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Risk Factors for Lymphedema after Thigh Sarcoma Resection and Reconstruction

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Background: Secondary lymphedema can be a lifelong and debilitating consequence of lower extremity oncologic resection and reconstruction. The goal of this study was to identify risk factors for the development of lymphedema in patients treated for thigh sarcoma.

Methods: A retrospective review analyzed all patients who underwent thigh sarcoma resection and reconstruction by a plastic surgeon at the Mayo Clinic between 1997 and 2014. Patient demographics, tumor characteristics, surgical management, adjunctive therapies, and complications of patients who did and did not develop postoperative lymphedema were compared.

Results: A total of 148 patients were identified. Twelve percent of patients developed lymphedema postoperatively during an average follow-up of 26 months. Risk factors for the development of lymphedema included defect location in the medial thigh ($P = 0.04$), arterial resection ($P = 0.001$), arterial reconstruction ($P = 0.027$), and a history of cardiac disease ($P = 0.03$). Twenty-two percent of patients who developed lymphedema also experienced wound dehiscence compared with 4.6% of patients without lymphedema ($P = 0.02$). There were no differences in age, body mass index, smoking, history of deep venous thrombosis or venous stasis, wound dimensions, or type of reconstruction performed in patients with and without lymphedema.

Conclusions: Lymphedema is common following major oncologic resection. Preexisting cardiac disease, tumor location in the medial thigh, and arterial resection and reconstruction were associated with a higher risk of postoperative lymphedema. Noninfectious wound dehiscence may be secondary to lymphedema or represent an early indicator of patients who will ultimately develop lymphedema.
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INTRODUCTION

Soft-tissue sarcomas (STS) occur throughout the body, but 40%–60% of STS are found in the lower extremities, with the majority of these in the thigh.[1,2] The management of extremity STS has shifted away from amputation toward limb-sparing functional resections and multimodal therapy. Retrospective and prospective randomized studies of STS showed no significant difference in psychologic and quality of life outcomes between amputation and limb salvage in the long term; however, patients who experienced complications reported decreased quality of life and function at 2 years.[3–5] The complications of lower extremity reconstruction for sarcoma have been well described[5–11]; however, there is a paucity of literature assessing lymphedema as the primary outcome. Lymphedema is a potential complication of limb salvage for STS and may confer severe, permanent disability.[12–14]

Proper patient education and selection are paramount to establishing realistic expectations and achieving optimal outcomes with limb salvage. It is important to understand the risks and benefits of limb-preserving treatment strategies; so patients can have an informed discussion with their physicians regarding the best management strategy. The goal of this study was to characterize the risk factors

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for lymphedema in patients with thigh sarcoma resection and reconstruction. This will help identify patients preoperatively who are at a higher risk of developing lymphedema, which may guide the decision-making process.

METHODS

After institutional review board approval, a retrospective review of all patients with thigh STS defects reconstructed by the Division of Plastic Surgery at Mayo Clinic (Rochester, Minn.) from 1997 to 2014 was conducted. Patients for whom plastic surgery was consulted to manage wound complications were omitted because this represented a different patient population and certain reconstructive options may no longer be available. Those patients with preexisting lymphedema were also excluded. The diagnosis was made by one of the treating surgeons, and affected patients were generally referred to their local lymphedema specialist. Patients who developed postoperative lymphedema were grouped and compared with those who did not develop lymphedema.

Age, sex, comorbidities, wound characteristics (including tumor location, tumor size, and exposure of critical structures), chemotherapy, radiotherapy, reconstructive procedure, and complications were analyzed. All defects were categorized by anatomical location into anterior, posterior, medial, or lateral thigh as well as proximal, mid, or distal thigh. When a defect spanned more than one area, the wound was classified by where the majority of the defect was located. Reconstructive procedures were categorized into 6 groups: primary closure, skin grafts, local thigh fasciocutaneous flaps, local thigh muscle flaps, regional (non-thigh) flaps, and free flaps. To assess whether different radiation strategies affected the development of lymphedema, patients were categorized into 4 groups: no radiation, neoadjuvant radiation, intraoperative radiation, and/or adjuvant radiation. Operative notes were reviewed to determine if vascular structures were resected or reconstructed. Descriptive statistics and *t* tests were performed with significance defined as a *P* value of <0.05. Fisher exact tests and odds ratios were calculated for identified risk factors.

