

Randomized Controlled Trials in Soft Tissue Sarcoma: We Are Getting There!



Andrea J. MacNeill, MD, MSc^a, Abha Gupta, MD, MSc^{b,c},
Carol J. Swallow, MD, PhD^{d,e,*}

KEYWORDS

- Randomized controlled trial • Soft tissue sarcoma • Extremity sarcoma
- Retroperitoneal sarcoma • Preoperative radiotherapy • Chemotherapy

KEY POINTS

- The rarity and heterogeneity of soft tissue sarcoma (STS) pose challenges to the design and conduct of randomized controlled trials (RCTs).
- The only level 1 evidence to guide the surgical management of STS is a small RCT that established the equivalence of limb salvage to amputation for extremity STS.
- Improved local control of extremity STS with radiotherapy (RT) has been demonstrated in 2 landmark RCTs, and the relative advantages of preoperative versus postoperative RT are documented in the NCIC SR2 trial. Level 1 evidence regarding the use of RT in retroperitoneal sarcoma is as yet pending, from the European Organization for Research and Treatment of Cancer-led STRASS trial.
- With the exception of specific histologic subtypes, there is a lack of evidence to support routine neoadjuvant/adjuvant chemotherapy as a standard of care for most adult STS. However, multiple agents have been shown to prolong survival in the metastatic setting.
- Large collaborations in pediatric oncology have generated robust level 1 evidence for the management of pediatric STS.

Disclosure Statement: The authors have nothing to disclose.

^a Division of Surgical Oncology, Department of Surgery, Diamond Health Care Centre, BC Cancer Agency, University of British Columbia, 5199-2775 Laurel Street, Vancouver, British Columbia V5Z 1M9, Canada; ^b Department of Hematology/Oncology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada; ^c Department of Medical Oncology, Princess Margaret Cancer Centre, 610 University Avenue, Toronto, Ontario M5G 2M9, Canada; ^d Department of Surgical Oncology, Mount Sinai Hospital/Princess Margaret Cancer Centre, 600 University Avenue, Suite 1225, Toronto, Ontario M5G 1X5, Canada; ^e Department of Surgery, University of Toronto, Stweart Building, 149 College Street, Toronto, Ontario M5T 1P5, Canada

* Corresponding author. Mount Sinai Hospital, 600 University Avenue, Suite 1225, Toronto, Ontario M5G 1X5, Canada.

E-mail address: Carol.Swallow@sinaihealthsystem.ca

Surg Oncol Clin N Am 26 (2017) 531–544

<http://dx.doi.org/10.1016/j.soc.2017.05.001>

1055-3207/17/© 2017 Elsevier Inc. All rights reserved.

surgonc.theclinics.com

INTRODUCTION

Soft tissue sarcoma (STS) is a family of rare malignant neoplasms with an incidence of 4 to 5 per 100,000. As these are of predominantly mesenchymal origin, they can occur in any anatomic location. This anatomic diversity has important implications for treatment, in particular with respect to operative considerations, such that extremity/trunk and retroperitoneal/intra-abdominal STS are in many ways distinct entities.

More than 70 histologic subtypes of STS are now recognized with widely variable biology and sensitivity to systemic treatments. Increasingly, the discovery of characteristic underlying molecular alterations is facilitating targeted treatment of individual subtypes. For these reasons, it is imperative to conceptualize STS as a family of disparate malignancies requiring treatment strategies tailored to individual patients and disease. The rarity and heterogeneity of STS pose a considerable challenge to the design, conduct, and interpretation of randomized controlled trials (RCTs). The STS literature is, therefore, limited in high-level evidence and in the general applicability of many of the existing RCTs.

Surgery remains the mainstay of curative-intent treatment of STS. The ability to achieve complete excision is the primary determinant of survival and overt local recurrence for most histologies.¹⁻³ Radiotherapy (RT) is often used to allow preservation of critical structures and to decrease local recurrence, but a survival benefit has not been shown.^{4,5} Chemotherapy has an important role in the primary treatment of specific chemosensitive subtypes of STS, including nonpleomorphic rhabdomyosarcoma (RMS) and Ewing sarcoma (ES), but in other subtypes its use is generally reserved for treatment of advanced or metastatic disease. The level 1 evidence available for each of these treatment modalities is discussed below.

SURGERY

Seminal work on the surgical approach to extremity STS was published in 1982 by Rosenberg and his colleagues⁶ at the National Institutes of Health (NIH). A total of 43 patients were randomized to either amputation (N = 16) or limb salvage with adjuvant external beam RT (N = 27). All patients received postoperative systemic chemotherapy. There was no significant difference in overall survival (OS) between the two groups, and local control in the limb salvage group was 85%. These results instigated a paradigm shift toward limb preservation that has long remained the standard of care.

The optimal extent of surgery for retroperitoneal sarcoma (RPS) has not been evaluated in a similarly rigorous fashion. The anatomic constraints of the retroperitoneum render microscopic margin negative resection difficult. In contradistinction to extremity/trunk STS, local failure remains a predominant pattern of RPS recurrence, leading to disease-specific mortality that continues to accrue even 20 years postoperatively.⁷ Based on retrospective data from multiple institutions, particularly in Europe, there has been an evolution in recent years toward more liberal en bloc resection of adherent but grossly uninvolved organs in an attempt to improve local control in RPS.^{8,9} However, this approach has not been compared with more conservative resection using true prospective data collection, even in an observational manner; it is difficult to imagine how a meaningful RCT could be conducted.

