumab + Doxorubicin with OS advantage in LA/metastatic STS.
* mTOR inhibitors: Sirolimus, temsirolimus, everolimus promising for perivascular epithelioid cell tumors (PEComas) and in patients with lymphangioleiomyomatosis or angiomyolipomas.
* Bevacizumab ± TMZ for recurrent epithelioid hemangiopericytoma and malignant solitary fibrous tumor (SFT).
  + Other drugs for Solitary Fibrous Tumors: Sunitinib [[George JCO '09](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2716937/), [Stacchiotti Ann Onc '12](https://academic.oup.com/annonc/article/23/12/3171/175474)], Sorafenib [[Valentin IND '13](https://link.springer.com/article/10.1007%2Fs10637-013-0023-z)], Bevacizumab + TMZ [[Park Cancer '11](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3135685/)]
* **Palbociclib**: inhibitor of CDK 4/6: Use in CDK4 amplified, well-differentiated or dedifferentiated liposarcoma (WD-DDLS).

* **ARST 1321** [[Chen JCO '19](https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.11070), [Weiss JCO '19](https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.11002)]: Phase II/III. **Preoperative RT** ± **Pazopanib** (+ chemo, if chemosensitive).

Pazopanib in combination with chemoradiation or RT alone was found to be safe in children and adults. The rate of near pCR was significantly greater with the addition of pazopanib to pre op CCRT in children and adults with IR and HR NRSTS. Awaiting results correlating pathologic necrosis with survival outcomes [[Wang JCO '17](#u8ch1u49og3r)].

* + 42 pts. Unresected trunk/extremity Non-RMS intermediate risk and high risk STS.
  + Chemotherapy cohort: Chemosensitive NRSTS > 5 cm, G2-3, including all synovial sarcoma.
  + Non-chemotherapy cohort: Insensitive NRSTS of any size, grade G2/3, or any chemosensitive NRSTS for whom no chemo was planned per discretion of patients and treatment teams.
    - Chemo: Pazopanib + Ifosfamide 7.5 and doxorubicin + 45/25 preop RT starting after cycle 2. Primary tumor resected at week 13, followed by chemo and pazopanib to week 25.
    - Non-chemo: Pazopanib + 50/25 preop RT. Primary tumor resected at week 10, and pazopanib continued to week 25.
  + MTD with chemo cohort at Level 1 (350 mg/m2 peds; 600 mg adults) with two DLTs in 10 patients.
  + MTD with non-chemo cohort at Level 2 (450 mg/m2 peds; 800 mg adults) with two DLTs in 10 patients.
  + For chemotherapy cohort, pathologic necrosis ≥ 90% of 22→ 58%.

## 

## [Metastatic STS](#_ysnuxhlm0ojt)

* The lung is the most common site for mets, but myxoid fibrosarcoma has a high rate of spinal metastasis.
* There is a growing role for SBRT in metastatic soft tissue sarcoma, in large part due to ineffective chemotherapy.
* What to expect with chemotherapy: 33% rate of distant metastasis with or without chemo. Nearly all patients progress.
* **EORTC 62012** [[Judson Lancet Oncology '14](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)70063-4/fulltext)]: First line **Doxorubicin ± ifosfamide**.  
  The vast majority of patients will progress if treated with chemotherapy alone.

Combined doxorubicin + ifosfamide is not supported unless the specific goal is tumor shrinkage.

* + 455 patients with advanced sarcoma. MFU nearly 5y.
  + No difference in OS between groups.
  + MPFS 4.6→ 7.4 mo. Progression in 88% of patients regardless of chemotherapy.
  + ORR 14→ 26%.
* **SBRT for spinal mets** [[Leeman J Neurosurg Spine '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5551386/)]:   
  Isolated local and adjacent segment failures are exceptionally rare for patients with metastatic sarcoma to the spine.

The majority of progression in the spinal axis occurs ≥ 5 vertebral levels away.  
Treatment to the involved level only is reasonable. Total spine imaging is necessary for surveillance post-treatment.

* + 88 patients. 2005-2012. MFU 14 mo.
  + 1y local FFS 86%. However, 83% of local failures occurred with distant segment failures.
  + 1y isolated local- / adjacent- / distant-FFS of 98→ 98→ 75%.
  + Over half of failures in the spinal axis occurs ≥ 5 vertebral levels away.
  + Of the 55 patients with any spinal progression, 25% had progression in a single vertebral level while 60% had progression at ≥ 3 sites within the spine simultaneously.
  + Treatment to a lower BED or presence of local failure independently predicted for distant spinal failure.
* **SBRT for spinal mets** [[Folkert IJROBP '14](https://www.ncbi.nlm.nih.gov/pubmed/24661662)]: **SBRT** (Low dose - 3-6 fx to 28.5 Gy) **vs. SRS** (24/1 - high dose).  
  Both multifraction and single fraction are acceptable.
  + 88 patients with 120 discrete metastasis. MFU 1y.
  + Not surprisingly, given the heterogeneity and low doses of SBRT, a single fraction did better.
* [[Dhakal IJROBP '12](https://www.ncbi.nlm.nih.gov/pubmed/21277105)], Mehta, Navarria, Frakulli, Baumann. SBRT to lung mets. LC from the high 80s to mid-90s. 50/5 reasonable.

## 

## [Follow-up](#_ysnuxhlm0ojt)

* Designing a rational follow up schedule for patients with extremity STS [[Wilson ASO '20](https://www.ncbi.nlm.nih.gov/pubmed/32152780)]:
  + Small low grade tumors should undergo annual follow-up for 5 years following definitive treatment.
  + Large G1 tumors and small G2-3 tumors should have f/u every 6 mo for the first 2y, then yearly to 10 years.
  + Large G2-3 tumors require f/u q3m for the first 2y, then q6mo for years 3-5, then annually until 10 years.
* 5y OS for I / II / III / IV of 90→ 80→ 55→ 20%.
* Low grade LR < 15%, OS >90%
* Int/High grade LR < 15%, G2 OS 80%, G3 OS 60%.
* RT brings LR from 25-30% to < 10%.
* PT/OT.
* Chest imaging q6m (CT chest).
* Imaging of primary depending on physical exam.
* H&P q3-6 mo x2 years.

# [STS: Extremity and trunk](#_ysnuxhlm0ojt)

* **NCI** [[Rosenberg ASO '82](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1352604/)]: **Amputation vs. LSS + RT**. All got adjuvant Adriamycin/Cytoxan→ MTX.

Amputation is equivalent to WLE and RT.

* + 43 pts. High grade STS of extremities.
    - RT 50 Gy to the entire compartment + 10-20 Gy boost to the tumor bed.
    - **5y LR ~0→ 15%** (p=0.06), **5y OS ~85%**. 5y DFS ~75%.
  + 65 pts on simultaneous prospective trial. **LSS + RT ± Chemo**.
    - 3y DFS 60→ 92%, 3y OS 74→ 95% for addition of chemo.

* **NCI** [[Yang JCO '98](http://ascopubs.org/doi/abs/10.1200/JCO.1998.16.1.197), [Beane ASO '14](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6293463/)]: **LSS ± PORT.** Add adjuvant doxo and cyclophosphamide for G3.

PORT improves LC for low grade\* and high-grade tumors. Desmoids may not require RT.

\*LC benefit for G1 tumors driven by inclusion of desmoid tumors. If desmoids are taken out, LC for G1 tumors disappears!

Adjuvant EBRT following surgery for STS of the extremity provides excellent local control with acceptable treatment related morbidity and no statistically significant improvement in overall survival.

* + 141 pts. 9 desmoids. 1983-1991. LG (n=50) HG (n=91). SM 1-2 cm. R2 or widely SM+ excluded. MFU 18y.
    - Strat for G2 vs G3 (30%), proximal vs. distal limb, SM ± 1mm.
    - PORT ± 45 Gy wide field + 18 Gy boost to the tumor bed.
    - Only 20% were greater than 10 cm while 40% were 5-10 cm.
  + 20y local recurrence 26.5→ 1.4%. 10y OS ~80%. 20y OS ~67%.
    - Of the 54 pts who completed telephone interviews at 20 years, only 1 patient recurred between 10 and 20y.
  + 5y DM for high grade tumors of ~20%.
  + Low grade (n=50): 24 surgery alone (8 recurred), 26 PORT (1 recurred).
    - 10y LC 67→ 96%. If the 9 patients with desmoid or dermatofibrosarcoma protuberans were excluded, then 6/19 not receiving XRT and 1/22 receiving XRT recurred locally (p=0.67).
  + High grade (n=91): 47 chemo alone (9 recurred), 44 PORT and chemo (0 recurred).
    - 10y LC 81→ 100%.
  + EBRT had a trend to more wound complications (~15%), clinically significant edema, and limb deficits (~15%).
* **MDACC** [[Pisters Ann Surg '07](https://www.ncbi.nlm.nih.gov/pubmed/17893504)]: **T1 STS LSS with Obs for R0, PORT for R1.**  
  Surgery alone may be acceptable for some patients so long as completely resected (e.g. ≤ 5 cm, superficial tumors).
  + 88 T1 STS. 60% G3. 70% superficial (old T1a) disease. R1 in 16% (n=14), R0 in 84% (n=74). MFU 6y.
  + For R0, LR at 5y / 10y of 8→ 11%. CSM at 5y / 10y of 3→ 3%.
  + For R1 + PORT, 5y LR 40%.

