
Isolated Limb Infusion as a Limb Salvage Strategy for Locally Advanced Extremity Sarcoma



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- BACKGROUND:** Treatment-resistant, locally advanced soft tissue sarcomas often require amputation for complete tumor extirpation. Isolated limb infusion (ILI) selectively delivers high-dose chemotherapy to the extremity in an attempt to achieve limb salvage. The aim of this study was to report perioperative and oncologic outcomes after ILI in patients with extremity soft tissue sarcomas.
- STUDY DESIGN:** From 1994 to 2016, 77 patients underwent 84 ILIs at a total of 5 institutions. Melphalan and actinomycin D were circulated for 30 minutes after complete tourniquet occlusion of the limb, then actively washed out to prevent systemic exposure.
- RESULTS:** The procedure was performed in an upper extremity on 19 patients (21 infusions) and in a lower extremity on 58 patients (63 infusions). The 3-month overall response rate (ORR) for the entire cohort was 58%, and there was a statistically significant difference ($p = 0.03$) between upper (37%) and lower extremity (66%) ORR. With median follow-up of 20.6 months (range 0.6 to 146.1 months), the overall limb salvage rate was 77.9%. For those who underwent amputation due to progression of disease, the median time to amputation was 4.5 months. With a median follow-up of 20.6 months, the median overall survival for the entire cohort was 44.3 months. The distant metastatic-free survival was longer for responders than nonresponders ($p = 0.01$), though the disease-specific survival was not different for the same groups ($p = 0.2$).
- CONCLUSIONS:** Isolated limb infusion for extremity soft tissue sarcoma results in an objective response for half of the patients who are otherwise facing amputation, and offers prolonged limb salvage for the vast majority of patients. The procedure is well tolerated without serious complications. (J Am Coll Surg 2017;224:635–642. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)
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Regional chemotherapy was developed as a strategy to treat patients with in-transit melanoma as a way to deliver chemotherapy to disease without systemic toxicity. The initial procedure described was hyperthermic isolated

limb perfusion (HILP) with open cannulation of the vessels at the proximal aspect of the extremity and a high-flow oxygenated perfusion,¹⁻⁴ but more recent efforts have focused on isolated limb infusion (ILI).⁵⁻¹¹ This

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Abbreviations and Acronyms

CPK	= creatine phosphate
DMFS	= distant metastatic-free survival
HILP	= hyperthermic isolated limb perfusion
ILI	= isolated limb infusion
LRFS	= local recurrence-free survival
NED	= no evidence of disease
ORR	= overall response rate
OS	= overall survival

technique involves the instillation of chemotherapy through percutaneously placed arterial and venous catheters in an extremity, with tourniquet occlusion of the extremity proximal to the catheter tips. The chemotherapy is circulated for 30 minutes, then washed out from the limb before restoring systemic circulation. The less invasive approach of ILI, in which the catheters can be placed percutaneously by radiographic guidance, was recently shown to have equivalent outcomes when retrospectively compared with HILP.¹²

Patients with locally advanced extremity soft tissue sarcoma have limited therapeutic options. In the absence of distant metastatic disease, amputation has been the standard treatment, reserving systemic chemotherapy for those patients who progress. Historically, amputation was standard for resectable high-grade extremity sarcoma as well, but chemotherapy and radiation therapy are now standard surgical adjuncts, making limb salvage the standard of care.¹³⁻¹⁶ Regional chemotherapy has been proposed as a limb salvage strategy for patients with locally advanced sarcoma. Initial reports using the HILP technique described limb salvage rates of 80%. The technique of ILI was initially described for sarcoma patients in the neoadjuvant setting, and an 85% to 100% objective response rate was reported for patients who underwent resection after infusion,^{5,6} with 65% obtaining a complete response in 1 study.⁶ Three recent reports of ILI as a treatment strategy apart from surgical resection report objective response rates ranging from 42% to 79%.^{9,10,17}

Despite encouraging results from these limited reports, long-term outcomes have not been reported for regional chemotherapy using ILI in patients with locally advanced extremity sarcoma. There is concern that without a complete response in the extremity, distant disease may flourish, resulting in decreased overall or distant metastatic-free survival (DMFS) for these patients compared with amputation. The purpose of this report was to describe the long-term outcomes from several high volume centers of ILI for patients with locally advanced extremity sarcoma.

