

Local Recurrence of Extremity Soft Tissue Sarcoma



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KEYWORDS

- Sarcoma • Recurrence • Metastasis • Radiation • Amputation • Limb salvage
- Isolated limb infusion • Hyperthermic isolated limb perfusion

KEY POINTS

- Multimodality management of recurrent extremity soft tissue sarcoma is dependent upon prior therapy and includes surgery, irradiation, brachytherapy and systemic chemotherapy.
- Amputation may provide local control and palliation of symptoms for recurrent extremity soft tissue sarcoma.
- Regional therapy in the form of hyperthermic isolated limb perfusion or isolated limb infusion has a role in the management of recurrent extremity soft tissue sarcoma to provide local control as a limb-salvage therapy treatment option.

INTRODUCTION

Soft tissue sarcomas (STSs) are a heterogeneous group of malignancies with distinct clinical and pathologic features, all characterized by mesodermal differentiation.¹ STS is relatively rare, accounting for only 1% of adult malignancies with an estimated 11,900 people diagnosed annually and approximately 4870 deaths in the United States.² More than 50 different subtypes have been identified with undifferentiated pleomorphic sarcoma, gastrointestinal stromal tumors, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors being the most common.³ These tumors may arise from the extremity, head or neck, truncal region, retroperitoneum or chest wall, as well as, other locations. The anatomic location of these tumors is important because it influences treatment and outcome. Several prognostic factors, such as tumor stage, size, grade, and anatomic location, have

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been demonstrated to have an impact on overall survival in the management of primary extremity STS.⁴⁻⁶ Similarly, margin of resection, low-grade histology, and the use of radiotherapy are important factors in achieving local disease control.⁷⁻⁹

Treatment involves a multidisciplinary effort by those specializing in the management of sarcoma. Surgery is the standard treatment of primary extremity STS. The objective of surgical resection is to obtain negative margins but this may be difficult in situations of abutment or involvement of critical neurovascular structures. In these situations, radiation therapy (RT) may be administered as either neoadjuvant therapy or in the adjuvant setting. Neoadjuvant RT is recommended in situations in which a microscopic positive margin is anticipated. The disadvantage of neoadjuvant RT is that it does result in an increased risk of wound healing complications. Positive margins after surgical resection are associated with an increased risk of local recurrence.^{10,11} Re-resection to negative margins is preferred but may not be possible, especially in situations of critical nerve or vascular involvement, or when resection may result in loss of function or significant impairment of the involved extremity. Postoperative RT is recommended and has been demonstrated to improve the local control of patients with positive surgical margins.^{12,13} Postoperative RT, although associated with a lower risk of short-term wound complications, is associated with higher rates of long-term treatment-related effects, possibly related to the higher dosages of radiation.¹⁴

The role of systemic chemotherapy in the management of primary extremity STS varies among institutions. The relative indications of systemic chemotherapy include high-grade tumors larger than 5 cm or intermediate-grade tumors larger than 10 cm, especially in younger patients. The use of chemotherapy in the treatment of primary extremity STS is controversial and has yielded inconsistent results. In a randomized controlled trial of preoperative chemotherapy followed by surgery compared with surgical resection alone of subjects with high-risk tumors, there was no difference in 5-year disease-free survival or overall survival.¹⁵ In smaller tumors in a retrospective cohort of subjects receiving neoadjuvant chemotherapy in high-grade extremity sarcomas, Grobmyer and colleagues¹⁶ demonstrated an improvement in disease-specific survival for tumors larger than 10 cm receiving neoadjuvant chemotherapy but not in smaller tumors. Generally accepted indications for adjuvant chemotherapy include synovial sarcoma and pediatric rhabdomyosarcoma, as well as situations of local recurrence and metastatic disease. Single-agent and anthracycline-based regimens are generally accepted and frequently used in situations of locally advanced, unresectable, or metastatic STS.¹⁷⁻²⁰

Despite appropriate aggressive multimodality therapy, local recurrence is not uncommon, affecting up to 7% to 24%.^{11,21,22} Management of recurrent STS is a challenge because often patients have undergone neoadjuvant therapy before surgical resection. Local recurrence for those who may not have undergone preoperative therapy may be associated with a better prognosis than for those treated with a combined multimodality initial approach.²³ Little is known about the effect of local recurrence on overall outcome. It is generally thought that local recurrence of STS is associated with a poor prognosis and has a negative impact on distant metastasis and survival.²⁴