## [Pre-Op vs Post-op RT](#_2i2n53rm2x1a)

Preop is preferred for most situations. Lower dose, smaller treatment volume therefore less irreversible long-term toxicity.

Preop has more post-op wound healing complications (~40%) but less long-term fibrosis (typically irreversible).

Lower doses are typically utilized in the preoperative setting.

Reserve upfront resection for uncertain histology after initial biopsy and additional information would drive systemic treatment, lower extremity STS in patients with comorbidities who are at high risk for wound complications and wound healing, or very small tumors with expectation that no RT will be required.

* **CAN-NCIC-SR2** [[O'Sullivan Lanc '02](https://www.sciencedirect.com/science/article/pii/S0140673602092929?via%3Dihub), [Davis RTO '05]](https://www.sciencedirect.com/science/article/pii/S0167814005000241?via%3Dihub): **3D PORT 66/33** **vs. Pre 50/25**. Preop gets 16 Gy PORT if SM+.

Preop and postop RT have equivalent OS and LC, though toxicity differs with more late toxicity in PORT arm.

Preoperative RT with doubled wound complications. This is especially pronounced for lower extremities.

Postoperative RT trended to more fibrosis, edema, and joint stiffness.

Initially better OS with pre-op due to deaths other than sarcoma in the post-op arm, but OS benefit washed out on 6y MFU.

* + 188 extremity pts. Of preop arm, 14/88 (16%) had SM+, 10/14 (11%) received 16 Gy post-op boost. MFU 6y.
    - Initially 5 cm CC to 50 Gy, then 2 cm around GTV for cone-down.
    - Pre-op got 16-20 Gy postop boost if SM+.
  + 3y LC ~93%. 3y DM ~25%, 3y PFS ~65%. *Not powered for differences in outcomes!*
  + **Wound complications 15→ 37%**, for LE / UE 43→ 5%. *Wound complications are usually reversible.*
    - Pre-op IMRT flap avoidance decreases the rate of LE wound complications to 30% [[O'Sullivan Cancer '13](#kix.pb06s79tdjvu)].
  + **2y G2+ fibrosis ~48→ 32%** (p=0.07). *Fibrosis, edema and joint stiffness are usually irreversible.*
  + 2y G2+ edema ~23→ 15%, 2y G2+ joint stiffness ~23→ 19% [NS].
  + Field size predictive of greater rates of fibrosis and joint stiffness, marginally predictive of edema (p=0.06). [RoR](#203njngpimdd)
* Multi-institutional [[Sampath IJROBP '11](https://www.sciencedirect.com/science/article/pii/S0360301610008850)]:Retro. **Post Op vs. Pre Op RT**
  + 821 patients. MFU 5y.
  + Preop RT is associated with significantly improved OS and CSS [HR 0.72 and 0.64]
  + 5y CSS 74→ 79%.
  + There is also an association with decreased LR and DM with pre-op RT.

## [Brachytherapy, IMRT](#_2i2n53rm2x1a) and IORT

* **MSKCC Brachytherapy** [[Harrison '93](https://www.sciencedirect.com/science/article/pii/036030169390236O?via%3Dihub), [Pisters JCO '96]](http://ascopubs.org/doi/abs/10.1200/JCO.1996.14.3.859): R0/1 superficial trunk or **LSS ± BT**.   
  Established use of BT for high grade, negative margins.

Brachytherapy improves LC for SM-, G3 only.  
Counterintuitive: For the subset of microscopic SM+ (15%), BT added no benefit!

* + 164 pts. LDR 42- 45 Gy over 4-6 days. 15% R1 resections.
    - Volume 2 cm sup/inf, 1.5-2 cm med/lat. Catheters implanted 1 cm apart and loading on POD #6.
  + 5y LC 69→ 82%. Subset: Only high grade benefits. 5y LC 66→ 89% (**5y LR 35→ 10%**).
  + 5y FFDM ~80%, 5y DSS ~83%, regardless of tumor grade.
* **MSKCC Brachy vs. IMRT** [[Alektiar Cancer '11](https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.25882)]: Retro. **LSS + BT vs. IMRT**.
  + 134 patients. 71 pts post op brachy from 1995-2003. 63 pts IMRT pre or post op 2002 - 2006. MFU 4y.
    - BT were smaller and more negative margins.
  + Around 15% required re-operation.
  + 5y LC 81→ 92%.
* **European pooled analysis for extremity STS** [[Roeder ASO '18](https://www.ncbi.nlm.nih.gov/pubmed/30276647)]: **R0→ IORT** (12 Gy) **+ EBRT** (45/25).
  + 259 pts. Median age 55y. Median size 8 cm. MFU 5y.
  + R0 70%. R1 30%. 5y LC 86%.
  + Limb preservation and good functional outcome were achieved in 95% and 81% of patients.

## IMRT and SBRT

IMRT, especially preop, significantly reduces late morbidity such as joint stiffness, lymphedema, and fibrosis. Utilizes a smaller volume, and a lower dose is used preoperatively.

* The idea to have less toxicity with IMRT; 5y LC is equivalent when comparing multiple trials.
* **MSKCC** [[Folkert JCO '14]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4178522/): Retro. **3D vs. IMRT**. Median dose 63 Gy.   
  LC is similar and may be better with IMRT, late toxicities such as edema and dermatitis appear to be lower with IMRT.

IMRT patients were more commonly high grade, SM+, older, more nerve manipulation, and still did better!

* + 319 patients. 1996-2010. Nearly 90% were post-op. MFU nearly 5y.
  + 5y LR 15→ 8%! MVA HR 0.45.

* **RTOG 0630** [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&Fil%20eID=9379), [Wang JCO '15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4486342/)]: Phase II. **Pre-op 3D** [[NCIC](#13fpkt8syajl)] **vs. IMRT**. 50/25.

Pre-op IMRT leads to a statistically significant improvement in fibrosis, edema, and joint stiffness over 3D.

* + 98 pts. Extremity STS. IMRT in 75%. Primary endpoint: Determine effect of reduced RT volume with AE.
    - G2-3 or ≥ 8 cm: CTV = GTV + 3 cm CC and 1.5 cm radial, including suspicious T2 edema.
    - G1 and < 8 cm: CTV = GTV + 2 cm CC and 1 cm radial.
    - Skin/subcutaneous tissue V20 < 50%, bone V50 < 50%.
  + 2y LC 94% even though 60% SM+. All LF within CTV, so expansions are legit.
  + Late G2+ for historical NCIC / 06-30 of 37→ 11%.
  + Fibrosis 32→ 5%, Edema 15→ 5%, Joint stiffness 18→ 3.5%.

* **RTOG 9514 and 0630** [[Wang JCO '17](https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.11012)]: **pCR is associated with improved survival**.

pCR is associated with improved survival outcomes, and should be considered as a survival surrogate for future STS studies.

[[ARST1321](#tpqmuunwkrww)] is investigating the correlation of pCR with improved survival with concurrent pazopanib.

* + 135 pts underwent surgery and 123 were evaluable for pCR. MFU 5y.
  + RTOG 95-14 (n=51): G3 STS ≥ 8 cm of extremities or body wall. 1997-2000. 3c NAC→ RT→ 3c post op chemo.
  + RTOG 06-30 (n=72): Preoperative RT without chemotherapy.
  + 95-14 had 28% pCR (n=14/51) while 06-30 had 19% pCR (n=14/72).
  + 5y OS for ± pCR of 77→ 100%. 5y LF for ± pCR of 10→ 0%.
  + pCR is associated with improved OS and DFS.
  + Leiomyosarcoma/liposarcoma/myxofibrosarcoma were associated with better OS.
  + Liposarcoma/myxofibrosarcoma were associated with better DFS.
* **Poland** [[Koseła-Paterczyk EJSO '14](https://www.ejso.com/article/S0748-7983(14)01094-4/fulltext)]: Prospective. **25/5→ surgery in 3-7 days**.
  + 272 pts. 2006-2011. Median size 8.5 cm. G3 65%. NACCRT in high risk patients (22%). MFU 3y.
  + LC 81%, worse for size > 10 cm, G3 or R1 resections.
  + CCRT had no impact on OS.
  + 42% (n=114) had Rx toxicity, most with tumors located on lower limbs.
  + 7% (n=21) required surgery for complications.
* **UCLA Pre-op SBRT** [[Kalbasi Clin Cancer Res '20](https://www.ncbi.nlm.nih.gov/pubmed/32054730)]: Phase II. **30/5 Pre-op**.

There were favorable rates of wound complications and G2+ toxicity after 2y of follow up.

* + 52 pts. MFU 2.5y.
    - CTV = GTV + 3 cm CC and 1.5 cm radial.
  + 2y LR 6% (n=2/35). 2y DM 21% (n=10/47), most of whom were G3.
  + Average pathological treatment effect of 44% (standard deviation 32%).
  + Late G2+ toxicity in 16% of patients.
  + Major wound complications in 32% (n=16/50). 19 germline SNPs in miRNA binding sites of immune and DNA damage response genes, in addition to lower extremity location, demonstrated strong predictive performance for major wound complications.

## [Toxicity](#_ysnuxhlm0ojt)

Predictors of wound issues: diabetes, > 10cm, < 3mm from skin, use of flap/STSG [[Baldini '13]](https://link.springer.com/article/10.1245%2Fs10434-012-2797-1). Surgery > 6 weeks? [[Griffin](https://link.springer.com/article/10.1245%2Fs10434-015-4631-z)]

Post Op 66/33 vs. Pre Op 50/25 with 15→ 37% wound complications, especially pronounced in the lower extremities. Late fibrosis ~50→ 30% (p=0.07), trend to less edema and joint stiffness with pre-op. Field size was predictive of greater rates of fibrosis and joint stiffness, marginally predictive of edema [[CAN-NCIC-SR2](#13fpkt8syajl)].

