Principles of Radiotherapy in Pediatric Soft Tissue Sarcoma

Dr. Archana Dutta

Consultant Oncologist

Punjab Institute of Medical Sciences- Jalandhar

Sacred Heart Hospital- Jalandhar

American Oncology Institute- Jalandhar

Background

Overview

- Originate from embryonic mesodermal tissues during differentiation into various mesenchymal tissue components.
- Constitute 6% to 8% of childhood cancers (<15 years old), slightly higher in Western countries compared to Asian countries.
- 50% to 60% are rhabdomyosarcoma (RMS), others are non-RMS soft tissue sarcomas (NRSTS) including various rare tumors.
- NRSTS category includes fibrosarcomas, synovial sarcomas, Ewing's family tumors, MPNSTs, IMTs, and Kaposi sarcoma (per International Classification of Childhood Cancers Version 3).

Age and Incidence

- Majority of RMS (2/3rd) cases diagnosed before age 6, incidence decreases with age.
- NRSTSs more common in older children, increasing during adolescent years.
- Higher incidence of Kaposi sarcoma in African countries with endemic HIV.

MPNST : Malignant Peripheral Nerve Sheath Tumors and IMT : Inflammatory Myofibroblastic Tumors

Sangkhathat S. Current management of pediatric sarcomas

Background

Associated Syndromes:

- Some cases associated with cancer predisposition syndromes, like Li-Fraumeni syndrome (linked to Tp53 mutations).
- Neurofibrosarcomas linked to neurofibromatosis type 1 (NF1) gene mutations, associated with embryonal RMS.
- Werner syndrome

Molecular Signatures:

- Specific chromosomal translocations and chimeric transcription factors seen in certain pediatric sarcomas.
- PAX-FOXO1 fusion characteristic of unfavorable histology/alveolar RMS.
- RB1 gene : leiomyosarcoma (<1 yr)
- SMARCB1 (INI1) : Extrarenal rhabdoid tumors

Improved Outcomes and Treatment:

- Pediatric soft tissue sarcoma outcomes significantly better over the past 3 decades.
- Prognosis of RMS in younger children better than adult sarcomas.
- Multidisciplinary therapeutic approach, evidence-based medicine, and modern treatments improve survival and organ preservation.

CLINICAL PRESENTATION AND DIAGNOSIS OF PEDIATRIC SOFT TISSUE SARCOMA

Soft Tissue Sarcomas: Localization

- These tumors can appear anywhere in the body (muscle, fascia, fat).
- Primary sites of rhabdomyosarcomas (RMSs):
    1. head and neck,
    2. genitourinary system,
    3. limbs.
- Common presentation:
    1. growing lump impacting nearby organs;
    2. organ-specific symptoms possible (e.g., frequent urination, obstructive jaundice).
- Tumor site and relation to surrounding organs determined by imaging (preferably MRI and/or CT).

Age Distribution of Soft Tissue Sarcomas in Children Aged 0 to 19 Years (SEER 2000–2015)

	Age <5 y	Age 5–9 y	Age 10–14 y	Age 15–19 y	Age <20 y	All Ages (Including Adults)
All soft tissue and other extraosseous sarcomas	**1,124**	**773**	**1,201**	**1,558**	**4,656**	**80,269**
Rhabdomyosarcomas	**668**	**417**	**382**	**327**	**1,794**	**3,284**
Fibrosarcomas, peripheral nerve, and other fibrous neoplasms	**137**	**64**	**112**	**181**	**494**	**6,645**
Fibroblastic and myofibroblastic tumors	114	33	41	77	265	4,228
Nerve sheath tumors	23	31	70	102	226	2,303
Other fibromatous neoplasms	0	0	1	2	3	114
Kaposi sarcoma	**2**	**1**	**2**	**10**	**15**	**7,722**
Other specified soft tissue sarcomas	**237**	**238**	**559**	**865**	**1,899**	**49,004**
Ewing tumor and Askin tumor of soft tissue	37	36	72	113	258	596
pPNET of soft tissue	24	23	42	56	145	402
Extrarenal rhabdoid tumor	75	8	9	4	96	205
Liposarcomas	4	6	37	79	126	10,749
Fibrohistiocytic tumors	43	73	142	223	481	13,531
Leiomyosarcomas	11	14	19	41	85	14,107
Synovial sarcomas	12	39	141	210	402	2,608
Blood vessel tumors	12	9	11	32	64	4,238
Osseous and chondromatous neoplasms of soft tissue	1	6	16	14	37	1,018
Alveolar soft parts sarcoma	4	5	22	33	64	211
Miscellaneous soft tissue sarcomas	14	19	48	60	141	1,339
Unspecified soft tissue sarcomas	**80**	**53**	**146**	**175**	**454**	**13,614**

pPNET = peripheral primitive neuroectodermal tumors; SEER = Surveillance, Epidemiology, and End Results.
aSource: SEER database.

Diagnostic Approaches and Resectability

- ***Imaging*** helps identify tumor location, proximity to vascular structures, and potential surgical impact.
- **Plain films :** extraskeletal osteosarcoma or synovial sarcoma.
- **Computed tomography (CT) :** Chest CT : presence of metastases. An abdominal CT can be used to image intra-abdominal tumors, such as liposarcoma.
- **Magnetic resonance imaging (MRI).** MRI can be used to image intra-abdominal tumors, such as liposarcoma, and is essential for extremity lesions.
- **PET scan and bone scan :**
  - In a retrospective study, 46 PET scans were completed in 25 pediatric patients with soft tissue sarcoma.
  - The positive predictive value of finding metastatic disease was 89%, and the negative predictive value was 67%.
  - A small retrospective study of nine patients with NRSTS suggested that PET-CT was more accurate and cost-effective than either modality alone in identifying distant metastatic disease.
- No serum markers available for sarcoma diagnosis.

Biopsy strategies

Diagnosis of Childhood NRSTS:

- NRSTS (non-RMS soft tissue sarcomas) differ pathologically from rhabdomyosarcoma and Ewing sarcoma.
- Classification of childhood NRSTS can be challenging due to distinct characteristics.

Biopsy Techniques:

- Core-needle biopsy, incisional biopsy, or excisional biopsy used for NRSTS diagnosis.
- Surgeon involvement crucial for biopsy decision, ensuring proper placement for negative margins.

Importance of Adequate Tissue Sampling:

- Core-needle biopsy or small incisional biopsy necessary for molecular analysis and conventional studies.
- Various analyses include histological, immunocytochemical, light/electron microscopy, cytogenetics, FISH, molecular pathology.

Core Needle Biopsy :

- Of 530 suspected soft tissue masses in (largely adult) patients who underwent ***core-needle biopsies***, 426 (80%) were proven to be soft tissue tumors, 225 (52.8%) of which were malignant.
- Core-needle biopsy was able to differentiate soft tissue sarcomas from benign lesions with a sensitivity of 96.3% and a specificity of 99.4%.
- Tumor subtype was accurately assigned in 89.5% of benign lesions and in 88% of soft tissue sarcomas.
- The biopsy complication rate was 0.4%.

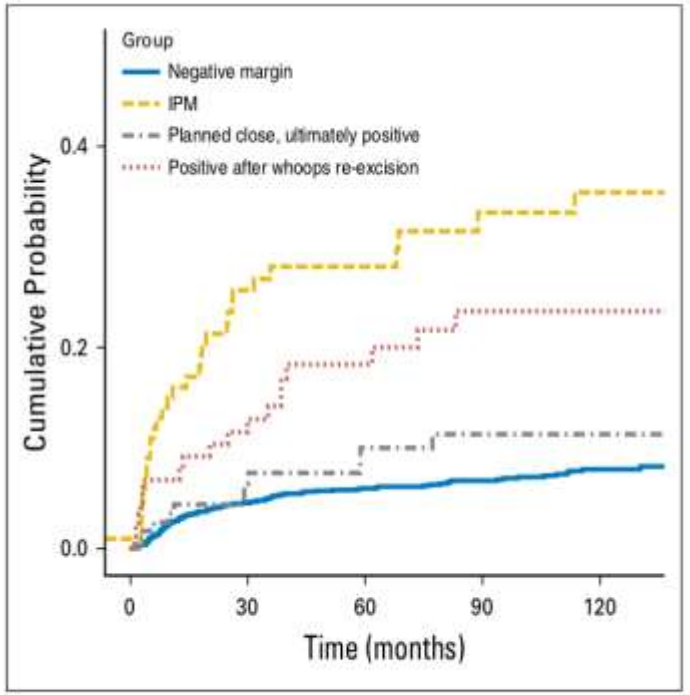


Fig 2. Cumulative probability of local recurrence by Toronto Margin Context Classification. IPM, inadvertent positive margin.

Strauss et al., J Surg Onc, 2010

Clinical Staging and Metastatic Work-up

- Pre-treatment staging categorizes disease based on ***tumor site, size, local invasion, regional lymph nodes, distant metastasis.***

Metastatic work-up includes :

- bone marrow aspiration/biopsy,
- bone scintigraphy,
- brain/lung/liver imaging (CT or MRI).

- Spinal tap for cerebrospinal fluid indicated for suspected parameningeal tumors.
- Functional imaging study (PET-CT) enhances pretreatment staging accuracy, especially for nodal status and distant metastasis.

Sentinel Lymph Node Biopsy

- Radio-tracer-based sentinel lymph node biopsy feasible and concordant with PET-CT in pediatric soft tissue sarcomas.

Strauss et al., J Surg Onc, 2010

AJCC 8th Edition Staging

T-staging

Sarcoma Type	T1	T2	T3	T4
Extremity and Retroperitoneum	<5 cm	5-10 cm	10.1-15 cm	>15 cm
Head and Neck	≤ 2 cm	>2 cm to ≤ 4 cm	>4 cm	Invasion (a versus b)
Arising in abdominal organs	Localized	Extension beyond organ	Invades another organ	Multifocal

N-staging | N0 vs N1

M-staging | M0 vs M1

Note: Staging also includes FNCLCC grade (1-3)

- Differentiation
- Mitotic Count
- Necrosis

Japanese Journal of Clinical Oncology, Volume 49, Issue 2, February 2019

Extremity

AJCC Anatomic Stage/Prognostic Groups

	T	N	M	G
Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
	T4	N0	M0	G1, GX
	T	**N**	**M**	**G**
Stage II	T1	N0	M0	G2, G3
Stage IIIA	T2	N0	M0	G2, G3
Stage IIIB	T3	N0	M0	G2, G3
	T4	N0	M0	G2, G3
Stage IV	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