RESULTS

A total of 161 patients were initially identified during the study period. Thirteen patients demonstrated preexisting lymphedema, presumed to be secondary to the tumor or associated treatment effects of chemotherapy and/or radiation, and were thus excluded. Tumors in these patients were fairly equally distributed throughout the thigh except relatively few were in the lateral thigh (Table 1). Of the remaining 148 patients, the average age was 57.4 years (range, 14–94) and the average body mass index was 28.9. The histologic subtypes of sarcoma in these patients are listed in Table 2. A total of 29.3% of patients had surgery for a recurrent tumor. Eighteen (12.2%) patients developed lymphedema after thigh sarcoma treatment (Figs. 1–2). The average time to lymphedema onset was 3.7 months. Patients with lymphedema were followed for an average of 44.1 months versus those without lymphedema 23.6 months ($P < 0.05$). The rates of lymphedema were fairly consistent throughout the study period; most years had 0–2 patients who were diagnosed with lymphedema with 3 patients being diagnosed who had surgery in 2000 and 4 who had surgery in 2011.

Table 1. Location of Tumor in Patients with Preexisting Lymphedema

Vertical Location within the Thigh	Horizontal Location within the Thigh			
	Anterior	Medial	Posterior	Lateral
Proximal third (n = 5)	2	3	—	—
Middle third (n = 5)	1	1	2	1
Distal third (n = 3)	1	—	2	—

Table 2. Histologic Subtypes of Sarcomas

Histology	No. Patients (%)
Malignant fibrous histiocytoma	38 (25.9)
Liposarcoma	25 (17.0)
Synovial sarcoma	10 (6.8)
Chondrosarcoma	4 (2.7)
Rhabdomyosarcoma	2 (1.4)
Osteosarcoma	3 (2.0)
Angiosarcoma	2 (1.4)
Dermatofibrosarcoma protuberans	2 (1.4)
Other	61 (41.5)

A summary of the potential risk factors for the development of postoperative lymphedema in patients with and without lymphedema can be found in Table 3.

Patients with lymphedema demonstrated a higher rate of cardiac disease (including coronary artery disease, previous myocardial infarction, or congestive heart failure) than those without lymphedema (odds ratio, 3.0; $P = 0.03$). Of the 7 patients in the lymphedema group, 4 patients had congestive heart failure and 3 patients had coronary artery disease. Echocardiogram data were available on only 1 of the 3 patients with coronary artery disease and did show some compromise of ejection fraction. It is possible that the other 2 patients also had some compromised function of their heart. In addition, coronary artery disease is likely a marker of underlying peripheral vascular disease, which may also impact the risk of developing lymphedema. In the no lymphedema group, 9 patients had congestive heart failure (CHF) and 7 patients had coronary artery disease. Beyond this, there were no differences in the 2 groups with regard to demographics or comorbidities, including rates of peripheral vascular disease, diabetes, and smoking status.

In terms of tumor characteristics, there was a higher rate of lymphedema associated with defect location in the medial thigh, which was statistically significant (odds ratio, 2.81; $P = 0.04$). There was a trend toward significance for decreased risk of lymphedema in patients with lateral thigh defects, but this did not reach statistical significance (odds ratio, 0.08; $P = 0.08$). There was no difference in the size of defects or the type of reconstruction performed between the lymphedema and no lymphedema groups. The depth of tumor resection stratified by tumor location is shown in Table 4. This shows that generally patients who develop lymphedema have tumors located in the moderate to deep depths, although this was not statistically significant.