See the [[Retroperitoneal](#_3lvr8tz9i1z3)] toxicity section for more information.

* **MSKCC** [[Alektiar IJROBP '05](https://www.redjournal.org/article/S0360-3016(05)00101-X/abstract)]: **WLE + PORT for** **Upper extremity vs. Lower extremity**.

There is a higher rate of reoperation with lower extremity sarcoma after CMT.

The UE site is associated with a greater rate of local recurrence compared with the LE site.

* + 369 patients. 1982-2000. Primary high grade extremity STS. MFU 4y.
  + Wound re-op 1→ 11%.
  + 5y LC 82%, 5y DMFS 61%, 5y OS 71%.
  + 5y LC 70→ 86%.
  + The two groups were comparable in regards to tumor size, prior excision, brachy or EBRT, and deep vs. superficial.
* **MSKCC** [[Rimner Cancer '08](https://www.ncbi.nlm.nih.gov/pubmed/19090010)]: **Subsite-specific complications in STS of the thigh: Anterior vs. Medial vs. Posterior**.  
  Medial (femoral vessels) or posterior compartment (sciatic nerve) of the thigh usually has more complications.
  + 255 patients. Primary STS of thigh. 1982-2002. More than 80% G3, deep, and > 5 cm. Close/SM+ 33%. MFU 6y.
  + 5y LC 89%, 5y DMFS 61%, 5y OS 66%.
  + Medial and posterior compartments have appear to have around 20% complications:
    - Medial compartment (femoral vessels) has more wound reoperation and edema.
    - Posterior compartment (sciatic nerve) has more wound reoperation and nerve damage.
    - Anterior compartment (femur) has almost no wound reoperation.
  + Wound reoperation (10%), edema (13%), joint stiffness (12%), nerve damage (8%), bone fractures (7%).
  + No difference in bone fracture, joint stiffness, DMFS, or OS between compartments.

* **Wound avoidance** [O'Sullivan Cancer '13]: Phase II. **Pre-op IMRT to reduce LE wound complications, morbidity**.  
  Pre-op IMRT flap avoidance decreases the rate of LE wound complications to 30% [[O'Sullivan Cancer '13](#kix.pb06s79tdjvu)].
  + 59 LE STS patients. 2005-2009. Median size 9.5 cm. 93% high grade. 98% deep. MFU 4y.
  + Prospectively determined 'virtual' flaps spared by IMRT, contoured by surgeon.
  + Wound complication 30%, as compared to 43% for LE in [[SR2](#13fpkt8syajl)].
  + 4y LR 7% with no recurrences near flaps.

### Bone fracture

* **MSKCC** [[Lin Cancer '98]](https://www.ncbi.nlm.nih.gov/pubmed/9635528): **Thigh STS**. **LSS + RT**.   
  Periosteal stripping + RT places patients at high risk for femoral fractures, especially females and receipt of chemo.
  + 205 patients. 1982-1997. 9 developed radiation induced fractures.
  + Only 4% developed femoral fracture.
  + Risk factors: periosteal stripping (5y fracture rate 29%). In periosteal stripping subset, nearly half of females or half of patients receiving chemo developed fractures.
* **Princess Margaret** [[Holt JBJS '05](https://www.ncbi.nlm.nih.gov/pubmed/15687153)]: **LSS/EBRT of Lower extremity**. No chemo.

Women more than 55y of age have a higher risk of fracture.

Frequency of pathologic fracture is associated with higher doses (60 Gy or 66 Gy) than 50 Gy.

* + 364 patients. RT pre, post, or pre with a post-op boost.
  + 27 fractures occurred in 23 patients.
  + Fractures for male / females of 2→ 6%.
  + Fractures for ± 55y of 1→ 7%.
  + Fractures for low dose (50 Gy) / high dose (60-66 Gy) of 1→ 7%
  + Median time to fracture 44 mo.

* **Dosimetric factors of bone fracture** [[Dickie IJROBP '09]](https://www.sciencedirect.com/science/article/pii/S0360301608038546?via%3Dihub): **Thigh STS**. **LSS + RT**.

Mean bone dose should be less than 37 Gy (compared to 40 Gy in Pak below).

* + 691 patients. 1989-2005. 31 developed radiation induced fractures.
  + Recommend bone V40 < 64%, mean bone dose < 37 Gy, max bone dose < 59 Gy.
* **Dosimetric factors of femoral fracture** [[Pak IJROBP '12](https://www.redjournal.org/article/S0360-3016(11)03320-7/abstract)]: **Thigh STS**. **LSS + RT**.

Femoral neck is at higher risk than other anatomic regions. Mean femoral neck doses > 40 Gy. Compared to [[Dickie](#kix.qfnzqho3b8yn)].

* + 131 patients. 1985-2006. 5 developed pathologic femoral fractures, 4 were analyzed.
  + Three of the four patients developed femoral neck fractures.
  + Mean femoral neck dose 23→ 58 Gy, V30 5→ 15 cc, V45 2.5→ 12 cc, V60 0.8→ 7.2 cc.
  + All fracture sites received mean doses greater than 40 Gy.
  + Prophylactic intramedullary pinning was performed in high-risk patients, with no significant difference in fracture rates between patients with and without periosteal excision.
* **PMH Nomogram for bone fracture** [[Gortzak Toronto Cancer '10]](https://www.sciencedirect.com/science/article/pii/S0360301608038546?via%3Dihub).
* **Observed vs. Expected risk** [[Folkert ASO '19](https://link.springer.com/article/10.1245%2Fs10434-019-07182-5)]: **Observed vs. PMH Nomogram Expected risk**. Median 63 Gy.

The PMH nomogram overestimates the risk of fracture when using IMRT.

Established predictors of fracture such as gender, tumor size, and dose of RT seem to have less impact in the IMRT era.

* + 92 thigh/groin STS. 2002-2010. Mostly post-op. MFU 6y.
  + 5y crude rate of fracture with IMRT of 6.7%.
  + Rate of fracture 7→ 26%. *The PMH nomogram vastly overestimated the rate of fracture.*
  + MTT fracture 23 mo.
  + Predictors of fracture age ≥ 60y and periosteal stripping.

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| **General treatment paradigm for extremity/trunk**:   * **G1**: **Surgery alone**. WLE, SM-: LR < 15%, OS >90%.   + Re-resect if will not have a significant impact on functionality.   + **PORT for SM < 1 cm** (2B recommendation).     - Atypical lipomatous tumor/WDLS guided by no tumor on ink.   + Indications for RT: SM+, LR s/p surgery alone, tumor location not amenable to subsequent salvage surgery. * **G2/3**: **RT→ LSS** (3-6w after) ± chemo ± boost. LR < 15%, survival varies by size, G2 vs G3.   + All pts should receive radiation therapy unless on clinical trial for surgery alone. * **IV** (< 4 lung mets / good KPS): RT→ Surgery, metastasectomy. Chemo.   + Doxorubicin + ifosfamide favored [[Pervaiz Cancer '08]](https://onlinelibrary.wiley.com/doi/abs/10.1002/cncr.23592).   + Pazopanib for non-lipgenic tumors if they have failed anthracycline.   **After pre-op, is there a benefit in the post-operative boost?**   * May not benefit select patients: low grade, WD-LS and focally, “planned” SM+. * Also, no benefit on LR, DM, and mortality [[Yami IJROBP '10](https://www.sciencedirect.com/science/article/pii/S0360301609027710?via%3Dihub), [Pan JSO '14](https://onlinelibrary.wiley.com/doi/abs/10.1002/jso.23741)]. * No randomized trial yet! |

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| **This Summary Box was made possible by the ACRO Resident Committee.**  **A more comprehensive collection of resources for all disease sites may be found at** [**http://www.acro.org/**](http://www.acro.org/)  Contouring   * eContour: [[Lower extremity STS](http://econtour.org/cases/115)] * ARRO: [[Sarcoma](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/ARROCaseSarcoma.pdf)] * Consensus Panel of MSK Anatomy of LE muscle compartments [[RTOG Contouring Atlas](https://www.rtog.org/LinkClick.aspx?fileticket=jzg6pjYoy7g%3d&tabid=402), [Paper](https://www.rtog.org/LinkClick.aspx?fileticket=joD6eB80xfs%3d&tabid=402), [Boundaries](https://www.rtog.org/LinkClick.aspx?fileticket=x0REg3QGcsg%3d&tabid=402), [Zaorsky](https://twitter.com/NicholasZaorsky/status/1226200148969213957?s=20)] * RTOG Extremity STS [[Contouring Atlases](https://www.nrgoncology.org/Portals/0/Scientific%20Program/CIRO/Atlases/RTOGsarcoma.pdf)] * Consensus on target volume delineation [[Wang IJROBP '11](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3205346/), [Haas IJROBP '12]](https://www.sciencedirect.com/science/article/pii/S0360301612001356?via%3Dihub). * RTOG preop extremity STS contouring of suspicious peritumoral edema target volume agreement [[Bahig IJROBP '15](https://www.ncbi.nlm.nih.gov/pubmed/23474110)]   Society Guidelines   * [[ESMO Guidelines](https://www.esmo.org/Guidelines/Sarcoma-and-GIST)] for Sarcoma and GIST. * ABS Consensus Statement for Sarcoma Brachytherapy [[Holloway ABS 13](https://www.americanbrachytherapy.org/consensus-statements/other/)]   Relevant Accessible Radiation Protocols   * RTOG 9514 [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&Fil%20eID=10606)]: G3 STS ≥ 8 cm of extremities or body wall. 1997-2000. 3c NAC→ RT→ 3c post op chemo. [RoR](#u8ch1u49og3r) * RTOG 0630[[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&Fil%20eID=9379)]: **Pre-op 3D** [[NCIC](#13fpkt8syajl)] **vs. IMRT**. 50/25. [RoR](#203njngpimdd) * CAN-NCIC-SR2 (Methods>Procedures) [[O'Sullivan Lanc '02](https://www.sciencedirect.com/science/article/pii/S0140673602092929?via%3Dihub)]. Preop vs PostOp extremity STS .[RoR](#13fpkt8syajl)   Quality of Life/Toxicity   * CAN-NCIC-SR2 (Tables 2/3) [[O'Sullivan Lanc '02](https://www.sciencedirect.com/science/article/pii/S0140673602092929?via%3Dihub)]. Preop vs PostOp extremity STS.[RoR](#13fpkt8syajl) * RTOG 0630 (Table 3) [[Wang JCO '15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4486342/)] IGRT for extremity STS toxicity. [RoR](#203njngpimdd) * Pre-op IMRT flap avoidance decreases the rate of LE wound complications from 43→ 30% [[O'Sullivan Cancer '13](#kix.pb06s79tdjvu)]. [RoR](#kix.pb06s79tdjvu) |