RADIATION

Extremity Soft Tissue Sarcoma

As in the limb-sparing approach supported by the landmark work of Rosenberg and colleagues,⁶ RT has for several decades been used to facilitate function-preserving surgery by allowing close/microscopically positive margins along critical neurovascular

structures. Two randomized trials in the 1990s helped to firmly establish the role of adjuvant RT in improving local control in extremity STS. Following macroscopically complete resection of extremity or superficial trunk STS, Pisters and colleagues⁴ randomized 164 patients intraoperatively to receive postoperative brachytherapy (BRT) or no additional treatment. They found a significant benefit to BRT in patients with high-grade tumors (5-year actuarial local control 82% compared with 69% without BRT, $P = .04$) but no benefit in low-grade tumors. There was no difference in OS for high or low grade. Similarly, in a trial involving 141 patients who had undergone complete resection of extremity STS, Yang and colleagues¹⁰ demonstrated significantly improved local control in the group randomized to postoperative external beam RT (XRT) versus no additional therapy; in this trial, a local control benefit was seen for both high- and low-grade tumors. The latter study also examined quality of life; the investigators suggested that, in patients at low risk of recurrence, XRT could likely be safely omitted. As with the Pisters and colleagues⁴ trial, no improvement in OS was seen with adjuvant RT. The magnitude of the improvement in local control observed by Yang and colleagues¹⁰ was interpreted by some as a signal that XRT was perhaps superior to BRT in the adjuvant treatment of STS. Long-term follow-up (median 17.9 years) of the XRT trial has confirmed the durability of improved local control with adjuvant RT, without a corresponding survival benefit.⁵

Sequencing of Radiotherapy and Surgery

The National Cancer Institute of Canada Sarcoma2 (NCIC-SR2) trial compared the delivery of 50 Gy of XRT in the preoperative setting ($n = 94$) versus 66 Gy XRT postoperatively ($n = 96$) for extremity STS and found higher rates of significant wound healing complications with preoperative XRT (35% vs 17%, $P = .01$).¹¹ Local recurrence rates were similar between groups, but, surprisingly and intriguingly, OS was slightly higher in the preoperative XRT group ($P = .048$). Longer follow-up revealed higher rates of late toxicities, such as fibrosis, joint stiffness, and edema after postoperative RT, with significantly lower limb function ratings.¹² Given that the acute wound healing complications seen with preoperative XRT are typically recoverable, whereas the late effects associated with postoperative XRT are more likely to be irreversible, these data supported consideration of preoperative RT for high-risk extremity STS. Other related advantages include more limited, targeted treatment volume.

Modified RT techniques to mitigate the earlier-described toxicities have been investigated in 2 recent nonrandomized trials. Using preoperative image-guided intensity-modulated RT (IG-IMRT) to minimize the dose to uninvolved tissues, O'Sullivan and colleagues¹³ compared wound healing in lower extremity STS ($n = 70$) with that documented in the NCIC's SR2 trial. Significant wound complications were observed in 30.5% (vs 43.0%, $P = .2$) and reoperations for wound complications were necessary in 33.0% (vs 43.0%, $P = .55$). The rate of primary wound closure was 93.2% in the IG-IMRT cohort (vs 71.4% in the SR2 trial, $P = .002$), which was associated with less need for tissue transfer. In another nonrandomized trial (Radiation Therapy Oncology Group [RTOG]-0630), image-guided radiation therapy (IGRT) to a reduced target volume resulted in late toxicity scores of grades 2 or greater in only 10.5% of 79 eligible patients with extremity STS, compared with the NCIC SR2 trial rate of 37% ($P < .001$); notably, there was no apparent increase in marginal-field recurrences, defined as recurrence at the edge of the clinical target volume.¹⁴

The increased rates of late toxicity observed with postoperative XRT have been attributed, at least in part, to the delivery of a higher biological equivalent dose (the prescribed dose of postoperative XRT was 66 Gy to the wound and tumor bed, as opposed to 50 Gy with the tumor in situ). The need for a higher dose in the

postoperative setting has recently been called into question, and an RCT designed to explore this issue is currently enrolling patients at Princess Margaret Cancer Centre, Toronto. The trial randomizes patients to 50 Gy XRT preoperatively or 50 Gy XRT postoperatively (NCT02565498). Deferring the decision about RT administration to the postoperative period allows due consideration of the final histopathologic analysis, including microscopic margin status. It is well accepted that select patients with STS of the extremities that have favorable features (<5 cm and/or low grade) can be appropriately treated with surgery alone.¹⁵ Recent retrospective series have questioned whether the indications for RT can be better tailored to avoid overtreatment of patients who undergo quality surgery.^{16,17} In a study that investigates the selection criteria for safe omission of RT, the French Sarcoma Group is currently accruing patients to an RCT (NCT00870701) in which patients who have undergone resection of extremity STS with final pathologic margins of 1 cm or greater are randomized to postoperative XRT versus no further treatment, regardless of tumor size or grade.

Retroperitoneal Sarcoma

Given the anatomic challenges in obtaining a microscopically complete resection of STS in the retroperitoneum, RT is conjectured to be of potential benefit; but there is currently no level I evidence to support its use. Two prospective, nonrandomized trials from Princess Margaret Cancer Centre (PMCC) and MD Anderson Cancer Center (MDACC) evaluated the safety and feasibility of preoperative XRT in RPS.¹⁸ These studies established that preoperative XRT for RPS was well tolerated in terms of acute RTOG toxicity scores. The associated oncologic outcomes seemed to compare favorably with historical controls. Concurrently, a phase I/II trial at PMCC investigated dose escalation in the form of postoperative BRT after preoperative XRT and complete macroscopic resection of RPS.^{19,20} Although it is important to note that the treatment groups were not randomized, it was clear that postoperative BRT entailed excessive toxicity without any apparent improvement in disease control.