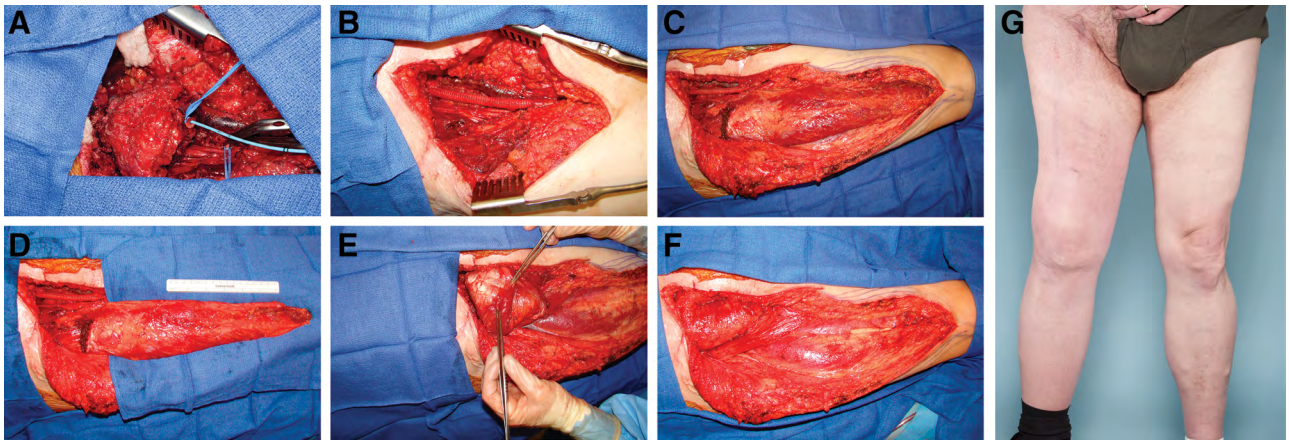

Fig. 1. Fifty-seven–year-old man with a history of retroperitoneal liposarcoma resected 8 years previously. He had an abdominal recurrence 2 years later and then a groin recurrence 3 years after that, both of which were excised. The patient underwent neoadjuvant and intraoperative radiation therapy for the disease in the right groin. Three years later, the patient was diagnosed with recurrent right groin liposarcoma. He underwent additional radiation before resection. Intraoperatively, the tumor was found to extend under the abdominal wall, deep to the inguinal ligament, requiring excision of a portion of the external oblique aponeurosis and the inguinal ligament, resulting in bowel herniation. A, In addition, the common femoral artery and the proximal deep and superficial femoral arteries were resected with the tumor. The femoral vein and nerve were exposed in the base of the wound but were intact. B, The femoral arteries were replaced with an 8-mm Hemashield interposition graft between the distal external iliac and the superficial femoral artery, and the deep femoral artery, including the lateral femoral circumflex branch, was replanted onto the posterior aspect of the interposition graft. After vascular reconstruction, the patient underwent intraoperative radiation. C–F, To reconstruct the defect, including that in the abdominal wall, and cover the femoral artery graft, the patient underwent a right rectus femoris pedicled rotational flap. Postoperatively, the patient required readmission for cellulitis, which was treated conservatively with antibiotics. He was also found to have occlusion of the great saphenous vein. The patient developed lymphedema within a few weeks after surgery. G, A 19-month postoperative photograph demonstrating right lower extremity lymphedema.

Arterial resection and reconstruction were associated with postoperative lymphedema ($P = 0.001$ and $P = 0.027$, respectively). Because arterial resection and reconstruction are dependent variables, it is intuitive that those patients with reconstruction would still have lymphedema, likely due to injury to the nearby lymphatics. However, patients who underwent reconstruction had a lower rate of lymphedema than those who did not undergo reconstruction. No statistically significant association was detected between venous resection or venous reconstruction and the development of postoperative lymphedema. In reviewing the operative notes, lymphatic resection was not described in any of the patients and no lymphatic reconstruction was attempted.