## [Treatment Planning](#_ysnuxhlm0ojt)

See Summary Box above and the [[Retroperitoneal Treatment Planning](#_f97qt7sc0qc6)] section.

* With neoadjuvant RT, the tumor may or may not regress but the pseudocapsule may thicken and become acellular. The goal is to make the mass peel off of neurovascular bundles easier at the time of surgery due to capsule formation.
* Timing of surgery:
  + After preoperative RT, a **3-6 week interval** is necessary before resection to allow acute reactions to subside and decrease risk of wound complications. Consider plastics involvement.
  + There is a trend to higher rate of complications if > 6 week interval to surgery [[Griffin ASO '15](https://link.springer.com/article/10.1245%2Fs10434-015-4631-z)].
  + Timing of PORT: **10-20d after surgery** for healing. Bolus scar/drain sites for the first 50 Gy unless tangential.
    - Do not wait > 8w beyond resection because of late fibrosis and proliferation.
* **Be prepared to re-sim for LE STS due to tumor growth** [[Dickie RTO '17]](https://www.sciencedirect.com/science/article/pii/S0167814016344802?via%3Dihub):

Around 33% will have a tumor change > 1 cm, usually around 2.5 weeks into treatment.

* + Prospective study. 70 pts. LE STS. IGRT 50/25 with daily CBCT.
  + 22/70 (around 33%) required a repeat CT prompted by tumor change >1 cm.
  + Mean tumor volume change was 45% for growing tumors and 33% for shrinking tumors.
  + CT2 prompted at a mean of 13 fractions.
  + [[Wong RTO '17]](https://www.thegreenjournal.com/article/S0167-8140(14)00325-9/fulltext): 188 CBCT from 39 pts. Mean GTV increased 6.6% in the first 2w, with a 4% decrease by the end of pre-op RT.
* Spare ≥ 1.5-2 cm strip of limb circumference (1 cm strip V20 < 50 %)
  + Never treat the entire circumference to > 50 Gy.
  + Spare 50% of XS of weight-bearing bone, entire or > ½ of joint cavities, and major tendons (patellar, Achilles).
* **General principles**:
  + The majority of tumor cells are within 1 cm of GTV [[White IJROBP '05]](https://www.sciencedirect.com/science/article/pii/S0360301604022886?via%3Dihub).
  + **Include peritumoral edema**, as though to be high risk to harbor sarcoma cells [[Bahig IJROBP '13]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3646910/).
  + The dermis overlying tumor deep to fascia is not a target, and its inclusion may increase wound complications.
  + Old standard: 4 cm CC and 1.5 radial, edit CTV at bone→ 5-10 mm for PTV.
  + New standard: At least 3 cm CC and 1.5 cm radial at least for initial 50 Gy per [[RTOG 06-30](#203njngpimdd)].
* **Preop**: No need in G1.
  + CTV\_50 = T1c + 3 - **4 cm CC and** 1- **1.5 cm radial** + peritumoral edema if feasible.
    - Consider 2 cm CC and 1 cm radial if < 8 cm and G1 per [[RTOG 06-30](#203njngpimdd)].
  + PTV\_50 = CTV + 0.5 cm with daily IGRT, + 1-1.5 cm without daily IGRT.
  + Give 16-18 Gy PORT boost if R1 vs 20-26 Gy if R2 *- boost controversial*.
    - Postoperative boost of 16 Gy after pre op can be considered in SM+

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| **Consider cone-down after 50 Gy for PORT**   * **VORTEX** [[Robinson IJROBP '16](https://www.redjournal.org/article/S0360-3016(16)30347-9/fulltext)]: **PORT 50 Gy** (5 cm CC / 2 cm radial)**→ 66 Gy vs. 66 Gy** (2 cm iso). There is no difference in the 2y limb function. Due to small events, it is not possible to evaluate LRFS.   2 cm margin is not standard yet. Still, it may be safe to reduce post-op target volume.   * + 216 pts. Extremity STS who underwent LSS. No chemo. MFU 5y.     - CTV1\_50: GTV + 5 cm CC and 2 cm axial.     - CTV2\_66: GTV + 2 cm.   + 5y LR ~15%, 5y OS ~72→ 67% (NS).   + 2y G2+ toxicity equivalent. *So, what's the point of smaller margins?*   + Not a non-inferiority study! Due to the small number of events. |

* **Postop**: Give if SM < 1 cm, consider for > 10 cm if no re-excision. ALT/WDLS guided by no tumor on ink.

See the Summary Box above. May consider cone down after 50 Gy.

* + 4-5 cm CC + 1.5-2 cm radial is standard. May cone down after 50 Gy, bringing 2 cm radial to 66 Gy.
  + CTV\_50 = bed + scar + pre-op T1c + (drain site) + 4-5 cm CC and 1.5-2 cm radial. If a subcutaneous tumor, then only need to expand into 5 mm into muscle.
    - Include drain site if CTV > 5 cm, G2-3, R1 resections - *controversial*  [[Haas IJROBP '12](https://www.sciencedirect.com/science/article/pii/S0360301612001356?via%3Dihub)].
  + CTV\_boost = pre-op GTV + **2 cm CC and 1.5 cm radial**.
  + CTV\_SM+\_>64 Gy due to association with improved LC [[Delaney IJROBP '07]](https://www.sciencedirect.com/science/article/pii/S0360301606034997?via%3Dihub).
* **Unresectable**: 50 Gy to large field, cone-down to 60 Gy, then to 70-76 Gy.
  + Consider decreasing RT total dose and dose/fx (1.8 Gy) if doxorubicin is given.
  + Delay RT >3 days from doxorubicin.

LDR 16 - 26 Gy, HDR 14-24 Gy; IORT 10-12.5 microscopic, 15 Gy macroscopic.

# [STS: Retroperitoneal](#_ysnuxhlm0ojt)

See the [[General STS](#_ysnuxhlm0ojt)] section.

The only proven treatment modality for retroperitoneal sarcoma is surgery.

Local control is only around 50% at 5 years after surgery alone. Negative margins are difficult, compartmental resection may reduce local recurrence to 30-40% [[Bonvalot JCO '09](https://www.ncbi.nlm.nih.gov/pubmed/19047280)].

Retroperitoneal WD-LS are typically quite large, but appear to be radiosensitive [[Gronchi](#kix.qnrsvadwmnzq), [STRASS](#kix.g4gie4g850us)].

Leiomyosarcomas and Dedifferentiated liposarcomas most commonly recur distantly [[MSKCC](#ynmu76q89xa6), [Gronchi](#kix.qnrsvadwmnzq)].

* 2.7 cases of retroperitoneal STS per 1 million people. 15% of all STS. Majority measure 15-20 cm in size (T4).
* Unlike Extremity STS where node-positive disease is stage IV, node-positive disease for retroperitoneal is stage III.
* Biopsy indicated for pts receiving preoperative RT or chemo, unless CT reveals homogeneous fat-density retro mass suggestive of WD-LS [[Lahat Cancer '09](https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.24045)].
* Role of RT and CT **unproven**… No proven role! Most centers aim to do **pre-op RT**.
* 50 Gy pre-op RT (tolerable for RP), 60-66 Gy post-op (too toxic for RP) by expert RT and surgeon panels.
* **Difficulties of surgery**: Proximity to critical organs, major neurovascular bundles. GTR in ~70% of primary tumors.
  + Absolute contraindications: Cord involvement, DM, peritoneal implants, involvement of SMV, extensive vascular involvement (e.g. aorta). Relative contraindications: involvement of IVC or iliac veins [[Jaques Ann Surg '90]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1358074/).
  + There appears to be no impact with R1 resections, suggesting many presumed R0 patients may have undetected positive margins.
  + Patterns of failure: **Predominantly LR: 50-80%**. DM to liver > lung [[Alldinger Anticancer Research '06](http://ar.iiarjournals.org/content/26/2B/1577.long)]. 5y OS 50-60%.
* **RT in Retroperitoneal Sarcoma Management** [[Haas JSO '17](https://onlinelibrary.wiley.com/doi/pdf/10.1002/jso.24892)]:
  + Only 25% of pts outside clinical trials receive RT, and nearly 90% of those in the post-operative setting.
* **MSKCC** [[Stojadinovic ASO '02](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1422449/)]: Retro.