In 2004, the American College of Surgeons Oncology Group opened a phase III trial (Z9031) of preoperative XRT plus surgery versus surgery alone for primary RPS, but the study closed prematurely because of poor accrual over the first year. Led by Sylvie Bonvalot,²¹ the European Organization for Research and Treatment for Cancer (EORTC) has succeeded in carrying out a similarly designed multi-institutional trial that has enrolled patients with primary RPS across Europe and North America, with target accrual completed as of early 2017 (EORTC 62092–22092 STRASS). The recently reported second interim safety analysis showed no statistically significant increase in adverse events with XRT.²¹

A German phase I/II trial is currently underway examining the addition of intraoperative RT (IORT) to preoperative IMRT in primary RPS, with an interim analysis reporting acceptable levels of toxicity and comparable oncologic outcomes with historical and contemporary series.²²

CHEMORADIATION

The combination of preoperative XRT and perioperative systemic treatment has been prospectively investigated in both extremity and retroperitoneal sarcoma but not in any RCT of which the authors are aware. After an encouraging single-institution pilot study, the RTOG conducted a phase II trial of neoadjuvant mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) interdigitated with 44 Gy of preoperative XRT, followed by resection and 3 cycles of postoperative MAID (RTOG 0514) in patients with high-risk extremity and body wall STS.²³ This regimen proved to have substantial

toxicity that precluded further study or use outside of a trial. Long-term follow-up of these patients revealed resolution of treatment-related toxicities within 1 year, with oncologic outcomes that compared favorably with other published series.²⁴

In 1996, Pisters and colleagues⁴ (MDACC) commenced a phase I trial of low-dose doxorubicin with concurrent preoperative XRT for high-grade RPS. The results were reported as a combined experience with PMCC, whereby 37 high-grade RPS were treated with preoperative XRT $\pm$ BRT in a phase I/II trial.¹⁸ Long-term results of the combined use of preoperative chemoradiation (CRT) for RPS at MDACC have not been reported, and the regimen is not currently used at that center. Gronchi and colleagues²⁵ reported a phase I/II trial of preoperative high-dose prolonged-infusion ifosfamide in combination with 50.4 Gy preoperative XRT for resectable RPS and found that only two-thirds of patients could complete the planned treatment regimen. Given the toxicity and feasibility concerns raised in these preliminary studies, further investigation of combined preoperative CRT for RPS has not been pursued in RCTs.

SYSTEMIC THERAPY

STS demonstrates widely variable sensitivity to cytotoxic chemotherapies. RMS and ES are highly responsive to chemotherapy, which forms a cornerstone of the multidisciplinary management of these diseases. These histologies, however, occur predominantly in children and young adults and are addressed separately below. The focus of the rest of this section is on adult STS.

Adjuvant Chemotherapy

The potential role of adjuvant chemotherapy in STS has been explored in numerous RCTs and 2 meta-analyses. The first meta-analysis summarized 14 trials including 1568 patients evaluating the efficacy of adjuvant doxorubicin-based therapy in localized, resectable STS²⁶ and demonstrated a significant improvement in recurrence-free survival (RFS) (hazard ratio [HR] 0.75, $P = .0001$) but only a 4% difference in OS at 10 years, which was not significant (HR 0.89, $P = .12$). Within the subgroup of patients with extremity STS, there was a 7% absolute difference in 10-year OS with adjuvant chemotherapy (HR 0.80, $P = .029$), suggesting that this population may derive marginal benefit from systemic treatment. In 2008, an updated meta-analysis considered 4 additional trials of adjuvant chemotherapy, all of which included ifosfamide, for a total of 1747 patients.²⁷ Small but significant absolute risk reductions again were seen for local (4%, 95% confidence interval [CI] 0%–7%, $P = .04$), distant (9%, 95% CI 5%–14%, $P = .000$), and overall recurrences (10%, 95% CI 5%–15%, $P < .001$). With the inclusion of the newer studies, there was also a significant improvement in OS (ARR 6%, 95% CI 2%–11%, $P = .003$). Whether this difference was the result of a larger sample size or the inclusion of ifosfamide remains unclear, but it should be noted that all of the newer trials included ifosfamide-based chemotherapy in contrast to only one study in the Sarcoma Meta-analysis Collaboration (SMAC). When weighed against the toxicity of combination chemotherapy, the marginal improvements noted in this meta-analysis were insufficient to shift practice toward routine administration. More recently, an EORTC phase III trial comparing adjuvant doxorubicin + ifosfamide to surgery alone for resected high-grade sarcomas failed to show a difference in RFS (HR 0.91, 95% CI 0.67–1.22, $P = .51$) or OS (HR 0.94, 95% CI 0.68–1.31).²⁸

Neoadjuvant Chemotherapy

The Italian and Spanish Sarcoma groups randomized patients to 3 versus 5 cycles of preoperative epirubicin + ifosfamide.²⁹ Despite noninferiority of the truncated

regimen, subgroup analysis revealed significant differences in outcome between histologic subtypes, prompting a subsequent phase III trial of histology-tailored chemotherapy in high-risk, resected STS (Italian Sarcoma Group-STS-1001). In this trial, patients with high-risk STS of the extremity or body wall were randomized to either 3 cycles of epirubicin + ifosfamide or 3 cycles of a histology-tailored regimen, all given preoperatively: gemcitabine + docetaxel for undifferentiated pleomorphic sarcoma, trabectedin for high-grade myxoid liposarcoma (LPS), high-dose prolonged-infusion ifosfamide for synovial sarcoma, etoposide + ifosfamide for malignant peripheral nerve sheath tumors, or gemcitabine + dacarbazine for leiomyosarcoma (LMS). The trial was closed early because of superior RFS and OS with the standard epirubicin + ifosfamide regimen compared with a histology-specific approach (RFS 0.62 vs 0.38, $P = .004$; OS 0.89 vs 0.64, $P = .033$).³⁰ Subgroup analysis showed that trabectedin had comparable activity to epirubicin + ifosfamide in myxoid LPS, which is now being further investigated because of the presumed lower toxicity of trabectedin compared with conventional chemotherapy.

