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Authors

Million, Lynn
Hayes-Jordan, Andrea
Chi, Yueh-Yun
et al.

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Local Control For High-Grade Nonrhabdomyosarcoma Soft Tissue Sarcoma Assigned to Radiation Therapy on ARST0332: A Report From the Childrens Oncology Group

Lynn Million, MD[#*], **Andrea Hayes-Jordan, MD**[#†], **Yueh-Yun Chi, PhD**[‡], **Sarah S. Donaldson, MD**[*], **Suzanne Wolden, MD**[§], **Carol Morris, MD**[‖], **Stephanie Terezakis, MD**[¶], **Fran Laurie, BS**[#], **Karen Morano, CMC, MPH**[#], **T.J. Fitzgerald, MD**[**], **Torunn I. Yock, MD**[††], **David A. Rodeberg, MD**[‡‡], **James R. Anderson, PhD**[§§], **Rose Anne Speights, MSA, CCRP**[‖‖], **Jennifer O. Black, MD**[¶¶], **Cheryl Coffin, MD**[##], **Mary Beth McCarville, MD**[‖‖], **Simon C. Kao, MD**[***], **Douglas S. Hawkins, MD**[†††], **Sheri L. Spunt, MD**[#*], **R. Lor Randall, MD**[#‡‡‡]

[*] Department of Radiation Oncology (LM, SSD) and Department of Pediatrics (SS), Stanford University, Stanford, California

[†] Department of Surgery, University of North Carolina, Chapel Hill, North Carolina

[‡] Department of Biostatistics, University of Southern California, Los Angeles, California

[§] Department of Radiation Oncology, Memorial Sloan Cancer Center, New York, New York

[‖] Department of Orthopedic Surgery, Johns Hopkins University, Baltimore, Maryland

[¶] Department of Radiation Oncology, University of Minnesota, Minneapolis, Minnesota

[#] Imaging and Radiation Oncology Core (IROC), Lincoln, Rhode, Island

[**] Department of Radiation Oncology, University of Massachusetts, Worcester, Massachusetts

[††] Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts

[‡‡] Department of Surgery, East Carolina University, Greenville, North Carolina

[§§] MERCK Research Laboratories, North Wales, Pennsylvania

[‖‖] St. Jude Children's Research Hospital, Memphis, Tennessee

[¶¶] Department of Pathology, Children's Hospital Colorado, Aurora, Colorado

[##] Department of Pathology, Vanderbilt University, Nashville, Tennessee

[***] Department of Radiology, University of Iowa, Iowa City, Iowa

[†††] Department of Pediatrics, Seattle Children's Hospital, Seattle, Washington

[‡‡‡] Department of Orthopedics, University of California Davis, Sacramento, California

Corresponding author: Lynn Million, MD, lmillion@stanford.edu.

This protocol is registered with ClinicalTrials.gov (registry no.: NCT00346164).

Data-Sharing Statement: Deidentified individual patient data from this clinical trial and a data dictionary defining each field in the data set will be made available on the National Cancer Institute NCTN/NCORP Data Archive (https://nctn-data-archive.nci.nih.gov/) within 1 year of print publication of this manuscript according to the NIH Data Sharing Policy (grants.nih.gov/grants/policy/data_sharing/).

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[#] These authors contributed equally to this work.

Abstract

Purpose: The ARST0332 trial for pediatric and young adults with nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) used risk-based treatment including primary resection with lower-than-standard radiation doses to optimize local control (LC) while minimizing long-term toxicity in those requiring radiation therapy (RT). RT for high-grade NRSTS was based on extent of resection (R0: negative margins, R1: microscopic margins, R2/U: gross disease/unresectable); those with >5 cm tumors received chemotherapy (CT; ifosfamide/doxorubicin). This analysis evaluates LC for patients assigned to RT and prognostic factors associated with local recurrence (LR).

Methods and Materials: Patients aged <30 years with high-grade NRSTS received RT (55.8 Gy) for R1 ≤5 cm tumor (arm B); RT (55.8 Gy)/CT for R0/R1 >5 cm tumor (arm C); or neoadjuvant RT (45 Gy)/CT plus delayed surgery, CT, and postoperative boost to 10.8 Gy R0 <5 mm margins/R1 or 19.8 Gy for R2/unresected tumors (arm D).

Results: One hundred ninety-three eligible patients had 24 LRs (arm B 1/15 [6.7%], arm C 7/65 [10.8%], arm D 16/113 [14.2%]) at median time to LR of 1.1 years (range, 0.11–5.27). Of 95 eligible for delayed surgery after neoadjuvant therapy, 89 (93.7%) achieved R0/R1 margins. Overall LC after RT were as follows: R0, 106 of 109 (97%); R1, 51 of 60 (85%); and R2/unresectable, 2 of 6 (33%). LR predictors include extent of delayed resection (P <.001), imaging response before delayed surgery (P < .001), histologic subtype (P <.001), and no RT (P = .046). The 5-year event-free survival was significantly lower (P = .0003) for patients unable to undergo R0/R1 resection.