RT is not routinely indicated in R1 disease; may use tissue displacement spacers to keep bowel out of volume.

* + 2,084 pts. 1982-2000. SM+ in 20%. MFU 4y.
  + SM+ for extremity / H&N / retroperitoneal sarcoma of 19→ 30→ 45%.
  + 72% of patients with positive margins had no recurrence.
  + Risk for local recurrence: Retroperitoneal sarcoma with HR 3.1.
  + For the majority of sarcoma anatomic sites and histologies, SM+ was a significant risk factor for local recurrence.
  + 229 pts with retroperitoneal sarcomas. There was no difference in LR with SM+. This suggests that although margins were nominally negative in 55% of patients, that many patients may have had undetected positive margins.
* One randomized trial: EBRT ± IORT… Not very useful.
  + Sindelar [[Arch Surg '93]](https://jamanetwork.com/journals/jamasurgery/fullarticle/595647): **± IORT→ EBRT**. Improved LC with IORT.
    - 35 pts. Surgically resected retroperitoneal STS. Single institution.
      * IORT 20 Gy→ low dose EBRT 35-40 Gy vs. 50-55 Gy EBRT alone.
    - MS ~48 mo, LRR 80→ 40% with IORT.

* **Preoperative IMRT + IORT** [[Roeder BMC Cancer '14](https://www.ncbi.nlm.nih.gov/pubmed/25163595)]: Phase I/II. **IMRT→ Surgery/IORT**.
  + 27 patients with primary/recurrent retroperitoneal STS (size > 5 cm, M0, at least marginally resectable). MFU 3y.
    - RT: SIB w 45-50 Gy to PTV and 50-56 Gy to GTV in 25 fx followed by surgery and IORT (10-12 Gy).
    - Liposarcomas 70%, G2 50%, G3 30%. Median size 15 cm.
  + 5y LC 72%. 5y DM 40%.
  + Severe postoperative complications in 33% (n=9), of whom 2 died after multiple re-interventions.
  + G3 toxicity in 6% of surviving patients after 1y and none after 2y.
* **Nomogram** [[Raut Cancer' 16](https://www.ncbi.nlm.nih.gov/pubmed/26916507)]: Retroperitoneal STS undergoing definitive resection (R0 / R1 / R2).  
  Interestingly, WD-LS had the highest rate of local failures. They likely did not receive radiotherapy.

Recall: Liposarcomas appear to benefit from radiation therapy, see [[STRASS](#kix.g4gie4g850us)].

* + 631 pts in validation set, 523 pts in development set. Around 60% liposarcomas. Only 30% received RT.
  + 7y DFS 38%, 7y OS 58%.
  + For DFS, Grade matters most. Size > 15 cm, LMS, UPS, WD-LS and multifocality are risk factors.
  + For OS, Grade matters most, followed by size > 15 cm. WD-LS is also a risk factor, less so extent of resection.

* **Patterns of Recurrence** [[Gronchi Ann Surg '16]](https://insights.ovid.com/pubmed?pmid=26727100): Primary retroperitoneal STS undergoing resection (R0/R1/R2).  
  LMS and solitary fibrous tumors have low LF, while UPS and WD/DD-LS (12q) recur much more frequently.

LMS, UPS, and DD-LS have the highest risk for DM.

Recall: Liposarcomas appear to benefit from radiation therapy, see [[STRASS](#kix.g4gie4g850us)].

* + 1007 pts. 8 different institutions. Resected STS. Only 5% R2.
    - WD-LS median size 27 cm. Appears to benefit from adjuvant RT.
    - LMS median size 12 cm.
  + OS at 5 / 8 / 10y of 67→ 56→ 46%.
  + LR at 5 / 8 / 10y of 26→ 31→ 35%.
  + 8y LR for LMS / WD-LS / G1-2 DD-LS 10→ 35→ 48%.

Predictors of LR: Age, size, R0, grade, tumor rupture, multifocality, RT, and histo subtype.

* + - 8y LR for WD-LS was only 5% in the one institution that routinely delivered RT.
    - 8y LR for LMS is less than 10%.
  + 8y DM **50% for LMS**, 32% DD-LS G3, 9% DD-LS G1-2, 0% WD-LS.

Predictors of DM: Size, grade, multifocality, histo subtype.

* **UAB selective dose escalation** [[Tzeng Cancer '06]](https://onlinelibrary.wiley.com/doi/abs/10.1002/cncr.22005): Pre-op 45/25 to tumor, **57.5 Gy boost** to areas HR for SM+.
  + 16 pts. All completed RT. 28 mo LR 2/16. 2y LC 80% (20% LR).
* **SEER** [[Bates Am JCO '15]](https://insights.ovid.com/pubmed?pmid=26703813): 144 retroperitoneal STS who received PORT.
  + MS 27→ 36 mo.
  + On MVA, adjuvant RT, male sex, age > 65 and stage were all prognostic factors for OS.
* **NCDB** [[Nussbaum Lancet '16]](https://www.sciencedirect.com/science/article/pii/S147020451630050X?via%3Dihub): Retro case-control study of nearly 10k pts from NCDB.

There is a suggestion of a 5y OS benefit of 8% with either pre or postoperative RT.

* + 5y OS for surgery alone / preop RT of 54→ 62%. Propensity score matching.
  + 5y OS for surgery alone / postoperative RT of 52→ 60%. Propensity score matching.
* **Mayo** [[Stucky JSO '14](https://onlinelibrary.wiley.com/doi/full/10.1002/jso.23576)]: ± RT→ Surgery with IOERT.
  + 63 primary or locally recurrent RPS. EBRT to 45-50 Gy. IOERT to 10-20 Gy to close or HR margin.
  + 5y LC 46→ 89% for any kind of radiation. This is unusually high - LC usually 20-50%!
  + 5y OS 60% for both groups.

* **STRASS I / EORTC 62092** [[NCT01344018](https://clinicaltrials.gov/ct2/show/NCT01344018), [Bonvalot ASCO '19](https://meetinglibrary.asco.org/record/174255/abstract)]: **± 50.4/28→ En bloc surgery**.  
  There was no apparent benefit for pre-operative RT in retroperitoneal sarcoma, although there may be a benefit with preoperative RT in the liposarcoma subgroup. High grade sarcomas and leiomyosarcomas do not seem to benefit from RT.
  + 266 pts, 75% liposarcomas. 2012-2017. Localized, previously untreated retroperitoneal STS. MFU nearly 4y.
    - Overall rate of reoperation ~10%.
    - Originally had defined local tumor progression while on RT as failure, but later
  + 3y abdominal RFS ~60%.
  + In the LPS subgroup, 3y abdominal RFS 60→ 72%.
  + Primary: RFS difference. Secondary: DMFS, pCR, toxicity.

* **STRASS II** [Needs source] will assess the role of NAC for high grade DD-LS and leiomyosarcoma.

"STRASS I included all "adult-type" primary RPS without distinguishing those with a high LRR from those with a more pronounced systemic risk. This is the main reason why the study failed to show a benefit of neoadjuvant radiation in the whole RPS family" - STRASS II.

See the [[Chemotherapy](#_3trempxorlhb)] section for a note on chemosensitivity.

* + Patients on this trial will not be receiving radiotherapy.
* IOERT [[NCT01566123](https://clinicaltrials.gov/ct2/show/NCT01566123)] for preop RT→ surgery + IORT for high-risk retroperitoneal sarcoma. Prelim w inc OS.
* **MGH** [[Delaney NCT01659203](https://clinicaltrials.gov/ct2/show/NCT01659203)]: Phase I/II. **Pre-operative IG-IMPT or IMRT with SIB to high risk margin for RPS**.
  + NACCRT is allowed.
  + 50.4/28 to lower risk CTV1, Dose-escalated SIB (60.2 - 61.6 - 63)/28 to high risk CTV2 margins.

## 

## [Toxicity](#_oejspbehx9b8)

See the [[Extremity and Trunk](#_39oy0omcq6ng)] toxicity section for more information.

* Toronto [[Wong Cureus '17]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5724811/): Cross-sectional retroperitoneallong-term QoL after preoperative RT and surgery.
  + 48 pts. QoL assessment. Median IMRT dose 45 Gy.
  + 54% acute GI toxicity, 92% G1-2, 8% G3.
  + 3y GI toxicity 88%, 19% G3.
* **Bowel OAR constraints** [[Mak PRO '16](https://www.practicalradonc.org/article/S1879-8500(15)00453-1/fulltext)]: 56 pts w pre-op RT. Delivered doses to bowel bag: ~70% exceeded V15 > 830cc, V25 > 650 cc, V45 > 195 cc and only 5% w ≥ G3 toxicity. The above constraints are likely too conservative!
  + This is important b/c EORTC 62092 has V45 < 195cc constraint to reduce dose from 50 to 45 Gy.
  + G3+ toxicity in 5%.
  + G2 toxicity in 64% (mainly nausea, less so diarrhea and pain).