Historically, local recurrences of extremity sarcomas were managed with amputation.²⁵ Amputation offers definitive local control but often at the expense of patient function, with potential for significant morbidity and a negative impact on overall quality of life. Furthermore, amputation does not have an impact on distant metastasis or overall outcome.²⁶⁻²⁸ For this reason many suggest that attempts to surgically manage local recurrence a second time should be more aggressive than the initial treatment approach. Re-resection of extremity STS recurrence is a treatment option,

as well as the repeated use of irradiation for those receiving radiation during initial management. Both of these treatment approaches are associated with a high risk of treatment-related morbidity and may negatively affect extremity function. Selecting an appropriate therapy that allows patients to maintain function and quality of life without negatively affecting long-term outcome is important. The regional delivery of chemotherapy, in the form of hyperthermic isolated limb perfusion (HILP) or isolated limb infusion (ILI), as a potential adjunct to surgical resection with RT, may be an additional treatment option for these complex patients.

How to most appropriately manage local recurrence remains an active area of debate among clinicians who devote their practices to the management of STS. This article focuses on the management of locally recurrent STS of the extremity.

MANAGEMENT OF RECURRENCE

Surgical Resection and Irradiation of Sarcoma Recurrence

Local recurrence after previous resection with or without previous radiation can be a devastating development for patients. Management of the local recurrence is complicated by previous therapies and development of the recurrence within a previously irradiated field. There is a growing trend toward limb-salvage therapy, even in the setting of recurrent disease, with an emphasis on the maintenance of extremity function and preservation of quality of life. Wide resection is important when treating local recurrence to prevent further local relapse from sarcoma. Unfortunately, positive margins are common after repeated resection for recurrence, as high as 30%.^{21,29,30} In addition, the risk of a second relapse after undergoing limb salvage for local recurrence is also high, up to 21%.^{22,31} Because many patients have undergone multimodality treatment before the development of recurrence, management of the recurrence is, therefore, associated with higher morbidity. This may limit repeated use of potential therapeutic modalities for the management of recurrent disease. These factors in the initial treatment of the primary sarcoma tumor, as well as others such as anatomic constraints, synchronous distant metastasis, and aggressive tumor biology, are present and must be considered in the management of the local recurrence.

Salvage treatment options after local recurrence include limited re-excision; radical surgical resection, often necessitating plastic surgery reconstruction; amputation; additional RT; and, in selected cases, systemic chemotherapy. Although many investigators report on the management of recurrence using combined modality therapies, one series in particular highlights the role of surgical management alone in managing these complex patients. A retrospective review was performed on 62 patients at MD Anderson Cancer Center who were treated for an isolated first recurrence of STS within a previously irradiated field.³² All subjects underwent previous resection and external beam radiation (EBRT) with a median time to development to recurrence of 25 months. The investigators attempted a conservative, limb-sparing approach to the management of the local recurrence and attempted to obtain a 1 to 3 cm negative surgical margin when possible. Twenty-five subjects underwent wide local excision (WLE) alone, 33 underwent WLE with brachytherapy (BCT), 3 had WLE with preoperative EBRT (45, 46, 50 Gy), and 1 had WLE with postoperative EBRT (64 Gy). When EBRT was used, a 5 to 7 cm treatment margin was administered to the tumor bed. There were 39 relapses (69%), 29 were local (12, WLE group and 17, RT group) resulting in a 5-year actuarial local control (LC) rate of 51%. The use of additional RT was associated with a higher rate of complication compared with WLE alone (80% vs 17%, $P<.001$) and was the only factor significant for late complication on multivariate analysis ($P<.001$). With respect to tumor biology and outcome, 71% of subjects had

high-grade tumors but only 27% developed distant metastasis and 50% developed local recurrence within 5 years. The investigators go on to suggest that consideration should be given to a surgery-alone approach when possible, primarily because of the toxicity associated with additional RT and lack of a local control benefit.