Conclusions: Risk-based treatment for young patients with high-grade NRSTS treated on ARST0332 produced very high LC, particularly after R0 resection (97%), despite lower-than-standard RT doses. Neoadjuvant CT/RT enabled delayed R0/R1 resection in most patients and is preferred over adjuvant therapy due to the lower RT dose delivered.

Introduction

Nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) accounts for 4% of pediatric cancers and <1% of all adult cancers, with a significant proportion affecting teenagers and young adults, an age group frequently underrepresented in clinical trials.[1–3] Surgical resection is the foundation for curative treatment of NRSTS, with the role for neoadjuvant and adjuvant radiation therapy (RT)/chemotherapy (CT) in children and young adults less well defined. This is in contrast to children with rhabdomyosarcoma and adults with soft tissue sarcoma (STS), where decades of clinical trials have standardized the approach to multidisciplinary management.[4,5]

The ARST0332 trial conducted by Childrens Oncology Group (COG) recently validated a treatment schema based on a risk stratification system for young patients with NRSTS using known STS prognostic factors including metastatic disease, tumor resectability, size, and grade. ARST0332 prioritized avoiding RT altogether but used lower-than-standard RT doses and field sizes to diminish long-term toxicity in those requiring it. An important study finding was high local control (LC) despite omission of RT: 96% after R0 resection for

low-grade tumors and 91% for <5 cm high-grade tumors. After R1 resection for low-grade tumors >5 cm the LC rates were lower (82%), but all patients were salvaged with further surgery ± RT, suggesting that the vast majority of young patients with R1 resection of a low-grade tumor can be cured without RT.[6] The goal for all other patients was to achieve high LC rates via R0 resection (upfront or delayed surgery) and highly conformal RT at lower-than-standard doses, with dose-intensive ifosfamide/doxorubicin CT for >5 cm tumors.

The Pediatric Oncology Group conducted 2 NRSTS trials more than 3 decades ago using age-adjusted RT doses for resected tumor (45–50 Gy) with positive margins and higher doses for unresected tumors (55–64.8 Gy), but outdated RT techniques and volumes with poor overall study compliance are not informative for contemporary radiation practice.[7,8]

RT doses >60 Gy routinely used for resected STS in adults have since been adopted in children[9–11]; however, data from sarcoma survivors suggesting a relationship between higher radiation dose (≥60 Gy) and increased risk for secondary malignant neoplasms (SMN) supported testing lower doses in a clinical trial.[12] Conformal target volumes (1.5 cm) had not been validated for children or young adults before ARST0332 enrollment; however, preliminary results from a single-institution prospective study suggested smaller RT volumes (1.5 cm) for pediatric NRSTS might be feasible and safe in a groupwide setting, with the final report after 3 year follow-up confirming no LR after R0 and 21% LR after R1 resection.[13]

For children with unresected NRSTS, strategies to facilitate resection have primarily relied on neoadjuvant CT with selective use of RT after surgery to avoid exposure in those patients who may not need RT, but local progression was a major cause of failure, supporting the need for more effective LC approaches.[14,15] Neoadjuvant RT ± CT has been successfully used for adults with STS of the extremity and trunk, with a >90% LC rate.[16–18] However, a high rate of wound complications after neoadjuvant therapy (18%−48%) is often cited as evidence to resect tumors at initial presentation.[19,20] Fewer long-term effects are anticipated with neoadjuvant therapy owing to the lower doses and smaller field sizes. Resection of the irradiated tumor bed may further reduce the risk of SMN.

This analysis evaluates LC for young patients with high-grade, nonmetastatic NRSTS assigned to RT and prognostic factors associated with local recurrence (LR).

Methods and Materials

Patient eligibility

Patient eligibility, risk stratification, treatment assignment, therapy delivered, toxicity, response, event-free survival (EFS), and overall survival (OS) outcomes have been previously reported.[6] This trial was approved by the National Cancer Institute Pediatric Central Institutional Review Board and by the institutional review boards of each participating institution, as required. Informed consent and assent as appropriate was obtained from parents, guardians, and patients, according to National Cancer Institute guidelines.

Figure 1 shows the risk stratification and treatment assignment algorithm. This LC analysis was restricted to patients with nonmetastatic, high-grade Pediatric Oncology Group or Federation Nationale des Centres de Lutte Contre le Cancer NRSTS arising at all anatomic sites assigned to treatment arms that included RT.[21,22] Patients with hepatic primary tumors and those who had undergone amputation before study entry were excluded because they did not receive RT. Patients <24 months of age for whom RT was optional were also excluded.

Primary tumor site treatment

Patients assigned to adjuvant RT (55.8 Gy in 31 fractions) included those enrolled on arm B (≤5 cm R1) and arm C (>5 cm, R0 or R1). Patients on arm C also received adjuvant CT (ifosfamide [6 cycles]/doxorubicin [5 cycles]) with concurrent ifosfamide alone during RT. Adjuvant RT started within 6 weeks of surgery.

Patients assigned to neoadjuvant RT (45 Gy in 25 fractions) were enrolled on arm D (unresectable or >5 cm high-grade tumor where delayed resection was planned). These patients also received concomitant neoadjuvant CT (ifosfamide [4 cycles]/ doxorubicin [2 cycles]) followed by surgery at week 13 and additional postoperative CT (ifosfamide [2 cycles]/doxorubicin [3 cycles]). Neoadjuvant RT began after the second cycle of CT at week 4; concurrent ifosfamide alone was administered at weeks 7 and 10.