At present, the role of routine (neoadjuvant/adjuvant) chemotherapy in the treatment of localized, resectable STS remains contentious. Although not standard, major consensus guidelines acknowledge that adjuvant chemotherapy can be considered in high-risk patients (high grade, deep, >5 cm); work is ongoing to better define what patient population may derive the most benefit from this treatment modality.³¹

Regional Techniques

Regional delivery of chemotherapy was explored by the University of California, Los Angeles sarcoma group in the treatment of distal extremity lesions. Doxorubicin was administered intra-arterially in the early experience and later via an intravenous route to the lower extremity before limb-preserving resection of distal STS.

The addition of regional hyperthermia (RHT) was subsequently investigated as a means of augmenting the efficacy of systemic treatment.³² An EORTC trial (62,961) compared perioperative etoposide + ifosfamide + doxorubicin (EIA) alone or in combination with RHT, in addition to best local control (surgery $\pm$ RT).³³ Patients with localized, high-risk STS of the extremity ($n = 149$) or nonextremity sites (trunk, retroperitoneum, head and neck; $n = 192$) were eligible, along with both primary and recurrent disease. The addition of RHT increased response rates, assessed radiologically after induction therapy according to World Health Organization's criteria (28.8% vs 12.7%, $P = .002$). Disease-Free Survival (DFS) was superior in the RHT group (HR 0.70 with EIA + RHT vs EIA alone, 95% CI 0.54–0.92, $P = .011$). Although there was no difference in OS with RHT in the intention-to-treat cohort, among those patients who actually completed induction therapy (4 cycles of EIA + 8 cycles of RHT vs 4 cycles of EIA alone; $n = 269$), OS was better in the combined therapy group (HR 0.66, 95% CI 0.45–0.98, $P = .038$). Long-term follow-up of the subgroup of patients with macroscopically completely resected (R0/R1) abdominal and retroperitoneal STS revealed significantly improved local progression-free survival (LPFS) and DFS in the group who received combined treatment with RHT (5-year LPFS 56% vs 45%, $P = .044$; DFS 34% vs 27%, $P = .027$), but no difference in OS.³⁴

Intraperitoneal Chemotherapy

The French Sarcoma Group investigated the role of intraperitoneal (IP) chemotherapy in combination with cytoreductive surgery for peritoneal sarcomatosis.³⁵ Patients who had undergone cytoreductive surgery were randomized to 5 days of postoperative IP doxorubicin and cisplatin or no IP therapy. There was no difference in local or

distant RFS or in OS between patients who received IP chemotherapy and those who did not.

Although several groups are using IP chemotherapy in addition to cytoreductive surgery for desmoplastic small round cell tumor, this has not been the subject of an RCT.

Advanced/Metastatic Disease

The management of locally advanced or metastatic STS is complex and requires individually tailored multidisciplinary care by a specialist sarcoma team. Systemic treatment can be administered with multiple possible objectives, including prolongation of life, relief of symptoms, or downsizing for possible resection. The goals of care should be identified at the outset, as decisions regarding type and duration of systemic therapy are contingent thereupon. As in the adjuvant setting, anthracycline-based regimens remain the standard of care for most STS. Multiple recent trials have investigated alternative agents or combinations; however, until very recently, none has demonstrated definitive superiority to single-agent doxorubicin particularly in terms of OS ([Table 1](#)). The EORTC 62012 trial investigated single-agent doxorubicin versus doxorubicin + ifosfamide for locally advanced, unresectable, or metastatic STS and found significant differences in the objective response rate and progression-free survival (PFS) but no difference in OS.³⁶ The addition of ifosfamide was advantageous if the goal of treatment was tumor shrinkage; failing this, there was no benefit to intensified treatment of palliation of patients with advanced STS. Similarly, the PICASSO III trial demonstrated that the addition of palifosfamide, an active metabolite of ifosfamide, to doxorubicin compared with doxorubicin alone in adults with metastatic sarcoma failed to improve PFS or OS but increased toxicity in the combination arm.³⁷ The GeDDIS trial also failed to demonstrate any advantage of gemcitabine + docetaxel over single-agent doxorubicin for locally advanced or metastatic STS but only higher toxicity in the experimental arm.³⁸ Aldoxorubicin, an albumin-binding prodrug of doxorubicin, was investigated as an alternative to doxorubicin in a phase II study of locally advanced or metastatic STS and found to have superior PFS with no difference in OS. The manageable side effect profile and lack of cardiotoxicity with aldorubicin warrants further investigation.³⁹

Gemcitabine in combination with docetaxel has been shown to be superior to single-agent gemcitabine but at the cost of increased toxicity.⁴⁰ LMS, especially of the uterus, has specific sensitivity to these regimens; both gemcitabine alone and in combination with docetaxel are reasonable options in women with advanced disease.⁴¹ The combination of gemcitabine and dacarbazine is better tolerated, and the addition of dacarbazine has been shown to improve PFS and OS compared with gemcitabine alone in adults with all STS.⁴² Trabectedin has recently been approved as second-line therapy, having demonstrated superior activity to dacarbazine in the treatment of adults with metastatic LMS and LPS.⁴³

In recent years, a variety of targeted therapies have been investigated in the treatment of advanced or metastatic STS. The phase III PALETTE trial demonstrated that pazopanib, a multi-agent tyrosine kinase inhibitor, offered significant improvement in PFS in patients with metastatic STS of nonadipogenic origin compared with placebo, permitting its registration as an approved drug for STS.⁴⁴ Eribulin was compared with dacarbazine in patients with metastatic LMS and LPS, with a small but significant improvement in OS in the eribulin group.⁴⁵ Finally, Tap and colleagues⁴⁶ compared single-agent doxorubicin to combination with olaratumab; the combination was associated with a highly significant 11.8-month survival benefit. Although this was only a phase II study, the remarkable benefit in OS facilitated rapid approval of olaratumab for STS.