## 

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| **This Summary Box was made possible by the ACRO Resident Committee.**  **A more comprehensive collection of resources for all disease sites may be found at** [**http://www.acro.org/**](http://www.acro.org/)  Contouring   * ARRO: [[Retroperitoneal Sarcoma](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/ARROcaseRPSarcoma.pdf)] * Treatment Guidelines for Preop RT of Retroperitoneal Sarcomas [[Baldini IJROBP '15](https://www.redjournal.org/article/S0360-3016(15)00180-7/abstract), [2017 ASTRO Refresher](https://www.astro.org/uploadedFiles/_MAIN_SITE/Meetings_and_Education/ASTRO_Meetings/2017/Annual_Refresher_Course/Content_Pieces/Sarcomas-Baldini.pdf)] * NRG retroperitoneal sarcoma target volume and OAR agreement [[Baldini IJROBP '15](https://www.ncbi.nlm.nih.gov/pubmed/26194680)]   Review Articles   * RT in Retroperitoneal Sarcoma Management [[Haas JSO '17](https://onlinelibrary.wiley.com/doi/pdf/10.1002/jso.24892)]. [RoR](#_oejspbehx9b8)   Society Guidelines   * [[ESMO Guidelines](https://www.esmo.org/Guidelines/Sarcoma-and-GIST)] for Sarcoma and GIST. * Transatlantic Australasian Retroperitoneal Sarco˜ma Working Group [[Papers](https://tarpswg.org/papers-from-tarpswg/)] * ABS Consensus Statement for Sarcoma Brachytherapy [[Holloway ABS 13](https://www.americanbrachytherapy.org/consensus-statements/other/)]   Relevant Accessible Radiation Protocols   * RTOG 0124 [[Protocol](https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&Fil%20eID=7540)]. Multimodality treatment in primary/recurrent RP sarcoma. * CAN-NCIC-SR2 (Methods>Procedures) [[O'Sullivan Lanc '02](https://www.sciencedirect.com/science/article/pii/S0140673602092929?via%3Dihub)]. Preop vs PostOp extremity STS .[RoR](#13fpkt8syajl)   Quality of Life/Toxicity   * Retroperitoneal preoperative SIB IMRT + IORT (Tables 4/5) [[Roeder BMC Cancer '14](https://www.ncbi.nlm.nih.gov/pubmed/25163595)] . [RoR](#o4newt6jv7wi) * Toronto [[Wong Cureus '17]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5724811/): Cross-sectional retroperitoneallong-term QoL after preoperative RT and surgery. [RoR](#ut210rk1hfa5) |

## [Treatment Planning](#_oejspbehx9b8)

See the Bowel OAR constraints paper in the section above for commentary on the recommended constraints below.

See Summary Box above and the [[Extremity Treatment Planning](#_mc8yn0g8kc4n)] section.

* **Treatment Guidelines for Preop RT of Retroperitoneal Sarcomas** [[Baldini IJROBP '15]](https://www.redjournal.org/article/S0360-3016(15)00180-7/abstract):
  + **Expand GTV by 1.5 cm**; crop at bone/retroperitoneal compart/kidney/liver interface and extend 5 mm into bowel and air cavity. Skin surface 3 - 5 mm and add 3 cm distally if it extends in the inguinal canal. If 4D is not available for the upper abdomen, expand CTV 2 - 2.5 cm CC and 1.5 - 2 cm radially.
  + PTV = ITV + 5 mm for IGRT or 9-12 mm if no IGRT.
  + OAR limits: Spinal cord, small/large bowel and/or bowel bag only contoured for PTV + 2 cm CC.
    - Stomach and duodenum V45 ≤ 100%, V50 < 50%, max dose 56 Gy.
    - Small and large bowel contoured as peritoneum: V15 ≤ 830 cc, V45 ≤ 195 cc.
      * Likely too conservative, see Mak study below.
    - Individual loop of small bowel: V15 < 120 cc, V55 < 20 cc.
    - Individual loop of large bowel: V60 < 20 cc.

# [STS: Future Directions](#_ysnuxhlm0ojt)

See NCTN Trial Portfolios by Disease Site: [[Sarcoma](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Sarcoma.pdf)].

* **EORTC 62921** [**QS**](http://www.quadshotnews.com/2018/02/comin-in-hot.html)[[Dewhirst JAMA Onc '18](https://jamanetwork.com/journals/jamaoncology/article-abstract/2672383)]: **Sandwich chemo (Doxo, ifos, and etoposide) ± regional hyperthermia**.
  + 341 pts. Region of interest was raised to 42C for 60 min concurrent with ifosfamide at each cycle.
  + Absolute OS advantage of 10% at both 5 and 10 years.
* **Act.in.Sarc** [[Bonvalot ASTRO '18](https://www.astro.org/ASTRO/media/ASTRO/Meetings%20and%20Education/PDFs/AM18/LBA18.pdf), [Lanc Onc '19](https://www.sciencedirect.com/science/article/pii/S1470204519303262?via%3Dihub)]: Phase II/III. **Pre-op 50/25 ± Halftium-Oxide nanoparticle** (NBTXR3)  
  NBTXR3 is a brilliant, albeit not cleverly-named, oncologic concept merging into one novel drug all your least favorite basic sciences: Chemo 101, Orgo, and...dun dun dun… Rad Bio. NBTXR3 is a suspension of nanoparticles containing the inorganic insoluble compound hafnium-oxide, best known for its use in ceramics. And now in soft tissue sarcoma (STS). The key here is that hafnium-oxide happens to emit tons of electrons when bombarded with X-rays, making for lots of free radicals in irradiated organic compounds.  
  TBL [QS](http://www.quadshotnews.com/2018/10/double-response-with-half-nium.html): Forget hyperthermia, hafnium-oxide is the career comeback disillusioned radiation biologists have been looking for.

TBL [QS](http://www.quadshotnews.com/2019/07/glass-hafnium-full.html): Get ready for a new chapter in Hall because there are currently no less than six open clinical trials across disease sites looking to replicate these promising results of NBTXR3-radiosensitization.

* + 180 pts. Locally advanced STS or extremity and trunk wall. Excludes abdominal wall or tumors > 3,000 cc.
    - Dosing at 10% of tumor volume at standard concentration.
  + pCR 8→ 16%.
  + R0 66→ 81%
  + Injection site pain in 14% of patients.
  + G3+ 30→ 39%. Hypotension 0→ 9%. Wound complications ~22%.
* See [[**NRG-DT001**](#apkrv8fvbw2k)]: Phase Ib. **Neoadjuvant AMG-232 (MDMi) + NART in P53wt STS** (typically liposarcoma).

See Figure 1 from [[Trino Front Pharmacol '16](https://www.frontiersin.org/articles/10.3389/fphar.2016.00491/full)] for more on MDM2 inhibition.

* + STS, G2-3, ≥ 5 cm. Biopsy sent for TP53 NGS. Patients with wild type p53 continue on study.
  + Two cohorts based on tumor location: Retroperitoneal/abdomen/pelvis vs. extremity/body wall.
* See [[**ARST 1431**](https://docs.google.com/document/d/17O0LOemBhckXGuuPBCh6u8vqBfc6lg88r46B8YctMXU/edit#bookmark=kix.cwg8nj2n0zj1)]: Phase III. **VAC/VI ± Temsirolimus** in patients with IR RMS.

VAC (actinomycin) is considered backbone chemo for IR RMS.

Should we be adding temsirolimus to VAC/VI? Currently accruing.

Cyclophosphamide is extremely important! This protocol was modified to add maintenance low dose cyclophosphamide/vinorelbine after consolidation chemo.

* + **ERMS**: **Stage 2-3 R2**; **Stage 4, Group IV, age < 10 years old**; Stage 1, R2 non-orbit; Stage 3, Group I/II (R0-1);  
    Intermediate risk now includes patients with metastasis if fusion negative and < 10 years old!

Intermediate risk now includes Subset 2 from [[0331](https://docs.google.com/document/d/17O0LOemBhckXGuuPBCh6u8vqBfc6lg88r46B8YctMXU/edit#bookmark=kix.l6kl6263ku4r)] given these patients did so poorly on that trial.

* + **ARMS**: **Stage 1-3, Group I-III**.
  + ARMS FOX01 negative, Stage 1-2 Group I-II, orbit: Single arm VAC/VA and RT.
  + Allows any RMS histology except pleomorphic.
  + All primary site RT begins at week 13.
    - This is due to no difference in timing in RT between IRS-IV, D9803, and ARST 0531. Week 13 was chosen to allow for assessment of feasibility of temsirolimus, complex RT planning, and possible delayed primary excision.
  + PET encouraged at week 9, but only required if CR without biopsy. PET scans do not impact treatment otherwise. If PET at 9 weeks is CR, then the dose of RT is reduced to 36 Gy. If PR, RT replanning allowed at 36 Gy. Delayed primary excision allowed at week 12 (debulking strongly discouraged). **For size > 5 cm, boost to 59.4 Gy**.
  + No early RT for high risk PM tumors. Emergent RT only in rare cases of failure to respond to chemo.
    - Protons and photons allowed: Expect 50/50.
    - Bone mets < 5cm: Optional SBRT.
      * Bone mets in SD/PR: PTV2 = GTV2 (35/5). PTV1 = CTV2 + 2mm (30/5).
        + After 15 Gy WLI: PTV2 = GTV2 (30/5). PTV1 = CTV2 + 2mm (25/5).
      * Bone mets in CR: PTV2 = GTV2 (30/5). PTV1 = CTV2 + 2mm (25/5).
        + After 15 Gy WLI: PTV2 = GTV2 (30/6). PTV1 = CTV2 + 2mm (20/5).
    - Lung mets: All pts with any lung mets or malignant pleural effusion should receive bilateral WLI to 15/10.
    - Metastatic lesions (all non-bone sites, all non-lung sites and bone > 5 cm)
      * CR: 40/20. SD/PR 50/25.
  + Patients < 2y old:
    - Adherence to guidelines encouraged, as outcomes were poor for these kiddos on 0531.
    - Deviation allowed for kiddos ≤ 24 mos who are FOX01 negative.
  + Temsirolimus (mTOR inhibitor) shows activity in relapsed RMS pts.