Others investigators, however, have identified that limb salvage after initial conservative treatment is possible and that additional radiation in the management of recurrence results in improved local control with acceptable toxicity. Catton and colleagues²⁹ reported on 25 subjects treated with surgery alone or surgery and re-irradiation for locally recurrent STS. Two subjects with synchronous metastasis were treated palliatively, whereas 7 subjects were managed with early amputation. Eleven subjects underwent conservative resection without irradiation, 7 of which relapsed, and 5 underwent subsequent conservative surgery and irradiation. A total of 10 subjects were treated with combined surgery and irradiation (Brachy-6, Brachy/EBRT-3, EBRT-1). The investigators reported a local control of 91% with 36% local control for conservative excision alone (4/11) and 100% for excision with reirradiation (10/10). Sixty percent of the reirradiation group did develop significant postirradiation complications but 3 eventually recovered function. Although the numbers are small, the investigators suggest that inappropriate initial management is a risk factor for relapse and the use of combined conservative surgery with re-irradiation provides superior local control and a better functional outcome to amputation.

The initial treatment of primary extremity STS has an impact on the subsequent management of recurrence. Additional cumulative radiation is associated with potential increased morbidity. Furthermore, obtaining negative margins may be difficult and incomplete resection of isolated recurrences is associated with a high rate of relapse. Moureau and colleagues²² reported on 83 adult subjects with isolated local recurrence of STS sarcoma (74 located on the extremity). The recurrences were managed with wide excision (number [N] = 29), marginal resection (N = 43) and 5 required amputation. The margin of resection (R) was R0 (N = 33), R1 (N = 47), or R2 (N = 3). Twenty-three subjects received EBRT and 26 underwent BCT (22, BCT alone; 4, BCT plus EBRT). Thirty-seven subjects (45%) developed further local recurrence within a mean of 23 months, giving an actuarial local control rate of 42% at 5 years. The investigators note that when conservative treatment is feasible, it should combine surgery and radiotherapy with BCT being best used in previously irradiated patients. The use of BCT may decrease the high complication rates associated with reirradiation but recognize that the cumulative dose of radiation is high and late complications may develop.

One of the difficulties in managing patients with isolated local recurrence after previous surgical resection and radiation is the high morbidity associated with subsequent treatment. Repeated irradiation carries the potential for significant complication and many of these complications may require subsequent reconstructive surgery or even amputation.^{33,34} One study reported that 34% of patients previously irradiated required re-intervention for wound healing complications.³⁵ The University of Florida reported on 14 patients treated over a 30-year period with isolated recurrence after initial primary conservative resection and irradiation.³⁶ Thirteen of the 14 received EBRT with or without BCT and 1 received BCT alone. The incidence of serious complication requiring either reoperation or leading to permanent functional impairment was 50%.

To reduce the effect of compounded toxicity with repeat irradiation in the recurrent setting, advanced techniques such as intraoperative RT (IORT) and BCT have been used to deliver high-dose irradiation while minimizing normal tissue toxicity. IORT

has been well studied when combined with salvage limb-sparing surgery for recurrent disease with favorable local control, limb salvage, and overall survival results.^{37,38} Investigators from the University of California, San Francisco reported a 23% acute treatment-related toxicity and grade 3 late toxicity developing in 31% of subjects when using IORT for recurrence.³⁷ No grade 4 or 5 toxicity was observed and no subject required amputation for complication when treated with IORT for recurrence. Pearlstone and colleagues³³ reported on 26 subjects who developed sarcoma recurrence within a previously irradiated field treated with re-resection and BCT. Re-resection was performed with BCT with a mean dose of 47.2 Gy delivered at the implant procedure. Half of the subjects underwent tissue flap transfer over the resection bed. Complications, primarily wound breakdown, occurred in 5 subjects, 4 of whom required operative intervention. Each of the 4 had initially undergone primary closure without tissue transfer. The 5-year recurrence-free survival was good at 52%, suggesting that local control can be achieved with re-irradiation of recurrent STS by BCT with acceptable complication rates, potentially sparing the need for more radical surgery or even amputation.

