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The Landmark Series: Multimodality Treatment of Extremity Sarcoma

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Abstract

Multimodality treatment of primary soft tissue sarcoma has evolved over the last 50 years, including seminal studies in amputation versus limb-sparing surgery, incorporation of radiation therapy (XRT), and the continuing controversy over the utilization and efficacy of systemic chemotherapy. We review the landmark studies in the multimodality management of primary extremity and trunk soft tissue sarcoma.

Multimodality treatment of soft tissue sarcoma (STS), consisting of >70 histologic subtypes,^{1,2} is the standard of care for patients with localized disease. Seminal works, including randomized studies evaluating limb-preservation, radiation sequencing, and systemic chemotherapy in the localized setting, have helped to inform the current recommendations. In this Landmark article, we review seminal studies in surgery, radiation therapy, and systemic chemotherapy to highlight the critical studies informing practice to date.

SURGERY AND RADIATION THERAPY

Amputation Versus Limb-Sparing Resection for Localized Extremity Soft Tissue Sarcoma

Purpose and Rationale—The infiltrative nature of STS results in local recurrence of 30–50% when simple excision alone is performed for high-grade tumors. These high recurrence rates led to the use of amputation or radical compartment resections for primary treatment of STS, which resulted in a reduction of local recurrence to < 5%, although with significant long-term morbidity. However, it was noted that, following complete resection via amputation, up to 40% of patients developed distant metastatic disease primarily to the lungs, leading to the introduction of wide local resection followed by radiation therapy (XRT) as an alternative option to obtain local control. This randomized trial was designed to compare local control following amputation versus limb-sparing surgery (LSS) + XRT in patients with localized extremity STS.³

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Study Design and Endpoints—Patients with extremity STS treated at the National Cancer Institute (NCI) between 1975 and 1981 were randomized 2:1 to limb-sparing surgery + XRT versus amputation. Patients were stratified based on primary tumor histology, tumor grade, time from diagnosis, and location (proximal or distal in the extremity). Amputation was performed at or above the joint and included all muscle groups. Patients in the LSS group underwent wide resection to include all gross tumor with several centimeters of surrounding normal tissue. Clips were placed in the resection bed to guide postoperative radiation therapy at a dose of 6000–7000 rads (Gy). Of note, the study also included a nested randomized trial of chemotherapy versus no chemotherapy.

Results: Primary and Secondary Endpoints—Sixteen patients were randomized to amputation and 27 to LSS + XRT. Although patients that underwent LSS were more likely to develop local recurrence (0% vs. 15% $p = 0.06$), there was no difference in 5-year disease-free survival (78% amputation vs. 71% limb-sparing, $p = 0.75$) or overall survival (88% vs. 83%, respectively; $p = 0.99$).

Conclusions—Limb-sparing surgery + XRT is an effective treatment for patients with soft tissue sarcomas of the extremities.

Commentary—Based on this important trial, limb-sparing surgery is the standard of care for patients with primary extremity STS. Although amputation is associated with better local control, this does not translate into differences in long-term survival, which is dictated by the development of distant metastatic disease. Although primary amputation is still necessary in < 5% of patients with primary STS, the 43 patients in this trial who were willing to undergo randomization to amputation or limb preservation should be really commended as they contributed to the preservation of limbs of countless subsequent patients, which should not be understated.

Adjuvant Brachytherapy in Soft Tissue Sarcoma

Purpose and Rationale—Noting the toxicity associated with postoperative XRT in the NCI trial, the brachytherapy (BRT) technique of XRT delivery was investigated by the group at Memorial Sloan-Kettering Cancer Center (MSKCC) as a way to provide adjuvant XRT with smaller total treatment volumes.⁴

Study Design and Endpoints—Between 1982 and 1992, 164 patients with localized extremity and trunk STS were randomized intraoperatively after complete surgical resection to BRT versus no BRT. Randomization was stratified by tumor grade, tumor size, tumor location (superficial or deep), proximal or distal extremity site, and primary versus locally recurrent disease. BRT catheters were placed intraoperatively in the tumor bed, with a target region to be irradiated 2 cm circumferentially and catheters implanted approximately 1 cm apart and fixed with sutures. Postoperative localization films were obtained, dosimetry was performed, and BRT to a dose of 42–45 Gy was delivered over 4–6 days, starting no sooner than postoperative day 6.