# [Gastrointestinal Stromal Tumors (GIST)](#_wrgwa2aop5jm)

* Paradigm: Surgery→ imatinib (400 mg qday).
  + Consider preop imatinib if downsizing is required.
  + If on Imatinib with SD, then don't stop as high risk of progression.
* Use CT w contrast for patients on TKIs (sunitinib).
* Stomach (60-70%), SI (30%); duodenum (4-5%), rectum (4%), esophagus (< 1%), colon and appendix (1-2%).
* Liver mets and dissemination within the abdominal cavity; LN mets rare.
  + Be careful during biopsy; hemorrhage and intra-abdominal tumor dissemination are of concern
* 95% have KIT (CD117) expression. Most have **KIT** mutation, less have **PDGFRA** RTK mutation. 10-15% are wild-type (preferred SDH-deficient GIST). BRAF exon 15 (V600E) also reported.
  + Adjuvant Imatinib for 3 years recommended in c-KIT positive tumors if high risk (as below).
* MEKi (binimetinib) in addition to imatinib may improve response rates in advanced GIST [[Chi'ASCO '20](https://meetinglibrary.asco.org/record/185566/abstract)]
* **SSGXVIII/AIO** [[Joensuu JAMA Onc '20](https://pubmed.ncbi.nlm.nih.gov/32469385/)]: **R0→ Imatinib for 1y vs. 3y**.

About 50% of deaths can be avoided during the first decade of follow up after surgery with 3y of imatinib.

* + 397 pts. 2004-2008. MFU 10y.
  + 5y RFS 53→ 71%. 10y RFS 42→ 53%.
  + 5y OS 86→ 92%. 10y OS 65→ 79%.
* Avapritinib is now [[FDA approved](https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-avapritinib-gastrointestinal-stromal-tumor-rare-mutation)] for PDGFRA mutations as of January 2020 with ORR approaching 90%.
* Prognosis: size >10 cm, >5 cm with >5 mitosis/hpf, mitotic rate (>10 mitoses per 50 HPF), tumor rupture, and location (Worse: SI, rectal).
* **Carney-Stratakis**: AD predisposed to GISTs and paragangliomas.
  + Loss of function of succinate dehydrogenase (SDH) gene subunits (SDHB, SDHC, SDHD) identified in GISTs.
  + No association with KIT/PDGFRA mutations! They are SDHB negative.

**Misc**

* Li-Fraumeni (STS, osteosarcoma, breast cancer, leukemia, brain tumors, and adrenocortical carcinoma <45 yo).
  + STS in 12-21% of individuals.
  + RMS <6 years and undifferentiated pleomorphic sarcoma >50 years.
* Hereditary retinoblastoma (RB1)
  + Leiomyosarcoma is the most frequent STS subtype (78% of leiomyosarcomas diagnosed >30 years after Rb dx).
* NF-1, NF2
  + 5% develop STS. Most commonly, MPNSTs.

#### 

# [Desmoid Tumor (aggressive fibromatosis)](#_wrgwa2aop5jm)

[**StatPearls: Dermatofibrosarcoma Protuberans**](https://www.ncbi.nlm.nih.gov/books/NBK513305/) *Last update: 2/14/2019.*

[**StatPearls: Desmoid Tumor**](https://www.ncbi.nlm.nih.gov/books/NBK459231/)*Last update: 7/31/2019.*

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| **Desmoid Tumor Working Group** [[Eur J Cancer '20](https://www.ncbi.nlm.nih.gov/pubmed/32004793)]: **The Management of Desmoids: A Global consensus-based guideline**.   * Active surveillance is a well-established primary approach to primary/recurrent sporadic/familial desmoid tumors. An initial "active surveillance" approach does not appear to influence the efficacy of subsequent treatments. Persistent progression may be a triggle for treatment. Scan with MRI within 1-2 months, then in 3-6 month intervals. Generally speaking, you should try to wait one year from diagnosis unless RECIST criteria for progressive disease is met. The type of treatment varies with site:   + Abdominal wall: Surgery is the first choice.   + Intra-abdominal/retroperitoneal/pelvis: Systemic therapy should be considered.   + Extremity/girdles/chest wall: Surgery should not be first line unless expected morbidity is very low, systemic therapy is preferable. Isolated limb perfusion also may be considered as opposed to radiotherapy.   + H&N/intrathoracic: medical therapy is generally considered as the first line.   + In selected conditions (elderly, patient intolerance/preference, comorbidities, lesions growing rapidly and threatening vital organs, etc.), radiotherapy is a reasonable and effective first line alternative. * Surgery is the accepted second-line treatment only for sporadic tumor desmoid tumors located in the abdominal wall failing observation. Wide microscopic margins should be the goal, but positive microscopic margins can be accepted when function or cosmesis is an issue. However, if positive microscopic margins can be anticipated, other management than surgery should be preferred. If R1 is obtained, there is little data supporting re-resection or adjuvant radiotherapy. * Medical therapies are second-line treatments for sporadic tumor desmoid tumors located at all other sites and for all familiar tumor desmoid tumors failing observation. * Local ablative treatments such as cryotherapy or radiotherapy options that can be considered as an alternative to medical therapies on an individual basis. * Pain control is paramount to improve quality of life, independently of the use of active treatment against the disease. * Diagnosis of desmoid tumors: CTNNB1 mutations and APC mutations are mutually exclusive. CTNNB1 wild-type status should raise suspicion for FAP, especially if intra-abdominal. * FAP associated tumors (Gardner syndrome) seems to be more aggressive and multifocal, and tends to be treated more aggressively in terms of medical management. In the setting of confirmed APC mutation, a mesenteric mass may likely be a desmoid tumor, particularly if the patient had prior surgery. FAP patients should be jointly managed by sarcoma specialists and experts in GI cancer. Small bowel transplantation should be discouraged. * There is a lack of evidence that pediatric patients need to be treated differently than adults. * There is a lack of comparative studies for systemic therapy. Randomised data only exists for sorafenib (TKI), pazopanib (TKI), and methotrexate plus vinblastine. Prospective phase II data exists for the administration of low dose chemotherapy with MTX plus vinblastine and imatinib. In general, it is reasonable to employ less-toxic agents followed by more toxic agents in a stepwise fashion. |

* 900 cases/year at a peak age of 30-40y. < 5% of all STS.
* After surgery alone, extra-abdominal wall tumors have a higher risk of recurrence. However, 5y LR < 10% for abdominal wall tumors after surgery alone [[Crago Ann Surg '14](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4096320/)].
* Abdominal wall type: From rectus. Young women, often peri or post partum. May regress w antiestrogens.
* Intraabdominal type: From iliac fossa, pelvis, or mesentery (Gardner's, often > 10 cm). Unrelated to gestation.
* They do not have histopathologic features necessary to classify as sarcomas, but are categorized as low grade sarcomas because of their high tendency to recur locally after excision. **Surgical margins 2 cm desired**.
  + There are no differences in imaging characteristics as compared to malignancy.
* Incisional bx by your friendly ortho onc, as may discover sarcoma on path.
* **CTNNB1** gene encoding the beta-catenin pathway (for sporadic) is identified in 85% of those with desmoid tumors.
* FAP results from mutations in APC gene on 5q21 - APC mutations account for 5-15% of desmoids [[Nieuwenhuis IJC '10](https://onlinelibrary.wiley.com/doi/abs/10.1002/ijc.25664)].
  + Colorectal polyps that progress to cancer at age 35-40.
  + **Gardner’s syndrome** is a variant of FAP with osteomas, skin cysts, congenital hypertrophy of RPE, and desmoid tumors (aggressive fibromatosis). Mutation in CTNNB1, B-catenin.
  + Desmoid tumors reported in 7.5-15% of patients with FAP.
  + Median age of diagnosis of 31y.
* Proposed staging system for FAP-associated retroperitoneal desmoid [[Cleveland clinic](https://www.ncbi.nlm.nih.gov/pubmed/18322756)]:
  + Stage I: Asx, < 10 cm, stable.
  + Stage II: ADLs ok, < 10cm, stable.
  + Stage III: Sx but no hospital, or GI/GU obstruction, or 10-20 cm slow grower.
  + Stage IV: Hospital, septic such as fistula/abscess, or > 20 cm and rapidly growing.
    - 5y OS 76% for intra-abdominal FAP-associated stage IV [[Quintini Ann Surg '12]](https://insights.ovid.com/pubmed?pmid=22323009).
* **Heidelberg** [[Seidensaal Rad Onc '20](https://ro-journal.biomedcentral.com/articles/10.1186/s13014-020-01565-9)]: Retro. Median 54 Gy.

RT in the treatment of desmoids can lead to long term control. Treatment of patients with abdominopelvic desmoids should be avoided due to the risk of higher grade complications.

