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REVIEW ARTICLE

Local Control of Soft Tissue and Bone Sarcomas

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A B S T R A C T

Sarcomas of soft tissue and bone are mesenchymal malignancies that can arise in any anatomic location, most commonly the extremity, retroperitoneum, and trunk. Even for lower grade histologic subtypes, local recurrence can cause significant morbidity and even disease-related death. Although surgery remains the cornerstone of local control, perioperative radiation and systemic therapy are often important adjuvants. This review will summarize the current therapeutic approaches for local control of soft tissue and bone sarcomas.

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INTRODUCTION

Sarcomas are a diverse group of malignancies arising within soft tissue and bone. With more than 80 different histologic subtypes that develop from or within muscle, fat, nerves, cartilage, and bone, these mesenchymal malignancies present unique therapeutic challenges. When feasible, patients with suspected sarcoma should be evaluated by a multidisciplinary sarcoma program including a sarcoma pathologist, medical oncologist, radiation oncologist, radiologist, and experienced sarcoma surgeon. The multidisciplinary approach has been shown to improve clinical outcomes in multiple sarcoma studies performed in Europe and the United States[1] and facilitates referral to histology-specific clinical trials when indicated. In a study of 375 patients with extremity and retroperitoneal sarcoma, patients not treated at a sarcoma center had a 2.4-fold higher risk of local recurrence compared with those treated at a sarcoma center.[1]

Local control refers to treatment approaches focusing on the primary site of disease. Although we review the impact of surgery, radiation, chemotherapy, targeted therapy, and immunotherapy on local control, it should be noted that seemingly focal treatments such as surgery and radiation may have systemic effects (abscopal) and systemic therapies such as chemotherapy can affect local control. Although local control is not necessarily synonymous with focal treatment, the therapeutic goals of local control are to improve patient survival and minimize or eliminate the morbidity associated with the primary tumor.

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SOFT TISSUE SARCOMA

In general, local control of soft tissue sarcoma (STS) involves the appropriate utilization of perioperative radiation and surgery. The role of systemic treatments, such as chemotherapy, targeted therapy, and immunotherapy, on local control is not as clearly defined. We will review each therapeutic modality as it relates to local control.

Surgery

Proper surgical resection remains the cornerstone of local control in STS. Similar to systemic therapies, the extent of surgical resection has increasingly become histology specific and has generally moved away from overly morbid operations, highlighting the importance of evaluation by a sarcoma surgeon.

For extremity STS, early studies showed that wide local excision (WLE) alone was associated with local recurrence rates as high as 30% to 50%.[2,3] Given poor local control with WLE alone, amputation became common practice until the use of perioperative radiation therapy (XRT) enabled effective limb-sparing surgery. A seminal National Cancer Institute trial compared amputation with WLE and XRT in patients with high-grade extremity STS. In a 1:2 randomization, 16 patients underwent amputation and 27 patients were treated with WLE and XRT. Both groups were also treated with adjuvant doxorubicin-based chemotherapy.[4] Despite a local recurrence rate of 15% with WLE and XRT and 0% with amputation, there was no difference in overall survival. Because amputation did not

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provide a survival benefit, WLE and XRT became the standard for primary high-grade extremity STS.

Unlike extremity STS, most patients with retroperitoneal STS die of local or regional recurrences. Optimizing local control may improve disease-specific survival for retroperitoneal STS.[5-8] In an STS study demonstrating this, disease-specific mortality was caused by local recurrence without synchronous metastasis in 77% of patients with retroperitoneal STS, compared with only 9% of patients with extremity and trunk STS.[9] Because the completeness of resection is the primary determinant of local recurrence in retroperitoneal STS, there has been interest in extending surgical margins. As a result, there is an ongoing debate as to the potential benefit of extended surgical resection, which is defined as resection of uninvolved adjacent organs (typically the psoas muscle, colon, and kidney) to obtain a rim of normal tissue surrounding the tumor[10,11] (Fig 1). In multivariate analysis of a large retrospective series of 382 patients, extended surgical resection showed a 3.3-fold lower rate of local recurrence compared with simple complete resection but was not associated with improved overall survival.[12] Follow-up analysis of the same series, however, reported a 66% overall survival rate among the extended surgical resection cohort compared with a 48% overall survival rate in historic controls.[13-16] A major limitation of this approach, beyond the nonrandomized nature of the data, is the morbidity associated with the operation. In a series of 249 patients, 30% required a reoperation or invasive procedure for a complication related to surgery, and 3% of patients died of postoperative complications.[17] Additional high-quality studies are required to evaluate the optimal surgical margins for local control of retroperitoneal STS.

