Management of Extremity Soft Tissue Sarcomas

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Soft tissue sarcomas are relatively rare tumors, with approximately 9220 cases anticipated in the United States in 2007 [1]. Although soft tissue sarcomas can arise in virtually any anatomic site, patients with extremity sarcomas represent almost half of all patients [2]. In a series of 3442 patients from Memorial Sloan-Kettering Cancer Center, 33\% of all soft tissue sarcomas originated in the lower extremities and 14\% in the upper extremities [2].

Given the rarity of presentation at other anatomic sites, much of the treatment of sarcomas at non-extremity sites has been extrapolated from evidence in clinical trials of patients with extremity sarcomas. This extrapolation of treatment is largely defined by the use and timing of adjuvant therapy such as radiotherapy and systemic chemotherapy. An understanding of the management of extremity sarcoma is a keystone to optimal treatment of patients with soft tissue sarcomas at other anatomic sites.

This article provides an understanding of the evaluation, staging, and management of patients with extremity sarcoma. Although there are straightforward guidelines to the management of patients with extremity sarcoma, each patient presents with unique considerations for tumor control, functional outcome, and potential toxicities. As is true for patients diagnosed with sarcoma at other anatomic sites, a multidisciplinary team

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approach streamlines care with attention to the complexities and intricacies of choosing and delivering optimal therapy.

**Staging**

Although soft tissue sarcomas are, in fact, a heterogeneous mixture of histologies and presentations, the sixth edition of the American Joint Committee on Cancer (AJCC) staging system applies to all soft tissue sarcomas with the exception of angiosarcoma, dermatofibrosarcoma, infantile fibrosarcoma, and malignant mesenchymoma. Histologic grade, tumor size, and depth are the primary determinants of AJCC stage (Table 1). The central importance of histologic grade in the staging system is unique to soft tissue sarcoma. The presence or absence of distant or nodal disease completes the staging system. Although the histologic subtype and anatomic site of origin clearly influence outcomes [3–5], these factors are not included in the staging system; histologic subtype does help influence the analysis of histologic grade and is thus indirectly measured.

<table>
<thead>
<tr>
<th>Parameter</th>
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<tr>
<td>Primary tumor</td>
<td>TX: Primary tumor cannot be assessed; T0: No evidence of primary tumor; T1: Tumor ≤ 5 cm in greatest dimension; T1a: Superficial tumor; T1b: Deep tumor; T2: Tumor &gt; 5 cm in greatest dimension; T2a: Superficial tumor; T2b: Deep tumor</td>
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<td>Regional lymph nodes</td>
<td>NX: Regional lymph nodes cannot be assessed; N0: No regional lymph node metastases; N1: Regional lymph node metastases</td>
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<td>Distant metastases</td>
<td>MX: Distant metastases cannot be assessed; M0: No distant metastases; M1: Distant metastases</td>
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<td>Stage grouping</td>
<td>Stage I: G1-2, T1a, 1b, 2a, 2b, N0, M0; Stage II: G3-4, T1a, T1b, T2a, N0, M0; Stage III: G3-4, T2b, N0, M0; Stage IV: Any G, Any T, N1, M0; Any G, Any T, Any N, M1</td>
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Superficial defined as above and not invading the superficial fascia; deep defined as invading fascia (retroperitoneal and visceral lesions and most head and neck lesions are considered deep). 

**Abbreviation:** G, grade.

Although histologic grade can be measured on a two-, three-, or four-tiered system, the staging system incorporates all of these grades. This approach allows simplification to the more common use in everyday clinical application of a two-tiered system, low (G1, G2) or high (G3, G4) grade. This incorporation of histologic grade into the staging system reflects the finding in comparative multivariate analyses that histologic grade is the most important factor in predicting the risk for distant metastasis and tumor-related death [5,6].

Tumor size is defined by whether the sarcoma is greater than 5 cm measured clinically or radiographically. Tumor size has been shown to be an important predictive factor in determining metastasis-free and overall survival [7]. Tumor size is further subcategorized by the depth, that is, “a” if superficial (lack of involvement of superficial investing muscular fascia of the extremity) or “b” if deep (deep to, or involves, superficial fascia). Sarcomas located deep to the investing muscle fascia have been shown to have a worse prognosis [5,6].

Of all the applicable anatomic sites, the AJCC staging system is best designed for extremity sarcomas. In the sixth edition, the AJCC reclassified tumors that were T2b, G1-2, N0, M0 as stage I instead of stage II. In the current modification, the four different stages are divided by the following descriptions: (1) stage I tumors are low grade (G1-2), small or large, and superficial or deep; (2) stage II tumors are high grade (G3-4), small and superficial, or deep or large and superficial only; (3) stage III tumors are high grade (G3-2), large, and deep; and (4) stage IV tumors involve metastasis to a distant site or regional nodes.