Results: Primary and Secondary Endpoints—Actuarial estimates of freedom from local recurrence for the entire cohort at 60 months were 82% and 69% for the BRT and no BRT groups, respectively ($p = 0.04$). However, when low-grade and high-grade tumors were analyzed separately, patients with high-grade tumors were significantly less likely to develop local recurrences in the BRT arm, whereas there was no impact of BRT on local control in patients with low-grade tumors. Similar to previous studies evaluating XRT for local control, there were no differences in distant recurrence between the treatment arms, with 5-year disease-specific survival rates of 84% in the BRT arm compared with 81% in the no BRT arm.

Conclusions—Adjuvant BRT improves local control after complete resection of soft tissue sarcomas, though the benefit appears to be limited to patients with high-grade tumors.

Commentary—The study by Pisters et al. from MSKCC demonstrated the benefit of adjuvant BRT in patients with localized extremity and trunk STS undergoing limb-sparing surgery. Although BRT had theoretical advantages of decreasing treatment volume possibly leading to reduced long-term toxicity, the complexity of catheter placement, the required inpatient hospitalization during XRT, and the development of sophisticated XRT modalities, such as intensity-modulated radiation therapy (IMRT), have significantly reduced the use of BRT in current practice. However, this trial is significant for its ability to perform a randomized trial in the treatment of patients with a rare disease.

Benefit of Adjuvant Radiation Therapy in the Treatment of Soft Tissue Sarcomas of the Extremity

Purpose and Rationale—Following the replacement of amputation with limb-sparing surgery followed by high-dose XRT as the standard of care for localized extremity sarcoma, it was noted that high-dose XRT to the extremity was costly and resulted in significant functional impairment of the limb and, in some cases, complications leading to amputation. Therefore, a randomized study of surgery with or without postoperative XRT was designed to evaluate local recurrence, disease-free survival, and overall survival in patients with low-grade and high-grade extremity soft tissue sarcoma.^{5,6}

Study Design and Endpoints—Between 1983 and 1991, 91 patients with high-grade extremity sarcoma and 50 patients with low-grade STS were randomized to receive postoperative XRT versus no XRT. All patients with high-grade sarcoma received postoperative chemotherapy (doxorubicin and cyclophosphamide) given concurrently with radiation. Concurrent prospective quality-of-life and functional studies were performed to evaluate the effects of XRT.

Results: Primary and Secondary Endpoints—In the initial publication by Yang et al.⁵ at a median follow-up of 9.6 years, there were no local recurrences in patients with high-grade sarcoma treated with XRT compared with nine local recurrences in patients randomized to not receive XRT, with an estimated actuarial local failure rate at 10 years of 22% in the no XRT arm. Similarly, patients with low-grade sarcoma treated with adjuvant XRT were significantly less likely to recur than those treated with surgery alone ($p = 0.016$).

In a long-term follow-up study,⁶ at a median of 17.9 years, the incidence of local recurrence was 25% in the surgery alone group compared with 1.4% in patients treated with postoperative XRT ($p = 0.0001$). However, patients treated with XRT were more likely to have wound complications, clinically significant edema, and functional limb deficits long term.

Conclusions—Postoperative XRT is highly effective in preventing local recurrences. However, there is significant long-term toxicity that may be permanent.

Commentary—This trial (confirmed with the subsequent long-term follow-up) established the inclusion of XRT for optimal local control in the multimodality treatment of patients undergoing limb-sparing surgery for extremity STS. However, it was noted that there was significant short-term and long-term toxicity associated with XRT, including edema and reduced limb function. In addition, the overall risk of local-only recurrence was relatively low ($< 25\%$ for low- and high-grade tumors), suggesting that patients with very low risk of local recurrence could be considered for omission of XRT if the risks outweigh the benefits. A longitudinal study by Pisters and the MD Anderson Cancer Center (MDACC) sarcoma group demonstrated a local recurrence risk of $< 10\%$ for tumors < 5 cm resected with negative margins,⁷ supporting the consideration of surgery alone for patients with small, superficial STS resected with widely negative margins. In addition, there is growing evidence that, in experienced centers, limb-sparing surgery alone can result in excellent local control regardless of the malignancy grade, size, or depth of the tumor.^{8,9} However, histologic subtype should be factored into the decision, highlighting the importance of regionalization of sarcoma care to high-volume centers, where the highest surgical skills and knowledge of the disease are available.¹⁰

Preoperative Versus Postoperative Radiation Therapy in the Treatment of Extremity and Trunk STS