Amputation for Sarcoma Recurrence

Although limb-salvage therapies offer local control in up to 85% to 90% of patients, the development of local recurrence may make conservative management difficult. Tumors involving proximal nerves or vessels may compromise local control if limited resection is attempted and limb-salvage, therefore, may not be possible. Furthermore, the development of treatment-related toxicities, such as wound healing complications or nonhealing wounds, may represent a source of significant pain and render the involved extremity functionless. Fungating, foul-smelling tumors, bleeding, or intractable pain may further complicate patient quality of life and management of recurrent STS tumors.³⁹ Amputation in this setting may offer palliation of tumor or treatment-related symptoms. Investigators from the University of California, Los Angeles (UCLA), found the development of local recurrence to be extremely morbid with 38% of subjects eventually requiring amputation.⁸ Some subjects, unfortunately, are not amenable to resection at presentation and require early amputation for management of recurrent disease.²⁹

Distal extremity amputations range from resection of individual digits to above-elbow or above-knee amputations. In situations of proximal vascular or neural involvement, forequarter or hindquarter amputation may be required. Forequarter amputation, or interscapulothoracic disarticulation, involves the removal of the whole upper limb girdle, including the humerus, scapula, distal clavicle, and chest wall musculature. Hindquarter amputation, or hemipelvectomy, involves removal of the femur and the bony pelvis, typically through the sacroiliac joint.

Morbidity after radical amputations, especially hindquarter, may be significant occurring in up to 60% or more of patients.^{40,41} Most commonly, wound healing complications and flap necrosis have been described. Hernia formation may also develop long term.⁴¹ Complications after forequarter amputation are generally fewer. Mortality is also high for those undergoing hindquarter amputation but a more recent report of 40 subjects undergoing radical amputation demonstrated a 2.5% mortality with only one subject succumbing to postoperative sepsis.⁴² Phantom pain may be a problem after amputation, especially in those who present with significant pain preamputation.⁴³ However, for those who present with symptomatic, disabling disease, radical amputation may offer palliation of symptoms with improvement in pain in up to 78%.⁴² Advances in limb prostheses allow restoration of limited function, cosmesis, and maintenance of independence for motivated patients.

Although there is no effect on overall survival for patients who undergo amputation for recurrence, for those who have exhausted all other treatment options, amputation remains a treatment option. Local and distant recurrences are high after amputation and likely reflect aggressive tumor biology.⁴² The palliation of complex wounds, improvement of pain, and potential impact on improved quality of life renders amputation a reasonable treatment option for the symptomatic patient.

Chemotherapy for Sarcoma Recurrence

The routine use of adjuvant chemotherapy in the treatment of recurrent extremity sarcoma continues to be an area of active debate. In general, the regimens commonly used in the management of primary extremity STS are highly toxic and have failed to demonstrate a sustained long-term survival benefit. Although individual center results vary widely, a meta-analysis of 1568 subjects demonstrated a benefit to local recurrence (6%) and distant recurrence (10%) at 10 years when doxorubicin-based chemotherapy regimens were combined with surgery for local control.⁴⁴ There was no benefit when overall survival was analyzed at 10 years. A retrospective review from Memorial Sloan-Kettering and MD Anderson Cancer center demonstrated a statistically significant benefit when chemotherapy was used for stage III extremity STS with respect to local control, distant metastases, overall disease-free survival, and disease-specific survival at 1 year.⁴⁵ The benefits were not maintained overtime, however, and were not observed at 5 years.

One of the difficulties in interpreting and broadly generalizing these results is that various histologic subtypes are frequently treated in these series, hence confounding results. Certain histologic subtypes have demonstrated more chemosensitive behavior, notably pediatric rhabdomyosarcoma and synovial sarcoma. Synovial sarcoma has been found to respond favorably to adjuvant chemotherapy and metastatic lesions are also sensitive to chemotherapy.^{46,47} Pediatric rhabdomyosarcoma also responds favorably and when treated with chemotherapy has a 5-year overall survival of 71%.⁴⁸ Broadly accepted indications for systemic chemotherapy include pediatric rhabdomyosarcoma, synovial sarcoma, local recurrence, and distant metastasis.

In the setting of recurrent disease, recommendations are less clear. The National Comprehensive Cancer Network (NCCN) guidelines for limited metastasis confined to a single organ or disseminated metastases are similar to those of stage IV disease at presentation; that is, doxorubicin based regimens.⁴⁹ There are limited data on the use of systemic chemotherapy in patients who undergo metastasectomy and results suggest minimal impact on survival of patients with metastatic extremity STS who undergo metastasectomy.⁵⁰ NCCN guidelines describe the use of systemic chemotherapy in the recurrent setting as a category 2B recommendation, suggesting that the intervention may be appropriate based on lower-level evidence. Despite a lack of consensus, several centers have suggested a potential benefit to the use of systemic chemotherapy for the management of local recurrence. Investigators from McGill University demonstrated that local recurrence occurred at or before the development of distant metastasis in 34% of patients.³¹ Eilber and colleagues⁸ from the UCLA Sarcoma Research Group noted that local recurrence was the most significant factor for decreased survival and, therefore, patients should be strongly considered for adjuvant systemic chemotherapy. Patients who develop recurrence should undergo referral to a multidisciplinary team that specializes in the management of these complex patients with consideration for clinical trial enrollment.