XRT

As discussed earlier, local control is improved with perioperative XRT in patients with extremity STS. For local recurrence, the indication for XRT differs from patients with primary disease depending on whether XRT was previously administered. For patients who did not receive XRT with initial resection, reresection and XRT are indicated.

The timing of XRT, whether preoperative or postoperative, remains a debate. Both approaches have similar local control efficacy, but preoperative XRT results in lower rates of long-term fibrosis and lymphedema and improved joint mobility[18] compared with postoperative XRT. This may be attributed to the smaller volume of irradiated tissue[19] and the lower XRT doses[20,21] used in the preoperative setting. A disadvantage of preoperative XRT, however, is the increased rate of wound complications. In a randomized trial of 200 patients with STS, patients receiving preoperative XRT had more wound complications compared with patients treated with XRT postoperatively (35% *v* 17%, respectively).[22]

Whether XRT can improve local control in retroperitoneal STS is under investigation. The potential benefit of XRT in reducing local recurrence must be weighed against toxicity to adjacent organs, primarily bowel and kidney.[23,24] Two prospective trials have evaluated the role of neoadjuvant XRT on local control in patients with retroperitoneal STS.[25,26] Collectively, 54 patients with intermediate- to high-grade STS were treated with neoadjuvant XRT followed by an R0 resection; the local recurrence rate at 5 years was 40%.[27] An ongoing, multi-institutional, randomized, phase III trial (named STRASS by the European Organisation for Research and Treatment of Cancer) is evaluating preoperative XRT plus surgery versus surgery alone for patients with retroperitoneal STS with the primary end point of abdominal recurrence-free survival (ClinicalTrials.gov identifier: NCT01344018).

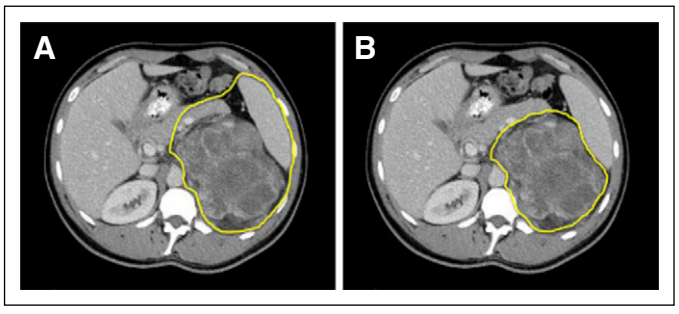

Fig 1. Cross-sectional imaging showing retroperitoneal sarcoma. (A) Yellow line shows boundary of an extracompartmental resection of tumor that includes splenectomy and distal pancreatectomy. (B) Yellow line shows boundary of conventional resection of tumor. In both cases, the medial margin is the same where the tumor abuts spine and aorta. Reprinted with permission.[5]

Chemotherapy

Individual studies evaluating local control of STS with perioperative chemotherapy have produced mixed results. A meta-analysis of 14 randomized trials, comprising 1,568 patients with retroperitoneal and extremity STS (median follow-up, 9.4 years), demonstrated that adjuvant doxorubicin-based chemotherapy was associated with a slight decrease in local recurrence (hazard ratio, 0.73; 95% CI, 0.56 to 0.94).[28] Subsequent individual trials with combinations of anthracycline-based regimens (doxorubicin or epirubicin) and ifosfamide have also demonstrated inconsistent findings. A meta-analysis in 2008 included all trials from the prior meta-analysis and patients from four additional trials (n = 1,953) treated with ifosfamide and doxorubicin. This study confirmed the marginal efficacy of chemotherapy in improving local control of patients with STS (hazard ratio, 0.73; 95% CI, 0.56 to 0.94).[29]

Emerging Treatments: Targeted Therapy and Immunotherapy

Sarcomas are increasingly being classified by the molecular abnormalities thought to drive pathogenesis. The following three core molecular mechanisms have been described in sarcomagenesis: DNA copy number abnormalities, somatic mutations in key signaling pathways, and transcriptional dysregulation from chimeric transcriptional factors.[30] Although there are many agents under investigation, the importance of understanding genetic alterations for the sarcoma clinician is to maintain familiarity with experimental trials using novels agents for patients with local recurrence who have experienced treatment failure with conventional therapy. Immunotherapy has shown promise in treating metastatic synovial cell sarcoma.[31] There are ongoing trials evaluating the role of immunologic checkpoint inhibitors, such as anti–programmed death ligand 1 (PD-L1) and anti–cytotoxic T-cell lymphocyte-4, on local control. The Neoadjuvant Durvalumab and Tremelimumab Plus Radiation for High-Risk STS (NEXIS) trial will evaluate WLE and XRT versus WLE and XRT