Table 1

Randomized trials investigating the use of systemic therapy in the treatment of locally advanced or metastatic soft tissue sarcoma

Trial	Study Design	N	Objective Response Rate	Progression-Free Survival	OS	Conclusions
Maki et al, ⁴⁰ 2007	Phase II: Gemcitabine + docetaxel vs gemcitabine	122	16% vs 8%	6.2 mo vs 3.0 mo	18 mo vs 12 mo	Combination superior but has increased toxicity (prohibitive of long-term use)
Garcia-Del-Muro et al, ⁴² 2011	Phase II: Gemcitabine + dacarbazine vs gemcitabine	113	49% vs 25% <i>P</i> = .009	4.2 mo vs 2.0 mo <i>P</i> = .005	16.8 mo vs 8.2 mo <i>P</i> = .014	Combination superior and well tolerated, no increased toxicity
PALETTE Van der Graaf et al, ⁴⁴ 2012	Phase III: Pazopanib vs placebo in nonadipocytic STS	369	6% vs 0%	4.6 mo vs 1.6 mo <i>P</i> < .0001	12.5 mo vs 10.7 mo <i>P</i> = .25	Superior disease control with pazopanib, acceptable toxicity
EORTC 62012 Judson et al, ³⁶ 2014	Phase III: Doxorubicin + ifosfamide vs doxorubicin	455	26% vs 14% <i>P</i> < .0006	7.4 mo vs 4.6 mo <i>P</i> = .03	14.3 mo vs 12.8 mo <i>P</i> = .076	No benefit to combination for palliation of advanced STS unless the goal of treatment is tumor shrinkage
GeDDiS Seddon et al, ³⁸ 2015 (abstract only)	Phase III: Gemcitabine + docetaxel vs doxorubicin	257	N/A	5.5 mo vs 5.4 mo <i>P</i> = .07	14.5 mo vs 16.4 mo <i>P</i> = .67	Increased toxicity with combination with no difference in disease control
Chawla et al, ³⁹ 2015	Phase II: Aldoxorubicin vs doxorubicin	123	25% vs 0%	5.6 mo vs 2.7 mo <i>P</i> = .02	15.8 mo vs 14.3 mo <i>P</i> = .21	Superior disease control with aldoxorubicin with manageable adverse effects and no cardiotoxicity
Demetri et al, ⁴³ 2016	Phase III: Trabectedin vs dacarbazine in LPS and LMS	518	9.9% vs 6.9% <i>P</i> = .33	4.2 mo vs 1.5 mo <i>P</i> < .0001	12.4 mo vs 12.9 mo <i>P</i> = .37	Superior disease control with trabectedin; led to FDA approval
PICASSO III Ryan et al, ³⁷ 2016	Phase III: Doxorubicin + Palifosfamide vs Doxorubicin	447	28.3% vs 19.9%	6.0 mo vs 5.2 mo <i>P</i> = 0.19	15.9 mo vs 16.9 mo <i>P</i> = 0.74	Increased toxicity with combination with no difference in oncologic outcomes
Tap et al, ⁴⁶ 2016	Phase II: Doxorubicin + olaratumab vs doxorubicin	133	18.2% vs 11.9% <i>P</i> = 0.3421	6.6 mo vs 4.1 mo <i>P</i> = .06	26.5 mo vs 14.7 mo <i>P</i> = .0003	Highly significant 11.8-mo survival benefit with olaratumab
Schoffski et al, ⁴⁵ 2016	Phase III: Eribulin vs dacarbazine in LPS and LMS	452	4% vs 5% <i>P</i> = .62	2.6 mo vs 2.6 mo <i>P</i> = .229	13.5 mo vs 11.5 mo <i>P</i> = .0169	Survival benefit with eribulin in LPS and LMS

Abbreviation: FDA, Food and Drug Administration N/A, Not Accessed.

CHEMOSENSITIVE SOFT TISSUE SARCOMAS: RHABDOMYOSARCOMA AND EWING SARCOMA

RMS and ES belong to the family of small, round, blue cell tumors characterized by much higher sensitivity to chemotherapy than most STS. Both are typically treated with multimodal therapy consisting of chemotherapy plus surgery and/or RT. Although these subtypes of STS occur predominantly in children and young adults, they are discussed here because of the considerable body of level 1 evidence available to guide their treatment. This large body of evidence is the result of international and multidisciplinary collaboration between large cooperative pediatric oncology groups, which could serve as an exemplar for the adult STS academic community seeking to generate a similarly robust literature.