Radiation did not affect the development of lymphedema. Overall, 86.5% of patients underwent radiation; 30.4% underwent some combination of neoadjuvant, intraoperative, and adjuvant radiation (most were a

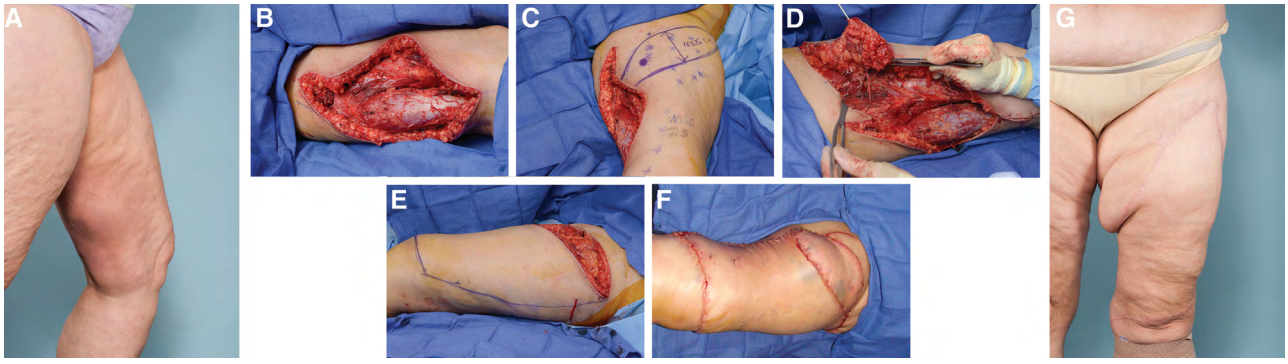

Fig. 2. A 51-year-old woman with a left medial mid-thigh sarcoma. A, preoperative photograph. B, She underwent neoadjuvant chemotherapy and radiation and then tumor resection. The great saphenous vein was sacrificed because it traversed the tumor. C, Reconstruction was completed with a freestyle superficial femoral artery perforator flap. D, The perforators can be seen on the deep surface of the flap. The distal 10 cm of the flap was found to be ischemic on SPY angiography; so this portion was excised and discarded. E, Given that additional tissue was needed, a keystone flap was designed using tissue from the anterolateral thigh. F, Final inset of the perforator and keystone flaps. She developed left lower extremity lymphedema within a few months postoperatively. G, A 7-month postoperative photograph. Two weeks later, she underwent scar revision and liposuction and debulking of the perforator flap and the thigh.

Table 3. Evaluation of Possible Risk Factors for the Development of Lymphedema after Thigh STS Resection