Regional Lymphadenectomy for Sarcoma Recurrence

Regional lymph node metastasis (RLNM) is a rare event in the natural history of STS with an estimated incidence of less than 5% of all patients.⁵¹ For this reason, elective lymphadenectomy is generally not indicated in the initial management of STS.^{52,53} Certain subtypes, however, are more commonly associated with regional nodal metastasis. Lymph node metastasis as regional recurrence is more common for epithelioid sarcoma, synovial sarcoma, and rhabdomyosarcomas, particularly in the pediatric population.^{53–55} The predilection for regional metastasis has led some investigators to suggest the routine use of sentinel lymph node biopsy (SLNB) in the management of these particular histologies.^{56–58} Results have been inconclusive, however, and limited to single-institution, small-volume, retrospective series. Most likely, a multicenter trial will be required to demonstrate any effect of routine SLNB on overall STS outcome for at-risk pathologic conditions.

Although lymph node metastasis is rare, in the absence of distant disease, formal lymphadenectomy may offer potential for cure and is recommended. In one of the larger series reported, Fong and colleagues⁵¹ reported on 1772 sarcoma subjects treated at Memorial Sloan-Kettering Cancer Center with lymph node metastasis from STS. Forty-six subjects (2.6%) were identified with lymph node metastasis over a 10-year treatment period. The most common histologies included angiosarcoma, embryonal rhabdomyosarcoma, and epithelioid sarcoma. Leiomyosarcoma and malignant fibrous histiocytoma were also common but, because of a higher prevalence of these tumors, represented a smaller percentage overall. Forty-five of the 46 subjects had high-grade tumors. Thirty-one subjects went onto radical lymphadenectomy with the remainder undergoing either simple excision or noncurative procedures. Those who underwent radical lymphadenectomy had an improved outcomes compared with those with noncurative procedures (16.3 months survival vs 5.9 months survival, $P = .027$). Although the 5-year survival for nodal metastasis was poor (34%), radical lymphadenectomy did offer the potential for long-term survival in a select few with isolated lymph node metastasis.

Results from the United Kingdom give additional insight on the impact of RLNM and the outcome of STS in adults. Seventy-three subjects who developed RLNM of 2127 patients with STS were reported.⁵⁹ The most common histology was similar to that of the Memorial Sloan-Kettering series and also included angiosarcoma. Fifty-seven subjects (78%) had lymph node metastasis alone as the site of initial spread, whereas 16 subjects (22%) had regional and distant metastasis. Forty-two subjects presented with synchronous RLNM with the primary tumor. The remainder presented with RLNM a median of 13.5 months from diagnosis of the primary tumor. Most interesting, the 1-year survival for RLNM alone was 77.5% compared with 36% for those with regional and distant metastasis at initial diagnosis ($P = .005$) suggesting that those with RLNM only fare better. The investigators also identified that those who presented with RLNM at the time of initial diagnosis had a poorer outcome than those who presented with metachronous RLNM metastasis.

Regional Therapy for Sarcoma Recurrence

For patients with STS who present with bulky recurrent tumors involving critical neurovascular structures, or with concomitant distant disease, selecting an appropriate therapy that provides local control without compromising quality of life, limb function, or long-term outcome is a challenge. Amputation, as previously mentioned, may provide local control at the expense of loss of function but does nothing to address distant disease and has no impact on overall outcome.^{26,60} There has been a growing trend

over the last several decades toward limb-preservation therapies when treating these complicated patients with recurrent or unresectable STS. Regional delivery of chemotherapy can be used as an adjunct to surgical resection with RT for advanced STS of the extremity. Furthermore, regional therapy offers the potential for local control, especially in situations of unresectable, isolated recurrent disease or recurrent disease in the presence of distant metastasis.