Although tumor grade, size, and depth are important prognostic factors for metastasis-free and overall survival, the most important factor in predicting local recurrence is the presence of positive margins on surgical excision [7]. Although tumor grade, size, depth, and histotype are the strongest factors for metastasis-free and overall survival, data suggest that positive margin status may also affect systemic control and disease-free survival [8,9]. Both of these points argue for re-resection to negative surgical margins whenever possible, because radiotherapy typically can compensate for inadequate resections.

**Presentation and natural history**

The most common presentation of a soft tissue sarcoma is a painless mass. Surgeons routinely evaluate patients with soft tissue masses of the extremities, and the majority of these masses are benign. For benign masses, a simple excision results in cure. Occasionally, the surgeon encounters a patient with either a preoperatively suspicious mass or an unexpected sarcoma after local excision and pathologic review. Patients with sarcomas have a high rate of local recurrence and mortality; therefore, it is crucial that the treating surgeon understand the appropriate diagnostic, staging, and treatment options.
Ideally, the soft tissue mass is identified as a possible sarcoma before plans for biopsy (or excision), because both the technique for biopsy and the pretreatment confirmation of malignancy are crucial to ensure optimal outcomes. Multidisciplinary evaluation and planning of the treatment of patients with sarcoma should be performed before initiation of any therapy. The natural history of sarcomas may help the surgeon identify suspicious masses upon examination. Extremity sarcomas most commonly occur proximally in the hip and shoulder regions [10]. A rapid rate of growth in combination with areas of differing consistency and fixation may alert the clinician to the possibility of sarcoma, but slow growth does not rule out malignancy. It is not unusual for such proximal extremity sarcomas to grow to a large size before the patient recognizes the need to seek medical attention. The patient may first notice the mass when an unrelated injury occurs to the affected extremity. Distal extremity soft tissue masses are generally identified sooner; therefore, they are usually smaller in size on presentation [11]. When the sarcomas become large enough, involvement of critical nearby neurovascular structures or locally compressed muscles may cause symptoms of radiating pain, numbness, or swelling [12].

The histology of extremity sarcoma is often related to the site of origin. The most common histologic subtypes seen in proximal extremity sarcoma are malignant fibrous histiocytomas, liposarcomas, and leiomyosarcomas [6]. Distal extremity sarcomas tend to be of different histologic subtype in comparison with more common proximal extremity sarcomas and include synovial sarcomas, epithelioid sarcomas, and clear cell sarcomas, which occur more frequently in the hands and feet. The most common histology occurring in the hand is epithelioid sarcoma [13], whereas synovial sarcoma and clear cell sarcoma occur more commonly in the feet. Most epithelioid, synovial, and clear cell sarcomas occur in the distal extremities [13,14]. Each of these histologic subtypes is associated with distinct clinical and biologic behavior.

Lymph node spread by sarcomas is generally rare (<3%) but is more commonly seen in patients with epithelioid sarcomas (up to 15%) and occurs with increased frequency in patients with clear cell sarcomas [15].

Most patients with extremity sarcoma present with clinically localized disease. Approximately 10% of patients have evidence of metastatic disease after staging evaluation [16,17]. The most common site of metastases for extremity sarcomas is the lung. Other sites of metastases include the lymph nodes and bone [15,17].

The most common site of metastasis after primary treatment of an apparently localized extremity sarcoma is the lung. Metachronous lung metastases usually occur within 2 to 3 years after resection. Patients with larger (greater than 5 cm), deeper (deep to superficial fascia), and higher grade tumors, as well as patients with high-risk histologic subtypes, are at increased risk for distant metastasis. The survival for patients with stage IV sarcoma is poor. Local control does not govern overall survival, and most patients with extremity sarcoma die of systemic manifestations of the disease.
Diagnosis and evaluation

The use of pretreatment biopsy is often helpful but not always necessary. Knowledge of the histology and grade of the tumor, recognizing the possibility of sampling error with a minimally invasive biopsy, helps plan multidisciplinary treatment. Pretreatment biopsy is mandatory when the tumor seems to involve critical structures or when neoadjuvant therapy is considered. Additionally, evidence suggestive of metastatic disease may prompt biopsy. With the insight of the grade and histology of the tumor obtained from biopsy, the surgeon can help plan the optimal margins for the best oncologic and functional outcome. Although several options for biopsy exist, one should preferably use the least invasive method sufficient to obtain a definitive histologic subtype and grade. The site of biopsy can also be crucial; the biopsy needle tract can result in local recurrence if this area is not excised during definitive surgical therapy [18]. Most commonly, core needle biopsy is used and provides adequate tissue diagnosis [19].