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plus anti–PD-L1/anti–cytotoxic T-cell lymphocyte-4 on local control in patients with high-grade truncal STS (ClinicalTrials.gov identifier: NCT03116529). A multi-institutional randomized phase II trial will evaluate WLE and XRT versus WLE and XRT plus anti–PD-L1 in patients with high-risk extremity STS (ClinicalTrials.gov identifier: NCT03092323; Table 1).

Surveillance of Local Recurrence

STS local recurrences occur in approximately 10% of patients treated with margin-negative resection and perioperative XRT. Most recurrences occur within the first 2 years.[21,32,33] Patients with a local recurrence have a poorer prognosis compared with patients who remain disease free, but it is not clear whether recurrence is part of a stepwise progression to metastatic disease or merely a marker of aggressive biology. The optimal time interval to surveil for local recurrence after resection of a primary tumor has not been well studied, but consensus-based National Comprehensive Cancer Network guidelines recommend cross-sectional imaging with magnetic resonance imaging (with and without contrast) every 4 to 6 months. Because STSs have a predilection to metastasize to the chest, a computed tomography (CT) scan of the chest (with contrast) is also performed. Although the role of fluorodeoxyglucose positron emission tomography/CT for surveillance is under investigation, it has proven to be effective in monitoring response to therapy in STS.[34-36]

BONE SARCOMA

The overall therapeutic approach for local control of bone sarcomas is histology dependent, but the mainstay of therapy remains surgical. The three predominant primary bone sarcomas—osteosarcoma, Ewing sarcoma, and chondrosarcoma—have dramatically different susceptibilities to adjuvant chemotherapy and XRT; as such, adjuvant protocols are histologically determined. The impact of emerging systemic treatments such as targeted therapy and immunotherapy on local control is not well established. We will review each therapeutic modality as it relates to local control of primary bone sarcoma.

Surgery

Historically, before the integration of chemotherapy, overall survival in osteosarcoma was dismal (< 20%) despite the use of amputation for negative-margin local control.[37] This changed dramatically in 1986, when a landmark study showed an increased 6-year overall survival rate from 11% to 61% with the

Table 1. Selected Clinical Trials of Neoadjuvant Therapy for Local Control of Soft Tissue Sarcoma

Institution and Trial Name	Location	Site	Trial Design	ClinicalTrials.gov Identifier
Radiation therapy				
University of Iowa	Iowa City, IA	All	Phase I/II: XRT + intratumor injections of talimogene laherparepvec	NCT02453191
German Cancer Research Center (RETRO-WTS)	Heidelberg, Germany	Retroperitoneal	Phase I/II: neoadjuvant + intraoperative XRT	NCT01566123
Radiation Therapy Oncology Group	Multiple institutions	Trunk and extremity	Phase II: image-guided XRT	NCT00589121
Technische Universität München (PREMISS)	Munich, Germany	Extremity	Phase II: image-guided, intensity-modulated XRT ± brachytherapy	NCT01552239
Targeted therapy				
University of California at Davis	Davis, CA	Trunk and extremity	Phase I/II: XRT + sorafenib	NCT00864032
German Cancer Research Center (SunRaSe)	Heidelberg, Germany	All	Phase I: XRT + sunitinib	NCT01498835
Heidelberg University	Mannheim, Germany	All	Phase II: pazopanib	NCT01543802
Massachusetts General Hospital	Boston, MA	All	Phase II: bevacizumab + XRT	NCT00356031
Oregon Health & Science University Cancer Institute	Portland, OR	Extremity	Phase I: sorafenib + epirubicin/ifosfamide + XRT	NCT00822848
University of Vermont	Burlington, VT	All	Phase I/II: docetaxel/gemcitabine + pazopanib	NCT01719302
National Cancer Institute	Bethesda, MD	All	Phase III: XRT + ifosfamide/doxorubicin *v* XRT + pazopanib	NCT02180867
University of Washington	Seattle, WA	Extremity	Phase I: chemotherapy + XRT + pazopanib	NCT01446809
Immunotherapy				
University of Maryland (NEXIS)	Baltimore, MD	Trunk	Phase I/II: XRT + anti–PD-L1/anti–CTLA-4 + WLE	NCT03116529
Moffitt Cancer Center	Tampa, FL	Trunk and extremity	Phase II: XRT + intratumor dendritic cell injections	NCT00365872
SARC (SU2C-SARC032)	Durham, NC	Extremity	Phase II: XRT + anti–PD-L1 *v* XRT	NCT03092323
Mayo Clinic	Rochester, MN	Extremity	Phase II: chemotherapy + XRT + sargramostim	NCT00652860