Purpose and Rationale—Although the aim of combined modality XRT and surgery is to obtain maximum control while preserving function, differences were noted in complications (short term and long term) between preoperative and postoperative XRT. Preoperative XRT required a smaller field with lower doses but was thought to have higher wound complications, whereas postoperative radiation was thought to have higher long-term toxicity. This multicenter randomized trial by the Canadian Sarcoma Group and NCI Canada was designed to evaluate whether preoperative versus postoperative XRT affected the rate of wound complications.^{11,12}

Study Design and Endpoints—One-hundred ninety patients were randomized to preoperative (50 Gy in 25 fractions) versus postoperative (66 Gy in 33 fractions) XRT, stratified by maximum tumor dimension. The primary endpoint was rate of wound complications within 120 days of surgery, defined as: secondary operation, invasive wound management, readmission for wound care, or persistent deep packing. Secondary endpoints included metastatic failure, acute toxicity, and function/general health utilizing the Musculoskeletal Tumor Society rating scale, the Toronto extremity salvage score (TESS), and the short form-36.

Results: Primary and Secondary Endpoints—At a follow-up of 3.3 years, 35% patients undergoing preoperative XRT developed a wound complication compared with 17% in the postoperative group ($p = 0.01$). Patients with larger tumors and those with tumors located in the lower extremity were more likely to develop wound complications. However, 68% patients in the postoperative group had acute toxic skin effects compared with 36% in the preoperative group ($p < 0.0001$). Although patients undergoing postoperative XRT had greater function at 6 weeks after surgery, there was no difference between treatment groups at later time points. Further, in a follow-up study,¹² patients in the postoperative arm had greater fibrosis, joint stiffness, and edema, with lower function scores on all measures compared with those in the preoperative arm. There was no difference in local recurrence or distant failure between the groups.

Conclusions—Preoperative XRT is associated with greater risk of wound complications than postoperative XRT, but patients treated with postoperative XRT had greater long-term fibrosis, joint stiffness, and edema related to radiation field size. There is no difference in local or distant recurrence related to the timing of XRT. Choice of XRT regimen for patients with STS should take into account the timing of surgery and radiotherapy, as well as the size and anatomical site of the tumor.

Commentary—The study by O’Sullivan et al. demonstrated equivalent oncologic outcomes between preoperative and postoperative XRT. However, preoperative XRT is associated with worse short-term outcomes, but postoperative XRT is associated with worse long-term functional outcomes. The interpretation of these data varies significantly by institution, whereby some sarcoma centers almost exclusively perform preoperative XRT, whereas others almost exclusively perform postoperative XRT. The decision for treatment sequencing is dependent upon institutional and patient factors. As a matter of fact, postoperative radiotherapy (RT) is delivered at higher doses (usually 60–66 Gy in 30–33 fractions) and to a larger field size. As a result, long-term edema and fibrosis are more frequent, but wound complications are less frequent, and tumor tissue is better assessable in terms of malignancy grade and other possible biological factors. On the contrary, preoperative RT can be delivered at lower doses (usually 50 Gy in 25 fractions—attempts to reduce further the dose in sensitive histologic subtypes are presently underway) and to smaller fields size. As a result, long-term edema and fibrosis are less frequent, and the limb function is better. However, the wound complication rate is high (over 30%), although in recent years, thanks to the introduction of intensity modulated RT able to spare more normal tissue, the wound complication rate has been reduced. In addition, one should consider the expected quality of surgical margins, as there is growing evidence that preoperative XRT can offset the negative prognostic impact of a microscopically positive margin when the positive margin is planned in advance on a critical structure.^{13,14}

Combination Chemoradiation in the Treatment of Extremity and Trunk STS

Purpose and Rationale—Multimodality therapy including margin-negative surgical resection with adjuvant XRT results in local control in 80–95% of patients. However, patients with high-grade tumors over 5 cm are at significant risk for distant failure, which increases with tumor size. As the role of adjuvant chemotherapy remains controversial (see

below), a pilot study by Spiro et al. was performed evaluating an aggressive chemotherapy regimen interdigitated with radiotherapy with impressive 5-year local control, disease-free survival, and overall survival rates. Based on these data, the Radiation Therapy Oncology Group (RTOG) initiated a phase II trial to evaluate the efficacy and toxicity of a modified mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) regimen in a multiinstitutional setting (RTOG 9514).^{15,16}

Study Design and Endpoints—One-hundred ninety patients with high-grade primary or locally recurrent STS > 8 cm were included. Patients were to receive three cycles of the modified MAID chemotherapy interdigitated with 44 Gy of preoperative XRT. Surgery was planned for 80 days after the initiation of the first cycle of chemotherapy. Postoperatively, three additional cycles of modified MAID were given between 21 and 35 days following surgery. Endpoints included wound complications, clinical response assessed by the response evaluation criteria in solid tumors (RECIST) criteria, and the logic response according to the percentage of viable tumor and chemotherapy and radiation-associated toxicity.