An essential step once the diagnosis of sarcoma is made is to assess the extent of local disease and the presence or absence of distant disease. For the assessment of local disease burden, physical examination provides an estimation of tumor size and depth and of the proximity of the tumor to critical structures such as bone, tendon, nerves, and blood vessels. A high-quality MRI or CT scan should confirm the clinical suspicion of proximity to vital structures and the local extent and will provide the most reliable information for operative planning. At the same time, this imaging may help guide plans for biopsy. Both CT and MRI provide detailed information of the tumor in relationship to surrounding anatomy. Although MRI is often thought to be superior in evaluation of soft tissue masses, at least one study has shown MRI and CT to be equally efficacious in local staging [20]. This equal ability to provide anatomic detail allows both CT and MRI to delineate tumors from vessels, nerves, bone, and muscle groups, suggesting that the surgeon should use the imaging that he or she and the collaborating radiologist feel most comfortable interpreting. This local staging should guide operative planning and help determine the possibility for limb- and function-preserving wide local excision, which is possible in approximately 95% of patients.

Given the predilection of sarcoma to metastasize to the lung, the systemic disease burden is most appropriately evaluated with radiographic imaging of the chest. Based on current guidelines, a chest radiograph may be sufficient and is the minimum requirement (National Comprehensive Cancer Network practice guidelines, www.nccn.org), however a CT scan is generally preferred. Depending on the histologic subtype, grade, depth, and size, coupled with the clinician’s preference, some experts may argue for high-resolution chest CT. Positron emission tomography (PET) has an increasing role in the management of sarcoma, particularly in assessing for evidence of metastatic disease and the response to therapy, but is currently not performed as part of standard staging [21–23]. As a reflection of this increasing role,
a large prospective study is currently accruing patients with soft tissue sarcoma who are receiving neoadjuvant chemotherapy to determine the value of the FDG-PET scan (combined with CT) in predicting disease-free survival (www.cancer.gov/clinicaltrials/UMN-2005LS080).

**Limb function-preserving surgery for extremity sarcoma**

Surgical resection with negative margins is the mainstay of therapy for extremity sarcomas. Historically, successful local control of extremity sarcomas has been obtained with amputation [24]. Although amputation provides local control in the vast majority of patients, functional and psychologic consequences may be significant. Contemporary approaches to surgical management of extremity soft tissue sarcomas have focused on functional resections with wide negative margins with the addition of radiotherapy when appropriate to provide local control. In suitable patients, the use of limited surgery and radiotherapy can provide a function-preserving alternative without sacrificing local control or survival when compared with amputation [25].

Successful conservative resection obtains negative surgical margins while preserving limb function. Microscopic and grossly positive surgical margins are associated with inferior outcomes, including a significantly increased risk of local recurrence [7,26,27]; therefore, careful preoperative planning and a realistic determination of the likelihood of a margin-negative resection with primary surgical management should be undertaken before intervention. As described previously, preoperative MRI and CT can be helpful in planning the surgical approach and determining whether initial surgery is likely to provide adequate resection margins of at least 1 to 2 cm. MRI may be most useful for determining the extent of soft tissue and neurovascular invasion, whereas CT can be useful for determining the extent of local invasion as well as the extent and degree of any bone invasion.

At the time of surgery, care must be taken to excise all sites of known and suspected disease and prior areas of violation. Most often, this region includes the biopsy site and the tumor mass with a wide margin of normal appearing tissue. Soft tissue sarcomas often appear on gross inspection to be contained within a well-defined capsule; however, on histologic evaluation microscopic disease is often appreciated outside of this pseudocapsule. Removal of the tumor mass and pseudocapsule without a margin of normal appearing tissue is associated with a high incidence of positive margins and frequently requires a second operation to obtain negative margins.

Several principles of surgical resection can help the practitioner provide an adequate oncologic resection while maintaining maximal function. The resected tissue should include the unviolated tumor, pseudocapsule, and reactive zone with a wide margin. In addition, any previous biopsy site or scars should be contained within the final specimen. In general, incisions should be placed longitudinally to facilitate resection with minimal violation.
of normal tissues and to minimize the toxicity of eventual radiotherapy. Drain sites should be placed in proximity to the surgical incision to facilitate the safe inclusion in radiotherapy field.

The concept of a barrier to spread is an important component of surgical resection guidelines [28]. A barrier to tumor infiltration can include tissues such as fascia, joint capsule, tendon, epineurium, and the vascular sheath. In general, the guidelines dictate that if a barrier to spread exists, the tumor should be removed outside of that barrier (ie, without violation). If there is no barrier to spread, the tumor is removed with a broad margin.

