Function and Health Status Outcomes Following Soft Tissue Reconstruction for Limb Preservation in Extremity Soft Tissue Sarcoma

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ABSTRACT

Background. While advances in reconstructive surgery have facilitated limb preservation in extremity soft tissue sarcoma (ESTS), limited information exists as to the functional outcome of patients with these reconstructed extremities. The primary objective of this study is to evaluate the impact of flap reconstruction on postoperative function and health status in patients undergoing limb-salvage surgery for ESTS.

Methods. Clinical and outcome data for eligible patients were extracted from a prospectively maintained database of sarcoma patients. Four outcome measures were used to assess three domains of function (impairments, activity limitations, and participation restrictions), and health status. The effect of soft tissue reconstruction on function and health status at 1–2-year follow-up was analyzed using univariate and multivariate regression.

Results. Two hundred and forty-seven patients met eligibility criteria, including 56 patients receiving flap reconstruction and 191 patients treated with primary closure. Patients receiving flaps had larger (9.8 versus 7.1 cm; $P = 0.003$), higher-grade (93% versus 72%; $P = 0.001$) tumors, and more frequently received radiotherapy (89% versus 72%; $P = 0.007$), and bone (20% versus 4%;

$P = 0.001$) and motor nerve resection (21% versus 10%; $P = 0.032$). Flap reconstruction was associated with more postoperative impairments [Musculoskeletal Tumor Society (MSTS) score 30.4 versus 32.2; $P = 0.004$] and activity limitations [Toronto Extremity Salvage Score (TESS) score 83.3 versus 89.5; $P = 0.0132$] on univariate analyses, but did not significantly predict postoperative function or health status outcomes on multivariate analyses.

Conclusions. Flap reconstruction was not an independent predictor of function and health status outcomes in patients with ESTS. However, ESTS patients receiving flaps had other clinical features placing them at risk for worse postoperative outcomes.

Extremity soft tissue sarcomas (ESTS) are rare malignant neoplasms that account for up to 2% of all cancer-related deaths.^{1,2} While patients with ESTS were historically treated by amputation, current multimodal approaches combining wide surgical resection with (neo)adjuvant radiotherapy and/or chemotherapy allow limb preservation in 90–95% of patients, without compromising disease recurrence and survival.^{3–10} However, managing tumors with a limb-salvage approach can create complex soft tissue defects susceptible to wound healing difficulties in the postoperative period.^{11,12} Reconstructive surgery in the form of pedicled and free tissue transfers has become paramount to the success of limb preservation in these difficult cases. Indeed, surgical flaps help to attain wound closure, fill surgical dead space, protect critical

structures (i.e., nerves, tendons, joints), and promote wound healing.^{11–15}

Although current evidence suggests that patients requiring soft tissue reconstruction for extremity salvage can achieve good oncologic outcomes, little is known regarding the function and quality-of-life outcomes of patients with these reconstructed extremities.^{16–18} Most prior research investigating function and health status in ESTS has focused on patients treated by simple wound closure techniques.^{5,9–21} Additionally, the small number of studies evaluating postoperative function in patients treated with extremity reconstruction are limited by small sample sizes and methodological approaches that fail to control for bias imparted by nonrandomization, lack of adjustment for confounders, and cross-sectional sampling.^{18,22–24}

Importantly, no study has directly compared the function or health status outcomes of ESTS patients receiving soft tissue reconstruction versus primary wound closure for limb preservation. This information is necessary to inform patients regarding the risks and benefits of extremity reconstruction, as well as to manage patient expectations in the perioperative period. Furthermore, reconstructive techniques may themselves detrimentally affect function or quality-of-life outcomes in patients with ESTS, by harvesting healthy muscle tissue, delaying postoperative recovery, impairing use of clothing and footwear, and altering cosmesis. A better understanding of the impact of soft tissue reconstruction on function and health status is required to identify if and how reconstructive approaches can be modified to ultimately improve outcomes in this population.

The primary objectives of this study are therefore: (1) to compare postoperative function and health status in ESTS patients undergoing limb salvage with and without soft tissue reconstruction, and (2) to examine the effect of surgical flaps on function and health status at 1–2-year follow-up. Additionally, this study examined the relationship between soft tissue reconstruction and postoperative complications in ESTS patients undergoing limb-preserving surgery.