Not routinely

Yes, probably

Need *to discuss with a radiation oncologist?*

Always

Japanese Journal of Clinical Oncology, Volume 49, Issue 2, February 2019

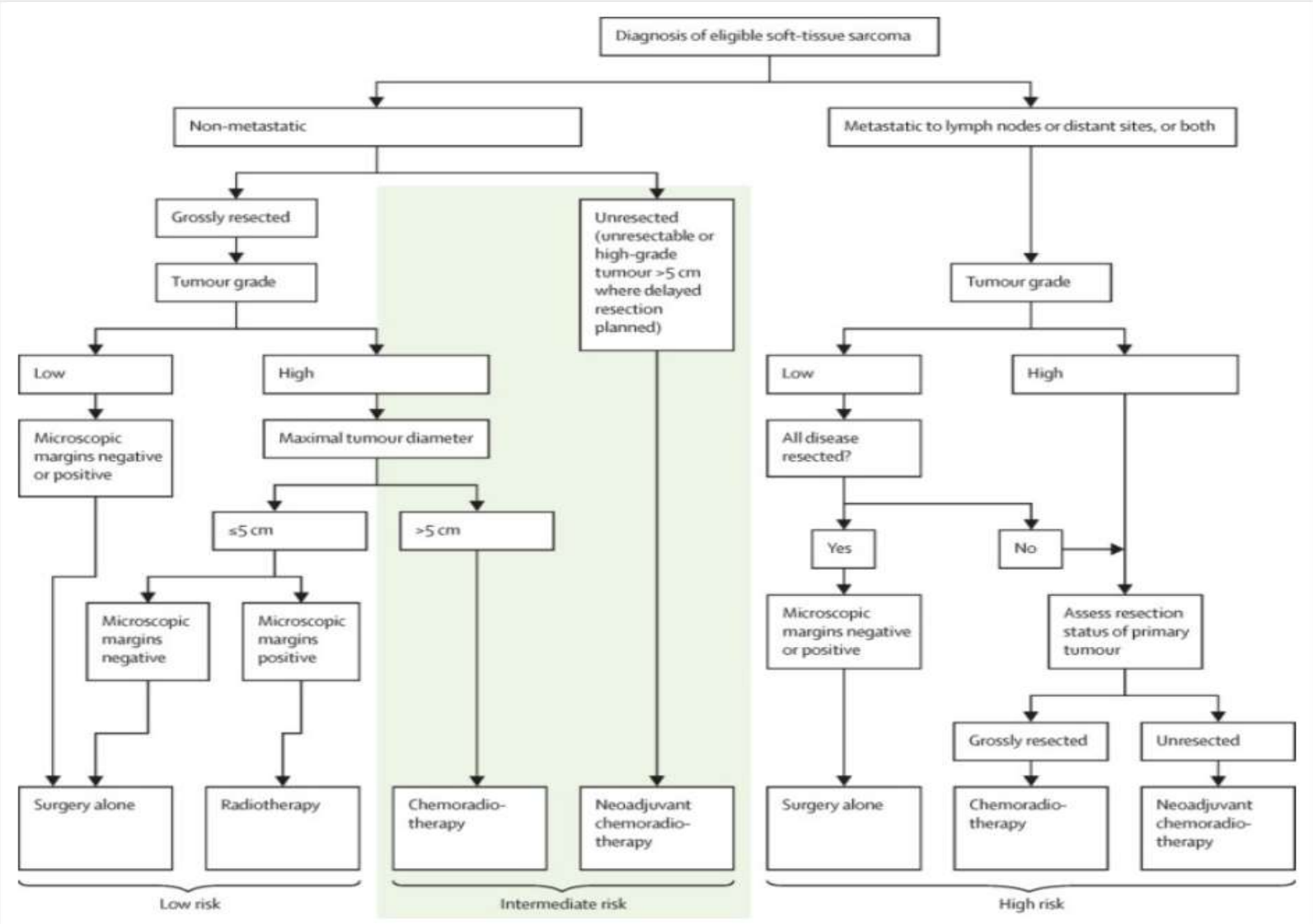
Prognostic features

- Size > 5 cm (< 5cm best indicator of benign “bump”)
- Report of increasing size (increasing size best indicator of “malignancy”)
- Pain
- Deep location

Symptom	Sensitivity (SE)	Specificity (SE)	Accuracy (SE)
Size > 5 cm	0.81 (0.02)	0.63 (0.03)	0.72 (0.02)
Pain	0.41 (0.03)	0.80 (0.03)	0.61 (0.02)
Increase size	0.63 (0.03)	0.82 (0.02)	0.73 (0.02)
Deep to fascia	0.94 (0.01)	0.31 (0.03)	0.60 (0.02)

Johnson et al., Am R Coll Surg Engl, 2001

Prognosis based on the Children's Oncology Group (COG) ARST0332 trial : Treatment Plan



Risk group and treatment assignment for the Children's Oncology Group ARST0332 trial. Reprinted from The Lancet Oncology, Volume 21 (Issue 1), Spunt SL, Million L, Chi YY, et al., A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study, Pages 145–161, Copyright © 2020, with permission from Elsevier.

Survival Results for the Children's Oncology Group ARST0332 Trial

	5-Year Event-Free Survival		5-Year Overall Survival	
Risk Group	**Events/Patients**	**Estimate, % (95% CI)**	**Events/Patients**	**Estimate, % (95% CI)**
Low	26/222	88.9 (84.0–93.8)	10/222	96.2 (93.2–99.2)
Intermediate	84/227	65.0 (58.2–71.8)	55/227	79.2 (73.4–85.0)
High	63/80	21.2 (11.4–31.1)	52/80	35.5 (23.6–47.4)
Surgical Margin				
R0	44/252	83.6 (78.3–89.0)	22/252	92.8 (89.1–96.5)
R1	29/81	66.2 (54.8–77.5)	17/81	79.7 (70.0–89.5)
R2	100/196	49.2 (41.4–57.0)	78/196	62.7 (55.2–70.3)

Prognosis based on the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) NRSTS 2005 study

Surgery alone group		
Synovial sarcoma	IRS group I, tumour size ≤5 cm	Initial resection only, no adjuvant treatment
Adult-type non-rhabdomyosarcoma soft tissue sarcomas	IRS group I, tumour size ≤5 cm, any tumour grade	
	IRS group I, tumour size >5 cm, tumour grade 1	
	IRS group II, any size tumour, tumour grade 1	
Adjuvant radiotherapy group		
Adult-type non-rhabdomyosarcoma soft tissue sarcomas	IRS group I, tumour size >5 cm, tumour grade 2	Radiotherapy 50·4 Gy
	IRS group II, tumour size ≤5 cm, tumour grade 2–3	Radiotherapy 54·0 Gy
	IRS group II, tumour size >5 cm, tumour grade 2	
Adjuvant chemotherapy group (with or without radiotherapy)		
Synovial sarcoma	IRS group I, tumour size >5 cm	I+D I+D I+D I+D
	IRS group II, tumour size ≤5 cm	I+D I+D I+D Radiotherapy 50·4 Gy
	IRS group II, tumour size >5 cm	I+D I+D I+D I I Radiotherapy 54·0 Gy I+D
	Axial site or resected N1	
Adult-type non-rhabdomyosarcoma soft tissue sarcomas	IRS group I–II, tumour size >5 cm, tumour grade 3 or resected N1	
Neoadjuvant chemotherapy group (with or without radiotherapy)		
Synovial sarcoma	IRS group III (unresected disease) or unresected N1	I+D I+D I+D S I I Radiotherapy 50·4–59·4 Gy I+D ± I+D
Adult-type non-rhabdomyosarcoma soft tissue sarcomas		

Treatment plan for patients with synovial sarcoma or adult-type non-rhabdomyosarcoma soft tissue sarcomas. Patients were divided into four treatment groups based on surgical stage, tumour size, nodal involvement, tumour grade (according to the Fédération Nationale des Centres de Lutte Contre le Cancer grading system for adult-type non-rhabdomyosarcoma soft tissue sarcomas), and tumour site (for synovial sarcoma). I+D = ifosfamide (3.0 g/m2 per day intravenously for 3 days) plus doxorubicin (37.5 mg/m2 per day intravenously for 2 days). I = ifosfamide (3.0 g/m2 per day intravenously for 2 days). IRS = Intergroup Rhabdomyosarcoma Study. N1 = nodal involvement. S = delayed surgery. Reprinted from The Lancet Child & Adolescent Health, Volume 5, Issue 8, Ferrari A, van Noesel MM, Brennan B, et al., Paediatric non-rhabdomyosarcoma soft tissue sarcomas: the prospective NRSTS 2005 study by the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG), Pages 546-558, Copyright 2021, with permission from Elsevier.

Survival Outcomes by Treatment Groups in the EpSSG NRSTS 2005 Study

Treatment Group	5-Year Event-Free Survival Rate (95% CI)	5-Year Overall Survival Rate (95% CI)	Local Recurrence Rate
Surgery alone	91.4% (87.0%–94.4%)	98.1% (95.0%–99.3%)	
Adjuvant radiation therapy alone	75.5% (46.9%–90.1%)	88.2% (60.6%–96.9%)	6.7% (1/15)
Adjuvant chemotherapy ± radiation therapy	65.6% (54.8%–74.5%)	75.8% (65.3%–83.5%)	10.8% (7/65)
Neoadjuvant chemotherapy ± radiation therapy	56.4% (49.3%–63.0%)	70.4% (63.3%–76.4%)	14.2% (16/113)

The Lancet Child & Adolescent Health, Volume 5, Issue 8, Ferrari A, van Noesel MM, Brennan B, et al., Paediatric non-rhabdomyosarcoma soft tissue sarcomas: the prospective NRSTS 2005 study by the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG), Pages 546-558, Copyright 2021,

Radiation Therapy

- The decision for radiation therapy hinges on the potential of surgery, with or without chemotherapy, to achieve local control while preserving critical organs, functions, and psychological well-being.
- **Factors Influencing Considerations:**

1. **Patient Variables:**
    - Age and sex of the patient play a role in treatment decisions.
2. **Tumor Variables:**
    - Histopathology, site, size, and grade of the tumor impact treatment choices.
3. **Use of Surgery and Margin Status:**
    - The utilization of surgery and the status of surgical margins influence the feasibility and necessity of radiation therapy.
4. **Expectations for Radiation-Induced Morbidities:**
    - Potential complications resulting from radiation, such as impaired bone/muscle development, organ damage, or later neoplasms, are considered.

Radiation Therapy Approaches:

- Radiation therapy can be administered preoperatively, postoperatively, or as definitive therapy if surgery is not possible.
- Radiation field size and dose are determined by patient and tumor characteristics, as well as the surgical procedure.

Improved Survival with Combined Approaches:

- Preoperative or postoperative radiation therapy has been linked to improved overall survival (OS) compared to surgery alone.
- OS benefits observed when radiation therapy is integrated into treatment plans.

Specialized Techniques:

- Brachytherapy and intraoperative radiation options are available in specific cases.
- Consideration for these techniques depends on the individual situation and tumor characteristics.

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Principles of RT Planning

Determine appropriate patient position

- Reproducible
- Patient comfort
- Supine, neutral positions preferred
  - Exceptions: tumors of back, prone

Rigid immobilization (custom cast)

- Immobilize foot for LE, hand for UE

Position patient keeping in mind:

- Spare strip of limb circumference (<20 Gy)
- Minimize dose to bone and joint
- Minimize subcutaneous hot spots

Preoperative RT

- **Advantages of Preoperative Radiation Therapy:**
- **Excellent Local Control Rates:** Preoperative radiation therapy has shown high rates of controlling the tumor locally.
- **Treating Smaller Tissue Volumes:** This approach targets smaller tumor volumes, avoiding the need to treat the postsurgical bed.
- **Lower Radiation Doses:** Relative hypoxia from surgical disruption isn't present, allowing lower radiation doses.
- **Reduced Fibrosis:** Preoperative radiation therapy might lead to less fibrosis due to smaller treatment volume and dose.

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Preoperative RT

Wound Complications and Fibrosis:

- **Wound Complications:** Preoperative radiation therapy has been linked to increased wound complications in adults, particularly in lower extremity tumors.
- **Degree of Complications:** The extent of these complications remains uncertain and might vary.

Comparison with Postoperative Approaches:

- **Fibrosis Reduction:** Preoperative radiation therapy could result in less fibrosis compared to postoperative treatments, possibly due to smaller treatment volume and dose.

Radiation Technique:

- **Impact on Normal Tissues:** Radiation technique affects the sparing of normal tissues.
- **Intensity-Modulated Radiation Therapy (IMRT):** IMRT, compared to 3-dimensional conformal radiation therapy, has the potential to reduce radiation dose to skin and epiphysis in extremity sarcomas.

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Postoperative radiation therapy

Postoperative Radiation Therapy:

- Administered after tumor removal.
- Indicated for inadequate surgical margins and larger, high-grade tumors.

Surgical Margins and High Grades:

- Vital for high-grade tumors with margins < 1 cm.

Combined Surgery and Radiation:

- Surgery plus radiation achieves strong local control rates.
- Extremity sarcomas: ~90% local control.
- Retroperitoneal sarcomas: ~70-75% local control.
- Overall: ~80% local control.