	Lymphedema (n = 18)	No Lymphedema (n = 130)	*P*
Demographics and comorbidities			
Age (y)	57.4	56.3	0.81
BMI (kg/m²)	29.3	28.6	0.70
Male gender, n (%)	11 (61)	68 (52)	0.62
Smoking, n (%)	6 (33.3)	40 (30.8)	0.79
Coronary artery disease, congestive heart failure, or history of myocardial infarction,* n (%)	7 (38.9)	21 (16.1)	**0.03**
Peripheral vascular disease, n (%)	2 (11.1)	3 (2.3)	0.11
Diabetes, n (%)	2 (11.1)	7 (5.4)	0.60
History of DVT, n (%)	1 (5.6)	7 (5.4)	1.00
Renal disease, n (%)	1 (5.6)	10 (7.7)	1.00
Asthma/COPD, n (%)	0 (0)	4 (3.1)	1.00
Prealbumin <15 or albumin <3.5, n (%)	0 (0)	4 (3.1)	1.00
Location of tumor, n (%)			0.06
Anterior thigh	5 (28.8)	35 (26.9)	1.00
Posterior thigh	3 (16.7)	22 (16.9)	1.00
Medial thigh*	10 (55.6)	40 (30.7)	**0.04**
Lateral thigh	0 (0)	33 (25.4)	0.08
Location of tumor, n (%)			0.32
Proximal third of thigh	10 (55.6)	52 (40.0)	0.31
Middle third of thigh	5 (28.8)	35 (26.9)	1.00
Distal third of thigh	3 (16.7)	43 (33.1)	0.19
Average defect size (cm) (range)			
Length (range)	16.9 (5–31)	18.4 (1–50)	0.99
Width (range)	12.7 (2–33)	10.6 (2–30)	0.67
Depth (range)	5.5 (1–12)	5.4 (1–17)	0.99
Vascular resection/reconstruction, n (%)			
Arterial resection*	8 (44.4)	16 (12.3)	**0.001**
Arterial reconstruction*	3 (16.7)	5 (3.8)	**0.027**
Vein resection	7 (38.9)	24 (18.5)	0.053
Venous reconstruction	0 (0)	1 (0.1)	0.706
Method of reconstruction, n (%)			
Primary closure	2 (11.1)	24 (18.5)	0.24
Skin graft	1 (5.6)	19 (14.6)	1.00
Local fasciocutaneous flap	1 (5.6)	12 (9.2)	1.00
Local muscle flap	9 (50)	42 (32.3)	0.26
Regional flap	3 (16.6)	28 (21.5)	0.57
Free flap	2 (11.1)	5 (3.8)	0.21
Radiation, n (%)			
Any	16 (88.9)	112 (86.2)	1.00
Neoadjuvant	16 (88.9)	112 (86.2)	0.53
Intraoperative	8 (44.4)	80 (61.5)	0.06
Adjuvant	8 (44.4)	32 (24.6)	0.49
Chemotherapy, n (%)			
Any	7 (38.9)	56 (43.1)	0.74
Neoadjuvant	6 (33.3)	48 (36.9)	0.76
Adjuvant	1 (5.6)	15 (11.5)	0.69
Postoperative complications, n (%)			
Any complication	9 (50)	66 (50.8)	1.00
Infection	3 (16.7)	29 (22.3)	0.76
Dehiscence*	4 (22.2)	6 (4.6)	**0.02**
Seroma	0 (0)	7 (5.4)	0.60
Hematoma	1 (5.6)	4 (3.1)	0.48
DVT	1 (5.6)	2 (1.5)	0.32
Partial flap loss	1 (5.6)	5 (3.8)	0.55
Total flap loss	0 (0)	1 (0.8)	1.00
Unplanned procedure	3 (16.7)	13 (10.0)	0.42
30-d readmission	2 (11.1)	18 (13.8)	0.42

*$P < 0.05$.

Values in boldface have a significant *p*-value.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis.

combination of neoadjuvant and intraoperative radiation); and 13.5% did not undergo any radiation.

There was no difference in the overall complication rate between patients who did and did not develop lymphedema. Interestingly, nearly a quarter of patients with wound dehiscence also had lymphedema. Our subgroup analysis revealed that the odds ratio of noninfectious wound dehiscence in the lymphedema group was 4.8 compared with patients who did not develop lymphedema ($P < 0.05$). It is not possible to determine whether the wound dehiscence caused the lymphedema or the presence of lymphedema is the underlying reason for the wound dehiscence.