Two techniques, HILP and ILI, allow the regional administration of chemotherapy, delivering drug concentrations 15 to 25 times higher than systemic dosages without the systemic side effects.⁶¹ There are numerous potential indications for regional therapy for STS, most notably: multifocal primary tumors,⁶² recurrent disease,⁶³ those undergoing previous resection with irradiation,⁶⁴ bulky primary tumors,^{65,66} or high-grade tumors.⁶⁵ Elderly patients⁶⁷ and those with distant metastasis treated in a palliative setting⁶⁸ have been shown to gain a benefit in local control and limb-salvage rates using regional therapy.

HILP, first reported in the 1950s for treating melanoma patients with regional in-transit disease, was the first regional chemoperfusion therapy to demonstrate improved salvage rates in patients with extremity STS.⁶¹ The technique is invasive and requires an extracorporeal bypass circuit.⁶⁹ HILP requires surgical exposure and cannulation of the iliac or femoral vessels for lower extremity disease or subclavian or axillary vessels for upper extremity tumors. The cannulae are connected to an extracorporeal circuit that contains a membrane oxygenator and a heat exchanger. To ensure vascular isolation and target tumor perfusion, a pneumatic cuff or esmarch tourniquet is applied proximally on the affected extremity. Systemic leakage is measured continuously throughout the procedure by a precordial Geiger counter that monitors ⁹⁹Tc radiolabeled human serum albumin or red blood cells previously injected into the perfusate. Flow rates are set as high as possible, generally 35 to 40 mL/L of limb volume per minute. The procedure is performed under hyperthermic conditions (38.5–40°C). Melphalan is the drug of choice for HILP and dosage is calculated according to the liter-volume method.⁷⁰ In many European centers, a combination of melphalan (10 mg/L for lower limb and 13 mg/L for upper limb), as well as TNF- α (2–4 mg) is commonly used.^{63,65,66} Actinomycin-D is frequently used with melphalan in most centers in the United States.⁷¹ Chemoperfusion is performed for a total of 90 minutes. At the completion of HILP, the limb is flushed with 2 to 4 L of isotonic saline solution, tourniquets are released, and vascular anatomy is reconstructed. Patients are observed in an intensive care setting for monitoring of systemic toxicity and reperfusion injury. Average postoperative length of stay ranges from 8 to 10 days.

ILI is a less invasive approach for administering regional chemotherapy and was first reported on by the Sydney Melanoma Unit.⁷² ILI, first described for the treatment of in-transit metastases in melanoma patients, is a less complex procedure with overall response rates close to those observed with conventional HILP. ILI is essentially a low-flow HILP performed under hyperthermic, nonoxygenated conditions by percutaneously placed catheters. High-flow 5Fr to 6Fr arterial and 6Fr to 8Fr venous catheters are inserted by way of the uninvolved lower extremity and advanced fluoroscopically into the involved extremity. This may be done preoperatively by interventional radiology or by vascular surgery after the induction of general anesthesia. Heparin is administered to achieve full systemic anticoagulation with a target activated clotting time (ACT) greater than or equal to 350 seconds. The catheters are connected to an infusion circuit that consists of a heat exchanger and bubble excluder. Once subcutaneous temperatures of greater than 37°C are achieved, a pneumatic tourniquet or an Esmark wrap is placed on the proximal aspect of the limb to be infused, isolating the limb from the systemic circulation. Papaverine (60 mg) is injected into the arterial

catheter and chemoperfusion is initiated. The cytotoxic agents, often melphalan and actinomycin D, are circulated for 30 minutes. After infusion is complete, the limb is manually flushed with 1 L of isotonic crystalloid solution, heparinization is reversed with protamine, and the catheters are removed when the ACT is at or near baseline. Patients are monitored daily for regional toxicity with serial creatine phosphokinase (CPK) measurements and discharged home when CPK levels peak and decrease back towards baseline, generally within 4 to 6 days.⁷³