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Postoperative radiation therapy

Retroperitoneal Sarcomas:

- Unique due to bowel's sensitivity.
- Postoperative radiation riskier due to bowel injury risk.

Bowel Sensitivity and Risk:

- Bowel sensitivity raises risk with postoperative radiation.
- Postoperative adhesions and immobility heighten risk.

Preoperative Approach:

- Preoperative radiation shifts bowel away from field.
- Displacement may reduce bowel exposure.

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Treatment Volumes

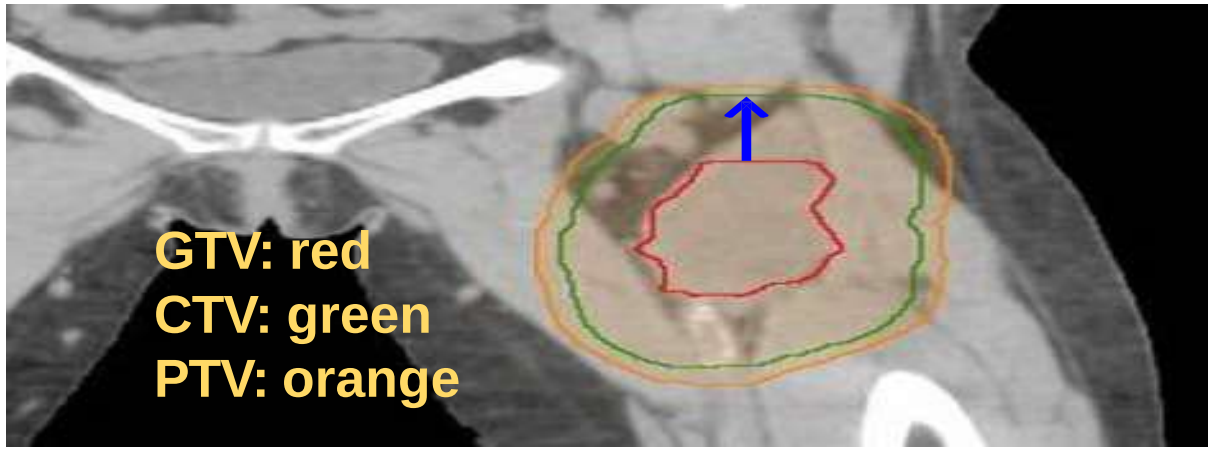
- Pre-op RT Volumes

GTV

- **Use MR T1 post-gadolinium images**

CTV

- **Expand GTV per guidelines**
- **Include T2 peri-tumoral edema if feasible**



- RT Volume for Pre-op RT Traditional Margins

CTV

- **GTV + 4 cm proximal/distal,**
- **1.5 cm radial**
- **Edit CTV at bone**

PTV

- **CTV + 5-10mm per institutional standard**

Haas, IJROBP 2012; 84:572

Reduced RT Volume for Pre-op RT

RTOG 0630*

- Prospective, multi-center Phase II trial
- 50 Gy pre-op RT
- Daily image guidance: kV, MV or CBCT

- **79 patients, 57 assessed for 2-yr late toxicity**
- **Median FU 3.6 yrs**
- **84% Grade 2/3**
- **75% IMRT, 25% 3D**

2 yr Local Control: 94% (all LF were within CTV)

≥ Grade 2 late toxicity: 10.5%

Compared to 37% for NCIC pre-op arm

Fibrosis 5.3%, Joint Stiffness 3.5%, Edema 5.3%

Authors' Conclusion:

"The significant reduction of late toxicities and absence of marginal-field recurrences suggest the target volumes used in RTOG-0630 are appropriate for pre-op IGRT for extremity STS"

This may be practice changing, confirmatory data are awaited

*Wang JCO 33:2231; 2015

RT Volumes, Doses & Margins for Post-op RT

- First Course-
- Contour GTV and operative bed
- CTV = op bed + 1.5 cm radially, 4 cm longitudinally
- Cone Down
- CTV = GTV + 1.5 cm radially and 2 cm longitudinally
- CTV to PTV expansion = 5-10 mm

Pre-operative RT (2 Gy)

Pre-operative volume 50 Gy

Post-operative RT (1.8 - 2 Gy)

First Course 45-50.4 Gy
Cone Down 16-20 Gy
Total Dose 60-66 Gy

Positive Margins (M+) >>> higher LR

For patients with positive margins:

Dose	5-yr Local Control	
Dose > 64 Gy	85%	
Dose ≤ 64 Gy	66%	p<.05

Negative Margins

- 60-66 Gy is acceptable

*Haas, IJROBP 84:572; 2012
DeLaney, (MGH) IJROBP, '07

Dose and volume : Recommendation for Pediatrics

Radiation volume and dose depend on the patient, tumor, and surgical variables noted above, as well as the following:

- Patient age and growth potential.
- Ability to avoid critical organs, epiphyseal plates, and lymphatics (but not the neurovascular bundles that are relatively radiation tolerant).
- Functional/cosmetic outcome.

Radiation Doses and Strategies:

- Preoperative radiation doses: 45 Gy to 50 Gy.
- Postoperative boost: 10 Gy to 20 Gy if positive resection margins.
- Planned brachytherapy for subtotal resection.
- Additional boost: 60 Gy for areas at risk of residual disease.

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Dose and volume

Boost Techniques:

- Simultaneously Integrated Boost (SIB): Higher dose area within larger lower dose volume.
- Small field of radiation after initial volume treated with 45 Gy to 50 Gy.

Postoperative Boost with Positive Margins:

- Efficacy data for postoperative boost to microscopically positive margin areas are limited.
- Postoperative radiation doses:
    - R0 resections: 55 Gy to 60 Gy.
    - R1 resections (microscopic positive margins): Up to 65 Gy.
    - Higher doses for unresectable gross residual disease, depending on treatment goals.

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Pre-op *vs* Post-op RT: Efficacy & Toxicities

- ***Efficacy : EQUIVALENT***
- Several non-randomized trials have shown similar local control rates
- Canadian RCT* 7 yr update showed:
- Similar LC rates (92%, 93%)
- Similar DFS and OS rates

- ***Toxicity : DIFFERENT***

PRE-OP

- **More acute wound complications (35% vs 17%*)**
- **Usually reversible**

POST-OP

- **More long-term edema, fibrosis, decreased ROM**
- **Usually irreversible**

Treatment approach should be individualized

Preference to Pre-op RT for most situations

– lower dose, smaller treatment volume less irreversible long-term toxicity

*O'Sullivan Lancet 2002;359:2235; JCO 2004;22(14S):9007

RT techniques : 3D vs IMRT

- *IMRT*
  - *Maintain or improve local control rates achieved with 3D*
  - *Reduce morbidities*

  – Edema, joint stiffness, fibrosis, wound complications, fracture, etc.

- **MSKCC retrospective series**
- **1996-2010c**

	3D RT	IMRT*	
N	154	165	
Median FU	90 mos	42 mos	
5-yr LR	15.1%	7.6%	p=0.05

Local Control Rates for Modern Series
3D Conventional and IMRT: Similarly Excellent

	5-yr LR	RT Modality
NCIC RCT, 2004 O' Sullivan	6%, 7%	3D (100%)
BWH/DFCI, 2013 Baldini	10%	3D (84%)
MSKCC, 2014 Folkert	15.1%	3D (100%)
MGH, 2010 Kim	11.5%	3D (88%)
PMH, 2013 O' Sullivan	11.8%	IMRT (flap sparing, 100%)
MSKCC, 2014 Folkert	7.6%	IMRT (100%)
RTOG 0630, 2015 Wang	11.4% (2-yr)	IMRT (75%)

- Multivariate analysis: IMRT independent favorable predictor for LC (HR for LR 0.46, p=0.02)
- Patients who received IMRT had more unfavorable features:

  – older, more high grade tumors, close/positive margins, and nerve manipulation

Folkert JCO 2014;32:3236

Late Toxicity Results

	IMRT			3D
Institution	**PMH***	**MSKCC****	**RTOG 0630&**	**Pre-op Arm NCIC#**
Treatment Modality	100% IMRT (sparing flap)	100% IMRT (79% post-op)	75% IMRT	100% 3D
≥ Grade 2: Subcutaneous Fibrosis	9.3%	NS	5.3%	31.5%
Joint Stiffness	5.6%	14.5%	3.5%	17.8%
Edema	11.1%	7.9%	5.3%	15.1%

- **Use of IMRT may be the main reason for reduced toxicity**

O'Sullivan Cancer 2013, 119:1878; **Folkert JCO 2014, 32(29):3236
& Wang, JCO 2015, 33(20):2231; #O'Sullivan Lancet 2002, 359:2235

STS of Extremity and Trunk

Low Grade :

- Generally surgery alone
  - Wide resection, Neg margins >>> LR <15%
  - Survival rate typically > 90%
- Indications for RT
  - Positive margins
  - LR s/p prior surgery alone
  - Location not amenable to salvage surgery

Treatment for High Grade (G2/3) STS of Extremity and Trunk

- **Limb-Sparing Surgery (LSS) and RT**

Rosenberg Ann Surg 1982
Yang, JCO 1998
Harrison, IJROBP 1993

High Grade STS Extremity/Trunk

- 3 classic randomized trials established the role for LSS + RT for high grade (G2/3) STS

NCI (Rosenberg Ann Surg 1982)

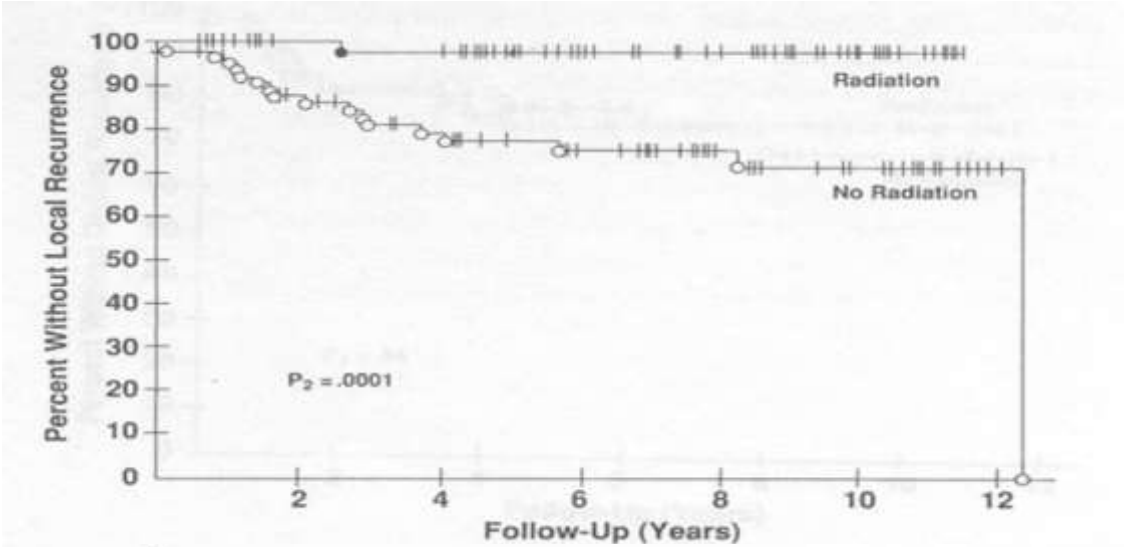
- **Amputation vs LSS + RT**
- **LR with LSS + RT: 15%; Equivalent OS**