DISCUSSION

Complications after limb-sparing surgery for extremity STS are common and are highest for tumors located in the thigh.[9,15–21] Lymphedema is one of the worst potential long-term complications and can decrease a patient's quality of life.[12–14] The underlying cause of

Table 4. Depth of Resection Based on Tumor Location*

Tumor Location	Depth (cm)	No. Patients with Lymphedema (n = 14)	No. Patients without Lymphedema (n = 72)
Proximal third of thigh			
Anterior	0–2.4	1	1
	2.5–4.9	2	2
	5–7.4		4
	7.5–9.9	2	3
	>10		
Medial	0–2.49		2
	2.5–5		2
	5–7.5	1	2
	7.5–10		6
	>10	1	1
Posterior	0–2.49	1	
	2.5–5		2
	5–7.5		1
	7.5–10		
	>10		1
Lateral	0–2.49		
	2.5–5		2
	5–7.5		1
	7.5–10		
	>10		
Middle third of thigh			
Anterior	0–2.4		2
	2.5–4.9		2
	5–7.4		1
	7.5–9.9		
	>10		2
Medial	0–2.49		
	2.5–5	1	2
	5–7.5	1	1
	7.5–10	1	
	>10		
Posterior	0–2.49		
	2.5–5		1
	5–7.5	1	1
	7.5–10		2
	>10		
Lateral	0–2.49		1
	2.5–5		2
	5–7.5		
	7.5–10		
	>10		1
Distal third of thigh			
Anterior	0–2.4		1
	2.5–4.9		3
	5–7.4		
	7.5–9.9		
	>10		
Medial	0–2.49		2
	2.5–5	1	3
	5–7.5		5
	7.5–10		
	>10		
Posterior	0–2.49		1
	2.5–5		1
	5–7.5		1
	7.5–10	1	
	>10		1
Lateral	0–2.49		2
	2.5–5		3
	5–7.5		
	7.5–10		
	>10		

*Data are not available for all patients.

lymphedema can be secondary to direct injury to the lymph nodes, lymphatic vessels, blood vessels, or as a result of fibrosis from radiation therapy.[22] There have been relatively few studies that address the risk factors for the development of postoperative lymphedema, especially in the thigh.

This study shows an incidence of 12% for the development of lymphedema in patients with thigh STS resection. The principal risk factors for the development of lymphedema identified in this study were medially located thigh defects, arterial resection and reconstruction, and a history of cardiac disease. When all 3 risk factors were present, 3 of 7 patients (43%) developed lymphedema. When none of the risk factors were present, 4 of 76 patients (5.3%) developed lymphedema. Ten of 50 patients (20.0%) with medial thigh defects, 8 of 24 patients (33.3%) with arterial resection, and 7 of 28 patients (25.0%) with cardiac disease developed lymphedema. This would indicate that the development of lymphedema is multifactorial and that risk is likely cumulative.

Defects of the medial thigh comprised more than half of the lymphedema group. In contrast, the lateral thigh seems to be a relatively safe zone because there were no cases of lymphedema in patients with lateral thigh tumors. This finding is consistent with the anatomic distribution of lymphatic channels, which are of highest density in the medial thigh and of low density in the lateral thigh. A previous report on STS wound complications found that complications occurred after an average of 21 days from the operation, with complication rates being the highest if tumors were in the adductor compartment.[16] The authors hypothesized that lymphatic disruption was the underlying etiology of these later surgical complications.

The risk of lymphedema was also higher in patients with previous cardiac disease. It may be that venous outflow from the lower extremity normally compensates for lymphatic disruption and patients with greater venous backpressure do not exhibit this capability. This hypothesis is supported by findings from a recent study in which patients who underwent a major vein resection were at a higher risk of lymphedema with an odds ratio of 2.7.[23] Therefore, it is unclear how much patients with congestive heart failure or other pathology resulting in decreased venous return would benefit from lymphovenous bypass. Furthermore, one may infer that maneuvers that improve venous return may improve lymphedema.

Wound dehiscence is also related to lymphedema, but it is unclear as to whether this represents a risk factor for or a sequela of lymphedema.

The incidence of lymphedema in patients who underwent radiation therapy was 8 times the rate of patients who underwent no radiotherapy; however, this study was likely underpowered to detect this difference. There was a relatively small number of patients with lymphedema in combination with a high number of patients treated with radiation.