There are treatment-related toxicities to HILP and ILI that are worth discussion. In general, the toxicity of HILP is more severe than that experienced by patients who undergo ILI procedures. Systemic toxicities are more commonly observed with HILP procedures and are related to the type of chemotherapy used and the amount of leakage of the chemotherapeutic into the systemic circulation. Leakage rates less than 3% to 4% are generally well tolerated. Continuous precordial monitoring for systemic leakage is mandatory for patients undergoing HILP procedures. TNF- α , commonly used in many European centers, is thought to be responsible for many of the systemic toxicities experienced with HILP. Systemic leakage of TNF- α can induce a severe systemic inflammatory response syndrome with hypotension and shock-like symptoms, which necessitates aggressive hydration and vasopressor resuscitation. Systemic toxicity related to ILI is much less common than HILP. Rhabdomyolysis, as measured by serum CPK, may be encountered in patients undergoing this form of regional therapy. CPK levels often increase greater than 1000 IU/L and require daily blood urea nitrogen and creatinine level monitoring to avoid myoglobin-induced renal failure. Aggressive hydration with isotonic saline and maintaining urine output greater than 0.5 mL/kg/h may reduce the risk of renal failure caused by myoglobinuria.⁷⁴ Patients with CPK levels greater than 1000 IU/L are hydrated and given corticosteroids to decrease muscle edema or inflammation and monitored until CPK levels decrease towards baseline. Regional toxicity after HILP or ILI is more common than systemic toxicity. A commonly used classification system characterizing acute tissue reactions was first reported by Wieberdink and colleagues⁷⁰ and has standardized regional toxicity reporting for patients undergoing HILP or ILI therapy (Table 1). Acute regional toxicity-related symptoms are seen within the first 48 hours after HILP, or 72 to 96 hours after ILI.^{72,75} Typical reactions to either therapy include mild erythema, edema, and pain (Wieberdink II-III). Mild to moderate blistering is frequently seen up to several days post-therapy. The development of compartment syndrome progressing to the need for amputation has been reported but is generally uncommon.

Table 1
Wieberdink toxicity

Grade	Clinical Characteristics
I	No subjective or objective evidence of reaction
II	Slight erythema or edema
III	Considerable erythema or edema with some blistering; slightly disturbed motility permissible
IV	Extensive epidermolysis or obvious damage to the deep tissues causing definite functional disturbances; threatened or manifest compartmental syndromes
V	Reaction that may necessitate amputation

From Wieberdink J, Benckhuysen C, Braat RP et al. Dosimetry in isolation perfusion of the limbs by assessment of perfused tissue volume and grading of toxic tissue reactions. *Eur J Cancer*. 1982;18:906; with permission.

Table 2

Treatment and outcome data for regional therapy for advanced extremity soft tissue sarcoma

Author, Year	Number of Subjects	Modality	Chemotherapy	Follow-up (mo)	ORR (%)	CR/PR/SD (%)	Limb Preservation (%)
Eggermont et al, ⁶⁵ 1996	186	HILP	TNF- α INF- γ (N = 55) Melphalan	22	82	29/53/18	82
Eggermont et al, ⁸⁷ 1996	55	HILP	TNF- α INF- γ Melphalan	26	87	36/51/13	84
Gutman et al, ⁶⁶ 1997	35	HILP	TNF- α Melphalan	14	91	37/54/9	85
Olieman et al, ⁶⁸ 1998	34	HILP	TNF- α INF- γ Melphalan	34	94	35/59/6	85
Lejeune et al, ⁸⁰ 2000	22	HILP	TNF- α INF- γ (N = 4) Melphalan	19	82	18/64/18	86
Noorda et al, ⁷⁷ 2003	49	HILP	TNF- α INF- γ (N = 4) Melphalan	26	63	8/55/35	57
Rossi et al, ⁸⁸ 2005	21	HILP	TNF- α Doxorubicin	30	62	5/57/38	71

Grunhagen et al, ⁶⁴ 2005	53	HILP	TNF- α Melphalan	22	88	42/45/13	82
Bonvalot et al, ⁸⁹ 2005	100	HILP	TNF- α Melphalan	24	65	36/29/35	87
Lans et al, ⁹⁰ 2005	26	HILP	TNF- α Melphalan	22	70	20/50/30	65
Grunhagen et al, ⁷⁶ 2006	197	HILP	TNF- α Melphalan	22	75	26/49/25	87
Hegazy et al, ⁶² 2007	40	ILI	Doxorubicin	15	85	—/85/—	83
Moncrieff et al, ⁷⁸ 2008	21	ILI	Melphalan Actin D	28	90	57/33/10	76
Turaga et al, ⁷³ 2011	12	ILI	Melphalan Actin D	8.6	78	14/64/—	78
Vohra et al, ⁷⁹ 2013	26	ILI	Melphalan Actin D	11	42	24/18/18	71
Rastrelli et al, ⁹¹ 2016	117	HILP	Doxorubicin (N = 47) TNF/Doxorubicin (N = 30) TNF/Melphalan (N = 40)	36	—	47/30/—	78

Abbreviations: Actin D, actinomycin D; CR, complete response; ORR, overall response rate; PR, partial response; SD, stable disease.