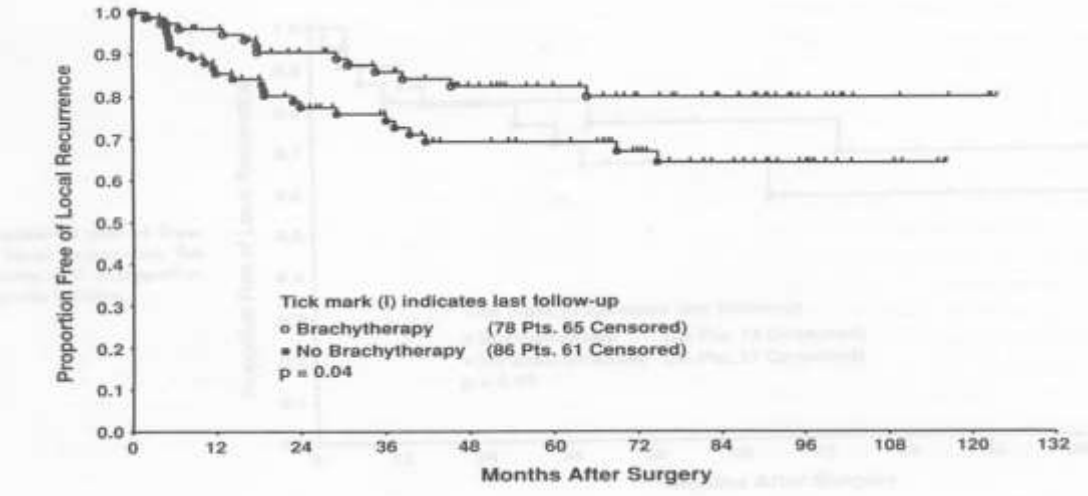
NCI (Yang, JCO 1998)

- **LSS alone vs LSS + RT**
- **Improved local control with RT; Equivalent OS**

MSKCC (Harrison, IJROBP 1993)

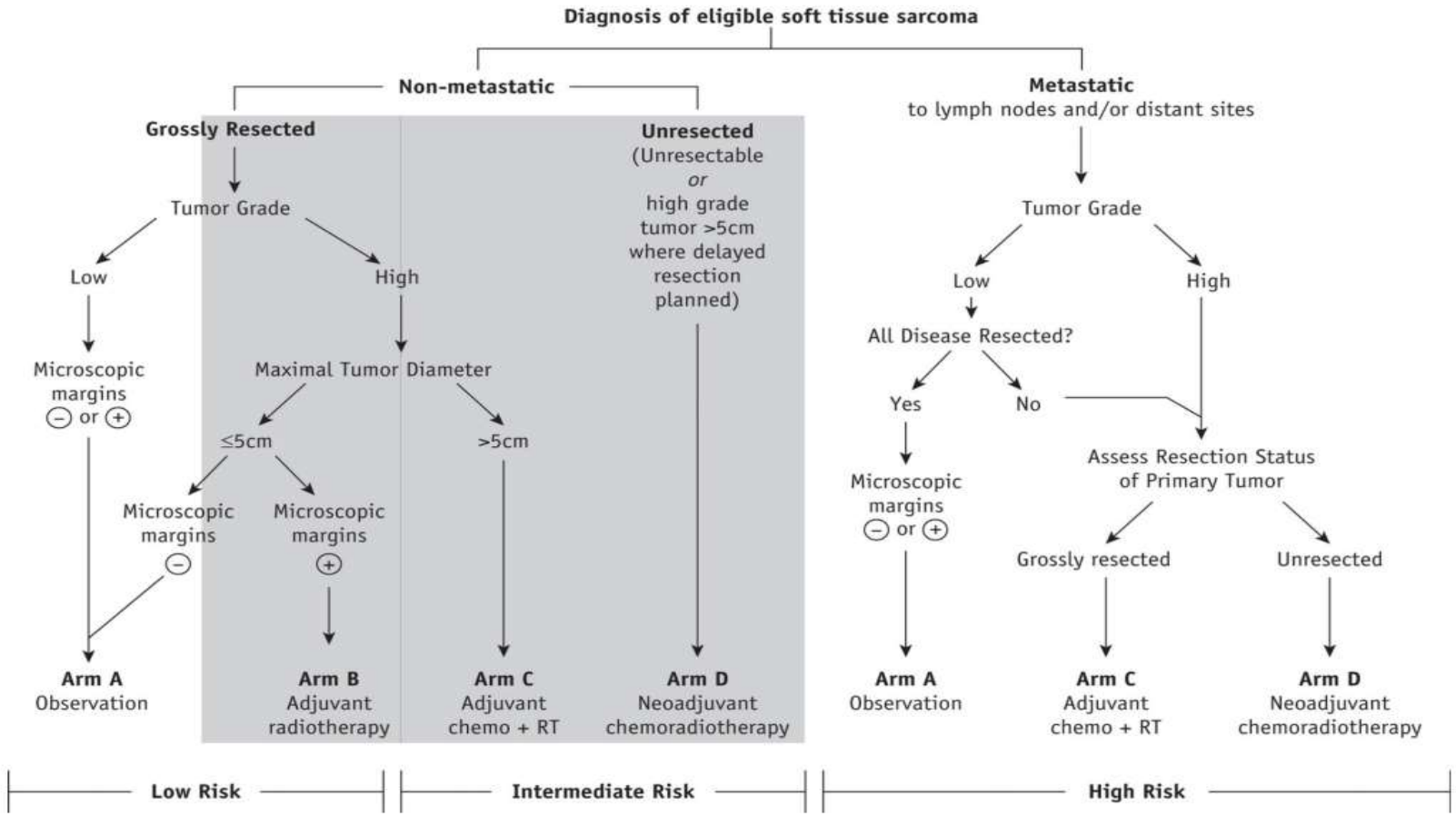
- **LSS alone vs LSS + BRT (brachytherapy)**
- **Improved local control with BRT; Equivalent OS**





ARST0332 Trial

•**NRSTS Treatment Analysis:**
•The Children's Oncology Group studied local recurrence (LR) in NRSTS patients treated on ARST0332.
•**Treatment Arms:**
•Patients under <30 years with high-grade NRSTS were divided into treatment arms based on tumor characteristics and treatment approach.



Spunt SL, Million L, Chi YY, Anderson J, Tian J, Hibbitts E, Coffin C, McCarville MB, Randall RL, Parham DM, Black JO, Kao SC, Hayes-Jordan A, Wolden S, Laurie F, Speights R, Kawashima E, Skapek SX, Meyer W, Pappo AS, Hawkins DS. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. Lancet Oncol. 2020 Jan;21(1):145-161. doi: 10.1016/S1470-2045(19)30672-2. Epub 2019 Nov 27. PMID: 31786124; PMCID: PMC6946838.

Cumulative incidence for local recurrence & Event-free survival by treatment arm and Extension of resection

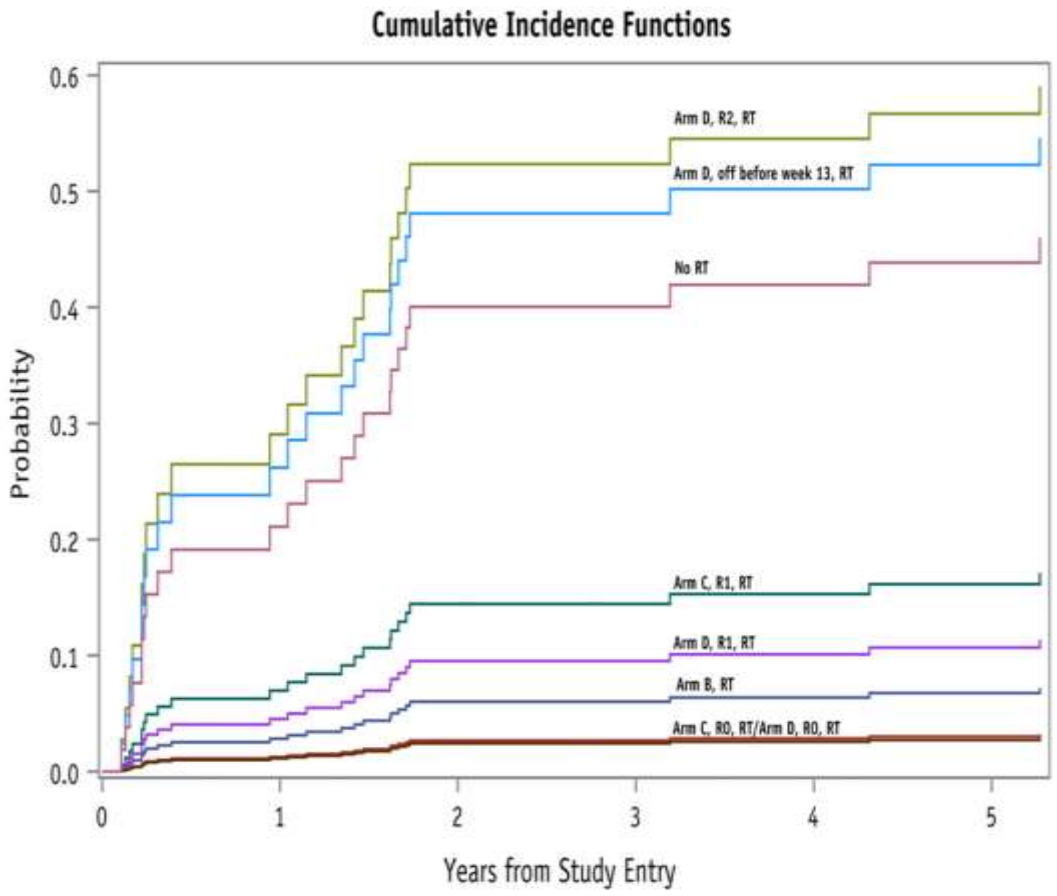
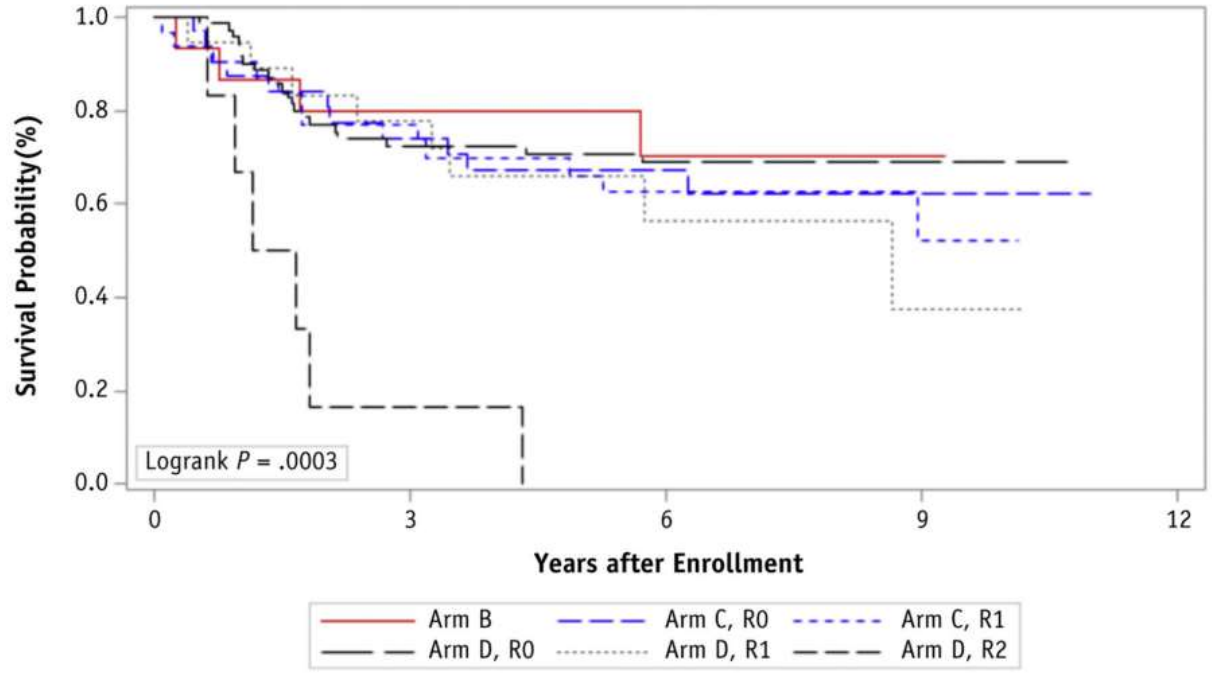


Fig 2.
Cumulative incidence for local recurrence by treatment arm, extent of resection, and radiation therapy (45 Gy, 55.8 Gy, 64 Gy, no radiation therapy).