Definitive primary tumor resection was performed at week 13 with the goal of achieving R0 resection, defined as a cuff of nonmalignant tissue of at least 5 mm surrounding the tumor. CT was restarted 2 to 5 weeks after surgery, with a primary site RT boost delivered after the first postoperative CT including 10.8 Gy in 6 fractions for R0 with <5 mm margins/R1 and 19.8 Gy in 11 fractions for R2/unresected tumors. Patients deemed unresectable after 45 Gy could continue with 19.8 Gy boost without interruption of radiation treatment.

For arm D patients, wound complications were reported for failure to initiate postoperative CT within 5 weeks of surgery, requiring removal from protocol therapy. Enrollment on arm B and C required that patients start RT at week 4 (arm C CT at week 3); if patients were unable to meet these study requirements owing to wound complications, they would not be eligible for enrollment.

Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Adverse event reporting was required for grade 5 and grade 4 adverse events. Serious (grade 3) wound complications were not recorded on this study unless they caused a delay in protocol therapy. Patients who developed an SMN were removed from protocol therapy.

RT planning and target volume definition

Computed tomography volumetric-based planning was required. Clinical target volume (CTV1) included gross tumor volume (GTV) + 1.5 cm uniform expansion in all directions. The planning target volume (PTV1) included CTV1 + 0.5 cm. For arms B and C, a volume reduction after 45 Gy was permitted to include the GTV + 1 cm = CTV2. Arm D postoperative boost volume included known positive surgical margins determined by operative/pathology reports and imaging studies. Daily image-guided RT was encouraged.

Photons, protons, intraoperative RT, and brachytherapy were allowed. High-dose-rate brachytherapy was prescribed to 34 Gy in 3.4 Gy per fraction delivered twice daily for 10 fractions.

Imaging, RT, and surgery review

RT target volumes and dosimetry were centrally reviewed for compliance to protocol guidelines at the Imaging and Radiation Oncology Core within 3 days of the start of RT and at the end of treatment using a digital submission platform. A major deviation was>10% of protocol dose, 90% isodose covering <100% of CTV, or a portion of the GTV not being included in the treatment volume; a minor deviation was 6% to 10% difference from the protocol dose, >10% of the PTV receiving >110% of protocol dose, or CTV/PTV margins less than specified by protocol. Primary tumor imaging response was evaluated after neoadjuvant therapy and coded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) using centrally reviewed volumetric measurements of the primary tumor.[23] Operative notes and pathology reports were centrally reviewed by COG sarcoma surgeons after week 13 surgery to confirm extent of resection (R0, R1, R2, unresected).

Statistics and endpoints

LR was documented by magnetic resonance imaging or computed tomography, with biopsy confirming recurrence being recommended. EFS and OS rates were estimated using the Kaplan-Meier method with confidence intervals estimated by the Peto-Peto method and were compared between groups using the log-rank test.[24–26] Prognostic factors were evaluated with the log-rank test. Cumulative incidence of LR was estimated using a subdistribution proportional hazards analysis, with regional/distant failures, second malignancy, and death as competing risks.[27] Follow-up was current to June 30, 2018 when the study database was frozen for analysis.

Results

Clinical features and treatment

Two hundred thirty-eight patients with nonmetastatic high-grade NRSTS assigned to RT ± CT were enrolled between February 5, 2007 and February 10, 2012. Median follow-up was 6.71 years (range, 0.01–10.98). Forty-five were excluded from the analysis for hepatic primary (n = 36), age <24 months (n = 7), or upfront amputation (n = 2). Table E1 shows patient and tumor characteristics of the 193 eligible/evaluable patients enrolled on arm B (n = 15), arm C (n = 65), and arm D (n = 113).

Eighty patients had undergone gross total resection at study entry: 38 R0 and 42 R1. Among 113 patients receiving neoadjuvant CT/RT on arm D, 18 (16%) went off protocol therapy before week 13 evaluation: 7 with PD and 11 owing to parent, patient, or physician preference. Ninety-four arm D patients had imaging to assess response to neoadjuvant treatment before week 13 surgery (CR, n = 2; PR, n = 30; SD, n = 51; and PD, n = 11). Delayed surgery outcomes for 95 patients remaining on protocol therapy at week 13 were as follows: R0, n = 71; R1, n = 18; R2, n = 1; and unresectable, n = 3. A postoperative boost

of 10.8 Gy was given to 16 of 71 R0 and 13 of 18 R1 patients; 19.8 Gy was given to 3 of 6 with R2/unresectable tumors. Nine of 113 patients (8%) receiving neoadjuvant RT/CT experienced significant wound complications: unexpected grade 4 (n = 1) and inability to initiate postoperative CT within 5 weeks of surgery (n = 8). Nine SMNs were reported in 193 patients; all occurred in patients who received RT: 1 in the RT field (chondroblastic osteosarcoma, 55.8 Gy), 1 at the RT field margin (55.8 Gy) for spinal cord astrocytoma in a patient with Li-Fraumeni syndrome, 1 with an uncertain relationship to the RT field (acute myeloid leukemia), and 6 outside of the RT field including 5 malignant peripheral nerve sheath tumor (MPNST) in patients with NF-1.