Long-term toxicity is infrequently reported and may include paresthesias or permanent nerve dysfunction.

The treatment and outcome data for patients undergoing regional therapy for extremity STS are listed in [Table 2](#). Tumor response rates range from 68% to 91% for patients with advanced extremity STS previously only considered for patients with amputation who undergo HILP.^{65,66,76,77} Early results for ILI therapy for limb-threatening STS have also produced encouraging results comparable with those for HILP. Tumor response rates range from 79% to 90% for patients treated with ILI.^{62,73,78} In general, despite similar overall response rates, HILP is thought to produce more complete responders than ILI.

In addition to tumor response, both HILP and ILI spare these complex patients the potential morbidity and need for amputation with well-documented limb-salvage rates. HILP limb preservation rates have been consistently reported to range from 57% to 87% when treating advanced extremity STS.^{65,68,76} ILI also is an attractive limb-sparing alternative to amputation for extremity STS recurrence with equal salvage rates to HILP and without the potential toxicity. Four of the larger ILI series for STS sarcoma document limb-preservation rates of 71% to 83%.^{62,72,73,79} Local or regional recurrence after HILP and ILI treatment have been reported and can occur as high as up to 42% to 48%, respectively.^{62,65,78,80} Additional regional therapy remains an option for patients who may recur or progress after previous HILP or ILI. Repeat HILP or ILI, for instance, offers the potential for local control, even in the presence of distant metastases. Furthermore, both procedures can be used either as definitive treatment or neoadjuvant therapy combined with surgery and radiation for advanced, unresectable or metastatic STS.

OVERALL SURVIVAL AFTER LOCAL RECURRENCE

The impact of local recurrence on overall outcome remains an area of active debate. Randomized clinical trials have not demonstrated an impact on overall survival whereas others have demonstrated conflicting results ranging from no impact to decreased survival.^{11,81–84} Although no consensus exists, the long-term prognosis after development of local recurrence is guarded. Determinants of survival, such as grade, size, location, and histologic type, have all been well described for primary extremity STS.^{11,27,28,85} Many of these primary tumor factors are also at play in the management of recurrent disease. Recurrence is a marker of high-grade tumor biology is associated with the development of additional recurrence and is associated with distant metastasis. Indirectly, therefore, these factors do potentially have a negative impact on survival. The UCLA Sarcoma Research Group demonstrated that local recurrence in subjects with high-grade extremity STS is associated with the development of subsequent local recurrences.⁸ When reporting on 753 subjects treated over a 20-year period, subjects who developed local recurrence were 3 times more likely to eventually die of disease compared with those who had not developed a local recurrence. Local recurrence was the most significant factor associated with decreased survival.

Local recurrence may also present with concomitant distant disease in up to 30% of patients.^{30,31,86} The management of local recurrence in the setting of distant metastasis is a challenging problem. The synchronous development of local recurrence in the setting of distant failure represents a grave prognosis. Furthermore, although many subjects in the aforementioned studies represent those who undergo additional treatment, these studies may not capture patients with recurrence that rapidly progress locally or systemically, or fail to complete treatment, and are thus excluded. In

the setting of local recurrence, referral to a multidisciplinary regional sarcoma center is strongly recommended with consideration for clinical trial enrollment.

SUMMARY

Local recurrence of extremity STS is a difficult clinical entity to treat. Treatment should aim for limb-salvage therapies when possible. Resection and irradiation of recurrence are associated with potentially significant morbidity that may negatively affect function. Amputation may be required for management of the recurrence or of complications related to treatment of the recurrence; however, it has no impact on survival and a potentially negative impact on patient function and quality of life. Regional therapies in the form of HILP and ILI are attractive treatment options as either definitive or adjuvant therapy, especially in the presence of distant disease. Local recurrence has a guarded prognosis and early referral to a center specializing in the management of these complex patients is warranted.

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