Number at Risk

Arm B	15	11	7	2	0
Arm C, R0	33	22	15	2	0
Arm C, R1	32	22	15	5	0
Arm D, R0	71	47	35	8	0
Arm D, R1	18	13	6	2	0
Arm D, R2	6	1	0		

Fig 3.
Event-free survival by treatment arm (B, C, and D) and extent of resection (R0/R1/R2 or unresected).

Spunt SL, Million L, Chi YY, Anderson J, Tian J, Hibbitts E, Coffin C, McCarville MB, Randall RL, Parham DM, Black JO, Kao SC, Hayes-Jordan A, Wolden S, Laurie F, Speights R, Kawashima E, Skapek SX, Meyer W, Pappo AS, Hawkins DS. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. Lancet Oncol. 2020 Jan;21(1):145-161. doi: 10.1016/S1470-2045(19)30672-2. Epub 2019 Nov 27. PMID: 31786124; PMCID: PMC6946838.

Conclusion

Local Recurrence Analysis:

- Out of 193 eligible patients, 24 experienced local recurrences.
- Local recurrence rates in different treatment arms:
  - Arm B: 1 of 15 (6.7%)
  - Arm C: 7 of 65 (10.8%)
  - Arm D: 16 of 113 (14.2%)
- Median time to local recurrence: 1.1 years (range: 0.11–5.27 years).

Delayed Surgery Outcomes:

- Among 95 patients eligible for delayed surgery post neoadjuvant therapy, 89 (93.7%) achieved R0/R1 margins.

Overall Local Control after Radiation Therapy:

- R0 margins: 106 of 109 cases (97%)
- R1 margins: 51 of 60 cases (85%)
- R2/unresectable cases: 2 of 6 cases (33%)

Conclusions:

- Risk-based treatment for young high-grade NRSTS patients on ARST0332 yielded high local control rates.
- R0 resection achieved particularly high local control (97%).
- Despite lower-than-standard radiation doses, very high local control was achieved.

Spunt SL, Million L, Chi YY, Anderson J, Tian J, Hibbitts E, Coffin C, McCarville MB, Randall RL, Parham DM, Black JO, Kao SC, Hayes-Jordan A, Wolden S, Laurie F, Speights R, Kawashima E, Skapek SX, Meyer W, Pappo AS, Hawkins DS. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. Lancet Oncol. 2020 Jan;21(1):145-161. doi: 10.1016/S1470-2045(19)30672-2. Epub 2019 Nov 27. PMID: 31786124; PMCID: PMC6946838.

Pathologic response in children and adults with large unresected intermediate- or high-grade soft tissue sarcoma receiving preoperative chemoradiation with or without pazopanib (ARST1321; PAZNTIS): a multicentre, randomised, open-label, phase 2 trial

Aaron R. Weiss[1],
Maine Medical Center, Portland, ME, USA

Yen-Lin Chen[1],
Massachusetts General Hospital, Boston, MA, USA

Weiss AR, Chen YL, Scharschmidt TJ, Chi YY, Tian J, Black JO, Davis JL, Fanburg-Smith JC, Zambrano E, Anderson J, Arens R, Binitie O, Choy E, Davis JW, Hayes-Jordan A, Kao SC, Kayton ML, Kessel S, Lim R, Meyer WH, Million L, Okuno SH, Ostrenga A, Parisi MT, Pryma DA, Randall RL, Rosen MA, Schlapkohl M, Shulkin BL, Smith EA, Sorger JI, Terezakis S, Hawkins DS, Spunt SL, Wang D. Pathological response in children and adults with large unresected intermediate-grade or high-grade soft tissue sarcoma receiving preoperative chemoradiotherapy with or without pazopanib (ARST1321): a multicentre, randomised, open-label, phase 2 trial. Lancet Oncol. 2020 Aug;21(8):1110-1122. doi: 10.1016/S1470-2045(20)30325-9. Epub 2020 Jul 20. PMID: 32702309; PMCID: PMC7745646.

Study Design and Patient enrollment

Key Study Details:

- The COG and NRG Oncology cancer consortia conducted a randomized trial.
- The trial investigated pazopanib in combination with neoadjuvant chemotherapy (doxorubicin and ifosfamide) and preoperative radiation therapy.
- Patients of pediatric and adult age with NRSTS were included.
- Eligibility criteria: Tumors larger than 5 cm, intermediate- or high-grade disease.

Trial Outcome:

- The trial aimed to assess the pathological tumor response after adjuvant therapy.
- The study was terminated early due to the crossing of the pathological response boundary in the interim analysis.

Patient Enrollment and Data:

- A total of 81 patients were enrolled in the study.
- Only 42 patients (52%) were available for response data.
- 17 patients from each group discontinued therapy due to reasons like disease progression, unacceptable toxicity, or patient/physician choice.

Weiss AR, Chen YL, Scharschmidt TJ, Chi YY, Tian J, Black JO, Davis JL, Fanburg-Smith JC, Zambrano E, Anderson J, Arens R, Binitie O, Choy E, Davis JW, Hayes-Jordan A, Kao SC, Kayton ML, Kessel S, Lim R, Meyer WH, Million L, Okuno SH, Ostrenga A, Parisi MT, Pryma DA, Randall RL, Rosen MA, Schlapkohl M, Shulkin BL, Smith EA, Sorger JI, Terezakis S, Hawkins DS, Spunt SL, Wang D. Pathological response in children and adults with large unresected intermediate-grade or high-grade soft tissue sarcoma receiving preoperative chemoradiotherapy with or without pazopanib (ARST1321): a multicentre, randomised, open-label, phase 2 trial. Lancet Oncol. 2020 Aug;21(8):1110-1122. doi: 10.1016/S1470-2045(20)30325-9. Epub 2020 Jul 20. PMID: 32702309; PMCID: PMC7745646.

Result and Conclusion :

Necrosis and Treatment Response:

- Control Group: 4 out of 18 patients (22%) had >90% necrosis at resection.
- Pazopanib Group: 14 out of 24 patients (58%) showed >90% necrosis at resection.
- This significant difference in response led to the early stopping of the study.

Toxicity and Wound Complications:

- Greater toxicity observed in the pazopanib group.
- Mainly due to increased myelosuppression (bone marrow suppression).
- Higher incidence of wound complications in the pazopanib group.

Follow-up and Outcomes:

- Longer follow-up required to assess differences in Overall Survival (OS) and Event-Free Survival (EFS).
- More time needed to determine the impact of treatment on long-term outcomes.

Weiss AR, Chen YL, Scharschmidt TJ, Chi YY, Tian J, Black JO, Davis JL, Fanburg-Smith JC, Zambrano E, Anderson J, Arens R, Binitie O, Choy E, Davis JW, Hayes-Jordan A, Kao SC, Kayton ML, Kessel S, Lim R, Meyer WH, Million L, Okuno SH, Ostrenga A, Parisi MT, Pryma DA, Randall RL, Rosen MA, Schlapkohl M, Shulkin BL, Smith EA, Sorger JI, Terezakis S, Hawkins DS, Spunt SL, Wang D. Pathological response in children and adults with large unresected intermediate-grade or high-grade soft tissue sarcoma receiving preoperative chemoradiotherapy with or without pazopanib (ARST1321): a multicentre, randomised, open-label, phase 2 trial. Lancet Oncol. 2020 Aug;21(8):1110-1122. doi: 10.1016/S1470-2045(20)30325-9. Epub 2020 Jul 20. PMID: 32702309; PMCID: PMC7745646.

Retroperitoneal Liposarcoma

- Is there a role for Radiation?

- *Non-randomized trials have assessed post-op RT, pre-op RT, +/- IORT or BRT*
- *Some suggest a benefit with RT, but none are definitive*
- *… There is no clear role for RT*

NCDB Case-Control Analysis

- **9,068 pts National Cancer Data Base**
- **Primary RPS: pre-op RT, post-op RT, no RT**
- **Case-control propensity score-matched analysis**

*Nussbaum, Lancet Oncol 2016; 17(7):966

Retroperitoneal Liposarcoma

- Is there a role for Radiation?

- *Non-randomized trials have assessed post-op RT, pre-op RT, +/- IORT or BRT*
- *Some suggest a benefit with RT, but none are definitive*
- *… There is no clear role for RT*

NCDB Case-Control Analysis

- **9,068 pts National Cancer Data Base**
- **Primary RPS: pre-op RT, post-op RT, no RT**
- **Case-control propensity score-matched analysis**

- **Both pre-op RT and post-op RT associated with significant survival benefits**
  - **Pre-op RT: HR 0.70 (p<0.0001)**
  - **Post-op RT: HR 0.78 (p<0.0001)**

*Nussbaum, Lancet Oncol 2016; 17(7):966

Since Many Centers Give Pre-op RT, How Should it be Delivered for RPS?

- *There were no standard guidelines*
- *An expert panel was convened to develop guidelines*

Perform 4D CT for tumors above iliac brim Expand GTV-4D symmetrically by 1.5 cm

Edit CTV:

- **Bone, RP Compartment, Kidney, Liver: 0 mm**
- **Bowel and Air Cavity: 5 mm**
- **Skin Surface: 3-5 mm**
- **If tumor extends through inguinal canal, add 3 cm distally (as per extremity STS)**

Dose

50 – 50.4 Gy

1.8 - 2 Gy fractions

Baldini IJROBP 2015; 92:603

Liposarcoma, well-differentiated, not otherwise specified (NOS)

- Liposarcoma is rare in the pediatric population and accounts for 3% of soft tissue sarcoma in patients younger than 20 years.
- In a review of 182 pediatric patients with adult-type sarcomas, only 14 had a diagnosis of liposarcoma.
- A literature review of 275 cases of pediatric liposarcoma showed that :
    - About 70% of patients with myxoid and well-differentiated liposarcoma were treated with surgery only. The overall clinical outcomes for these groups of patients were excellent, with no evidence of disease in 114 of 127 patients.
    - In contrast, more than 50% of patients with pleomorphic liposarcoma received radiation therapy and chemotherapy in addition to surgery, and their clinical outcome was suboptimal, with no evidence of disease in only 5 of 10 patients.

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Conclusion : RPS

Standard of Care for RPS:

- Best attempt at R0 resection

<u>Role of RT: unproven</u>

- Best assessed on trial (EORTC)

<u>If RT Given off Trial >> Give Pre-op</u>

- Follow expert consensus guidelines
  - 50 Gy; CTV: GTV-4D + 1.5cm margins
- Boost to high risk margins best on protocol
- Post-op RT is discouraged

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Rhabdomyosarcoma (RMS)

- RMS is the **most common pediatric soft tissue sarcoma**
  - 40% of all pediatric soft tissue sarcomas
- Slight male predominance
- Peak age is between 2 – 5 years of age

Genetics

- **Embryonal**
  - Loss of heterozygosity of **11p15.5**
- **Alveolar**
  - Translocations of:
    - **t(2:13)**
      - Chromosome 2: PAX3
      - Chromosome 13: FOX01 (Forkhead box protein O1, also called FKHR or FORKHEAD)
    - **t(1:13)**
      - Chromosome 1: PAX7
      - Chromosome 13: FOX01 (Forkhead box protein O1, also called FKHR or FORKHEAD)
  - These translocations result in **PAX-FOXO1 Fusion Genes** = **Forkhead fusion patients have a worse prognosis**

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Clinical Presentation and Workup

- RMS usually presents as an **asymptomatic mass**, but this is site dependent

- Universal:
  - H&P with CBC, CMP, LFTs, UA
  - **CT/MRI of the primary site**
  - **PET CT** (or CT CAP and bone scan)

  - **Biopsy the primary site**
  - **Bone marrow biopsy**

- Site Dependent
  - Lumbar puncture if parameningeal tumor (if CSF positive, obtain MR spine)
  - Sentinel lymph node biopsy for extremity cases
  - Ipsilateral retroperitoneal lymph node dissection for paratesticular sites in boys age greater than 10

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Risk Stratification

In RMS, there is pre-operative staging and post-operative grouping

- Combining these will lead to a risk group (low, intermediate, high) which will determine treatment

Staging

TABLE 56.5: IRSG Staging System

Stage	Sites	Size	N	M	3-yr Failure-Free Survival[19]
I: Favorable site	Orbit Head and Neck (non-PM) GU (non-bladder/prostate) Biliary tract	Any size	Any N	M0	86%
II: Unfavorable site, N0 and ≤5 cm	Bladder/Prostate Extremity Parameningeal Other (including: RP, perineal, perianal, intrathoracic, GI) Liver (nonbiliary)	≤5 cm	N0 or Nx	M0	80%
III: Unfavorable site, >5 cm or node-positive	Same as Stage II	≤5 cm	N1	M0	68%
		>5 cm	Any N	M0	
IV: Metastatic	All	Any size	Any N	M1	25%

T1, Confined to anatomic site of origin; T2, Extension and/or fixation to surrounding tissue; a, ≤5 cm in diameter; b, >5 cm in diameter; N0, Not clinically involved; N1, Clinically involved; Nx, Clinical status unknown; M0, No distant metastases; M1, Distant metastases.