METHODS

After obtaining IRB approval, data were collected from 5 centers to complete a retrospective analysis of patients who underwent ILI for locally advanced soft tissue sarcoma from 1994 to 2016. Data collected included demographic details, sarcoma histologic subtype, procedure details, post-operative course with toxicity, 3-month response to treatment, and long-term oncologic outcomes.

Preoperative assessment

Patients were considered candidates for ILI if they had a locally advanced extremity sarcoma, no objective evidence of vascular disease in the affected extremity, and no evidence of distant metastatic disease on imaging studies. Before surgery, limb volume was calculated with either circumferential measurements of the extremity at 1- to 2-cm intervals or by volume displacement. Volume measurements were used to determine the dose of chemotherapeutic agents, which included a combination of actinomycin (range 3.5 to 13.6 mg/L limb volume) and melphalan (range 46.1 to 142.9 µg/L limb volume).

Intraoperative isolated limb infusion procedure

Under fluoroscopic guidance, arterial and venous catheters were placed from the contralateral groin or brachium into the affected limb, with catheter tips positioned distal to the level of the tourniquet to ensure adequate isolation of the extremity. Patients were transported to the operating room and general anesthesia was induced. The extremities were warmed with either external warming blankets, warming pads, or heating lamps. Temperature probes were placed in the subcutaneous tissue and a tourniquet was placed proximal to all disease in the extremity. Unfractionated heparin was given intravenously to achieve an activated clotting time greater than 400 seconds. The tourniquet was inflated (250 mmHg upper extremity, 350 mmHg lower extremity) when the temperature of the extremity reached 37°C, and 60 mg of papaverine was given through the arterial catheter.

Arterial and venous catheters were connected to a closed circuit with 1-way valves or 3-way stopcocks to ensure flow in 1 direction. Chemotherapy was infused through the arterial catheter over a 5-minute period and then circulated for 30 minutes manually using a 20- to 30-mL syringe connected in line to the closed circuit (Fig. 1). The blood of the extremity was then drained through the venous catheter by infusing saline into the extremity and displacing the chemo-laden blood until the effluent was clear. Heparinization was reversed using protamine to reach an activated clotting time back to baseline. Catheters were removed and manual pressure—with or