Based on these general guidelines, specific scenarios are described [28]. For superficial lesions, the tumor is removed with a wide margin where there is no barrier (ie, along the subcutaneous path) and at the barrier where a barrier is present (ie, fascia). For deep lesions, the tumor and pseudocapsule are removed with a wide margin along muscle. The resection of other structures and the desired margin for deep tumors depend on the presence or absence of a barrier instead of physical distance.

For most superficial sarcomas, a deep negative margin can be obtained by resecting the underlying fascia. Care should be taken to avoid violation of uninvolved compartments and inappropriate violation of fascia, because this may necessitate additional surgical resections, removal of a larger volume of tissue, and the addition of radiotherapy if not already required, all with the potential of associated negative functional consequences. Deep tumors by definition invade or are beneath the superficial fascia; therefore, they necessitate violation of the fascia investing the involved compartment. If a positive margin is obtained at the time of resection, a re-resection should be performed with the goal of obtaining a negative margin. Zagars and colleagues [9] from the M.D. Anderson Cancer Center reported on a series of 666 consecutive patients with localized extremity soft tissue sarcoma referred after macroscopic resection. All of the patients received adjuvant radiotherapy. Among the 295 patients who underwent re-resection, residual tumor was found in 46%; final negative margins were found in 87%. Local control was significantly improved at 15 years (82% versus 73%) in patients undergoing re-resection, as were metastasis-free and disease-free survival. These data highlight the importance of the final surgical margin for determining local control. If surgical resection with wide negative margins is not considered possible based on imaging, preoperative radiation therapy should be considered to improve the likelihood of achieving a margin-negative resection.

The intricacies of the general guidelines for surgical resection underscore the complexity of the surgical approach for soft tissue sarcomas, suggesting a need for these surgeries to be completed at centers with significant experience in the management of sarcoma. In a series of 4205 patients with operatively managed sarcoma, significantly lower rates of 30- and 90-day mortality, higher median survival, and lower amputation rates were found when surgery was performed at high-volume centers, even though
significantly more high-grade tumors and tumors larger than 10 cm were managed at these centers [29]. An additional benefit present at most high-volume centers is the availability of a multidisciplinary sarcoma team. This team can help address and appropriately plan the therapy of patients with advanced or potentially technically challenging primary tumors.

**Reconstruction**

Determination of the appropriate surgical intervention is often dictated by the extent of local invasion on preoperative imaging. Instances in which amputation may be required or may be the preferred option include the involvement of major neurovascular structures by tumor, anticipated poor functional outcomes following adequate surgical resection and radiotherapy, and patient preference.

Although these general guidelines can assist in determining whether amputation is an appropriate option, they should not dictate therapy. In some instances, vascular reconstruction can be performed to effectively salvage a limb. Ghert and colleagues [30] reported on a series of 19 patients who underwent vascular resection and reconstruction as part of definitive surgery for soft tissue sarcoma of the extremities. Patients undergoing vascular reconstruction were more likely to experience wound complications (68% versus 32%), edema (87% versus 20%), and deep venous thrombosis (26% versus 0%) than matched controls. Amputation was also more common in the vascular reconstruction group (16% versus 3%); however, there was no significant difference in local or distant recurrence between the two groups, suggesting that vascular reconstruction can allow limb preservation in appropriately selected cases.

Significant defects of skin and soft tissue may result from the resection of large superficial extremity sarcomas. In this setting, the use of grafts and flaps may assist in wound closure. If a surgical defect is anticipated, the case should be discussed with a plastic surgeon before the definitive procedure to allow for determination of an appropriate closure technique and donor site. In addition, preoperative radiotherapy should be considered as an alternative to postoperative radiotherapy in this setting to minimize the potential for long-term complications of the combined therapy [31]. In general, patients with an anticipated need for extensive reconstruction should be referred to an institution with a multidisciplinary sarcoma team with experience and expertise in this area.

**The role of radiotherapy for local control**

Radiotherapy is frequently used as part of the multidisciplinary treatment of extremity sarcomas. Radiation can be used to improve the local control obtained with conservative surgery for soft tissue sarcomas, to improve the
resectability of advanced tumors, and to treat unresectable disease. Radiation can be delivered with a variety of techniques, including external beam radiation and brachytherapy, and can be delivered preoperatively, intraoperatively, or postoperatively. The optimal timing (preoperative versus postoperative) and the type of radiotherapy (external beam versus brachytherapy) are controversial and may depend on the available technology, as well as patient and tumor characteristics.