Grouping

TABLE 56.6: IRSG Grouping Classification

Group I	Localized disease, completely resected A: Confined to muscle or organ of origin B: Infiltration outside the muscle or organ of origin
Group II	*Gross total resection with:* A: Microscopic residual disease B: Regional LN spread, completely resected C: Regional LN resected with microscopic residual
Group III	*Incomplete resection with gross residual disease* A: After biopsy only B: After major resection (>50%)
Group IV	Distant metastasis at onset

Crist WM, Garnsey L, Beltangady MS, et al.

COG Risk Stratification

- Stage 4, Group 4 is High Risk
  - Unless you are fusion negative and less than 10 years old
- Alveolar is Intermediate Risk
- For Embryonal, to fall into low risk….you must fusion negative AND:
  - All BONG
  - Not BONG, Not Gross Residual

Table 60.7: Risk Stratification Based on Pre-Op Staging + Post-Op Grouping

Risk Group	Involved Groups
Low (~35%)	Favorable histology (embryonal) *and* PAX/FOX01 fusion negative *and* – Favorable site (stage I): groups I–III – Unfavorable site (stages II–III): groups I–II
Intermediate (~50%)	– Favorable histology (embryonal), PAX/FOX01 fusion negative, unfavorable site (stages II–III): groups III – Favorable histology (embryonal), PAX/FOX01 fusion positive, any site (stages I–III): groups I to III – Unfavorable histology (alveolar), PAX/FOX01 fusion positive or negative, any site (stages I–III): groups I–III – Stage IV, group IV, PAX/FOX01 fusion negative, <10 years old
High (~15%)	– Stage IV, group IV, PAX/FOX01 fusion negative, ≥10 years old – Stage IV, group IV, PAX/FOX01 fusion positive, any age

Source: Adapted from American Cancer Society. Rhabdomyosarcoma. 2020. https://www.cancer.org/cancer/rhabdomyosarcoma.html

Crist WM, Garnsey L, Beltangady MS, et al.:

Radiation - Doses

Clinical Group	Dose
I, Embryonal or FOX01 fusion negative	0 Gy
I, FOX01 fusion positive	36 Gy
II	36 Gy
III, < 5 cm	50.4 Gy
III, > 5 cm	59.4 Gy

Notes:

***Omission of radiation is only allowed for node negative patients**

***A complete response (CR) will receive 36 Gy**

***A cone-down is allowed if the dose exceeds 36 Gy; pre-chemotherapy volume will receive 36 Gy, post-chemotherapy volume will receive the higher dose**

***A CR in the orbit will receive 45 Gy; otherwise 50.4 Gy**

Radiation – Doses post DPE

	Total Dose - Gy		post DPE - Dose Gy		
Clinical Group	if no CR at Week 9**	if CR at Week 9**	if GTR post DPE with negative margin	if GTR post DPE with microscopic margin	if post DPE, gross residual disease
I, FOXO1 +	36	36	N/A	N/A	N/A
II	36	36	N/A	N/A	N/A
III, ≤5cm*	50.4	36	36	41.4	50.4
III, >5cm*	59.4	36	36	41.4	59.4

CR response doses

A positive margin will require slight dose escalation

Gross disease doses

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Radiation - Target Volumes

- Radiation Target Volumes
  - GTV1
    - **The volume is defined as disease <u>prior</u> to any surgical debulking or chemotherapy***
      - Post-operative radiation: tumor bed and any bone or soft tissue that was involved with the tumor prior to surgical resection
      - Definitive Radiation: tumor prior to any chemotherapy
  - CTV1
    - GTV + 1 cm
    - When lymph nodes are clinically or pathologically involved with tumor, the entire lymph node drainage chain should be included in the CTV.
  - PTV1
    - Minimum of 0.3 cm

- Radiation Target Volumes 2: these volumes are utilized when the prescription dose is higher than 36 Gy
  - GTV2
    - **The volume is defined as disease <u>after</u> chemotherapy (this is the cone-down)**
  - CTV2
    - GTV + 1 cm
  - PTV2
    - Minimum of 0.3 cm depending on immobilization

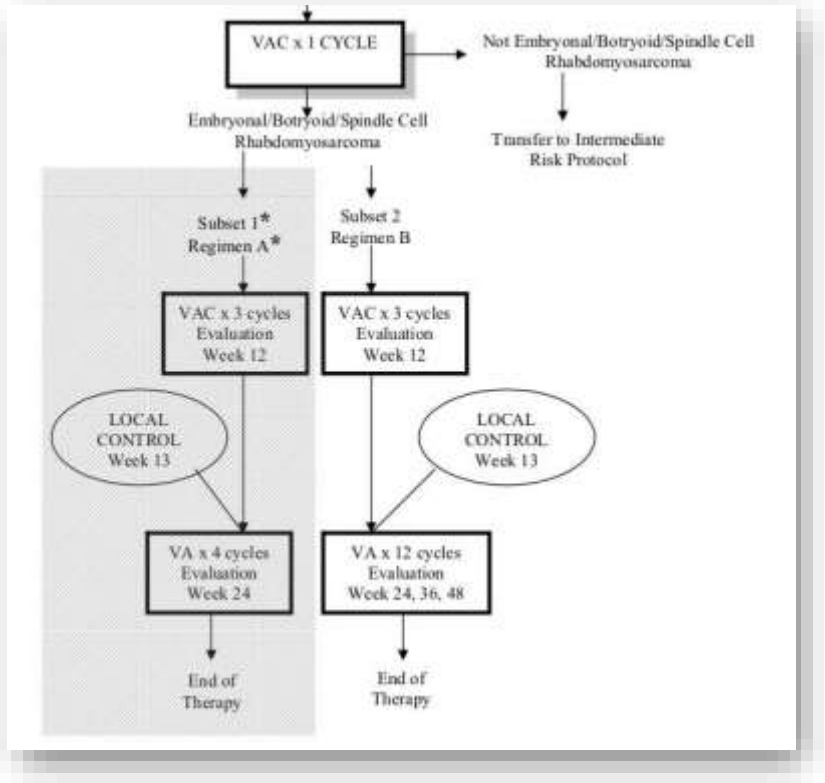
PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Radiation Timing

- Radiation Timing
  - Low and Intermediate Risk = Week 13
  - High Risk = Week 20
  - Patients with cord compression, visual loss, intracranial extension, cranial neuropathies = Day 0 per ARST 0431
    - However, in many cases emergent chemotherapy will relieve symptoms as quickly as radiation and delaying radiation should be assessed on a case by case basis

ARST 0331 – Low Risk Protocol

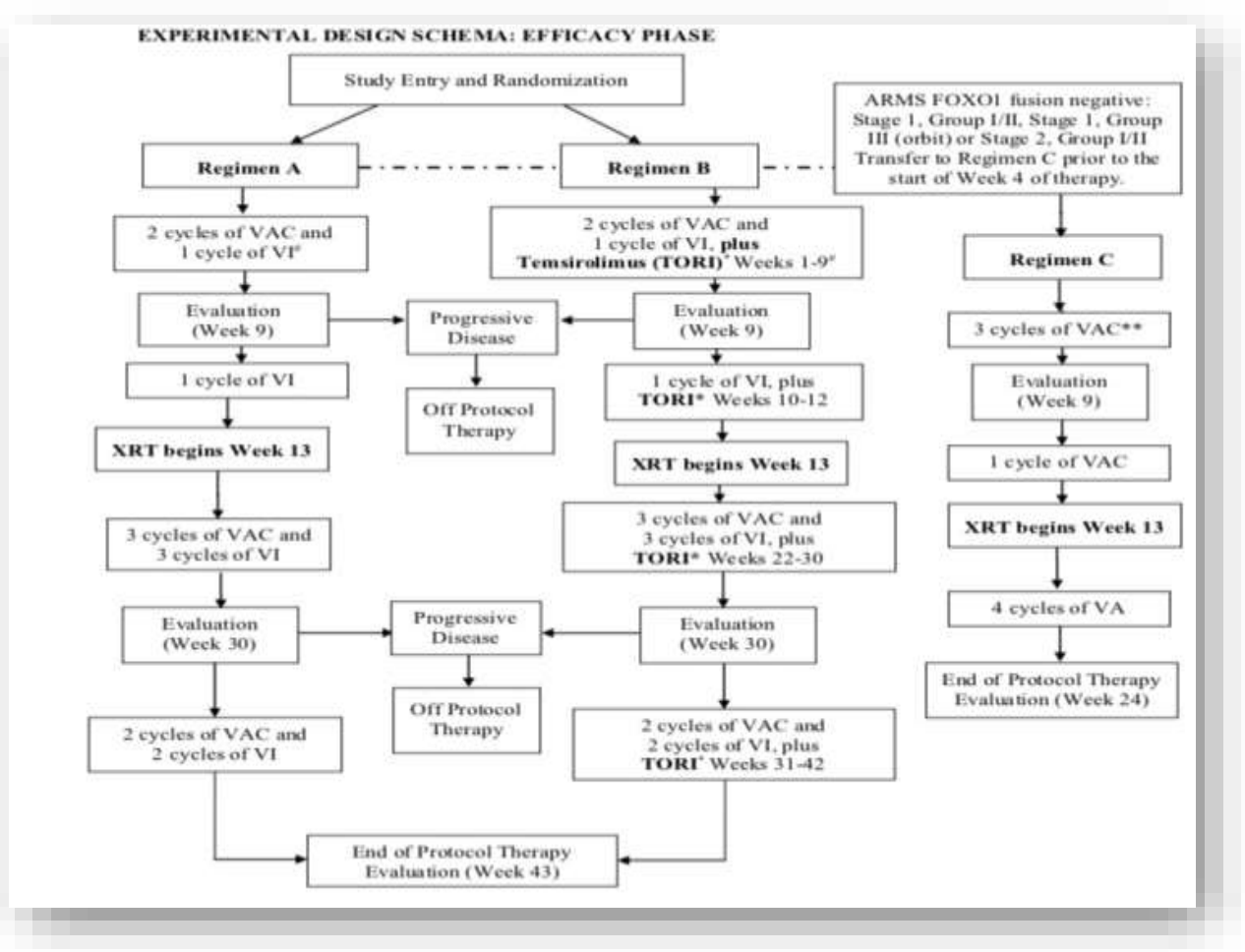
1. Biopsy/Surgery
2. VAC chemotherapy
3. **XRT** starts at week **13**
4. VA chemotherapy



Bradley, Julie A.; Kayton, Mark; Breneman, John; Chi, Yueh-Yun; Donaldson, Sarah; Hawkins, Douglas S.; Rodeberg, David; Walterhouse, David; Wolden, Suzanne (2018). Treatment Approach and Outcomes in Infants With Localized Rhabdomyosarcoma (RMS): Analysis of Children's Oncology Group (COG) Protocols ARST 0331 and ARST0531.