Results: Primary and Secondary Endpoints—Sixty-six patients from 31 institutions were enrolled between 1997 and 2000. Patients treated on this protocol were high risk, with a median tumor size of 15 cm and 80% grade 3 tumors. Only 59% of patients received all six cycles of chemotherapy, mainly related to treatment toxicity. There were three deaths (5%) associated with treatment, two of whom developed acute myelogenous leukemia secondary to chemotherapy. Of all patients, 84% experienced grade 4 toxicity, and 97% experienced grade 3 or higher toxicity. At a median follow-up of 7.7 years in surviving patients, 22.2% of patients developed local failure, and distant metastases were identified in 28.1% of patients.

Conclusions—Although the toxicity is significant, the long-term outcomes were potentially better than might be expected in such high-risk STS patients.

Commentary—Combination chemoradiation is used in a variety of solid tumors with improved efficacy over either modality alone. RTOG 9514 utilized an aggressive preoperative and postoperative chemotherapy regimen in combination with preoperative XRT, in which up to 40% of patients were not able to complete all cycles of therapy due to toxicity. The survival outcomes were favorable for this high-risk group, but the significant toxicity must be balanced with efficacy. It is worthy to mention that there are some other experiences combining XRT with anthracycline + ifosfamide, showing a more favorable toxicity profile.¹⁷ In addition, these combinations seem of particular benefit when a margin over a critical structure is expected to be close/positive and function preservation is the goal.¹⁸ New combinations are currently being tested, with histology-specific drugs (i.e., trabectedin and XRT in myxoid liposarcoma),¹⁹ different classes of drugs (tyrosine kinase inhibitors and XRT in unselected soft tissue sarcoma),^{20–22} immunotherapy and XRT in undifferentiated pleomorphic sarcoma or dedifferentiated liposarcoma (NCT03092323),²³ or devices (nanoparticles and XRT in unselected soft tissue sarcoma).²⁴ As we continue to

evaluate novel treatment regimens, these studies serve as basis for combination multimodality therapy.

SYSTEMIC THERAPY

Sarcoma Metaanalysis Collaboration (SMAC)

Purpose and Rationale—Several randomized clinical trials were conducted before 1997 to examine the efficacy of adjuvant doxorubicin-based chemotherapy after complete resection of STS. However, individually, these trials failed to show a significant benefit of adjuvant chemotherapy, although there were some trends towards improved outcomes. Therefore, the Sarcoma Meta-analysis Collaboration was initiated to assess whether a metaanalysis of the individual data from these trials would lead to more definitive evidence for the use of adjuvant chemotherapy in localized STS.^{25,26}

Study Design and Endpoints—A comprehensive literature search was performed to identify randomized controlled trials (RCTs) of adjuvant chemotherapy after resection of localized STS. The updated data from individual patients from all available randomized trials was collected, after which a quantitative metaanalysis was performed. The primary endpoints were set at overall survival, recurrence-free survival, and local and distant recurrence-free survival. Also, a potential beneficial effect of chemotherapy was analyzed for several patient and tumor characteristics such as age, sex, disease status at randomization, disease site, histology, grade, tumor size, extent of resection, and use of radiotherapy.

An update was performed in 2008, in which four additional RCTs were identified.²⁶ In the newer trials, doxorubicin was combined with ifosfamide, while in the 14 trials analyzed in the original SMAC, only 1 out of 14 combined doxorubicin with ifosfamide. Therefore, the objective was to update the 1997 metaanalysis to assess the efficacy of doxorubicin-based chemotherapy both with and without ifosfamide, as well as to assess differences between doxorubicin regimens without ifosfamide and doxorubicin with ifosfamide.