The duration of therapy is different depending on the technique employed. External beam radiation is delivered Monday through Friday over the course of 6 to 7 weeks. Brachytherapy is usually employed postoperatively with treatment delivered over several hours or days. Brachytherapy for extremity sarcomas is technically challenging, and its use is often limited to referral centers with a multidisciplinary sarcoma team.

Radiation was first used in the definitive management of extremity sarcomas to provide an alternative to amputation when combined with conservative surgery [25,32]. In this setting, the wide excision of soft tissue sarcomas followed by adjuvant radiotherapy results in local control rates in excess of 80%. Since the initial trials demonstrating that wide excision and radiation were an acceptable treatment option for soft tissue sarcoma, the appropriate indications and timing for the delivery of radiotherapy have been clarified to some extent. In general, the use of radiotherapy is associated with an improvement in local control after surgical resection without any influence on overall survival or distant metastases.

External beam radiation can be delivered in the preoperative or postoperative setting. If radiation is to be delivered, there are several possible benefits of preoperative radiation versus postoperative radiation, even though local control appears to be similar with both approaches [33]. Preoperative radiotherapy may provide a higher likelihood of obtaining a margin-negative resection for large tumors or those in close proximity to vital structures. Radiation doses used preoperatively tend to be lower than those used postoperatively (typically, 50 Gy compared with 60 to 70 Gy). In addition, radiation fields tend to be smaller in the preoperative setting because postoperative treatment fields often include the entire tumor bed, surgical scars, and drain sites with additional margin. Taken together, these factors may explain the reduced long-term toxicity seen with the preoperative approach when compared with the postoperative approach [31]. In contrast, postoperative radiotherapy has less risk of surgical wound complications and allows selection of patients at the highest risk for recurrence based on surgical pathology. The decision of which sequencing to employ is best made after consideration of patient and tumor characteristics by a multidisciplinary sarcoma team.

In patients with large, marginally resectable lesions, a preoperative approach is typically preferred to improve the likelihood of a margin-negative resection and to allow a greater likelihood of function preservation. These important goals are generally an acceptable trade-off for an anticipated
higher risk of wound complications. For patients in whom the risk of wound complications is prohibitively high, especially in smaller more readily respectable lesions, a postoperative approach may be preferred to decrease this risk while accepting an increased risk of late toxicity. For patients with small, superficial, or low-grade lesions or those with a questionable pathologic diagnosis, a postoperative approach may be preferred to allow a determination of the appropriateness of adjuvant radiotherapy.

An alternative method for delivering radiation at the time of surgery (intraoperatively) or shortly thereafter is brachytherapy, which involves placing catheters within the tumor bed at the time of surgery. Radioactive sources can then be placed in the catheters to deliver radiation to the tissues surrounding the resection cavity, typically after postoperative day 5 to minimize wound complications [34]. The radiation dose delivered with this technique can be supplemented with preoperative or postoperative external beam radiation if desired. This method has been found to be effective in providing excellent rates of local control for high-grade tumors; however, it does not appear to be effective in the management of low-grade tumors [34]. The major benefit of brachytherapy is that more normal surrounding tissue can be spared from radiation when compared with that exposed with external beam radiation. As described previously, brachytherapy is technically challenging and should only be used by practitioners familiar with its use in this setting.

Although radiation can enhance local control after surgical resection, several series support the argument that radiotherapy does not compensate for suboptimal resection. Local recurrence is significantly higher for patients who undergo a margin-positive resection even if they receive adjuvant radiotherapy [9,25]. Radiotherapy appears most beneficial for improving local control in the setting of a margin-negative resection; therefore, the use of adjuvant radiotherapy should not be seen as the alternative to a margin-negative resection, even if re-resection is required.

Although radiation is effective in improving local control after surgical resection, several series suggest that a subset of patients who have extremity sarcoma have adequate local control with surgical resection alone and do not benefit from radiotherapy [11,35–37]. The ability to accurately select patients at low risk of local recurrence after surgery would allow these patients to avoid the potential toxicity of radiotherapy. Pisters and colleagues [38] reported the results of a prospective trial of surgical therapy alone for T1 soft tissue sarcomas of the extremities or trunk that were resected with negative margins. In the 74 patients treated with surgery alone, 58% were high-grade lesions and 68% were superficial. The local recurrence rate at 10 years was 5.6%, and sarcoma-specific death occurred in 3.2%, suggesting that surgery alone is an appropriate option in selected patients. Pisters and colleagues suggested reserving radiotherapy for patients with final R1 resection and for patients with local recurrence. In contrast, a recent report from the Scandinavian Sarcoma Study Group in which records from 1093
patients with extremity and trunk wall sarcomas were reviewed failed to identify a subset of patients with extremity sarcoma that did not benefit from radiotherapy [39].