ARST 1431 – Intermediate Risk Protocol

1. Biopsy/Surgery
2. VAC chemotherapy (this study also this study investigates use of temsirolimus (an mTOR inhibitor))
3. **XRT** starts at week **13** (allowed for DPE)
4. Consolidation chemotherapy

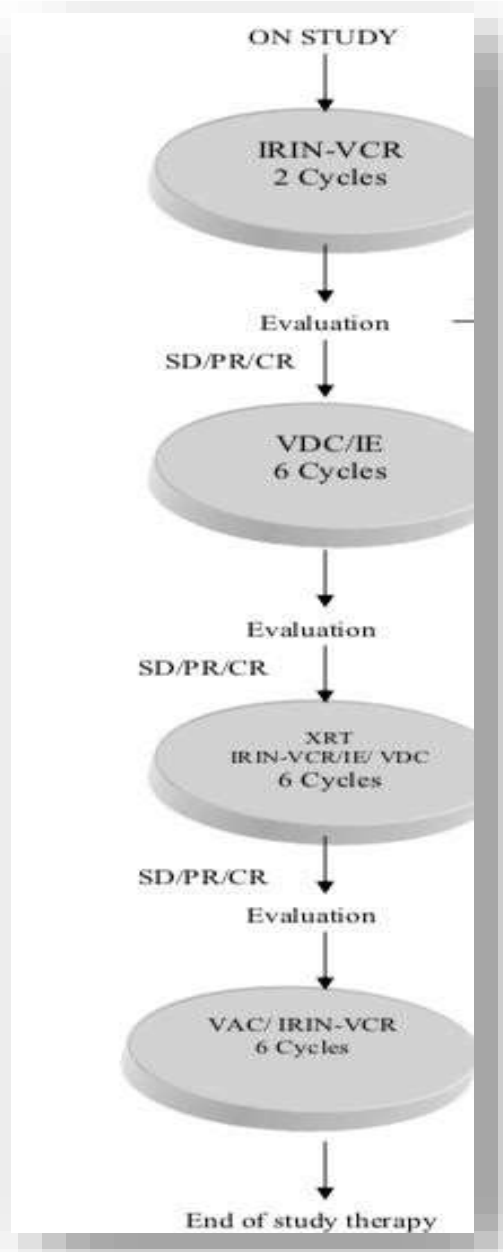


Bradley, Julie A.; Kayton, Mark; Breneman, John; Chi, Yueh-Yun; Donaldson, Sarah; Hawkins, Douglas S.; Rodeberg, David; Walterhouse, David; Wolden, Suzanne (2018). Treatment Approach and Outcomes in Infants With Localized Rhabdomyosarcoma (RMS): Analysis of Children's Oncology Group (COG) Protocols ARST 0331 and ARST0531.

ARST 0431– High Risk Protocol

- **Local control is achieved by radiation;** resection is rarely indicated

- Week 1-6
  - Vincristine/irinotecan
- Week 7 to 19
  - Vincristine/doxorubicin/cyclophosphamide alternating with etoposide/ifosfamide
- **Week 20** - 25
  - **Radiation** with vincristine/irinotecan
- Week 26 – 34
  - Vincristine/doxorubicin/cyclophosphamide alternating with etoposide/ifosfamide
- Week 38 - 46
  - Vincristine/dactinomycin/cyclophosphamide
- Week 47 – 62
  - vincristine/irinotecan



Bradley, Julie A.; Kayton, Mark; Breneman, John; Chi, Yueh-Yun; Donaldson, Sarah; Hawkins, Douglas S.; Rodeberg, David; Walterhouse, David; Wolden, Suzanne (2018). Treatment Approach and Outcomes in Infants With Localized Rhabdomyosarcoma (RMS): Analysis of Children's Oncology Group (COG) Protocols ARST 0331 and ARST0531.

Prognosis - Event Free Survival (EFS)

- Low Risk EFS = 90%

- Intermediate Risk EFS = 70%

- High Risk EFS = Less than 30%

– Remember, these are the metastatic patients

Bradley, Julie A.; Kayton, Mark; Breneman, John; Chi, Yueh-Yun; Donaldson, Sarah; Hawkins, Douglas S.; Rodeberg, David; Walterhouse, David; Wolden, Suzanne (2018). Treatment Approach and Outcomes in Infants With Localized Rhabdomyosarcoma (RMS): Analysis of Children's Oncology Group (COG) Protocols ARST 0331 and ARST0531.

Mesenchymal Chondrosarcoma

- A single-institution retrospective review identified 43 cases of mesenchymal chondrosarcoma from 1979 to 2010.
- Thirty patients with localized disease were evaluated. The mean age at diagnosis was 33 years (range, 11–65 years).
  - The 5-year OS rate was 51%, and the 10-year OS rate was 37%.
  - Younger age (<30 years) and male sex were associated with poorer OS and disease-free survival (DFS).
  - **Patients who did not receive adjuvant radiation therapy were more likely to have a local recurrence.**

PDQ Pediatric Treatment Editorial Board. Childhood Soft Tissue Sarcoma Treatment (PDQ®): Health Professional Version. 2023 Aug 18.

Desmoid Tumor

- Rare cancers, 3% of soft tissue tumors
- Most are sporadic,

but 5-15% of desmoids due to FAP or Gardner Sx

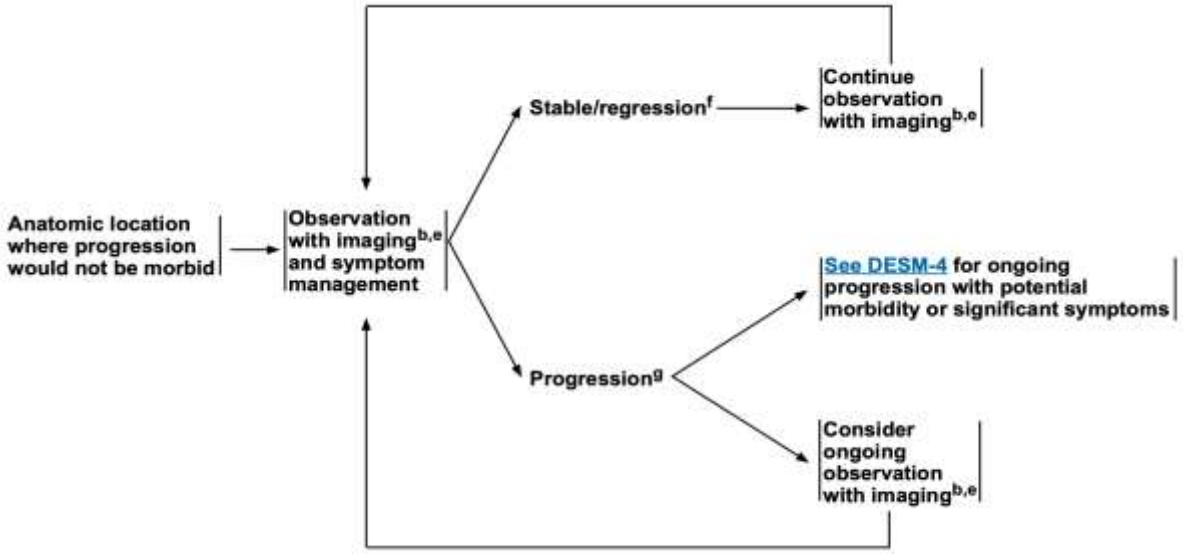
- Therapy

TABLE 1. Desmoid Tumor Staging System

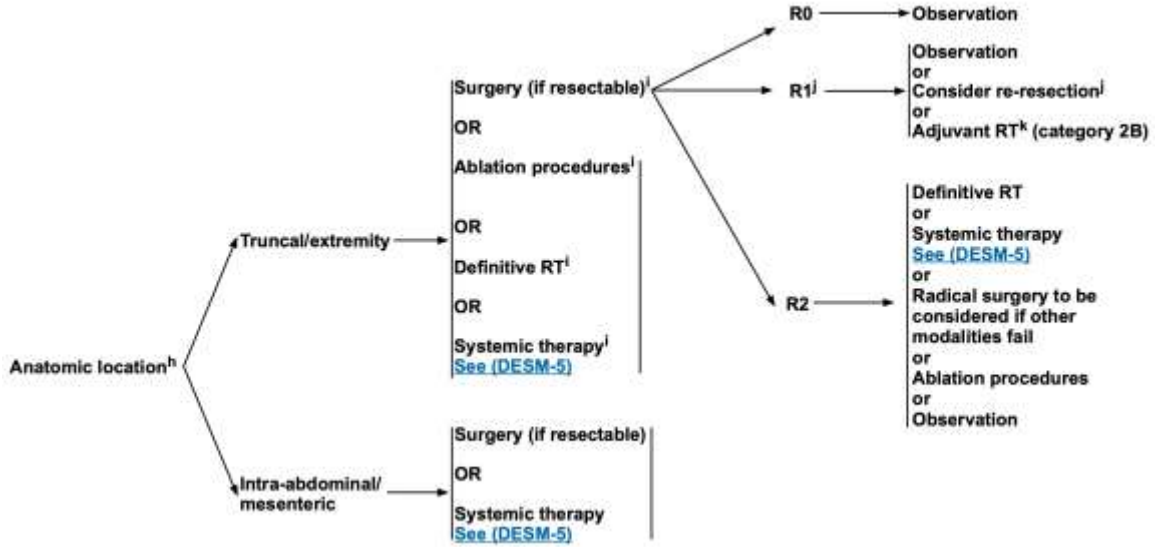
Stage	
I	Asymptomatic, <10 cm maximum diameter, and not growing
II	Mildly symptomatic,* <10 cm maximum diameter, and not growing
III	Moderately symptomatic,† or bowel/ureteric obstruction, or 10 to 20 cm, or slowly growing
IV	Severely symptomatic,‡ septic complications such as fistula and abscess, or >20 cm or rapidly growing

*Mildly symptomatic = sensation of mass, pain, but no restriction
†Moderately symptomatic = sensation of mass, pain; restrictive but not hospitalized
‡Severely symptomatic = sensation of mass, pain; restrictive, and hospitalized