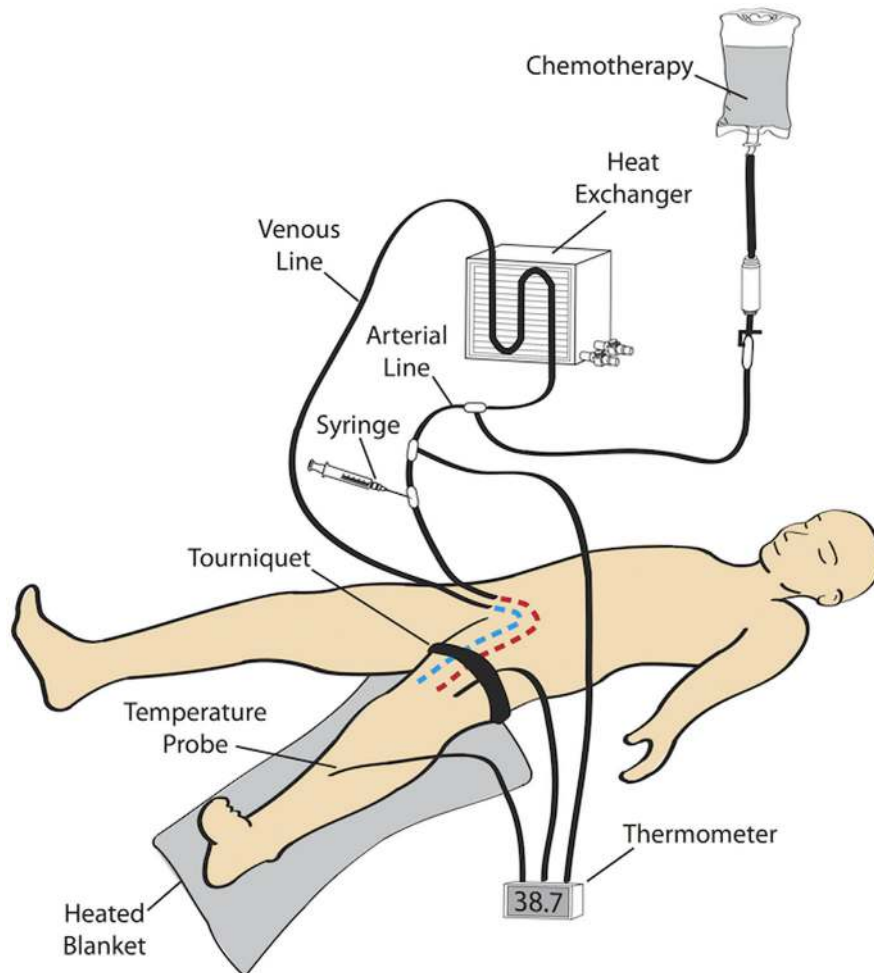


Figure 1. Isolated limb infusion technique for locally advanced soft tissue sarcoma. Arterial and venous catheters are placed from the contralateral limb and the tips are advanced just distal to the level of the tourniquet, which is placed proximal to the extent of disease. Chemotherapy is instilled over a 5-minute period and then circulated, with the extremity actively warmed, over a 30-minute period. All blood from the extremity (including the chemotherapy residue) is drained before systemic circulation is restored. (Image courtesy Jeffrey M Farma, MD, Fox Chase Cancer Center.)

without a percutaneous arteriotomy closure device—was applied to ensure hemostasis.

Postoperative care

Patients were admitted to the step down unit or the ICU, and extremity neurovascular checks were performed hourly for the first 12 hours, and then every 4 hours for the next 12 hours. Creatine phosphokinase (CPK) levels were checked every 12 hours throughout the inpatient stay to document the peak level. Normal saline (to maintain urine output > 0.5 mL/kg) and corticosteroids (dexamethasone 4mg every 6 hours) were administered if CPK levels exceeded 1,000 U/L. Patients who required

corticosteroids were discharged on a tapered dose of oral methylprednisolone. The length of inpatient stay was dictated by the CPK response after therapy, and patients were discharged after 2 documented decreasing CPK levels. Limb toxicity was measured throughout the hospital stay and also at 6 and 12 weeks postoperatively using the Wieberdink scale (Table 1). The highest grade toxicity was recorded and patients were stratified by high toxicity (grade III to V) or low toxicity (grade I to II).

Outcomes measurements

The response rate to therapy was measured at 12 weeks after ILI on cross-sectional imaging using RECIST

Table 1. Wieberdink Toxicity Scale (As Described by Wieberdink and colleagues¹⁸)

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

(Response Evaluation Criteria in Solid Tumors) v1.1 criteria for deep lesions or direct measurement for cutaneous and palpable lesions. In one center, the response was assessed as the best response, observed twice, more than 4 weeks apart postoperatively. Patients were seen every 3 months to determine the duration of response to treatment. Long-term oncologic outcomes such as overall survival, time to in-field progression, time to out-of-field progression (distant metastasis) were also collected.

Results

From 1994 to 2016, 77 patients underwent 84 ILI procedures for advanced soft tissue sarcoma of the extremity, 21 (25%) of which were for upper extremity tumors and 63 (75%) were for lower extremity tumors. For the entire cohort, the median age was 68.9 years (range 18.5 to 93.6 years) at the time of initial ILI, and 48 patients (62.3%) were female. The median follow-up was 20.6 months (range 0.6 to 146.1 months). Within 90 days preceding the procedure, 21 (27.2%) patients received systemic cytotoxic chemotherapy and 39 (50.6%) received external beam radiation therapy. Isolated limb infusion was performed for several sarcoma subtypes (Table 2); the most common was undifferentiated pleomorphic sarcoma (44.2%) followed by synovial sarcoma (6.5%), leiomyosarcoma (6.5%), and angiosarcoma (5.2%).

Intraoperative outcomes

The median limb volume for patients with upper extremity disease and lower extremity disease was 2.1 L (range 1.1 to 3.3 L) and 6.5 L (range 3 to 11.0 L), respectively. During the procedure, patients received a median of 7.2 mg/L (range 3.5 to 13.6 mg/L) melphalan and 88.5 µg/L (range 46 to 142 µg/L) actinomycin D. The median tourniquet time was 51 minutes (range 44 to 90 minutes), though the circulation time was 30 minutes in all patients. No additional chemotherapeutic drugs

were infused for any patients. The median initial limb temperature was 37.5°C (range 34.1 to 39.8°C) and was a median 38.9°C (range 36.5 to 40.6°C) at 30 minutes after infusion of chemotherapy. The arterial pH at 30 minutes for upper and lower extremity patients was median 7.09 (range 7.00 to 7.25) and median 7.13 (range 6.97 to 7.28), respectively (Table 3).