LR

Table 1 shows LR based on treatment arm, patient and tumor characteristics, extent of surgery, and RT. There were 24 (12.4%) LRs among 193 eligible patients at a median time to LR of 1.10 years (range, 0.11–5.27 years). Significant predictors of LR included histology ($P < .001$), imaging response after neoadjuvant therapy ($P < .001$), extent of resection at delayed surgery ($P < .001$), and no RT to the primary site ($P = .046$). Figure 2 shows the cumulative risk for LR based on treatment arm, extent of surgical resection, and delivery of RT. Figure 3 shows the EFS based on treatment arm and extent of surgery. All R2/unresected patients experienced events by 5 years (log-rank $P = .0003$).

The clinical features, treatment, and outcomes of patients with LR are shown in Table 2 (arms B/C) and Table 3 (arm D). Among the 80 patients assigned to adjuvant RT, 7 of 8 LRs occurred after R1 surgery, 5 of 8 had imaging to review the location of LR in relation to the RT field, and 4 recurred in the 100% isodose distribution. Among the 113 patients assigned to neoadjuvant therapy, 12 had an isolated LR and 4 experienced local and metastatic recurrence. Six developed isolated LR before week 13 delayed surgery, including 2 salvaged with surgery (6.5 and 9.4 years follow-up); 2 eventually died of metastatic disease, 1 died in a car accident, and 1 was lost to follow-up. Isolated LR occurred in 2 patients after R0 resection after week 13 surgery. Isolated local progression of disease occurred in 4 of 6 patients with R2/unresectable tumors; only 1 of these patients was alive at 9.8 years after 64.8 Gy definitive RT.

RT compliance

Of the 193 patients assigned to receive RT, 181 (94%) received it. There were 10 major and 12 minor deviations. Four patients who received RT did not have adequate records to assess compliance. Twelve patients who did not receive RT were enrolled on arm B (n = 1), arm C (n = 4), and arm D (n = 7). RT was not given for the following reasons: removal from protocol therapy for parent, patient, or physician preference (n = 8); PD (n = 1); consent withdrawal (n = 2); and protocol deviation (n = 1).

RT technique included 3-dimensional (3D) conformal (n = 96), intensity modulated RT (IMRT; n = 73), protons (n = 6), 3D/brachytherapy (n = 4), 3D/IMRT/brachytherapy (n = 1), and brachytherapy only (n = 1). Of the 95 patients eligible for week 13 surgery, 8 R0 patients with ≥5 mm margins did not require a boost. It was not possible to determine whether a boost was required for 20 R0 patients for whom the margin depth was not

recorded. The remaining 67 patients on arm D required a boost and 32 received it: 16 of 43 R0 with <5 mm margins, 13 of 18 R1, and 3 of 6 R2/unresected.

Discussion

This report confirms high LC rates for patients aged between 2 and 30 years treated on COG ARST0332, setting a new standard of care for young patients with high-grade nonmetastatic NRSTS. An important finding of this study is the high rate of LC achieved with neoadjuvant CT/RT and delayed resection in >5 cm high-grade tumors, with up to 94% of eligible patients remaining on protocol therapy at week 13 achieving R0/R1 resection.

An advantage of neoadjuvant therapy is that lower radiation doses (45 Gy) were used compared with adjuvant therapy (55.8 Gy), as were highly conformal target volumes (1.5 cm) which are smaller volumes than currently recommended for adult extremity soft tissue sarcomas.[17] Lower RT doses and more conformal fields have the potential to reduce normal tissue toxicity and the incidence of SMN. Only 6 of 113 patients who received neoadjuvant therapy experienced isolated local tumor progression before planned delayed surgery; 2 of 6 became long-term survivors, and none died of local tumor progression, suggesting deferring surgery until after neoadjuvant therapy is safe. We estimated a wound complication rate of 8% after neoadjuvant treatment based on adverse event grade 4 reporting or wound complications requiring removal from the treatment protocol. Our data are not directly comparable to adult wound complication rates after preoperative RT alone or sequenced with CT because grade 2 and 3 wound complications were not collected on this study.[18–20]

Our analysis found 4 predictors of LR, including histologic subtype, imaging response at week 13, no RT to the primary site, and extent of disease at delayed surgery. In keeping with their documented sensitivity to CT and RT, patients with synovial sarcoma had a low rate of LR (2.7%), whereas those with MPNST had a higher rate (27.9%).[14,28] PD on imaging after neoadjuvant therapy was highly predictive of LR, but radiographic response otherwise did not predict LR; patients with SD fared similarly to those with CR or PR. Less than 7% of patients who completed neoadjuvant therapy were unable to undergo R0/R1 resection at week 13. As expected, LC was very poor in this subgroup, with a significant adverse impact on survival. Similarly, poor LC and OS have been documented in adults treated with definitive RT for gross disease.[29] Three of 4 tumors in our study not amenable to R0/R1 resection after neoadjuvant therapy were MPNST, likely reflecting their frequent involvement of the brachial/lumbosacral plexus where surgical resection is challenging, explaining in part why this histology is a predictor of poor LC.