PATIENTS AND METHODS

This was a retrospective cohort study of ESTS patients undergoing limb-salvage surgery between September 2001 and July 2007 at two Canadian sarcoma centers (Toronto and Montreal). Study approval was obtained from the local ethics committee at each participating hospital, and informed consent was obtained from all participants. Patients were identified from a prospectively maintained database of extremity sarcoma patients and were classified into study groups according to the type of wound closure received at definitive limb-preserving surgery. The soft

tissue reconstruction group included patients receiving pedicled or free flap reconstruction for extremity salvage. The primary closure group included patients in whom limb preservation was achieved by simple wound closure techniques, including direct skin approximation and split-thickness skin grafting (STSG).

Patients were eligible for inclusion if they were over 16 years of age, fluent in English or French, and presented with a primary or locally recurrent soft tissue sarcoma of the upper or lower extremity (as diagnosed by an approved reference pathologist). Disease-free patients with function and health status assessments at 12–24 months following definitive surgery were included. One year was chosen as the minimum follow-up, based on previous work in ESTS demonstrating a plateau in functional outcomes 6–12 months following limb-salvage surgery.^{25,26}

Patients were excluded if they had concurrent malignancy, metastatic disease at presentation, or had received chemotherapy. Patients with atypical soft tissue sarcomas were also excluded, including aggressive fibromatosis, grade 1 liposarcoma, soft tissue osteosarcoma, Ewing's soft tissue sarcoma, embryonal rhabdomyosarcoma, primitive neuroectodermal tumor, dermatofibrosarcoma protuberans, and tumors of underdetermined malignant potential.

All outcome data and most clinical information were obtained from the prospectively maintained sarcoma database. Additional relevant information [patient comorbidities, American Society of Anesthesiologists (ASA) score] was obtained via chart review.²⁷

Outcomes

Outcomes of interest included function and health status at 1–2 years following limb-preservation surgery, as well as postoperative complications.

Function The World Health Organization (WHO) International Classification of Functioning Disability and Health (ICF) served as the conceptual framework for selecting functional outcome measures.²⁸ Impairments were measured using the Musculoskeletal Tumor Society Rating Scale (MSTS 1987), a clinician-rated scale with seven parameters.²⁹ Each item is rated on a scale of 0–5, with a maximum score of 35. Activity limitations were assessed using the Toronto Extremity Salvage Score (TESS), a patient-reported 30-item questionnaire that was specifically developed in patients with extremity sarcoma.³⁰ Each item is rated on a scale of 1–5, with the total score calculated as a percentage. Participation restrictions were measured using the self-report Reintegration to Normal Living Index (RNL).³¹ The RNL was developed to assess patients' perceptions of their ability to reintegrate into their life roles and situations after

illness or severe trauma. Its 11 items are scored on a scale of 0–10, with a maximum of score of 110. For all measures, higher scores represent better function.

Health Status Health status was evaluated using the patient-reported EQ5D-VAS, a visual analogue scale that measures individuals' perception of their global health state.³² EQ5D-VAS scores range from 0 to 100, with 100 being perfect health.

Postoperative Complications Postoperative complications were defined as any surgical complication requiring an interventional procedure (i.e., needle aspiration, incision and drainage, reoperation), any wound complication requiring deep packing for longer than 4 weeks, or any neurologic complication involving new motor deficits.

Statistical Methods

Descriptive statistics (frequencies, means, and standard deviations) were calculated for all variables. Baseline characteristics of patients in the soft tissue reconstruction and primary closure groups were compared using Student's *t*-tests for continuous variables, and chi-squared or Fisher's exact test for categorical variables. Nonparametric tests were performed when appropriate. Missing data were handled by simple (<5% missing) or multiple imputation ($\geq 5\%$ missing) techniques where necessary.

Differences in postoperative MSTTS (1987), TESS, RNL, and EQ5D-VAS scores between study groups were first assessed using the Wilcoxon rank-sum test. Multivariate linear regression analyses were then used to adjust for confounding in examining the association between type of wound closure and each function and health status measure. Potential confounders were identified from the literature and included: age, obesity, ASA score, baseline function and health status, tumor size, tumor grade, tumor depth, American Joint Committee on Cancer (AJCC, 5th edition) stage, tumor location, prior unplanned excision, radiotherapy, bone resection, motor nerve sacrifice, and complications.³³ Multivariate models were constructed according to a method described by Harrell et al., where covariates are sequentially added to a baseline model including the key predictor (type of wound closure) and outcome.³⁴ Covariates that changed the parameter estimate of the key predictor by 10% or more were included in the final model. Clinically important variables (age, tumor size, tumor location, baseline function/health status), determined a priori, were also retained in the final model, even if they failed to meet the above criterion. Two- and three-way interactions between type of wound closure, tumor size, and tumor location were also explored for each function and health status measure.