Ewing's Sarcoma

Standard chemotherapy for ES in North America consists of vincristine, doxorubicin, and cyclophosphamide (VDC) alternating with ifosfamide and etoposide (IE). This standard stems from the Intergroup-0091 trial, which showed significantly better 5-year RFS with the addition of IE to the standard regimen of VDC and dactinomycin in patients with localized ES.⁴⁷ Cyclophosphamide and ifosfamide were shown to be equally effective in the treatment of patients with standard-risk ES in the EICESS-92 study.⁴⁸ This study also suggested some benefit to the addition of etoposide in the treatment of high-risk ES. A Children's Oncology Group (COG) study investigated interval compression of standard chemotherapy and showed that VDC/IE delivered every 2 weeks was more effective than when given at 3-week intervals, with no increased toxicity.⁴⁹ It has been difficult to recapitulate this practice in older patients in the practical setting. The Euro-EWING99 study is a large international trial carried out by multiple cooperative groups consisting of three randomizations based on a backbone of vincristine, ifosfamide, doxorubicin, and etoposide. The Euro-EWING99-R1 trial showed that cyclophosphamide may be able to replace ifosfamide in consolidation treatment of standard-risk localized ES.⁵⁰ Euro-EWING99-R2 demonstrated improved outcomes with busulfan + melphalan chemotherapy in patients with localized ES with a poor histologic response to chemotherapy or with a large tumor volume.⁵¹ Euro-EWING99-R3 identified no benefit to busulfan + melphalan chemotherapy in patients with ES with lung or pleural metastases compared with conventional chemotherapy combined with lung irradiation.⁵²

Rhabdomyosarcoma

A series of RCTs carried out by the Intergroup Rhabdomyosarcoma Study Group (IRS) over the past 4 decades has compared various protocols of multi-agent chemotherapy, with or without surgery/RT, permitting refinement according to risk category.⁵³⁻⁵⁶ This evolution in RMS management is reflected in an improvement in OS for patients with localized RMS from 55% in IRS-I to 71% in IRS-IV. However, standard RMS chemotherapy has remained largely unchanged since the 1970s consisting of vincristine, actinomycin, and cyclophosphamide (VAC). Since IRS-IV, the COG, which has subsumed the IRS, has carried out 2 RCTs investigating modifications to standard RMS chemotherapy in intermediate-risk RMS. D9803 found no benefit to the introduction of topotecan into standard chemotherapeutic regimens.⁵⁷ In ARST0331, a regimen of alternating VAC with vincristine plus irinotecan (VI) was found to be as effective as standard chemotherapy but less toxic.⁵⁸ Ongoing trials within COG are continuing to investigate modifications to VAC/VI with the addition of novel, targeted agents in the treatment of RMS.

DISCUSSION

The evolution of STS care has been punctuated by a small number of practice-changing RCTs. Rosenberg and colleagues⁶ early demonstration of the feasibility of limb salvage in a very small cohort enabled further study of function-preserving techniques that have long since supplanted amputation as the standard of care for extremity STS.⁶ Pisters and colleagues⁴ and Yang and colleagues¹⁰ established the role of RT in enhancing local control; O'Sullivan and colleagues¹¹ comparison of preoperative versus postoperative RT shifted the default approach to RT in STS, thereby altering the late effects profile of this patient population. Numerous negative trials of adjuvant chemotherapy brought an end to the practice of routine administration of chemotherapy for all STS in many centers.^{26,27} However, there remain many outstanding questions in the multidisciplinary management of STS; as our understanding of this family of diseases deepens, it becomes increasingly apparent that the RCT paradigm may be prohibitive. The challenge of conducting RCTs in a disease with only 12,000 new diagnoses per year is compounded by the fact that the many histologic subtypes of STS can exhibit markedly different biological behavior and differential sensitivity to chemotherapy or RT and that even single subtypes can behave differently based on anatomic location. Acknowledgment of these limitations should inform future inquiry in several ways.

RCTs concerning systemic therapies should increasingly be tailored to individual or similar subtypes of STS. Recent evidence has elucidated subtype-specific behavior, such as the lack of efficacy of pazopanib in adipogenic STS and the relative resistance of LMS to ifosfamide, calling into question the generalizability of older trials including all STS and raising the possibility that adjuvant chemotherapy may in fact be beneficial in certain subtypes. The recent multicenter European RCT comparing standard chemotherapy to histology-driven regimens is evidence of a shift toward a more nuanced approach to systemic therapy in STS.³⁰ The pediatric sarcomas provide a model of the robust literature that can emerge from this type of subtype-specific focus.

Similarly, extremity/trunk and retroperitoneal STS should be differentiated in the design of future RCTs. The optimal extent of surgery and potential benefit of RT, for example, cannot be reasonably extrapolated from extremity data to an anatomic location in which local failure is the primary cause of disease-specific mortality. The EORTC STRASS trial represents a laudable international effort to overcome the barriers to level 1 evidence in RPS and provide disease-specific data in an area where there has long been clinical equipoise and considerable variability in institutional practice.

Recognizing the impracticality of RCTs in addressing many of the knowledge gaps in adult STS, it is worthwhile to acknowledge the value of high-quality observational data and the pivotal role they can play in informing the management of a rare disease. Most of the surgical literature in adult STS consists, at present, of single- or multi-institution series. In 2013, the Transatlantic RPS Working Group (TARPSWG) was convened to overcome the challenges of a rare disease and generate prospective, observational data to provide quality evidence surrounding the management of RPS. To date, the TARPSWG has published the largest reported retrospective experience of RPS^{59,60}; a prospective registry has been initiated, capturing data from more than 35 institutions in multiple countries. The potential of this type of large-scale collaboration has been demonstrated by the 4 decades of high-level evidence generated by the IRS/COG, which has directed a thoughtful, cohesive body of research in RMS. This model of multidisciplinary, international collaboration is vital to the creation of meaningful, reliable evidence to guide the complex management of STS.