For tumors resected at study entry, these ARST0332 trial results confirm the findings of a smaller single-institution prospective pediatric trial that using conformal target volumes after resection is a safe practice, with only 1 LR (<3%) after R0 resection.[30] This observation raises the question of whether further reduction of therapy is feasible in patients in whom an upfront R0 resection is anticipated. The European paediatric Soft Tissue sarcoma Study (EpSSG) NRSTS 2005 used a strategy that included CT but omitted RT in patients with synovial sarcoma and R0 margins, whereas other “adult-type” NRSTS histologies received adjuvant RT (50.4–59.4 Gy, depending on tumor size and surgical margins), with no local

failures reported among 13 patients with large (>5 cm) synovial sarcoma; EpSSG has not reported results yet for other histologies.[31]

A limitation of our study is incomplete institution reporting of the surgical margin depth, preventing us from confirming uniform adherence to the study definition of a negative margin (≥5 mm). However, our data suggest there is no difference in LC regardless of surgical margin depth as long as there is no tumor on the inked margin, a definition gaining acceptance in the literature on adult extremity and trunk STS when adjuvant RT is incorporated into the overall management.[32] A criticism of our study design is that radiation dose of resected tumors at study entry was the same regardless of the surgical margins (R0/R1), whereas in most practices the RT dose is higher for patients with R1 margins and lower for R0 margins. Because there is no planned successor ARST0332 trial for resected NRSTS, 55.8 Gy is the standard adjuvant dose for future comparisons, although we acknowledge testing lower radiation doses or omitting RT in certain subsets after R0 resection would be an important study question.

CT was safely delivered concurrently with RT in our trial, a practice we endorse that does not delay systemic therapy in patients at high risk for metastatic recurrence; however, due to limitations in study design and data collection, the rate of serious wound complications after this approach is unknown. Concurrent CT with RT is a practice not frequently used in adults owing to comorbidities and concerns about tissue/organ toxicity, as illustrated by a recent EORTC randomized trial delivering RT after the completion of adjuvant CT.[33] The majority of our patients (94%) received protocol RT with high compliance to guidelines, including 3D volumetric planning, contouring small target volumes, and IGRT in a cooperative group setting, suggesting practices that may be easily implemented outside of a clinical trial. IMRT was frequently used and provides improved target coverage and decreased dose to adjacent skin and joints compared with 3D conformal RT.[34] Our study could not provide evidence supporting a postoperative radiation boost for R0 <5 mm margins/R1 resections after neoadjuvant therapy because there were too few LRs. The long interval from the end of preoperative RT to the delivery of the postoperative boost, low doses delivered (10.8 Gy), and challenges with accurate target volume delineation are arguments for omitting boost in patients with close or R1 margins.[35] The recently completed COG ARST1321 NRSTS trial included guidelines to boost only gross disease (19.8 Gy) in high-grade extremity and trunk primary sites.

Conclusions

Risk-based treatment for high-grade NRSTS produced very high LC, particularly after R0 resection (97%), emphasizing the importance of oncologic resection as the foundational treatment for NRSTS. An adjuvant dose of 55.8 Gy produced high rates of LC in high-grade NRSTS, representing a modest decrease in RT exposure compared with doses typically used in adults. Neoadjuvant CT/RT with delayed resection was a successful strategy for patients requiring both treatment modalities, as nearly all unresected tumors at study entry underwent delayed resection with R0/R1 margins. For patients requiring both CT and RT, neoadjuvant therapy is preferred because a lower RT dose (45 Gy vs 55.8 Gy for adjuvant therapy) was effective, with much of the irradiated tissue excised at the time of delayed surgery and with