Differences in the proportions of patients experiencing complications in the reconstruction versus primary closure groups were compared using the chi-squared test. The relationship between type of wound closure and postoperative complications was then evaluated using multivariate logistic regression. The potential confounders of this relationship were also identified from the literature and included: age, ASA score, obesity, smoking, type II diabetes, peripheral vascular disease (PVD), tumor size, tumor location, prior unplanned excision, radiotherapy, and bone resection. The logistic regression model was also constructed according to the method of Harrell et al., as previously described.³⁴

All statistical analyses were performed by using SAS version 9.1 (2004; SAS Institute Inc., Cary, NC).

RESULTS

Patients

Two hundred and forty-seven patients met eligibility criteria, including 56 (23%) patients treated with soft tissue reconstruction and 191 (77%) treated by primary closure. In the primary closure group, 163 (85%) patients received direct wound closure and 28 (15%) patients had STSG. In the reconstruction group, 40 (71%) patients had reconstruction with pedicled flaps and 16 (29%) with free flaps. Five patients required two pedicled flaps to achieve wound closure, and thus a total of 45 pedicled flaps were performed in 40 patients. The majority of flaps involved harvesting muscle (69% myogenous, 8% myocutaneous). The most common donor sites were gastrocnemius (28%) and latissimus dorsi (15%).

Descriptive characteristics of the sample are provided in Table 1. The majority of patients ($n = 190$, 77%) were treated in Toronto and the remainder ($n = 57$, 23%) in Montreal. Study patients were representative of patients with ESTS in that they were predominantly male, middle-aged, and had deep, lower-extremity tumors. As expected, study groups also differed in terms of several baseline characteristics (Table 1). Of the 50 patients treated with radiotherapy and a flap, 49 (98%) were irradiated preoperatively and 1 (2%) postoperatively. In the primary closure group, 106 (77%) patients received preoperative radiotherapy, 16 (12%) received postoperative irradiation, and 15 (11%) received preoperative radiotherapy with a postoperative boost. Differences in timing of radiotherapy between study groups were statistically significant ($P = 0.004$). Median length of hospitalization was also significantly longer for patients treated with flap reconstruction versus primary closure (8.0 versus 5.0 days; $P < 0.0001$, Wilcoxon rank-sum test).

TABLE 1 Descriptive characteristics of ESTS patients receiving flap reconstruction versus primary closure for extremity salvage^a

	Flap reconstruction (<i>n</i> = 56)	Primary closure (<i>n</i> = 191)	<i>P</i> -value
Sex			
Male	25 (45%)	116 (61%)	0.032
Female	31 (55%)	75 (39%)	
Age (years), mean $\pm$ SD	58.2 $\pm$ 16.7	54.0 $\pm$ 16.9	0.099
Obese	7 (14%)	37 (23%)	0.161
Smoking status			
Current smoker	4 (7%)	33 (17%)	0.052
Ex-smoker	11 (20%)	45 (24%)	
Nonsmoker	28 (50%)	66 (35%)	
Type II diabetes	4 (7%)	14 (8%)	1.0 ^b
Peripheral vascular disease	–	4 (2%)	0.578 ^b
Presenting status			
Primary	53 (95%)	178 (93%)	1.0 ^b
Local recurrence	3 (5%)	13 (7%)	
Histology			
Malignant fibrous histiocytoma	20 (36%)	50 (26%)	0.147
Liposarcoma	16 (29%)	48 (25%)	
Leiomyosarcoma	3 (5%)	31 (16%)	
Other	17 (30%)	62 (33%)	
AJCC stage (5th edition)			
I	7 (13%)	45 (24%)	0.008
II	27 (48%)	108 (57%)	
III	22 (39%)	38 (20%)	
Tumor size (cm), mean $\pm$ SD	9.8 $\pm$ 5.4	7.1 $\pm$ 6.1	0.003
Tumor grade			
Low	4 (7%)	53 (28%)	0.001
High	52 (93%)	138 (72%)	
Tumor depth			
Deep to fascia	43 (77%)	137 (72%)	0.454
Superficial to fascia	13 (23%)	54 (28%)	
Tumor location			
Upper extremity, proximal	8 (14%)	32 (17%)	0.003
Upper extremity, distal	3 (5%)	21 (11%)	
Lower extremity, proximal	22 (39%)	104 (54%)	
Lower extremity, distal	23 (41%)	34 (18%)	
Prior excisional biopsy	12 (21%)	83 (43%)	0.003
Radiotherapy	50 (89%)	137 (72%)	0.007
ASA score			
1	10 (19%)	44 (24%)	0.834
2	27 (50%)	86 (48%)	
3	15 (28%)	44 (24%)	
4	2 (4%)	7 (4%)	
Bone resection	11 (20%)	8 (4%)	0.001 ^b
Motor nerve resection	12 (21%)	20 (10%)	0.032
Complications	23 (41%)	60 (31%)	0.179
Wound related	16 (29%)	46 (24%)	0.226