The exclusion of radiotherapy for patients with resected soft tissue sarcoma can be considered for patients with small low-grade lesions that are resected with widely negative margins (NCCN practice guidelines, www.NCCN.org). Patients with high-grade lesions, those with large lesions, and those with close or positive final margins should receive radiotherapy until more definitive data are available to make alternative recommendations. Within these guidelines, care should be taken to approach each individual patient with an understanding of the potential risks of radiation based on the location and size of the tumor, and one should weigh these risks with the expected gain in terms of local control.

**Special considerations: distal extremities**

Extremity sarcomas most often occur proximally at the hip and shoulder region. Distal extremity sarcomas present a unique challenge based on the anatomic and functional constraints. Because of the size and anatomy of the distal extremities, lesions involving the wrist, hand, ankle, or feet more frequently are in proximity to or involve vital neurovascular structures or muscles, joints, and tendons critical to function.

Similar to other extremity sarcomas, the evaluation of the extent of distal extremity lesions should be evaluated with MRI to assess the involvement of critical structures. MRI can be useful for biopsy planning and for evaluating the appropriateness of treatment options. Similar to other sites, biopsy should be carefully planned to avoid contamination of adjacent critical structures which would then need to be excised at the time of the definitive surgical procedure. Most often, an incisional biopsy is performed due to a perceived higher risk of contamination with core biopsies of lesions in these sites [40].

Because of the inability to achieve wide negative margins in many distal extremity sarcomas, most often, a combined modality approach is employed. Radiotherapy can be delivered pre- or postoperatively with the goal of enhancing local control from a definitive surgery. The preoperative radiotherapy approach allows the resection of less tissue adjacent to the tumor mass, potentially sparing critical structures, while also allowing a reduced dose of radiation to be delivered. This approach most likely provides the best functional outcome for patients when compared with definitive surgery followed by postoperative radiotherapy. Adjuvant radiotherapy is indicated in the setting of positive margins, close margins, or high-grade disease if not delivered preoperatively.

The use of surgery alone for patients with distal extremity lesions results in a higher rate of local recurrence if amputation is not employed. A series from Memorial Sloan-Kettering Cancer Center reviewed the outcomes of 50 patients managed with amputation or limited surgery for hand and
foot sarcomas [41]. Local recurrences occurred in 32% of patients treated with limited surgery and in none of the patients undergoing amputation. Most of the local recurrences in this series occurred in patients with close or positive final resection margins.

Several small series have reported the ability to preserve function with limited surgery and radiotherapy while achieving acceptable recurrence rates for sarcomas of the hand and foot [42,43]. A recent series from the University of Florida reported on the outcomes of 23 patients with nonmetastatic sarcoma of the hand-wrist or foot-ankle complex treated with surgical resection and radiotherapy [44]. The patients in this series received preoperative (n = 7) or postoperative radiotherapy (n = 16) and were followed up for a median of 11 years. Seven of these patients had tumors greater than 5 cm, and 18 were high-grade lesions. Surgery was repeated until negative margins were obtained (n = 20) or until amputation (n = 3). The 10-year local regional control and ultimate limb salvage rates in these patients were both 91%. No patient required an amputation for toxicity. The risk of severe edema or fibrosis was 5%, with moderate limitation in the range of motion seen in 7%. These data support the use of limited surgery and radiotherapy for sarcomas of the hand-wrist and ankle-foot complex to obtain local control while maintaining a functional distal extremity.

Limited surgery alone should be avoided due to the higher risk of local recurrence unless the use of radiotherapy is expected to result in unacceptable toxicity. Amputation remains an acceptable treatment option for patients who decline conservative surgery and radiotherapy, in instances in which negative margins cannot be obtained, and when amputation is expected to have minimal functional consequences (ie, ray amputation). In some instances, limited surgery with reconstruction may lead to inferior functional outcomes when compared with amputation with prosthesis. In these instances, amputation may be preferred.

The definitive surgical procedure aims to excise the tumor, prior biopsy site, and an area of normal tissue with at least 2 cm of margin. Frequently, this goal is not achievable due to the proximity of critical structures. Reconstruction of resected tissues is critical to achieving a functional extremity, often requiring bone allografts or autografts, vascular reconstruction, tendon grafts, nerve grafts, and skin grafts [44]. In these instances, preoperative consultation with a multidisciplinary team including orthopedic oncology, plastic surgery, and radiation oncology facilitates operative planning.