the potential to reduce the incidence of SMN. Additional research is needed to determine whether all patients with >5 cm tumors require RT after R0 resection, whether an RT boost is needed after delayed R1 resection, and how to improve LC for patients at high risk for LR, including those with MPNST and tumors still unresectable after neoadjuvant chemoradiation therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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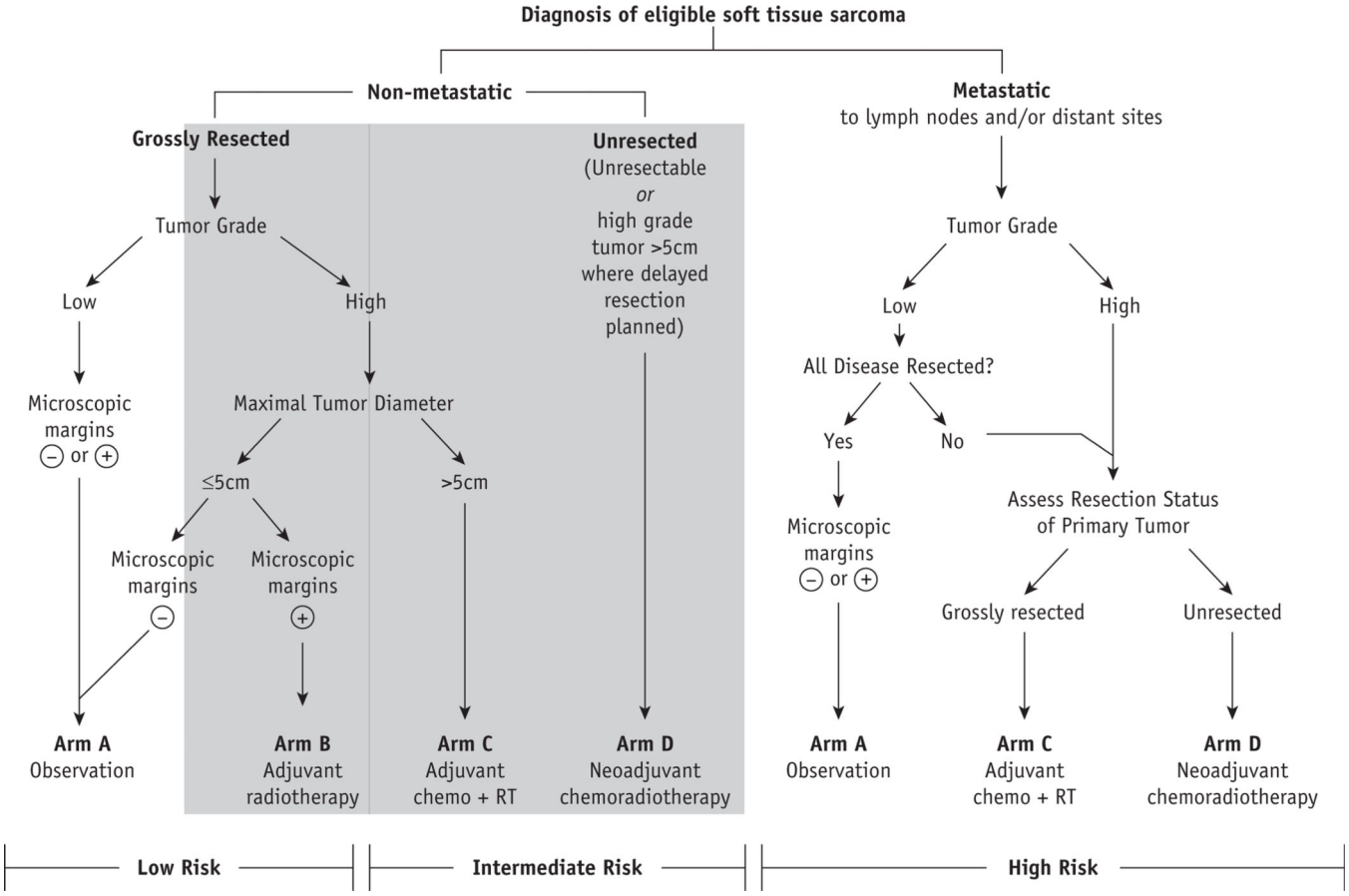


Fig 1.

Treatment algorithm for COG ARST0332 risk-based treatment for nonrhabdomyosarcoma soft tissue sarcoma in patients under age 30. The gray area highlights nonmetastatic treatment arms B,C, and D of patients assigned to radiation therapy.