AJCC American Joint Committee on Cancer, ASA American Society of Anesthesiologists

^a Values are frequencies (percentages) unless otherwise indicated. Percentages that do not add up to 100% are due to missing data or rounding

^b Fisher's exact test

TABLE 2 Preoperative and postoperative function and health status scores in ESTS patients treated with flap reconstruction versus primary closure for extremity salvage^a

Function and health status measures	Flap reconstruction (<i>n</i> = 56)	Primary closure (<i>n</i> = 191)	<i>P</i> -value ^b
Preoperative			
MSTS (1987)	31.6 ± 3.8 (33.0)	31.5 ± 4.0 (33.0)	0.895
TESS	84.5 ± 16.1 (90.0)	87.4 ± 20.2 (97.5)	0.006
RNL	86.8 ± 24.3 (96.0)	97.3 ± 18.3 (106.9)	0.007
EQ5D-VAS	76.0 ± 14.9 (80.0)	77.4 ± 18.8 (80.0)	0.301
Postoperative measures			
MSTS (1987)	30.4 ± 4.8 (31.0)	32.2 ± 4.0 (35.0)	0.001
TESS	83.3 ± 18.7 (91.4)	89.5 ± 14.9 (95.9)	0.007
RNL	93.9 ± 22.3 (108.0)	99.4 ± 19.5 (110.0)	0.140
EQ5D-VAS	79.3 ± 19.8 (85.0)	83.0 ± 14.7 (85.0)	0.450

MSTS Musculoskeletal Tumor Society Rating Scale, TESS Toronto Extremity Salvage Score, RNL Re-integration to Normal Living Index, EQ5D-VAS EQ5D visual analogue scale

^a Values are mean ± SD (median)

^b Statistical comparisons performed using the Wilcoxon rank-sum test

Function and Health Status

Univariate Analyses MSTS (1987), TESS, RNL, and EQ5D-VAS scores were negatively skewed in the study sample, and were relatively high. Table 2 presents preoperative and postoperative MSTS (1987), TESS, RNL, and EQ5D-VAS scores for each study group. At baseline, patients receiving flap reconstruction had significantly more activity limitations ($P = 0.006$) and participation restrictions ($P = 0.007$), as measured by TESS and RNL, respectively, than patients treated by primary closure. Postoperatively, patients receiving soft tissue reconstruction had significantly more impairments ($P = 0.001$) and activity limitations ($P = 0.007$), as measured by MSTS (1987) and TESS, respectively, than patients treated with primary closure. No significant differences in postoperative RNL or EQ5D-VAS scores were observed between study groups. Interactions between type of wound closure, tumor size, and tumor location were not statistically significant for any outcome measure.

Multivariate Analyses Type of wound closure (soft tissue reconstruction versus primary closure) did not significantly predict postoperative MSTS (1987), TESS, RNL, or EQ5D-VAS scores after controlling for confounding variables in multivariate regression analyses (Tables 3–6). Factors predictive of lower MSTS (1987) scores were large tumor size ($P = 0.050$), postoperative complications ($P = 0.003$), bone resection ($P = 0.034$), baseline impairments ($P = 0.001$), and older age at definitive surgery ($P = 0.0004$) (Table 3). Patients with deep tumors ($P = 0.019$), bone resection ($P = 0.015$), older age ($P = 0.003$), and more baseline activity limitations

($P < 0.0001$) had worse postoperative TESS scores (Table 4). The only significant predictor of postoperative RNL in the multivariate model was baseline RNL ($P < 0.0001$), with the overall model explaining only 16% of the variance in RNL scores (Table 5). Finally, complications ($P = 0.004$) and lower baseline health status ($P < 0.0001$) significantly predicted lower postoperative EQ5D-VAS scores in multivariate regression analyses (Table 6).