* + 40 patients who received 44 treatments from 2009-2018. 9 FAP associated. Median 967 cc. MFU 32 mo.
    - RT: 11 treated at diagnosis, 33 at time of progression/recurrence. PORT in 17 cases.
    - CTV is defined as GTV with 1-4 cm margin when feasible, depending on location and anatomy.
  + Local PFS at 3y / 5y of 76→ 64%.
  + PFS at 3y / 5y of 72→ 58%.
  + 5y OS 97%.
  + In the 31 patients with macroscopic tumor, PR 39% (n=12), CR 13% (n=4), PD 30% (n=13) predominantly at the margin of the PTV (n=5) followed by progression within the PTV (n=4).
  + Late toxicity was especially severe in patients with FAP and abdominopelvic desmoids including gastrointestinal fistula, perforation, and abscess.
* **Systemic therapy**: **NSAIDs**, TKIs, and "low-dose" or conventional chemo regimens including low dose doxorubicin.
  + Toremifene used in case reports after surgery. **Tamoxifen** + **sulindac** after surgery may be effective, but the only prospective phase II data on NSAIDs in addition to antihormonal therapy was [[negative](#szd5ds5w88is)].
  + There is a clinical benefit of TKIs, which may be more pronounced with **sorafenib** and pazopanib compared to imatinib and may be achievable with even low doses, limiting potential adverse effects.
  + **MTX + vinorelbine/vinblastine** has also been associated with prolonged stable disease in unresectable/recurrent dz.
  + Pegylated liposomal doxorubicin is an option.

### Treatment planning

* DEGRO guidelines for RT of non-malignant disorders [[Seegenschmiedt SuO '15](https://link.springer.com/article/10.1007%2Fs00066-015-0818-2)]
* **Progressive/recurrent desmoid**: Systemic treatment, resection ± PORT (50 Gy if no previous irradiation), RT alone (50-56 Gy, if not previously irradiated).
* **Local control** [[Nuyttens Cancer '00]](https://www.ncbi.nlm.nih.gov/pubmed/10738207): 22 studies for **± surgery ± RT**.

Ranges from 70-85% with gross or microscopic disease. Regression after RT may occur for up to 3y.

* + Surgery alone: 61%. LC for ± SM of 41→ 72%. *SM of 2 cm desired.*
  + Surgery + RT: 75%. LC for ± SM of 75→ 94%.
  + RT alone: 78%, w 3y LC ~80% for 56 Gy on another study [[Keus Ann Onc '13](https://academic.oup.com/annonc/article/24/10/2672/176873)].
* Consider PORT for R2 disease (R1 acts more like R0).
  + PORT microscopic dz to 50 Gy (NCCN).
  + Unresectable or R2 to 50-**56 Gy** (NCCN), though up to 65 Gy also used.
* Note: Desmoids can be observed if asymptomatic and not in areas that could lead to functional impairment with growth.

# [Benign](#_wrgwa2aop5jm)

## [Heterotopic ossifications (HO)](#_8l48cswry8jw)

* [**StatPearls: Heterotopic Ossification**](https://www.ncbi.nlm.nih.gov/books/NBK519029/)*Last update: 6/4/2019.*
* [**StatPearls: Radiation Therapy for Heterotopic Ossification Prophylaxis**](https://www.ncbi.nlm.nih.gov/books/NBK493155/)*Last update: 6/3/2019.*
* **Heterotopic ossification after hip arthroscopy (Review Article)** [[Amar J Hip Preservation Surg '15](https://academic.oup.com/jhps/article/2/4/355/2379457)].
  + Occurs 0-44% of the time after hip arthroscopy. Up to 80% if high risk.
    - Usually asymptomatic and incidental finding.
    - May begin to occur by 2w, maturing to solid bone by 3mo.
    - The lateral or anterolateral approach has greater risk for HO than posterior approach.
  + Most likely culprit is **mesenchymal stem cell** (MSC), which may mature into pathologic osteoblasts.
    - Goal to give RT within 24h preop or 72h postop to present mesenchymal cell differentiation.
  + **RF**: History of HO (80-100% risk), male, trauma, burns, acetabular fracture, Paget's disease, hypertrophic OA, skeletal hyperostosis, AS, prior hip surgery, T-type fracture, fracture with dislocation, multiple injuries, lateral/anterolateral approach, trochanteric or femoral osteotomy, extended iliofemoral approach.
* **Classifications**: [Brooker]
  + Grade 1: Isolated bone islands within soft tissues.
  + Grade 2: Bone spurs > 1 cm apart.
  + Grade 3: Bone spurs < 1 cm apart.
  + Grade 4: Complete ankylosis between proximal femur and pelvis.
  + This classification was criticized as bone that appears to be bridging may to either anterior or posterior to the hip and may not cause significant reduction to range of motion.
* **Fractionation**
  + **Historic studies**: Originally 20/10 based on peds knowledge of premature epiphyseal closure at > 20 Gy.
    - 20/10 vs. 10/5 within 96h no different [[Sylvester IJROBP '88](https://www.redjournal.org/article/0360-3016(88)90262-3/fulltext)], then 7/1 within 72h effective.
    - 10/5 vs. 8/1 within 96h no different, HO in 21% of patients in both arms [[Pellegrini '92](https://insights.ovid.com/pubmed?pmid=1541613)].
    - 8/1 < 4 h prior to or < 48h post-op no difference [[Gregoritch IJROBP '94](https://www.redjournal.org/article/0360-3016(94)90519-3/abstract)].
    - 7/1 vs. 5.5/1 within 72h post op, higher failure rate w 5.5 Gy [[Healy '95](https://insights.ovid.com/pubmed?pmid=7713977)].
    - Pre-op 7/1 < 4h vs. 17.5/5 within 72h postop w superiority of the latter.
      * Of note, pts with G3-4 treated with preop did worst.
    - 10/5 vs. 5/2 within 96h post op with no difference, though trend to worse w 5/2 [[Padgett '03](https://www.sciencedirect.com/science/article/pii/S0883540303002651?via%3Dihub)].
  + **Summary**:
    - Pre-op 7/1 within 4h (8h) pre-op or 72h (96h) post-op is effective [[Seegenschmiedt IJROBP '01](https://www.redjournal.org/article/S0360-3016(01)01640-6/fulltext)].
    - Post-op 5/2 may be effective, but 5.5/1 was not.
    - Preop 7/1 is effective for low disease burden if given < 4h prior to surgery.
    - Traditional size of field 14 x 14 cm, typically between the lesser trochanter and ischial ramus.
      * Sup: 3 cm above acetabulum, Inf outer ⅔ of shaft of implant.
    - It's OK to spare the medial ⅓ of the acetabular hardware component.
* **Post Op single fx**[[Lo Radiology '88]](http://pubs.rsna.org/doi/10.1148/radiology.168.3.3136510?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): **7/1 < 72h postop** w 4% failure rate (only 23 patients).
* [**Meta** [Pakos IJROBP '04]](https://www.sciencedirect.com/science/article/pii/S0360301603023101?via%3Dihub): **NSAIDs vs. RT**.
  + **RT may be better (HR 0.42), but absolute gain < 2%**.
  + Dose dependent, but 6/1 postop appears comparable to NSAIDs.
  + Based on the risk of G3-4 HO. Subgroups demonstrated early preop (16-20h) not effective, > 6 Gy better.
* **Meta** [[Milakovic RTO '15](https://www.sciencedirect.com/science/article/pii/S0167814015002893?via%3Dihub)]:
  + No difference for BED ± 25 Gy or between pre and post-op RT.
  + Multiple fractions may have lower prevalence of HO, but no difference in progression of HO.
* **Cochrane Review** [[Protocol - Liu '17](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012861/full)]: NSAIDs for preventing HO.
  + *Old Fransen Cochrane review pulled; awaiting this new review article.*
* **NSAID vs. postop single fx**[[Burd '01]](https://insights.ovid.com/pubmed?pmid=11741055): **Indomethacin vs. 8/1 < 72h**. G3-4 HO ~14→ 7% (p=0.22).
  + **Increased risk of bone nonunion following fracture w indomethacin** [[Burd '03]](https://www.ncbi.nlm.nih.gov/pubmed/12892193).
* NSAIDs are good: but... there's a catch (see above).
  + Randelli: 285 pts taking NSAIDS had no HO. 5/15 patients without prophylaxis had HO.
  + Beckman: naproxen 500 mg BID vs. nothing. HO 6→ 25%.
  + Wurzburg, Germany: 100 THA pts. 7/1 16-20h prior to surgery vs. diclofenac 75 mg/d BID x2w vs. historic controls without ppx.
    - HO 48→ 11% with NSAIDs. Brooker III-IV NS difference. Historical control 68%.

### [Treatment Planning](#_822mr8dchlbg)

* **Give 7/1 < 6h** (24h) **preop, or < 72h post op**.
* Roughly speaking, ~10-20% recur following RT.
* Only two case reports of RT-induced tumors after HO RT [[Farris Rad Onc '12](https://ro-journal.biomedcentral.com/articles/10.1186/1748-717X-7-140), [Mourad PRO '17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5461462/)]
* Use 6MV bc high Z of hardware will increase pair production w high E, which will increase scatter dose from positron annihilation reactions. The planning system will not model dose correctly w like 18MV due to high Z of hip hardware which may lead to underdosing.

## [Pigmented villonodular synovitis](#_8l48cswry8jw)

* DEGRO guidelines for RT of non-malignant disorders [[Seegenschmiedt SuO '15](https://link.springer.com/article/10.1007%2Fs00066-015-0818-2)]
* Proliferation in synovial cells of tendon sheaths and joint capsules.
* Synovectomy alone with LR 45%.
* RT 30-36 Gy with LR < 20%.