Results

Primary Publication-1997—A total of 1568 patients were identified from 14 trials with doxorubicin-based adjuvant chemotherapy.²⁵ Median follow-up time was 9.4 years. Sarcomas of all sizes and locations were included, and a minority of tumors were low grade. Out of these trials, six were performed with doxorubicin monotherapy, while the other trials used different combinations along with doxorubicin. For overall survival, the hazard ratio (HR) for the chemotherapy arm was 0.89, but this did not reach significance ($p = 0.12$). HRs for local recurrence-free survival, distant recurrence-free survival, and overall recurrence-free survival were 0.73, 0.70, and 0.75, respectively, all of which were significant ($p < 0.05$). The absolute risk reduction for distant metastases was 10% (5–15%) in the chemotherapy group compared with placebo. None of the analyzed characteristics was significantly correlated with a beneficial effect of chemotherapy, however sarcoma in the extremity seemed to benefit more.

SMAC Update-2008—A total of 18 trials representing 1953 patients were included.²⁶ All four new trials combined doxorubicin with ifosfamide. For overall survival, the odds ratio (OR) for adjuvant doxorubicin-based chemotherapy without ifosfamide was 0.84, which was not statistically significant. However, the OR for overall survival for doxorubicin + ifosfamide was 0.56 (0.36–0.85) in favor of chemotherapy. There were also benefits for local recurrence (0.66) and distant recurrence (0.61) in favor of chemotherapy which were significant. The absolute risk reduction in terms of overall survival was 11% (3–19%) in the doxorubicin + ifosfamide group when compared with placebo.

Conclusions—SMAC demonstrated that adjuvant doxorubicin-based chemotherapy significantly improves the time to local and distant recurrence. The addition of ifosfamide to doxorubicin-based chemotherapy is associated with significant, but modest, improvements in overall survival.

Commentary—Based on the original and updated SMAC, adjuvant doxorubicin-based chemotherapy is associated with improved local recurrence, distant recurrence, and overall survival in combination with ifosfamide. When considering adjuvant treatment for sarcoma, the combination of doxorubicin and ifosfamide should be considered standard of care. However, only a small minority of patients will benefit from adjuvant chemotherapy, and therefore balancing the benefits against toxicity and carefully selecting patients remains essential.

Adjuvant Doxorubicin and Ifosfamide Versus Observation for Intermediate- and High-Grade Sarcoma (EORTC 62931)

Purpose and Rationale—This study started before SMAC was published and aimed to address the unanswered question of whether adjuvant doxorubicin and ifosfamide would improve survival in intermediate- and high-grade sarcoma. A previous European Organisation for Research and Treatment of Cancer (EORTC) study²⁷ had shown no benefit of adjuvant chemotherapy on overall survival of both low- and high-grade sarcoma of all histologies but did show a benefit on relapse-free survival. However, the chemotherapy regimen in this study was suboptimal, and therefore EORTC 62931 was initiated to investigate the effects of doxorubicin and ifosfamide on overall survival.²⁸

Study Design and Endpoints—This multicenter randomized trial from the EORTC was performed in 12 European countries and Canada in 36 different sarcoma centers. Patients with completely resected intermediate- or high-grade (grade 2 or 3) primary or recurrent STSs at any site and with any size were included. Patients were randomized between five cycles of adjuvant doxorubicin, ifosfamide (5 g/m²), and lenograstim versus no adjuvant chemotherapy. Patients in both groups received radiotherapy after a resection with margins < 1 cm and for recurrent sarcoma, but radiotherapy was started in the treatment group after finalizing adjuvant chemotherapy. The primary endpoint was overall survival, and analyses were done by intention to treat.

Results: Primary and Secondary Endpoints—Between 1995 and 2003, 351 patients were randomly assigned to either adjuvant chemotherapy or no chemotherapy. Adjuvant

radiotherapy was equally given in both groups. Out of 163 patients starting chemotherapy, 130 patients (80%) completed all five cycles, and chemotherapy was in general well tolerated. There were no deaths due to toxic effects. In the control group, five patients did receive chemotherapy due to patient's choice, while in the treatment group, 44 patients did not receive chemotherapy or received it too late and were not eligible for analysis. Neither relapse-free nor overall survival differed significantly between both groups. The 5-year overall survival rate was 66.5% in the chemotherapy group versus 67.8% in the control group. However, when analyzing the effects of adjuvant chemotherapy for different prognostic factors, higher grade, larger size, and limb sarcoma were more likely to benefit from adjuvant chemotherapy.

Conclusions—This study showed no benefit of adjuvant chemotherapy with doxorubicin and ifosfamide after resection of STS in relapse-free survival or overall survival.