Postoperative Complications

Univariate Analyses Postoperative complications occurred in 23 (41%) patients receiving flap reconstruction and in 60 (31%) patients treated with primary closure (Table 1). The difference in proportion of complications between study groups was 0.1 [95% confidence interval (CI), –0.1 to 0.2; $P = 0.179$].

Most complications were wound related, occurring in 16 of 23 patients (70%) in the reconstruction group and in 46 of 60 patients (77%) in the primary closure group ($P = 0.226$). Other specific types of complications occurred infrequently. Vascular and neurologic complications each occurred in two patients receiving flaps and five patients treated with primary closure.

There were two flap failures in the reconstruction group. Total flap necrosis occurred in one patient with a pedicled latissimus flap, who then required delayed reconstruction with the contralateral latissimus muscle. The second patient was reconstructed with a free latissimus flap and femoral vein graft, and developed intraoperative venous thrombosis resistant to heparinization; conversion to pedicled flap reconstruction was therefore required for wound closure.

TABLE 3 Final multivariate regression model for MSTs (1987)

	Outcome = MSTs (1987) <i>n</i> = 243, mean R^2 = 0.322 [0.316–0.324] ^a	β (95% CI)	<i>P</i> -value
Type of wound closure (flap versus primary closure)		−0.4 (−1.7, 0.8)	0.488
AJCC stage I ^b		1.2 (−0.4, 2.8)	0.141
AJCC stage II ^b		0.8 (−0.4, 2.0)	0.199
Tumor location: proximal UE ^c		−0.1 (−1.6, 1.5)	0.950
Tumor location: distal UE ^c		0.6 (−1.2, 2.5)	0.504
Tumor location: proximal LE ^c		−0.04 (−1.3, 1.2)	0.952
Tumor size (cm)		−0.1 (−0.2, 0.0)	0.049
Prior incomplete excision (no versus yes)		−0.2 (−1.3, 0.8)	0.654
Radiotherapy (no versus yes)		0.6 (−0.6, 1.8)	0.361
Complications (no versus yes)		1.6 (0.6, 2.7)	0.003
Bone resection (no versus yes)		2.1 (0.2, 4.1)	0.034
Motor nerve resection (no versus yes)		0.8 (−0.6, 2.2)	0.267
Baseline MSTs		0.2 (0.1, 0.4)	0.001
Age (years)		−0.1 (−0.1, 0.0)	0.0004

MSTS Musculoskeletal Tumor Society Rating Scale, AJCC American Joint Committee on Cancer (5th edition), UE upper extremity, LE lower extremity

^a These values indicate the range of R^2 values across imputations

^b Reference category: AJCC stage III

^c Reference category: distal LE

TABLE 4 Final multivariate regression model for TESS

	Outcome = TESS <i>n</i> = 235, mean R^2 = 0.349 [0.333–0.364] ^a	β (95% CI)	<i>P</i> value
Type of wound closure (flap versus primary closure)		−0.8 (−5.5, 3.9)	0.731
AJCC stage I ^b		−2.4 (−9.2, 4.5)	0.500
AJCC stage II ^b		1.3 (−3.6, 6.1)	0.609
Tumor grade (high versus low)		−2.1 (−6.9, 2.7)	0.386
Tumor location: proximal UE ^c		0.4 (−5.5, 6.3)	0.889
Tumor location: distal UE ^c		3.0 (−4.0, 10.1)	0.401
Tumor location: proximal LE ^c		−0.4 (−5.1, 4.4)	0.883
Tumor depth (superficial versus deep)		5.8 (0.9, 10.6)	0.019
Tumor size (cm)		−0.2 (−0.5, 0.2)	0.331
Prior incomplete excision (no versus yes)		1.5 (−2.7, 5.7)	0.481
Radiotherapy (no versus yes)		3.5 (−1.5, 8.4)	0.167
Complications (no versus yes)		3.5 (−0.5, 7.6)	0.088
Bone resection (no versus yes)		8.6 (1.7, 15.5)	0.015
Motor nerve resection (no versus yes)		1.9 (−3.8, 7.6)	0.514
Baseline TESS		0.3 (0.2, 0.4)	<0.0001
Age (years)		−0.2 (−0.3, −0.1)	0.003

TESS Toronto Extremity Salvage Score, AJCC American Joint Committee on Cancer (5th edition), UE upper extremity, LE lower extremity

^a These values indicate the range of R^2 values across imputations

^b Reference category: AJCC stage III

^c Reference category: distal LE

Donor-site complications occurred in three patients with free flaps, including two seromas and one infection. No patients in the primary closure group required secondary flap reconstruction to achieve stable soft tissue coverage.