There are a few studies that have addressed lymphedema in patients undergoing extremity sarcoma resection. Early studies, some including upper extremity sarcomas, show rates of 0.1%–29.6%.[8,14,24–26] One of these early studies by Stinson et al[6] included 152 patients with extremity STS who underwent radiation therapy as part of 1 of the 6 clinical trials by the National Cancer Institute. They found a 19% rate of lymphedema with risk factors, including lower extremity location, radiation dose, and radiation field size length >35 cm. A study by Friedmann et al[27] of 289 patients

with upper and lower extremity STS demonstrated an incidence of 20% of mild lymphedema and 9% of moderate to severe lymphedema. They found tumor size >5 cm and tumor depth to be associated with the development of postoperative lymphedema. Another study by Rimner et al[28] with 255 patients with thigh sarcoma resection and postoperative radiation demonstrated a 13% incidence of lymphedema. On multivariate analysis, they found medial thigh location, female gender, and external beam radiation (compared with brachytherapy) to be associated with an increased risk of developing postoperative lymphedema; on univariate analysis, tumor size >10 cm and vessel resection were also associated with the development of postoperative lymphedema. A fourth study by Bedi et al[23] with 132 patients with upper and lower extremity sarcomas found a rate of postoperative lymphedema of 24%; the rate was highest for proximal lower extremity tumors (26.7%). They determined that the development of postoperative lymphedema was positively associated with sacrifice of a major vein and negatively associated with smoking status. The incidence of lymphedema in this study was 12%, which is consistent with these previously published studies.

There are several clinical implications of the findings in this study. When the tumor is located in the medial thigh, care should be taken to preserve the lymphatics in this region. Although our data do not support any association between the development of lymphedema and method of reconstruction, it would be prudent to consider the impact that the reconstructive method could have on the development of lymphedema, especially in high-risk areas like the medial thigh. If possible, especially with the use of neoadjuvant radiation, major arterial resection should be avoided, and if it is not possible, consideration should be given for arterial reconstruction. Patients with cardiac disease should be medically optimized, and a euvolemic status should be maintained. Patients with noninfectious wound dehiscence should be closely monitored for lymphedema because this could be an early predictor for the development of lymphedema. In addition, if lymphedema is identified postoperatively, prompt and aggressive treatment by a multidisciplinary team should be instituted to prevent complications and progression of the disease.

There are several limitations to our study. The major limitation is the short duration of follow-up; the rate of lymphedema could be higher than that reported in the long term because lymphedema can be a progressive disease that may take years to develop. In addition, lymphedema staging data were unavailable, which precluded analysis of effect size. The study was also underpowered for certain factors—for example, it was unclear whether the type of reconstructive procedure affected the incidence and progression of lymphedema. A larger population is needed to develop a reliable mathematical model to predict multivariate risk.

Lower extremity limb salvage for STS is associated with a high overall complication rate and has not been definitively shown to improve quality of life over amputation. The risks and possible sequelae of limb preservation must be weighed against the benefits for each patient. All patients, and particularly those at a higher risk for complications, should receive appropriate counseling preoperatively and be followed closely postoperatively. As surgical options for the management of lymphedema continue to evolve and improve, prophylactic measures at the time of resection and reconstruction may be considered in high-risk individuals.

CONCLUSIONS

The development of lymphedema after thigh sarcoma resection and reconstruction is not uncommon, and its etiology is likely multifactorial. This study identified defect location in the medial thigh, arterial resection and reconstruction, and history of cardiac disease as risk factors for the development of postoperative lymphedema. Wound dehiscence is also related to lymphedema, but it is unclear as to whether this represents a risk factor for or a sequela of lymphedema. Heightened awareness of these risk factors may facilitate the diagnosis of lymphedema in these patients because the clinical findings of early lymphedema may be subtle. Further work in this area may impact the way in which plastic surgeons manage these wounds, particularly high-risk wounds in high-risk patients. We recommend that physicians who care for these patients be familiar with the diagnosis of lymphedema and be able to provide care through a multidisciplinary team.

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