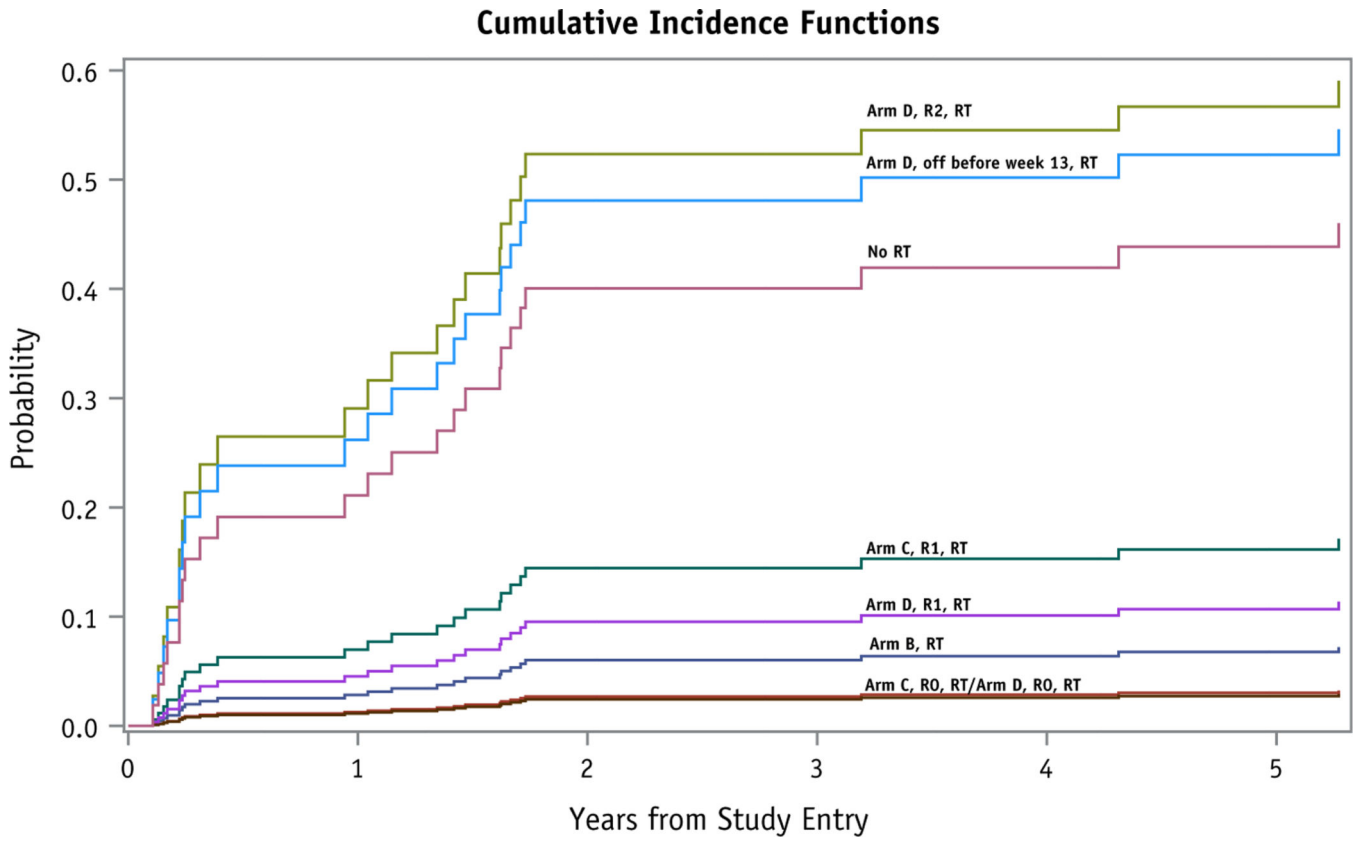
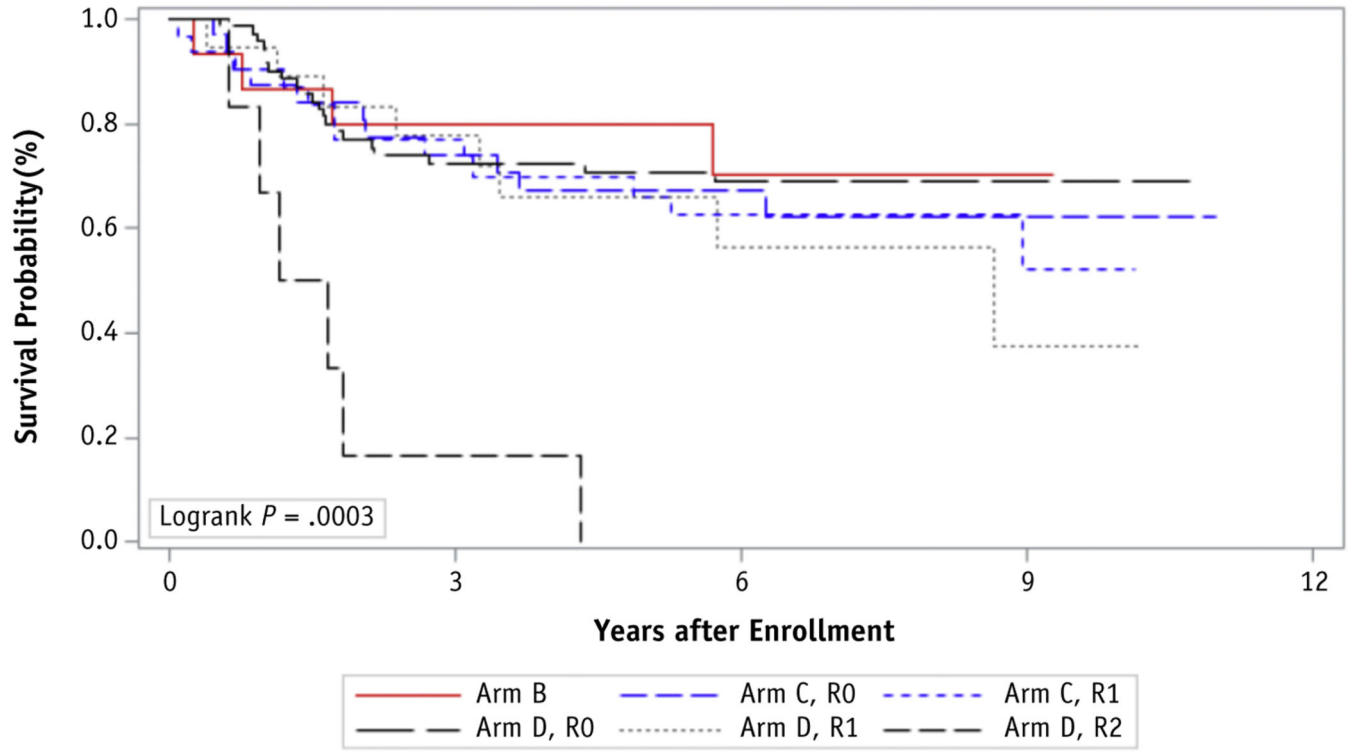


Fig 2.

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).