Abbreviations: CTLA-4, cytotoxic T-cell lymphocyte-4; PD-L1, programmed death ligand 1; SARC, Sarcoma Alliance for Research Through Collaboration; WLE, wide local excision; XRT, radiation therapy.

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addition of multiagent adjuvant chemotherapy.[38] Concurrently, a second study demonstrated that neoadjuvant chemotherapy provided a similar survival advantage.[39] Chemotherapy before surgery provides three secondary benefits that have had a lasting influence on how we treat osteosarcoma. Neoadjuvant chemotherapy provides manufacturing time for endoprostheses, a necessity in the era of all-custom implants; often decreases tumor size, lessening surgical morbidity and improving surgical margins; and provides prognostic information about treatment efficacy through pathologic response and necrosis. The protocols that allowed time to design and build implants made possible the era of functional limb salvage surgery. Coupled with advances in imaging and chemotherapy regimens, improved surgical techniques over the next decade improved the ability to achieve better oncologic and functional results.[40,41] Limb salvage surgery is now performed in nearly 90% of all patients with appendicular osteosarcoma,[42,43] with higher functional results and equivalent oncologic results to amputation.[44,45] At present, amputation is generally reserved for tumors for which a negative margin resection is not possible without creating a nonfunctional limb.[42] Nonetheless, surgical resection of all evidence of disease remains essential to achieving both local control and overall survival in osteosarcoma.[43,46,47]

In Ewing sarcoma, similar advances in chemotherapy, imaging, and surgical technique occurred over the past three decades. The surgical approach to Ewing sarcoma remains similar to osteosarcoma, with negative-margin surgical resection remaining the most widely used approach for local control.[48] Given the radiosensitivity of Ewing sarcoma, however, surgery is not mandatory in Ewing sarcoma, as it is in osteosarcoma. In a recent prospective clinical trial, surgery achieved a small but statistically significant advantage over XRT with respect to local control of disease.[49] Surgery also has an advantage in that it avoids risks of secondary malignancy caused by radiation, as well as a potential advantage in clarity in surveillance imaging. Nonetheless, if surgery is unlikely to achieve negative margins or carries undue morbidity, XRT remains an effective means for local control.

In chondrosarcoma, where XRT and chemotherapy are largely ineffective, negative-margin surgery represents the only approach for local control of primary disease. Given the predominance for axial locations, negative-margin surgery is often more technically challenging.[50,51] Nonetheless, complete resection is essential because any residual tumor cells will likely lead to local recurrence. With no adjuvant support from XRT or chemotherapy, marginal margins are extremely high risk.[50,51]

XRT

Since the original description by James Ewing in 1921, Ewing sarcoma has been in part defined by its sensitivity to XRT. Unlike osteosarcoma, definitive XRT offers reasonable success rates in local control of disease and can be used in lieu of surgery.[52] Nonetheless, recent work has shown small but statistically significant improved local outcomes with surgery over XRT and has led to recent recommendations from the Children's Oncology Group for "surgical resection when appropriate, whereas radiotherapy remains a reasonable alternative in selected patients."[49] (p467) In addition, there is a renewed interest in adjuvant XRT in association with surgery, especially in axial tumors with more challenging surgical margins.

Conversely, osteosarcoma and chondrosarcoma are relatively radiation-resistant tumors. XRT is generally reserved for patients in whom surgery is not acceptable to the patient or carries undo morbidity and is often palliative in nature.[53-57] A study of 31 patients with localized high-grade osteosarcoma who refused surgery and were treated with 60 Gy of XRT reported a 5-year local control rate of 56%.[58] The small-cell variant of osteosarcoma has been reported to be more sensitive to XRT,[59] but there is currently no role for XRT in patients with completely resected or resectable osteosarcoma.