Postoperative outcomes

The median length of stay after ILI was 7.0 days (range 3 to 28 days). Patients with an ILI performed for disease in the upper extremity had a shorter median length of stay than those with lower extremity disease (5 days vs 7 days; $p = 0.0169$). Toxicity by Wieberdink criteria was low (grade I to II) for patients after 51 procedures (60.7%), and there were no amputations performed for toxicity. The median peak postoperative CPK level for those with upper extremity disease was 372 U/L (range 54 to 11,783 U/L) and 1,068 U/L (range 1.5 to 10,656 U/L) for those with lower extremity disease. Toxicity, as measured by CPK level, resulted in \geq grade 3 toxicity in 47.6% of procedures (by CTCAE [Common Terminology Criteria for Adverse Events] v4.0 criteria). Seven patients (9.1%) underwent a repeat ILI procedure and there were no patients who underwent previous or subsequent HILP.

Disease response to isolated limb infusion

The overall response rate (ORR) at 3 months (complete response combined with partial response) for all patients who underwent ILI was 58.4% (45 of 77) patients, and 29.9% (23 of 77) had a complete response. Complete responders include 13 patients who were able to undergo a complete resection within 3 months of ILI to achieve this response. Additionally, 6 patients with a partial response at 3 months underwent resection later in their disease course, which left them with no evidence of disease (NED). Those who underwent ILI for lower extremity disease had a higher response rate compared with those with upper extremity disease (65.5% vs 36.8%; $p = 0.03$). There was no difference in ORR between patients who had a high toxicity after the procedure compared with those who had a low toxicity (66.7% vs 54.4%, respectively; $p = 0.3$) (Table 4).

In-field progression occurred in 54 (70.1%) patients and the median time, described as the local recurrence-free survival (LRFS), was 6.4 months. When subgroups were compared, a higher median LRFS was seen in those with a complete response compared with those with other responses (not-reached vs 3.7 months; $p < 0.0001$) and also in those with any response compared with those without a response (16.9 months vs 2.7 months, respectively; $p < 0.0001$). There was no difference in median

Table 2. Distribution of Sarcoma Histology Subtype

Sarcoma subtype	Isolated limb infusion		Amputation	
	n	%	n	%
Undifferentiated pleomorphic sarcoma	34	44.2	20	28.2
Angiosarcoma (1 epithelioid subtype)	6	7.7	4	5.6
Synovial sarcoma	5	6.5	5	7.0
Leiomyosarcoma	5	6.5	6	8.5
Epithelioid sarcoma	3	3.9	0	0
Kaposi's sarcoma	3	3.9	0	0
Myxofibrosarcoma	3	3.9	9	12.7
Myxoinflammatory fibroblastic sarcoma	3	3.9	0	0
Fibrosarcoma	2	2.6	2	2.8
Myxoid sarcoma, NOS	2	2.6	0	0
Clear cell sarcoma	2	2.6	1	1.4
Dedifferentiated liposarcoma	2	2.6	0	0
Osteosarcoma	2	2.6	11	15.5
Rhabdomyosarcoma (1 alveolar subtype)	2	2.6	0	0
Fibromyxosarcoma	1	1.3	0	0
Ossifying fibromyxoid sarcoma	1	1.3	0	0
Spindle cell sarcoma, NOS	1	1.3	0	0
Chondrosarcoma	0	0	7	9.9
Ewing sarcoma	0	0	2	2.8
Malignant peripheral nerve sheath tumor	0	0	2	2.8
Hemangiopericytoma	0	0	1	1.4
Chordoma	0	0	1	1.4
Total	77	100	71	100

NOS, not otherwise specified.

LRFS when those with lower extremity disease were compared with those with upper extremity disease (6.4 vs 7.1 months; $p = 0.6$) or those with low toxicity were compared with those with high toxicity (8.3 vs 6.4 months, respectively; $p = 0.2$).