Commentary—This trial evaluating the effects of adjuvant doxorubicin and ifosfamide failed to show a benefit in overall survival. However, 44 (25%) patients in the chemotherapy arm did not receive chemotherapy or started too late to be included but were included in the intention-to-treat analysis. The data suggest that future studies should focus on patients with larger, grade III, and extremity sarcomas, as the forest plots show a nonsignificant advantage for adjuvant chemotherapy in tumors with these characteristics. Interestingly, this study included tumors of all sizes and all locations, as well as both intermediate- and high-grade tumors. Also, the ifosfamide dose was relatively low, with 5 mg/m², while currently the most common dose is 9–12 mg/m². All of this might have influenced the outcome of this study, and this study teaches us that a potential benefit for (neo-) adjuvant chemotherapy will most likely only be found in high-risk tumors. It is worthy to note that patients included in the study were affected by a disease with a median risk of death in the 30% range. While this risk cannot be considered low, especially on a patient's perspective, the proportional (not only the absolute) risk reduction of the administration of chemotherapy looks lower when the baseline risk is lower.²⁹ This limits the potential of detecting the efficacy of chemotherapy when the population selected in the trial is marked by an intermediate risk. This study was recently revisited, and patients were stratified by the predicted overall survival using a validated nomogram.³⁰ When a cut-off of predicted risk of death of 40% was used, patients with a predicted overall survival inferior to 60% had a significant benefit in disease-free survival and overall survival by the administration of adjuvant chemotherapy.³¹ Tools like Sarculator to help select patients for future studies will have to be considered.

Three Cycles Preoperative Chemotherapy Versus Three Cycles Preoperative Followed by Two Cycles Postoperative Chemotherapy for High-Risk Extremity and Trunk Soft-Tissue Sarcoma (ETSTS)

Purpose and Rationale—A previous Italian randomized study in high-risk sarcoma patients had demonstrated an improved overall survival after five cycles of adjuvant chemotherapy with full-dose epirubicin and ifosfamide (included in SMAC).³² After this trial, there were suggestions that only the first three cycles of chemotherapy would be sufficient for distant-disease control, as the dose intensity of the latter two cycles had dropped significantly.³² Therefore, the Italian and Spanish Sarcoma Groups performed an

RCT comparing three cycles to five cycles of chemotherapy, also shifting towards a neoadjuvant or combined neoadjuvant/adjuvant approach. The hypothesis was that three cycles was noninferior to five cycles of standard chemotherapy, leading to an improved cost-benefit ratio towards three cycles.³³

Study Design and Endpoints—This randomized controlled trial was conducted in 13 Italian and Spanish sarcoma centers. Patients with a high-grade sarcoma > 5 cm, deeply seated, and high grade [grade 3 according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)] were randomized into two groups: patients in arm A would receive three preoperative cycles of epirubicin and ifosfamide, while patients in arm B were to receive the same three preoperative cycles followed by two postoperative cycles (three vs. five cycles). There was no preference for neoadjuvant or adjuvant radiotherapy, but this was left to the discretion of the individual centers. The primary endpoint was overall survival, and the trial was set up as a noninferiority study.

Results: Primary and Secondary Endpoints—Between 2002 and 2007, 328 patients were randomized between the two groups. Ten-year overall survival was 61% for the entire group, 64% in arm A and 59% in arm B. Three cycles of chemotherapy was not inferior to five cycles according to the intention-to-treat analysis. In arm A, 14% of all patients did not complete the chemotherapy cycles. In arm B, 8% of all patients did not complete the first three cycles, and 25% of the patients did not complete the postoperative chemotherapy cycles. Best responders were undifferentiated pleomorphic sarcoma (UPS), and worst responders were leiomyosarcoma (LMS). Response to therapy was confirmed to be associated with improved overall survival.

Conclusions—After 10 years of follow-up, this study shows no difference in overall or recurrence-free survival between three cycles of neoadjuvant epirubicin and ifosfamide and three neoadjuvant cycles followed by two adjuvant cycles.

Commentary—When considering preoperative or perioperative chemotherapy for high-risk sarcoma, this study confirms that three cycles of preoperative chemotherapy was noninferior to five cycles of perioperative chemotherapy. Of note, 25% of patients scheduled to get postoperative chemotherapy were not able to complete the postoperative treatment cycles. However, a per protocol analysis confirmed the noninferiority of three cycles against five cycles. When the goal of preoperative treatment is downsizing the tumor, more cycles can be considered in individual cases after a good response. However, there is no proven benefit on overall survival of administering more than three cycles even in responding patients as of yet. The fact that responders have a better outcome than nonresponders suggest that treating patients with neoadjuvant chemotherapy can provide insight into prognosis and tumor biology in individual patients. Finding good early markers predicting response is however essential to further personalize neoadjuvant chemotherapy.