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Table 1

Local control by patient and tumor characteristics of 193 eligible cases

Feature	Group	N	Local failure (%)	*P* value*
Stratum	B	15	1 (6.7)	
	C	65	7 (10.8)	
	D	113	16 (14.2)	
Age, y	<18	148	21 (14.2)	.30
	≥18	45	3 (6.7)	
Histology	Synovial sarcoma	75	2 (2.7)	<.001
	Malignant peripheral nerve sheath tumor	43	12 (27.9)	
	Undifferentiated	30	5 (16.7)	
	Other	45	5 (11.1)	
POG	Low	15	1 (6.7)	.70
	High	178	23 (12.9)	
FNCLCC	Low	1	0 (0.0)	1.00
	High	192	24 (12.5)	
Primary site	Body wall	29	3 (10.3)	.089
	Extremity	105	9 (8.6)	
	Head and neck	23	3 (13.0)	
	Visceral	36	9 (25.0)	
Tumor size	≤5 cm	24	2 (8.3)	.50
	>5 cm, ≤10 cm	103	11 (10.7)	
	>10 cm	66	11 (16.7)	
Extent of resection at study entry (arms B and C)	R0	38	1 (2.6)	.059
	R1	42	7 (16.7)	
Extent of resection at delayed surgery (arm D)	R0	71	2 (2.8)	<.001
	R1	18	2 (11.1)	
	R2/unresected	6	4 (66.7)	
Margins at study entry (arm B)	Positive (tumor on ink)	10	1 (10.0)	1.00
	Negative (<5 mm)	5	0 (0.0)	
Margins at study entry (arm C)	Positive (tumor on ink)	32	6 (18.8)	.16†

Feature	Group	N	Local failure (%)	*P* value*
	Negative (<5 mm)	17	0 (0.0)	
	Negative (≥5 mm)	4	0 (0.0)	
	Distance unknown	12	1 (8.3)	
Margins at after week 13 surgery (arm D)	Positive (tumor on ink)	18	2 (11.1)	.32†
	Negative (1–4 mm)	43	1 (2.3)	
	Negative (≥5 mm)	8	0 (0.0)	
	Distance unknown	20	1 (5.0)	
Imaging response at delayed surgery	CR	2	0 (0.0)	<.001
	PR	30	5 (16.7)	
	SD	51	0 (0.0)	
	PD	11	6 (54.6)	
RT on primary site	Yes	181	20 (11.1)	.046
	No	12	4 (33.3)	
RT performance	Major deviation	10	1 (10.0)	.73‡
	Minor deviation	12	2 (16.7)	
	No deviation	156	16 (10.3)	
	Off protocol therapy before RT	11	4 (36.4)	
	Unevaluable	4	1 (25.0)	

Abbreviations: CR = complete response; FNCLCC = Federation Nationale des Centres de Lutte Contre le Cancer; PD = progressive disease; POG = Pediatric Oncology Group; PR = Partial response; RT = radiation therapy; SD = stable disease.

*Fisher's exact test.

†Distance unknown excluded.

‡Comparison of major deviation, minor deviation, and no deviation.

Table 2

Local recurrences after adjuvant therapy (arms B and C)

Arm	Site	Histology	Extent of surgery	RT dose (Gy)	RT deviation	Relationship to RT field (isodose failure)	Mets at time of LR	Life status
B1	Thoracic	MPNST	R1	55.8	No	100%	None	Dead
C1	Thigh	Clear cell	R0	55.8	No	No imaging at LR	None	Dead
C2	Thoracic	Undifferentiated, spindle cell	R1	55.8	No	100%	Bone	Dead
C3	Paraspinal	Unclassified soft tissue sarcoma	R1	55.8	No	100%	None	Dead
C4	Pelvis	Undifferentiated, pleomorphic	R1	NE	No RT (off protocol therapy)	NE	None	Dead
C5	Retro-peritoneal	MPNST	R1	55.8	No	20%	None	Dead
C6	Hip	MPNST	R1	55.8	No	No imaging at LR	None	Alive
C7	Pelvis	Undifferentiated, epithelioid	R1	55.8	No	100%	Peritoneum, omentum	Alive

Abbreviations: LR = local recurrence; mets = metastases; MPNST = malignant peripheral nerve sheath tumor; NE = not evaluable; RT = radiation therapy.

Table 3

Local recurrences after neoadjuvant therapy (arm D): Off protocol therapy before week 13 surgery

Arm D	Site	Histology	Extent of surgery	RT dose (Gy)	RT deviation	Relationship to RT field (isodose failure)	Mets at time of LR	Life status
D1	Neck	MPNST	None	None	NE	NE	Leptomeninges	Dead
D2	Leg	Undifferentiated, pleomorphic	None	14.4	ND	NE	None	Dead
D3	Thigh	Unclassified soft tissue sarcoma	None	None	NE	NE	None	Dead
D4	Thigh	Unclassified soft tissue sarcoma	None	45	Minor	No imaging	None	Alive
D5	Thigh	MPNST	None	45	ND	No imaging	None	Alive
D6	Thigh	MPNST	None	None	NE	NE	None	Alive
D7	Retro-peritoneal	MPNST	None	45	ND	100%	Liver, peritoneum	Dead
D8	Forearm	Synovial Sarcoma	None	45	ND	100%	None	Dead

Abbreviations: mets = metastases; MPNST = malignant peripheral nerve sheath tumor; ND = no deviation; NE = not evaluable.