On diagnosis

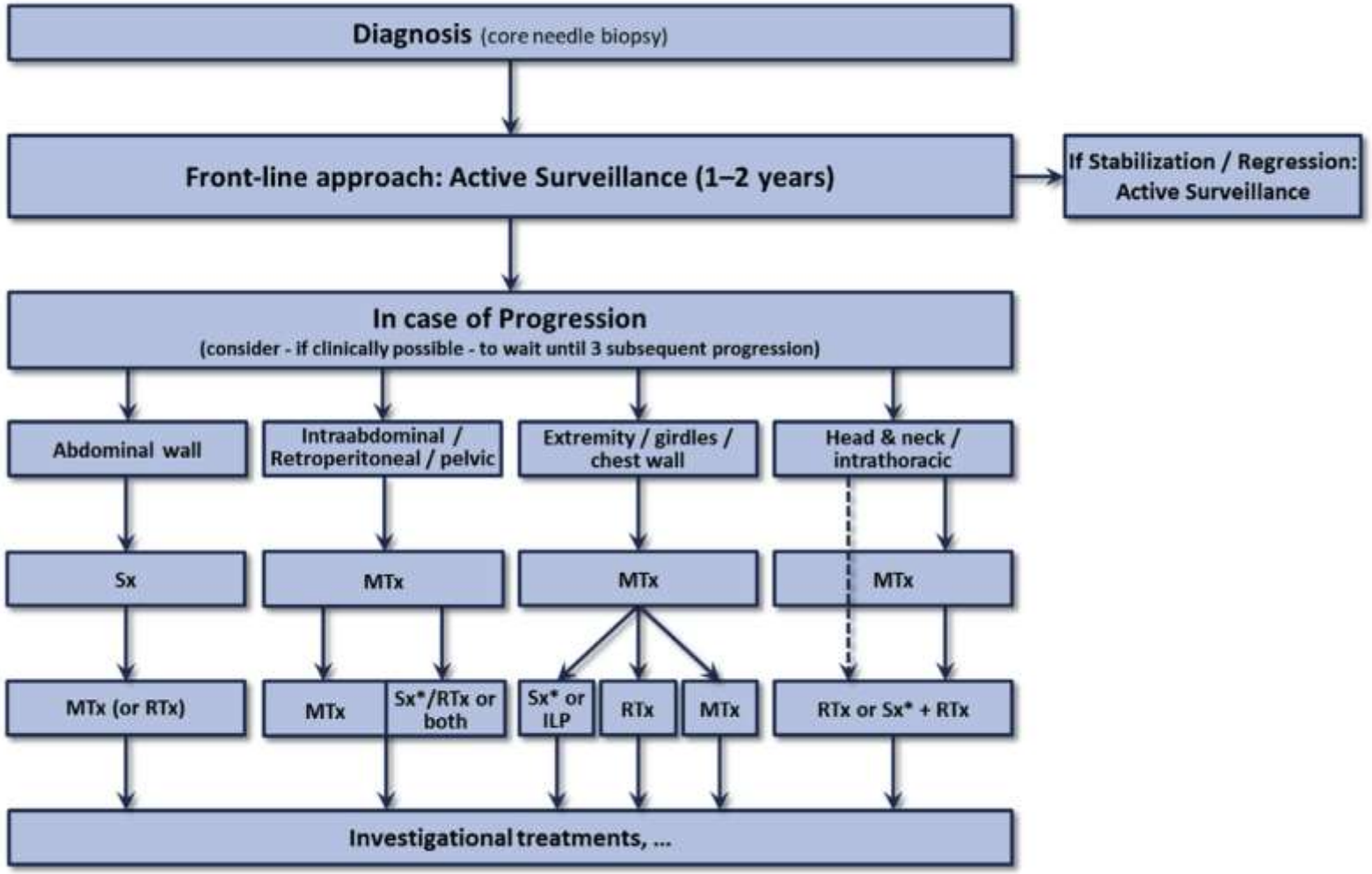


On progression



Cleveland Clinic Staging System
Quintini et al., Ann Surg, 2012
NCCN Soft Tissue Sarcoma v.2.2020

Therapy – Desmoid Tumour



Abbreviations: Sx: Surgery; Sx*: Surgery is an option if morbidity is limited; MTx: Medical treatment; RTx: Radiotherapy; ILP: Isolated limb perfusion.

Quintini et al., Ann Surg, 2012

Radiotherapy for Desmoid Tumor

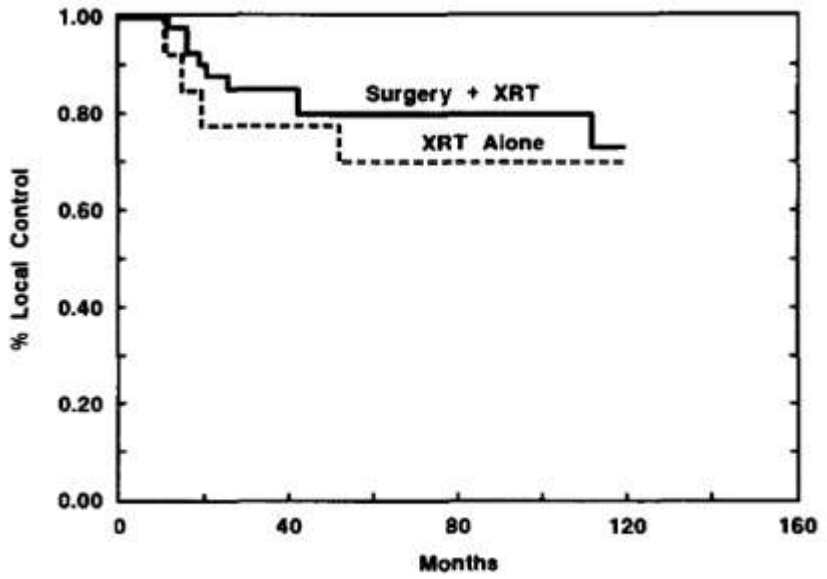


Fig. 2. Probability of local control by tumor status and treatment (Berkson-Gage Life Table Method).

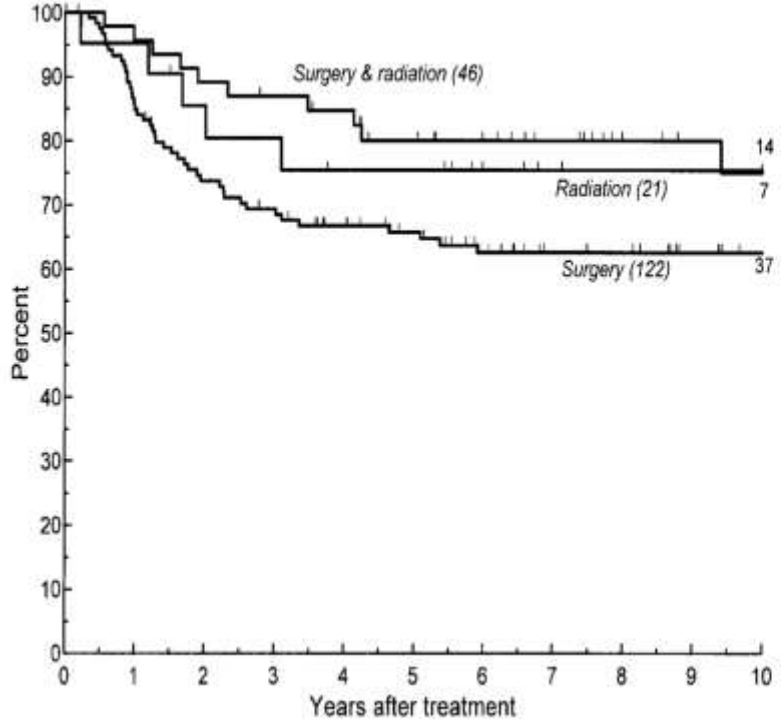
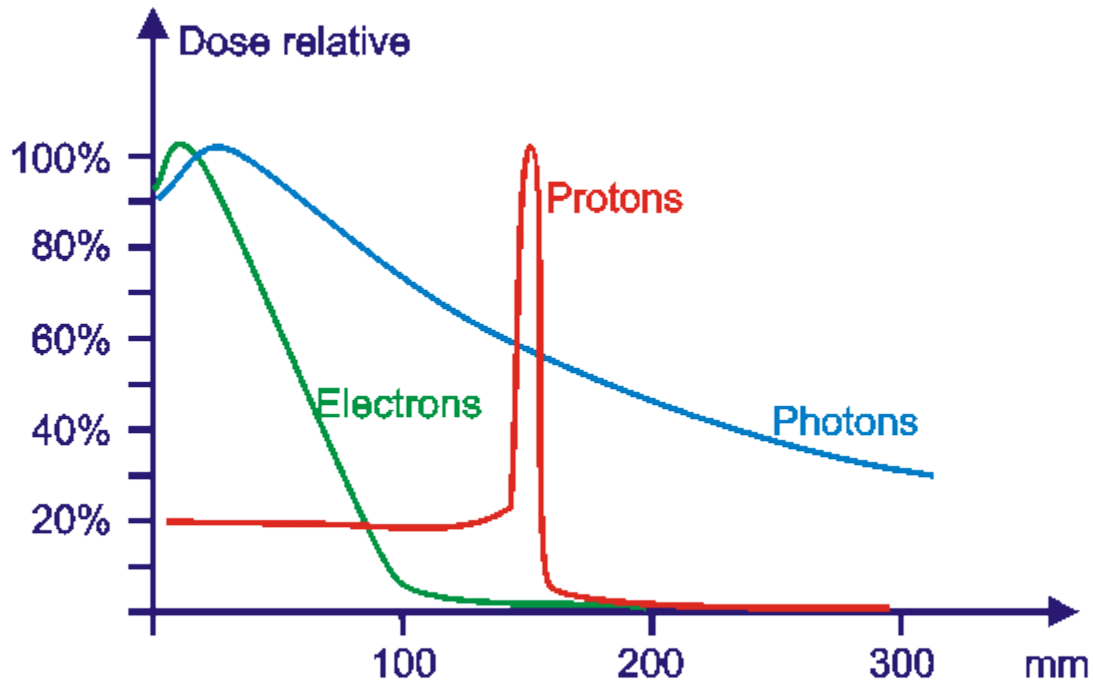


Fig 3. Freedom from relapse according to treatment strategy. The numbers at the end of each curve are the numbers of patients at risk at 10 years. These curves were not statistically significantly different from each other ($P = .111$).

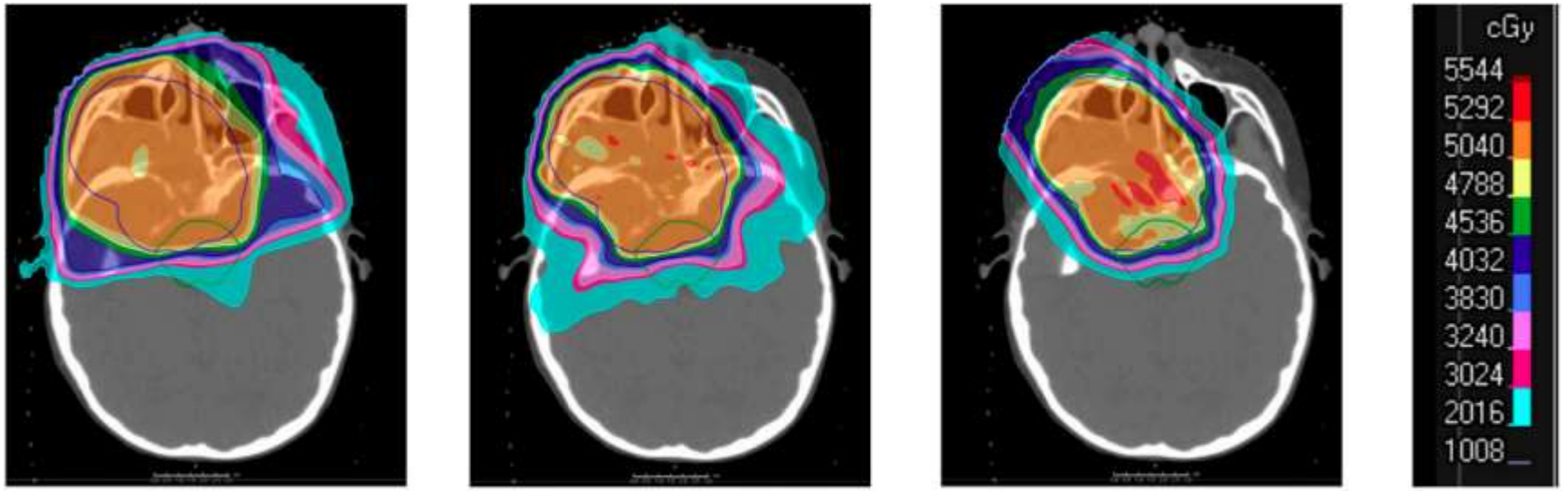
- Preferred dose is <u>50-56 Gy in 1.8-2 Gy fractions</u>
- Addition of RT likely does not improve local control when resected with negative margins, BUT…
  - Close/positive margins: Surgery +RT > Surgery alone
  - 5y LC: Surgery + RT = RT alone (75-85%)
- Radiotherapy for intra-abdominal desmoid tumor **should be avoided**

Ballo et al., JCO, 1999
Sherman et al., IJROBP, 1990

Physics of Proton Therapy...



Practical Implications of Physical Properties of Proton...



3D-CRT VMAT Proton

Thank You For Your Patience