REFERENCES

1. Lewis JJ, Leung D, Woodruff JM, et al. Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution. *Ann Surg* 1998; 228(3):355–65.
2. Heslin MJ, Lewis JJ, Nadler E, et al. Prognostic factors associated with long-term survival for retroperitoneal sarcoma: implications for management. *J Clin Oncol* 1997; 15(8):2832–9.
3. Stojadinovic A, Leung DHY, Allen P, et al. Primary adult soft tissue sarcoma: time-dependent influence of prognostic variables. *J Clin Oncol* 2002; 20(21):4344–52.
4. Pisters PW, Harrison LB, Leung DH, et al. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol* 1996; 14(3):859–68.
5. Beane JD, Yang JC, White D, et al. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. *Ann Surg Oncol* 2014; 21(8):2484–9.
6. Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of limb-sparing surgery plus radiation therapy compared with amputation and the role of adjuvant chemotherapy. *Ann Surg* 1982; 196(3):305–15.
7. Tan MCB, Brennan MF, Kuk D, et al. Histology-based classification predicts pattern of recurrence and improves risk stratification in primary retroperitoneal sarcoma. *Ann Surg* 2015; 263(3):593–600.
8. Gronchi A, Lo Vullo S, Fiore M, et al. Aggressive surgical policies in a retrospectively reviewed single-institution case series of retroperitoneal soft tissue sarcoma patients. *J Clin Oncol* 2008; 27(1):24–30.
9. Bonvalot S, Rivoire M, Castaing M, et al. Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control. *J Clin Oncol* 2008; 27(1):31–7.
10. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol* 1998; 16(1):197–203.
11. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet* 2002; 359(9325):2235–41.
12. Davis A, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol* 2005; 75(1):48.
13. O'Sullivan B, Griffin AM, Dickie CI, et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. *Cancer* 2013; 119(10):1878–84.
14. Wang D, Zhang Q, Eisenberg BL, et al. Significant reduction of late toxicities in patients with extremity sarcoma treated with image-guided radiation therapy to a reduced target volume: results of Radiation Therapy Oncology Group RTOG-0630 Trial. *J Clin Oncol* 2015; 33(20):2231–8.
15. Pisters PWT, Pollock RE, Lewis VO, et al. Long-term results of prospective trial of surgery alone with selective use of radiation for patients with T1 extremity and trunk soft tissue sarcomas. *Ann Surg* 2007; 246(4):675–81.

16. Cahlon O, Brennan MF, Jia X, et al. A postoperative nomogram for local recurrence risk in extremity soft tissue sarcomas after limb-sparing surgery without adjuvant radiation. *Ann Surg* 2011;255(2):343–7.
17. Gronchi A. Individualizing the use/non-use of radiation therapy (RT) in soft tissue sarcoma (STS): when abstention is better than care. *J Surg Oncol* 2014;111(2):133–4.
18. Pawlik TM, Pisters PWT, Mikula L, et al. Long-term results of two prospective trials of preoperative external beam radiotherapy for localized intermediate- or high-grade retroperitoneal soft tissue sarcoma. *Ann Surg Oncol* 2006;13(4):508–17.
19. Jones JJ, Catton CN, O'Sullivan B, et al. Initial results of a trial of preoperative external-beam radiation therapy and postoperative brachytherapy for retroperitoneal sarcoma. *Ann Surg Oncol* 2002;9(4):346–54.
20. Ridgway PF, Catton CN, Cannell AJ, et al. Combined management of retroperitoneal sarcoma with dose intensification radiotherapy and resection: long-term results of a prospective trial. *Radiother Oncol* 2014;110(1):165–71.
21. Bonvalot S, Raut CP, Pollock RE, et al. Technical considerations in surgery for retroperitoneal sarcomas: position paper from E-Surge, a master class in sarcoma surgery, and EORTC-STBSG. *Ann Surg Oncol* 2012;19(9):2981–91.
22. Roeder F, Ulrich A, Habi G, et al. Clinical phase I/II trial to investigate preoperative dose-escalated intensity-modulated radiation therapy (IMRT) and intraoperative radiation therapy (IORT) in patients with retroperitoneal soft tissue sarcoma: interim analysis. *BMC Cancer* 2014;14:617.
23. Kraybill WG, Harris J, Spiro IJ, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: radiation therapy oncology group trial 9514. *J Clin Oncol* 2006;24(4):619–25.
24. Kraybill WG, Harris J, Spiro IJ, et al. Long-term results of a phase 2 study of neoadjuvant chemotherapy and radiotherapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall. *Cancer* 2010;116(19):4613.
25. Gronchi A, De Paoli A, Dani C, et al. Preoperative chemo-radiation therapy for localised retroperitoneal sarcoma: a phase I-II study from the Italian Sarcoma Group. *Eur J Cancer* 2013;50(4):784–92.
26. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. *Sarcoma Meta-analysis Collaboration. Lancet* 1997;350(9092):1647–54.
27. Pervaiz N, Colterjohn N, Farrokhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer* 2008;113(3):573–81.
28. Woll PJ, Reichardt P, Le Cesne A, et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. *Lancet Oncol* 2012;13(10):1045.
29. Gronchi A, Frustaci S, Mercuri M, et al. Short, full-dose adjuvant chemotherapy in high-risk adult soft tissue sarcomas: a randomized clinical trial from the Italian Sarcoma Group and the Spanish Sarcoma Group. *J Clin Oncol* 2012;30(8):850–6.
30. Gronchi A, Ferrari S, Quagliuolo V, et al. Full-dose neoadjuvant anthracycline + ifosfamide chemotherapy is associated with a relapse free survival (RFS) and overall survival (OS) benefit in localized high-risk adult soft tissue sarcomas (STS) of the extremities and trunk wall: interim analysis of a prospective randomized trial. *Proceedings of the European Society for Medical Oncology. Copenhagen, Denmark, October 7–11, 2016.*