Histotype-Specific Neoadjuvant Chemotherapy Versus Standard Chemotherapy of Extremity and Trunk STS

Purpose and Rationale—As our understanding of the importance of sarcoma histology has evolved, it was recognized that previous trials were designed with the same standard chemotherapy regimens for all the different histological sarcoma subtypes, which might not necessarily reflect the differences in inherent tumor biology between the sarcoma subtypes. Therefore, an international, open-label randomized multicenter trial comparing three cycles of standard chemotherapy with three cycles of histology-tailored chemotherapy based on histological sarcoma subtypes, as determined by expert opinions, was performed. The hypothesis was that neoadjuvant histotype-specific chemotherapy would result in improved disease-free survival compared with standard chemotherapy.^{34,35}

Study Design and Endpoints—This phase 3 randomized controlled trial was conducted in 4 European countries at 32 centers. Patients with localized STS > 5 cm, deeply seeded, and high grade (grade 3 FNCLCC) were included in one of the following five histological subtypes: myxoid liposarcoma (MLPS), undifferentiated pleomorphic sarcoma (UPS), leiomyosarcoma (LMS), synovial sarcoma (SS), and malignant peripheral nerve sheath tumors (MPNST). Patients were to receive either three cycles of epirubicin/ifosfamide or the following regimens per subtype: trabectedin for MLPS, gemcitabine and docetaxel for UPS, gemcitabine and dacarbazine for LMS, high-dose ifosfamide for SS, and etoposide with ifosfamide for MPNST. The primary endpoint was disease-free survival, and safety was a secondary endpoint.

Results: Primary and Secondary Endpoints—A total of 287 patients were included between 2011 and 2016. The patients were diagnosed with MLPS ($n = 64$), UPS ($n = 97$), LMS ($n = 28$), SS ($n = 70$), and MPNST ($n = 27$). At the third futility analysis after a median follow-up of 12.3 months, patients treated with histotype-tailored chemotherapy had significant reduced disease-free survival and overall survival (4-year DFS and OS 38% and 64%, respectively) compared with those treated with standard chemotherapy (4-year DFS and OS 62% and 89%, respectively), and therefore the study was closed. Due to toxicity, 6% of patients in the standard arm and 4% in the histotype-specific arm interrupted treatment. On the final analysis, with a median follow-up of 52 months, the reduction in disease-free survival lost its significance (5-year DFS 47% against 55%, $p = 0.323$), while the difference in overall survival stood (5-year OS 66% against 76%, $p = 0.018$).

Conclusions—There was no benefit of histotype-tailored chemotherapy over standard chemotherapy for localized ETSTS belonging to the five histologic subtypes included in the study.

Commentary—Although histologic subtype is one (if not the most) important determinant of outcomes for patients with STS, the use of histotype-tailored chemotherapy was not superior over standard chemotherapy for localized ETSTS with currently available agents in the five histologic subtypes included in the study. However, care should be taken interpreting these data, since the definition of high-risk sarcomas is shifting from a set of fixed parameters to a more flexible prediction model for high risk with the developments of new

predictor tools for outcome (Sarculator app), and patients in this trial treated with standard chemotherapy had overall survival outcomes better than the control arm of the first Italian Sarcoma Group (ISG) study³² and the control arm of the high-risk subgroup analysis of the EORTC 62931 study.³¹ Also, the opinions and experience with other more histotype-specific drugs are developing further, potentially leading to other preferred systemic treatment regimens per subtype.

FUTURE DIRECTIONS FOR MULTIMODALITY THERAPY FOR SOFT-TISSUE SARCOMA

Margin-negative surgical resection remains the cornerstone of the management of localized STS. The use of radiation therapy, especially in the preoperative setting, in addition to surgery has led to increases in limb-sparing procedures and low risk of local recurrence. Trials evaluating short-course XRT, combination of XRT with immunotherapeutics (i.e., immune checkpoint blockade and intralesional therapy), and other novel agents are ongoing, with the aim to provide improved systemic control in these high-risk patients. The use of systemic cytotoxic chemotherapy should be considered in high-risk patients, but histotype-specific approvals for metastatic disease and new agents, including the incorporation of immunotherapy and other targeted agents, hold promise for moving the field further and minimizing toxicity (Tables 1, 2).