The efficacy of XRT for local control of bony sarcoma may need to be re-evaluated in light of new techniques including carbon ion XRT, proton-beam XRT, and intensity-modulated XRT.[60,61] Carbon ion XRT has shown therapeutic promise for chordoma.[54,55] Preliminary outcomes of proton-beam XRT for skull-based chondrosarcomas and chordomas have shown local control rates of 70% to 90% when combined with surgery.[62-64] Further study of these modalities will better delineate their role in local therapy for bone sarcoma.

Chemotherapy

Chemotherapy has been shown to have an important role in local control of high-grade osteosarcoma (ie, excluding parosteal osteosarcoma). In a review of 237 patients undergoing limb-sparing resections for osteosarcoma, the Rizzoli Institute reported a poor response to chemotherapy, not surgical margins, to be the strongest factor associated with local recurrence.[65] Recently, a retrospective review of 389 patients with osteosarcoma validated the importance of tumor response to chemotherapy on local control, further delineating that marginal surgical margins (< 2 mm) and poor tumor necrosis ($< 90\%$) are linked variables highly predictive of local recurrence.[66] In essence, these studies both demonstrate that chemotherapeutic response of the primary tumor likely protects patients from local recurrence in the setting of close or microscopically positive margins.

Given the often significant tumor size reduction with neoadjuvant chemotherapy, particularly with the soft tissue component of Ewing sarcoma, it can be considered critical to local control in this tumor type as well. In fact, recent literature has shown a reduction in local recurrence in pelvic Ewing sarcoma from 30% to 11% when modern doxorubicin, vincristine, cyclophosphamide, and dactinomycin are used with ifosfamide and etoposide.[67]

Chemotherapy has a limited role in the local treatment of chondrosarcoma. This chemotherapy-resistant sarcoma is primarily treated with surgery alone. However, using Response Evaluation Criteria in Solid Tumors (RECIST) to evaluate response in patients with chondrosarcoma being treated with chemotherapy, response rates varied dramatically depending on subtype, as follows: 31% for mesenchymal chondrosarcoma, 20% for dedifferentiated chondrosarcoma, 11% for conventional chondrosarcoma, and 0% for clear cell chondrosarcoma.[68] Given that more than 85% of chondrosarcomas are subtyped as conventional, few chondrosarcomas are treated with chemotherapy in practice.

Emerging Therapies: Targeted Therapy, Bisphosphonates, and Immunotherapy

The impact of novel therapies on local control of primary bone sarcoma remains investigational. Preclinical evidence

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suggests that targeting mammalian target of rapamycin and insulin-like growth factor 1 receptor may have synergistic antitumor activity against bone sarcoma. Although not designed to assess local recurrence, a phase II trial showed that cixutumumab and temsirolimus had modest clinical activity in patients with metastatic sarcoma.[69] In patients with metastatic human epidermal growth factor receptor 2 (HER2) –positive osteosarcoma, a phase II trial evaluating trastuzumab showed no significant difference in outcomes between HER2-positive and HER2-negative patients.[70]

A small phase II trial evaluating the efficacy of bisphosphonates on local control did not show any local recurrences after 5 years in patients with osteosarcoma treated with surgery, chemotherapy, and pamidronate.[71] However, the benefit of bisphosphonates on local control was not confirmed in a subsequent randomized trial of 318 patients with osteosarcoma treated with chemotherapy, surgery, and zoledronic acid.[72]

The presence of cytotoxic lymphocytes in the tumor microenvironment of patients with osteosarcoma correlates with survival, raising the possibility that perioperative immunotherapy may improve local control.[73,74] Preliminary results from the SARC028 study (ClinicalTrials.gov identifier: NCT02301039) showed a partial RECIST response to pembrolizumab in 19 patients with osteosarcoma.

Liposomal muramyl tripeptide phosphatidyl ethanolamine is an immunotherapy that induces endogenous interleukin-12 and has been shown to improve overall survival in a Children's Oncology Group phase III trial for osteosarcoma.[75]

Surveillance of Local Recurrence

There are few studies that have evaluated the optimal imaging schedule for surveillance after treatment of localized disease. Consensus-based National Comprehensive Cancer Network guidelines recommend physical evaluation, chest CT, and imaging of the surgical site as often as every 3 months during the first 2 years, with continued surveillance at increasing intervals thereafter.[76] This is often translated into practice with imaging every 3 months for 2 years, every 6 months for years 3 and 4, and annually thereafter. Similar to STS, relapse of disease, either at the surgical site or in the lungs, was identified in 20% to 30% of patients presenting with localized disease within 3 years.[77]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Local Control of Soft Tissue and Bone Sarcomas

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