**Adjuvant chemotherapy**

The high rates of eventual distant failure with high- and intermediate-grade sarcomas have led to an interest in delivering adjuvant chemotherapy to reduce the risk of distant failures. Several randomized trials and a meta-analysis have addressed the benefit of adjuvant chemotherapy in patients with sarcomas; however, its use remains controversial [45–49]. The Sarcoma
Meta-analysis Collaboration performed a meta-analysis of 14 randomized trials including 1568 patients with sarcoma to address the benefit of Adriamycin-based chemotherapy delivered in the adjuvant setting [45]. There was a significant improvement in distant relapse-free interval and in overall recurrence-free survival with the addition of Adriamycin-based adjuvant chemotherapy; however, there was no benefit in overall survival. The study has been criticized for the inclusion of multiple anatomic sites with differing prognoses and for the inclusion of patients at lower risk of distant failure.

An additional study published after the meta-analysis evaluated the role of chemotherapy (five cycles of epirubicin and ifosfamide) in 104 adult patients with grade 3 or 4 sarcomas measuring 5 cm or more involving the extremities or girdle [46]. Recurrent sarcomas were also included regardless of size. The disease-free survival was significantly improved with the addition of chemotherapy (48 versus 16 months), as was the median overall survival (75 versus 46 months). The absolute overall survival benefit of receiving chemotherapy at 4 years was 19%. The survival benefit has been questioned due to a similar metastatic rate in both arms.

Additional series evaluating the benefit of chemotherapy have tried to better define subsets of patients who might benefit from chemotherapy. A series of 101 patients with large, deep extremity synovial sarcomas from the Memorial Sloan-Kettering Cancer Center and UCLA found significantly improved disease-specific survival and distant recurrence-free survival with the addition of ifosfamide-based chemotherapy [47]. A similar series from the same institutions evaluated the effect of ifosfamide and Adriamycin-based chemotherapy in patients with resected high-grade, large, extremity liposarcomas. In that series, a benefit in disease-specific survival was found with the delivery of ifosfamide but not Adriamycin-based chemotherapy [48]. In contrast, a review of 674 patients with stage III soft tissue sarcoma of the extremities treated at Memorial Sloan-Kettering Cancer Center and M.D. Anderson Cancer Center suggested that the disease-specific survival benefits of chemotherapy do not persist beyond 1 year [49].

At this time, the role of chemotherapy for resected extremity soft tissue sarcomas is uncertain. Patients with a high risk of metastatic disease appear to benefit from chemotherapy. These patients include those with large, high-grade, and deep lesions. The recommendation to deliver chemotherapy must be individualized based on the risk of distant failure balanced with the risks of chemotherapy. In general, chemotherapy is often offered to young, healthy patients with high-risk tumors who are likely to tolerate the therapy well. Patients with medical comorbidities, specifically cardiac disease, may not be appropriate candidates for Adriamycin-based chemotherapy.

**Neoadjuvant therapy**

Chemotherapy has been evaluated as a mechanism to improve the resectability of locally advanced sarcomas when given alone or in combination
with radiotherapy preoperatively. Rates of disease response obtained with the combination of radiation and chemotherapy delivered preoperatively are promising; however, the toxicity associated with this approach is currently limiting.

In an attempt to determine the role of neoadjuvant chemotherapy alone, the M.D. Anderson Cancer Center treated patients with locally advanced or high-grade extremity sarcoma (stage IIIB) with three cycles of preoperative doxorubicin, dacarbazine, cyclophosphamide, and ADIC. In a comparison with patient outcomes in historical randomized studies using postoperative chemotherapy, patients who received three cycles of preoperative doxorubicin, dacarbazine, cyclophosphamide, and ADIC had similar disease-free and overall survival [50]. Unfortunately, even when the patients considered as responders to the neoadjuvant regimen were analyzed, no significant benefit in local recurrence-free survival, distant metastasis-free survival, or overall survival could be demonstrated. The final results of a European Organization for Research and Treatment of Cancer trial randomizing patients to preoperative chemotherapy consisting of doxorubicin and ifosfamide versus local treatment alone are pending (www.clinicaltrials.gov).

One of the most successful regimens combining radiotherapy and chemotherapy in the neoadjuvant setting was first reported by DeLaney and colleagues [51]. In this single institution series, a preoperative chemotherapy regimen consisting of mesna, Adriamycin, ifosfamide, and dacarbazine (MAID) alternating with radiotherapy was delivered to patients with locally advanced high-grade extremity soft tissue sarcomas, followed by resection and additional adjuvant chemotherapy. With this intensive regimen, the 5-year local control, freedom from distant metastases, disease-free survival, and overall survival were improved (58% versus 87%) in a comparison with historical controls.