Eight patients (14%) in the soft tissue reconstruction group and 17 patients (9%) in the primary closure group required reoperation for a complication. The difference in proportion of reoperations between study groups was 0.1 (95% CI, −0.2 to 0.3; P = 0.567). Only one patient (in the primary closure group) required amputation secondary to a complication.

Multivariate Logistic Regression Type of wound closure did not significantly predict postoperative complications when adjusting for confounders in logistic regression analysis (Table 7). Tumor size (P = 0.003), radiotherapy (P = 0.025), bone resection (P = 0.010), and patient age (P = 0.013) were significant predictors of complications in the multivariate model. Patients treated with radiotherapy and bone resection were 2.7 and 4.1 times more likely to have a complication, respectively. For each 1-cm increase in tumor size and 5-year increase in age, the odds of a complication increased by 8% and 10%, respectively.

TABLE 5 Final multivariate regression model for RNL

RNL Re-integration to Normal Living Index, AJCC American Joint Committee on Cancer (5th edition), UE upper extremity, LE lower extremity

^a These values indicate the range of R^2 values across imputations

^b Reference category: AJCC stage III

^c Reference category: distal LE

Outcome = RNL $n = 232$, mean $R^2 = 0.158$ [0.149–0.173] ^a	β (95% CI)	P -value
Type of wound closure (flap versus primary closure)	2.4 (–4.5, 9.3)	0.491
AJCC stage I ^b	1.4 (–8.1, 10.8)	0.778
AJCC stage II ^b	3.0 (–3.7, 9.7)	0.384
Tumor grade (high versus low)	–4.8 (–11.7, 2.0)	0.164
Tumor location: proximal UE ^c	3.7 (–4.7, 12.0)	0.394
Tumor location: distal UE ^c	7.7 (–2.2, 17.7)	0.127
Tumor location: proximal LE ^c	4.4 (–2.5, 11.3)	0.207
Tumor size (cm)	–0.2 (–0.7, 0.3)	0.429
Prior incomplete excision (no versus yes)	–0.5 (–6.5, 5.5)	0.865
Radiotherapy (no versus yes)	3.1 (–3.7, 9.8)	0.368
Complications (no versus yes)	2.8 (–3.0, 8.5)	0.346
Bone resection (no versus yes)	1.3 (–8.5, 11.0)	0.800
Baseline RNL	0.3 (0.2, 0.4)	<0.0001
Age (years)	–0.1 (–0.3, 0.0)	0.128

TABLE 6 Final multivariate regression model for EQ5D-VAS

EQ5D-VAS EQ5D visual analogue scale, AJCC American Joint Committee on Cancer (5th edition), UE upper extremity, LE lower extremity

^a These values indicate the range of R^2 values across imputations

^b Reference category: distal LE

Outcome = EQ5D-VAS $n = 224$, mean $R^2 = 0.165$ [0.152–0.179] ^a	β (95% CI)	P -value
Type of wound closure (flap versus primary closure)	–1.0 (–6.3, 4.4)	0.722
Tumor grade (high versus low)	–0.6 (–5.6, 4.4)	0.813
Tumor location: proximal UE ^b	–0.9 (–7.5, 5.7)	0.783
Tumor location: distal UE ^b	3.1 (–5.1, 11.4)	0.456
Tumor location: proximal LE ^b	0.2 (–5.3, 5.7)	0.951
Tumor size (cm)	0.0 (–0.4, 0.4)	0.934
Prior incomplete excision (no versus yes)	–0.4 (–5.1, 4.2)	0.858
Radiotherapy (no versus yes)	0.9 (–4.3, 6.1)	0.732
Complications (no versus yes)	6.6 (2.1, 11.0)	0.004
Baseline EQ5D-VAS	0.3 (0.2, 0.4)	<0.0001
Age (years)	–0.1 (–0.2, 0.0)	0.070