31. The ESMO/European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Surg Oncol* 2014;25(Suppl 3):102–12.
32. Selch MT, Kopald KH, Ferreiro GA, et al. Limb salvage therapy for soft tissue sarcomas of the foot. *Int J Radiat Oncol Biol Phys* 1990;19(1):41–8.
33. Issels RD, Lindner LH, Verweij J, et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. *Lancet Oncol* 2010;11(6):561.
34. Angele MK, Albertsmeier M, Prix NJ, et al. Effectiveness of regional hyperthermia with chemotherapy for high-risk retroperitoneal and abdominal soft-tissue sarcoma after complete surgical resection. *Ann Surg* 2014;260(5):749.
35. Bonvalot S, Cavalcanti A, Le Péchoux C, et al. Randomized trial of cytorreduction followed by intraperitoneal chemotherapy versus cytorreduction alone in patients with peritoneal sarcomatosis. *Eur J Surg Oncol* 2005;31(8):917–23.
36. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol* 2014;15(4):415–23.
37. Ryan CW, Merimsky O, Agulnik M, et al. PICASSO III: a phase III, placebo-controlled study of doxorubicin with or without palifosfamide in patients with metastatic soft tissue sarcoma. *J Clin Oncol* 2016;34(32):3898–905.
38. Seddon B, Whelan J, Strauss S, et al. GeDDiS: a prospective randomised controlled phase III trial of gemcitabine and docetaxel compared with doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft tissue sarcomas (EudraCT 2009-014907-29). *J Clin Oncol* 2015;33(suppl) [abstract: 10500].
39. Chawla SP, Papai Z, Mukhametshina G, et al. First-line aldodoxorubicin vs doxorubicin in metastatic or locally advanced unresectable soft-tissue sarcoma: a phase 2b randomized clinical trial. *JAMA Oncol* 2015;1(9):1272–80.
40. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of Sarcoma Alliance for Research Through Collaboration Study 002. *J Clin Oncol* 2007;25(19):2755.
41. Gupta AA, Yao X, Verma S, et al. Chemotherapy (gemcitabine, docetaxel plus gemcitabine, doxorubicin, or trabectedin) in inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma: a clinical practice guideline. *Curr Oncol* 2013;20(5):e448–54.
42. García-Del-Muro X, Lopez-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol* 2011;29(18):2528–33.
43. Demetri GD, Mehren von M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol* 2015;34(8):786–93.
44. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012;379(9829):1879–86.
45. Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet* 2016;387(10028):1629–37.

46. Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. *Lancet* 2016;388(10043):488.
47. Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med* 2003;348(8):694–701.
48. Paulussen M, Craft AW, Lewis I, et al. Results of the EICESS-92 Study: two randomized trials of Ewing's sarcoma treatment–cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. *J Clin Oncol* 2008;26(27):4385–93.
49. Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol* 2012;30(33):4148–54.
50. Le Deley M-C, Paulussen M, Lewis I, et al. Cyclophosphamide compared with ifosfamide in consolidation treatment of standard-risk Ewing sarcoma: results of the randomized noninferiority Euro-EWING99-R1 trial. *J Clin Oncol* 2014;32(23):2440–8.
51. Whelan J, Le Deley MC, Dirksen U, et al. Efficacy of busulfan-melphalan high dose chemotherapy consolidation (BuMel) in localized high-risk Ewing sarcoma (ES): results of EURO-EWING 99-R2 randomized trial (EE99R2Loc). *J Clin Oncol* 2016;36(suppl) [abstract: 11000].
52. Dirksen U, Le Deley MC, Brennan B, et al. Efficacy of busulfan-melphalan high dose chemotherapy consolidation (BuMel) compared to conventional chemotherapy combined with lung irradiation in Ewing sarcoma (ES) with primary lung metastases: results of EURO-EWING 99-R2pulm randomized trial (EE99R2-pul). *J Clin Oncol* 2016;34(suppl) [abstract: 11001].
53. Maurer HM, Beltangady M, Gehan EA, et al. The intergroup rhabdomyosarcoma study-I. A final report. *Cancer* 1988;61(2):209–20.
54. Maurer HM, Gehan EA, Beltangady M, et al. The Intergroup Rhabdomyosarcoma Study-II. *Cancer* 1993;71(5):1904–22.
55. Crist W, Gehan EA, Ragab AH, et al. The Third Intergroup Rhabdomyosarcoma Study. *J Clin Oncol* 1995;13(3):610–30.
56. Crist WM, Anderson JR, Meza JL, et al. Intergroup Rhabdomyosarcoma Study-IV: results for patients with nonmetastatic disease. *J Clin Oncol* 2001;19(12):3091–102.
57. Arndt CAS, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. *J Clin Oncol* 2009;27(31):5182–8.
58. Hawkins D, Anderson J, Mascarenhas L, et al. Vincristine, dactinomycin, cyclophosphamide (VAC) versus VAC/V plus irinotecan (VI) for intermediate-risk rhabdomyosarcoma (IRRMS): a report from the Children's Oncology Group Soft Tissue Sarcoma Committee. *J Clin Oncol* 2014;32(5 suppl) [abstract: 10004].
59. Gronchi A, Strauss DC, Miceli R, et al. Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS): a report on 1007 patients from the multi-institutional collaborative RPS working group. *Ann Surg* 2016;263:1002–9.
60. MacNeill AJ, Miceli R, Strauss DC, et al. Post-relapse outcomes after primary extended resection of retroperitoneal sarcoma: a report from the Trans-Atlantic RPS Working Group. *Cancer* 2017. <http://dx.doi.org/10.1002/cncr.30572>.