Based on the results obtained in this single institution series, a larger multi-institutional study was performed with the same regimen [52]. In that trial, 66 patients with large (> 8 cm), high-grade extremity sarcomas received three cycles of neoadjuvant MAID chemotherapy alternating with radiotherapy and three cycles of adjuvant MAID chemotherapy. Although 3-year rates of disease-free, distant disease-free, and overall survival were encouraging (56.6%, 64.5%, and 75.1%, respectively), the toxicity was significant. Eighty-four percent of patients experienced a grade 4 toxicity (mainly hematologic), and two patients required an amputation for treatment-related toxicity.

A continuous infusion Adriamycin and concurrent radiotherapy regimen was tested at the M.D. Anderson Cancer Center as neoadjuvant therapy for patients with localized, potentially resectable intermediate- or high-grade soft tissue sarcoma [53]. In this series of 27 patients, dermatologic toxicity was dose limiting, occurring in 30% of patients at 17.5 mg/m²/wk. Macroscopic complete resection was accomplished in all patients who underwent surgery (26 patients), and 50% of these patients had 90% or greater tumor
necrosis on pathologic evaluation. These results are encouraging, especially the rates of pathologic response.

Currently, the neoadjuvant approach remains investigational based on the lack of randomized data supporting its use and the significant toxicity that results from this approach. It is possible that the combination of radiation and chemotherapy may allow limb preservation with superior long-term functional outcomes in the setting of locally advanced high- or intermediate-grade sarcomas that are large or that are located in proximity to or invading critical structures.

**Recurrent disease**

Patients with recurrent disease may present in a variety of ways ranging from an isolated local recurrence to an isolated metastasis to widely disseminated disease. Patients who present with a local recurrence should be evaluated and treated similarly as patients who present with a new primary [54]. Patients who present with an isolated metastasis can be considered for metastatectomy with or without pre- or postoperative chemotherapy or radiotherapy. In combination with evaluation and treatment for the primary site, if a local recurrence exists simultaneously, metastatectomy includes removal of limited disease to a single organ and regional nodal dissection if this site represents the single site of metastasis. Billingsley and colleagues [55] showed that if all lung metastases are removed, median survival is lengthened to 33 months as compared with a median survival of 11 months in patients with pulmonary metastases who do not undergo surgery. Patients who present with widely disseminated disease should be considered for a variety of palliative therapies, including surgery, chemotherapy, radiotherapy, embolization, and ablation procedures. Patients who present with widely disseminated disease who are symptomatic are most appropriate for the consideration of additional therapy. If asymptomatic, observation is also appropriate and may be the optimal approach in the correctly selected patient.

**Follow-up evaluation**

Limited evidence supports the efficacy of specific surveillance strategies, but experts agree that surveillance is prudent to identify recurrences that are still potentially curable and while the limb and function can still be salvaged [56–58]. NCCN guidelines attempt to establish a rational schedule while avoiding an overabundance of tests. These guidelines recommend that patients should be followed up with a history and physical examination every 3 to 6 months for 2 to 3 years, every 6 months for the next 2 years, and then annually (NCCN practice guidelines, www.NCCN.org). For stage I tumors, chest imaging (radiography or CT) should be performed every 6 to 12 months; for stage II and III tumors, chest imaging should be performed more frequently, every 3 to 6 months for 5 years and then annually. Periodic
imaging with MRI or CT of the primary site should be considered if the combination of factors places the patient at increased risk for locoregional recurrence, especially if the location or depth of the lesion makes physical examination unreliable for this determination. Ultrasound, instead of MRI and CT, can also be considered as the mode of surveillance in these circumstances. After 10 years, the chance of local recurrence if the patient remains disease free becomes much smaller, and the requirement for surveillance imaging after this time point should be individualized.

Summary

For extremity sarcoma, limb salvage with the combination of function-preserving surgery and radiotherapy is the mainstay of treatment. The use of chemotherapy in the pre- or postoperative setting remains controversial and argues for an individualized approach to the patient and a multi-disciplinary approach by a dedicated team at a high-volume institution. The grade, depth, and histology of the sarcoma largely dictate the risk of the development of local recurrence and metastatic disease, but the loss of local control does not seem to determine the risk of metastatic disease. The addition of radiotherapy in the management of extremity sarcomas is a key development allowing function- and limb-preserving surgery with adequate rates of local control without an increase in the risk of systemic disease.

The anatomic site of the extremity sarcoma, proximal or distal, is associated with histologic subtypes that can be of vastly different biology and may determine a much different extent, sequence, and use of multimodality therapy for optimal outcomes. Given the complex factors associated with the determination of multimodality treatment coupled with the enormous heterogeneity and rarity of the disease, patients with extremity sarcomas should best be managed at high-volume specialized centers with multidisciplinary sarcoma teams.

References