The ILI procedure did not universally result in limb salvage and ultimately, 17 patients (22.1%) underwent amputation of the affected limb for disease. The median time to amputation for these patients was 4.5 months. As expected based on the LRFS comparisons, those with

a response at 3 months post-procedure had longer median time to amputation than those with no response (not reached vs 12.9 months; $p = 0.0001$) (Table 4).

Survival analysis

Because ILI is a regional procedure for a disease process with a propensity for distant spread, we analyzed the DMFS. A total of 26 (33.8%) patients ultimately developed distant metastatic disease. For patients who developed distant metastatic disease, the median time to

Table 3. Intraoperative and Postoperative Outcomes for Patients Who Underwent Isolated Limb Infusion for Advanced Extremity Sarcoma

Characteristic	Extremity	
	Lower (n = 63)	Upper (n = 21)
Sex, male, n (%)	20 (31.8)	10 (47.6)
Age, y, median (range)	70 (18–90)	72 (24–93)
CPK, U/L, median (range)	1,068 (1.5–10,656)	372 (54–11,783)
pH at 30 min, median (range)	7.13 (6.97–7.28)	7.09 (7.00–7.25)
Length of stay, d, median (range)	7 (4–28)	5 (3–21)
High toxicity (grade III–V), n (%)	25 (43.1)	5 (27.8)

Data analyzed by procedure.

CPK, creatine phosphokinase.

Table 4. Response Data Stratified by Extremity and Toxicity

Characteristic	Extremity			Toxicity*		
	Lower (n = 58)	Upper (n = 19)	p Value	High (n = 30)	Low (n = 46)	p Value
Overall response, n (%) [*]	38 (65.5)	7 (36.8)	0.0277	20 (66.7)	25 (54.4)	0.2855
Overall survival, mo, median	56.6	27.9	0.0389	32.4	52.8	0.9587
Disease-specific survival, mo, median	NR	27.9	0.2347	NR	NR	0.8867
Amputation, n (%)	10 (17.2)	7 (36.8)		9 (30)	8 (17.4)	
Disease status, n (%) [†]						
Alive with disease	18 (32.1)	3 (16.7)		8 (26.7)	13 (29.6)	
Died of disease	17 (30.4)	9 (50)		12 (40)	14 (31.8)	
No evidence of disease	17 (30.4)	3 (16.7)		7 (23.3)	13 (29.6)	
Died, not of sarcoma	4 (7.14)	3 (16.7)		3 (10)	4 (9.1)	

Data analyzed by patient.

*One patient with missing data.

[†]Three patients with missing data (2 lower extremity, 1 upper extremity).

NR, no response.

progression was 9 months. The median DMFS was longer for patients with a response at 3 months than for those without a response (not-reached vs 13.6 months; $p = 0.02$) and also for those with a complete response vs all others (not-reached vs 27.2 months; $p = 0.04$). There was no difference in median DMFS between patients with lower vs upper extremity disease (not-reached vs 27.2 months, respectively; $p = 0.7$) (Fig. 2).

At the time of the analysis, there were 21 patients (27.2%) alive with disease and 20 (25.9%) without

evidence of disease. With median follow-up of 20.6 months, the median overall survival (OS) for all patients was 44.3 months. Patients with lower extremity disease had a higher median overall survival than patients with upper extremity disease (56.6 months vs 27.9 months; $p = 0.04$), but there was no difference in median overall survival between responders and nonresponders after the procedure (44.3 months vs 32.2 months; $p = 0.9$). Of those patients who died (33, 42.9%), the vast majority (26, 78.8%) succumbed to disease rather than another medical