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TABLE 1

Landmark surgery and radiation trials

Year	Authors	RCT arms or study group	Major finding	Impact on practice
1982 ³	Rosenberg et al.	Amputation (<i>n</i> = 16) versus limb-sparing resection + postoperative XRT (<i>n</i> = 27)	No difference in disease-free survival. Increased local recurrence in limb-sparing group (0 vs. 15%, <i>p</i> = 0.06)	Limb-sparing surgery standard of care
1996 ⁴	Pisters et al.	Adjuvant brachytherapy (<i>n</i> = 78) versus no brachytherapy (<i>n</i> = 86) in patients with low- and high-grade ETSTS	Decreased 5-year local recurrence in brachytherapy group (89% compared with no brachytherapy (66%) in high-grade tumors No difference in local recurrence for low-grade tumors	Brachytherapy improved local control after complete resection of high-grade STS
1998 ⁵	Yang et al.	Postoperative adjuvant radiotherapy (<i>n</i> = 70) versus surgery alone (<i>n</i> = 71)	Decreased 10-year local recurrence with radiotherapy (0 vs. 22%, <i>p</i> = 0.003)	Adjuvant radiotherapy standard of care for STS
2010 ⁶	Beane et al.			
2002 ¹¹	O'Sullivan et al.	Preoperative 50 Gy versus postoperative 66 Gy external beam radiotherapy	No difference in local recurrence Increased acute wound complications in preop XRT group (35% vs. 17%). Increased late toxicity on postoperative XRT group (48.2% vs. 31.5%)	Preoperative or postoperative XRT acceptable as adjuvant therapy for localized STS. Increased acute toxicity with preop XRT, increased late toxicity with postop XRT
2005 ¹²	Davis et al.			
2006 ¹⁵	Kraybill et al.	Three cycles mesna, doxorubicin, ifosfamide, and dacarbazine + XRT preoperatively + three cycles postoperative chemotherapy.	97% grade 3 toxicity at 7.7 years follow-up. 28% distant metastasis, favorable compared with historic controls	Combination chemoradiation feasible, but with high toxicity. Better toxicity profile in recent experiences with doxorubicin-ifosfamide without dacarbazine combined to XRT ¹⁷
2010 ¹⁶	RTOG 9514			

TABLE 2

Landmark chemotherapy trials and metaanalysis

Year	Authors	RCT arms or study group	Major finding	Impact on practice
1997 ²⁵	Sarcoma metaanalysis collaboration	1568 patients from 14 trials of doxorubicin-based adjuvant chemotherapy	10% (5–15%) absolute risk reduction for distant in chemotherapy group compared with placebo	Adjuvant doxorubicin should be considered for patients with localized ETSTS
2008 ²⁶	Sarcoma metaanalysis collaboration—update	Added four trials to SMAC-1998; 1953 patients from 18 trials	1.1% (3–19%) absolute risk reduction for survival in doxorubicin + ifosfamide compared with placebo	Combination doxorubicin + ifosfamide potentially more efficacious than doxorubicin alone
2012 ²⁸	Woll et al. EORTC 62931	Adjuvant doxorubicin + ifosfamide (five cycles) versus observation	No difference in overall survival in the overall group. A trend towards better RFS in large high-grade STS of the extremity in the 10% range, mirrored by a subsequent unplanned analysis ³¹ stratifying patient by the predicted risk of death with a 20% absolute reduction of the risk of death in high-risk ETSTS patients (predicted OS < 60%) ³⁰	Adjuvant chemotherapy should be considered in high-risk ETSTS
2016 ³³	Gronchi et al. ISG-STS 0101	Preop epirubicin + ifosfamide; three cycles preop versus three cycles preop + two cycles postop (i.e., three vs. five)	No difference in survival. 25% in pre/post group did not complete postop chemo	Consideration of short-course preop chemo
2017 ³⁴ 2020 ³⁵	Gronchi et al. ISG-STS 1001	Three cycles preoperative standard chemotherapy (epirubicin + ifosfamide) versus histiotype-tailored chemotherapy	Reduced disease-free survival in histiotype-tailored chemotherapy group (38%) versus standard chemotherapy (62%)	No benefit of histiotype-tailored chemotherapy over standard chemotherapy for localized ETSTS