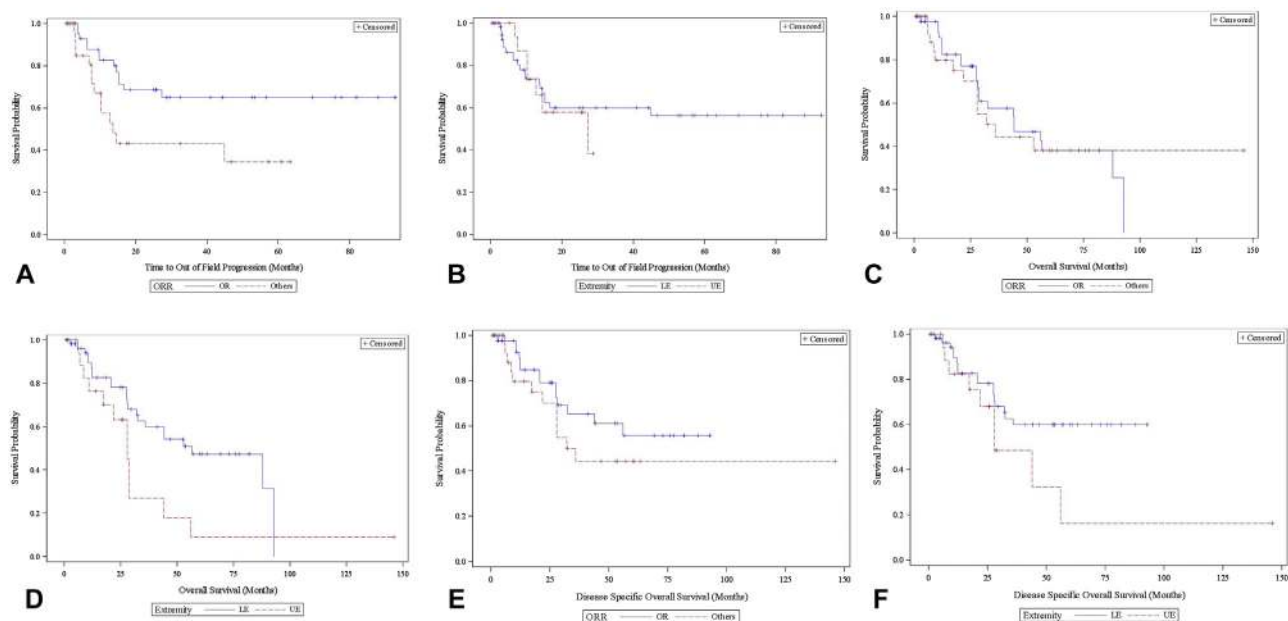


Figure 2. Survival curves for locally advanced soft tissue sarcoma patients who underwent isolated limb infusion (ILI). (A) Distant metastatic-free survival for responders compared with nonresponders and (B) upper compared to lower extremity ILI. (C) Overall survival for responders compared with nonresponders, and (D) upper extremity compared with lower extremity ILI. (E) Disease-specific survival for responders compared with nonresponders and (F) upper compared with lower extremity. LE, lower extremity; OR, objective response; ORR, overall response rate; UE, upper extremity.

condition. The median disease-specific survival was not reached for responders compared with a median disease-specific survival in those who did not respond to ILI of 32.2 months ($p = 0.2$). The disease-specific survival was 27.9 months in the upper extremity ILI group vs not reached in the lower extremity ILI group ($p = 0.08$).

As stated previously, ILI is a procedure designed to treat locally advanced disease in an extremity as an alternative to amputation. Given that this procedure does not result in a universal complete response (unlike amputation), there could be concern that residual disease might lead to a more rapid distant metastatic progression or decreased OS. To attempt to answer this concern, we included an independent, contemporary cohort of patients who underwent extremity amputation for locally advanced soft tissue sarcoma from 2006 to 2016 at Moffitt Cancer Center. In this group of 71 patients, 34 (48%) progressed with distant disease after amputation and, in these patients the median DMFS was 6.4 months. The median OS for all patients who underwent amputation was not reached.

DISCUSSION

Isolated limb infusion for locally advanced soft tissue sarcoma is a safe procedure that is well tolerated by patients. Patients remained hospitalized for a relatively few number of days and there were no procedure-related amputations required. We showed that ILI results in a meaningful overall response rate within the extremity, and the procedure can be repeated without any change in the toxicity or postoperative course. Almost one-third of patients have a complete response, and many are made NED because the ILI procedure has made the disease resectable. When the outcomes are judged against a reference set of patients who underwent amputation for locally advanced soft tissue sarcoma, there is no apparent impairment in the distant metastatic or overall survival.

This study represents the largest experience of the ILI technique for regional chemotherapy in patients with sarcoma. The conclusions from this dataset are enhanced due to the inclusion of multiple, high-volume centers that have expertise in regional chemotherapy. This includes the group responsible for first reporting this procedure. Further, the heterogeneity of histologic subtypes represents the breadth of disease encountered in a high-volume sarcoma practice, making these data applicable to a wide range of patients. The distribution of histologic subtypes is commensurate with the incidence of primary disease encountered. Finally, the time period of follow-up is sufficient to allow for long-term distant metastasis and overall survival analysis, endpoints that are the paramount concern to practitioners and patients. The

philosophy of regional therapy for advanced extremity sarcoma is important because one might question the use of a therapy that does not result in universal complete response (unlike amputation), and which, therefore, may hasten distant metastatic disease development and subsequently shorten OS. This view would suggest that amputation followed by systemic therapy would effectively treat distant disease in a group of patients with remarkable propensity to develop distant metastases. Advocates for ILI in these patients would argue that, with similar long-term survival data and meaningful overall response rates, patients would much prefer a treatment that preserves the affected extremity to one that does not. The reality is that those patients who develop metastatic disease after amputation or ILI likely already have distant microscopic disease at the time of the procedure, but the radiographic staging studies are not sensitive enough to detect it. In this sense, treatment of the extremity disease is not the determinant of long-term survival, and therefore, a limb salvage approach with ILI might be justified. There are some limitations to this study. First, the data are retrospective and collected over several years. That said, at the 2 largest centers, the data were collected prospectively as the cases and follow-up were completed, and a punctuated collection method such as this skews away from the inherent deficiencies encountered in acquiring data from the past. Second, there was no randomization of patients between ILI and amputation so direct comparison between these groups is not possible. The patients were heavily selected for ILI over amputation, and because the data for the 2 groups were not acquired in tandem, the reasons for this selection cannot be entirely elucidated.

CONCLUSIONS

Our report offers the largest report of a limb salvage approach, using the ILI technique of regional chemotherapy, for patients with advanced extremity sarcoma. These patients have very few systemic treatment options, and nearly all of those options are associated with significant toxicity and modest response rates. The ILI procedure is well tolerated and generally does not preclude future treatment options. For centers with experience in regional chemotherapy, our data suggest that expansion of this treatment to patients with sarcoma would result in a clinically relevant response for the majority of patients, allowing them to keep their limb with no detriment in overall survival.

Author Contributions

Study conception and design: Mullinax, Kroon, Thompson, Mosca, Farma, Bhati, O'Donoghue, Gonzalez, Zager

Acquisition of data: Mullinax, Kroon, Thompson, Nath, Mosca, Farma, Bhati, Hardmann, Sileno, Perez, Zager
 Analysis and interpretation of data: Mullinax, Naqvi, Chen, Gonzalez, Zager

Drafting of manuscript: Mullinax, Kroon, Mosca, Farma, Gonzalez, Zager

Critical revision: Mullinax, Kroon, Nath, Mosca, Farma, Bhati, Chen, Gonzalez, Zager

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Discussion



DR KEITH DELMAN (Atlanta, GA): The use of limb infusion for sarcoma is not as widely applied as it is for melanoma, so this work will hopefully help encourage sarcoma surgeons to consider this therapeutic approach in their armamentarium. I have just a few questions for the group.

You included data from Australia in your study. As you mentioned, tumor necrosis factor (TNF)- α is not approved for use in the US, but is routinely used for isolated limb infusion (ILI) in Europe, and I believe also in Australia. Can you please let us know if, in fact, the Australian contribution includes patients receiving TNF- α ? If so, was this considered in looking at your response? The European data generally show better responses in patients who receive TNF- α and, as a result, this information would be important to know.

Second, you report “low” Wieberdink toxicity, and the manuscript describes “low” as Grades 1 to 2. You also demonstrated you did have patients who had greater than Grade 3 Wieberdink toxicity. It was unclear to me whether the amputations that you reported were treatment related or they were related to therapeutic failure and progression of disease. Did any patient undergo amputation as a result of toxicity from therapy? Furthermore, did any patients suffer compartment syndrome or delay in discharge due to concerns of impending compartment syndrome? In other words, did the toxicity of the therapy have any impact on the patient?

Third, infusion was used as a last-resort therapy for limb salvage by your description, and 54 patients progressed infield. However, according to your manuscript, only 17 patients ultimately underwent amputation. I am curious, if you had infield progression in 54 patients and if this was actually implemented for limb salvage, why was amputation not implemented for the other patients? Additionally, 23 patients had a complete response. Although you characterize the complete response in your slides, can you please clarify these data? Of the 23 patients who had a complete response, how many occurred infield within your first 6 months? It is difficult to advocate, of course, for a procedure, albeit an apparently safe one in your series, which has a very short impact, even when