TABLE 7 Predictors of postoperative complications in logistic regression analysis (imputed data, $n = 247$)

AJCC American Joint Committee on Cancer (5th edition), OR odds ratio

Outcome = complications	Adjusted OR (95% CI)	P -value
Flap reconstruction versus primary closure	0.78 (0.39, 1.58)	0.488
Tumor size (cm)	1.08 (1.03, 1.14)	0.003
AJCC stage II versus I	1.36 (0.58, 3.18)	0.482
AJCC stage III versus I	1.28 (0.47, 3.50)	0.631
Prior incomplete excision (yes versus no)	0.84 (0.44, 1.61)	0.604
Radiotherapy (yes versus no)	2.67 (1.13, 6.27)	0.025
Bone resection (yes versus no)	4.06 (1.40, 11.74)	0.010
Age (years)	1.02 (1.01, 1.04)	0.013

DISCUSSION

This study is the first to directly compare function and health status outcomes between patients receiving soft tissue reconstruction and primary closure for limb

preservation in ESTS. Patients in the flap reconstruction group demonstrated significantly more impairments and activity limitations at 1–2 years postoperatively than patients in the primary closure group. A number of factors may contribute to this finding. Patients receiving flaps had

significantly larger and higher-grade tumors than patients treated with primary closure, and were more likely to have received preoperative irradiation, bone resection, and motor nerve resection. Each of these tumor and treatment factors has been associated with worse function and/or health status outcomes in at least one prior study of ESTS patients undergoing limb-salvage surgery.^{19,25,35,36} Additionally, patients in the reconstruction group had more preoperative activity limitations.

Considering these risk factors for poor functional outcome, it is perhaps surprising that postoperative MSTS (1987) and TESS scores in patients requiring extremity reconstruction were not substantially worse. Also interesting is the fact that patients requiring reconstructive surgery in this study reported similar participation (RNL) and health status (EQ5D-VAS) outcomes to patients treated with primary closure. This finding suggests that patients with reconstructed extremities are able to maintain similar social and occupational functioning and overall well-being compared with patients not requiring reconstructive surgery, despite greater restrictions in the physical and activity domains of function.

In fact, postoperative MSTS (1987), TESS, RNL, and EQ5D-VAS scores were relatively high in both study groups and compare favorably with those reported previously. Serletti et al. reported a mean MSTS (1987) score of 28.4, and Nelson et al. reported an average TESS score of 81, in 20 and 34 extremity sarcoma patients treated with limb salvage and reconstruction, respectively.^{22,24} Participation and health status outcomes have not been previously examined in ESTS patients requiring soft tissue reconstruction. In larger studies where the majority of patients were treated with simple wound closure techniques, MSTS (1987) scores range from 27.5 to 31.4, TESS scores range from 83% to 89%, RNL scores average 98.7, and EQ5D-VAS scores average 80.5.^{19,25,35,37–39} The fact that patients requiring soft tissue reconstruction demonstrated good function and health status outcomes in this study supports the value of limb-salvage approaches in these difficult cases.

This study is also the first to investigate the role of reconstructive surgery in influencing function and health status outcomes in extremity sarcoma. In this study, type of wound closure did not significantly predict postoperative impairments, activity limitations, participation restrictions, or health status after adjusting for confounding in multivariate regression analyses. Importantly, the confidence intervals for the adjusted differences (regression coefficients) in MSTS (1987), TESS, RNL, and EQ5D-VAS scores between the reconstruction and primary closure groups also exclude clinically meaningful differences in these outcome measures, based on what is currently known regarding their measurement properties.^{26,30–32,35,40} Thus,

in spite of the frequent use of myogenous and myocutaneous flaps in this study, flap reconstruction did not impair function and health status outcomes in patients undergoing limb salvage for ESTS.

Other factors predictive of impairments, activity limitations, and health status in this study are generally consistent with prior literature. Large tumor size, complications, bone resection, and older age have negatively impacted postoperative MSTS (1987) scores in prior studies of ESTS patients undergoing limb salvage.^{19,25,35} Along the same lines, deep tumors and bone resection have been previously associated with lower TESS scores, and complications have been significantly correlated with lower EQ5D-VAS scores.^{19,36,39} There are also important differences between the findings of this study and the literature, which may in part be explained by differences in patient population, method of multivariate model building, definition of predictor variables, selection of outcome measures, or lack of adjustment for baseline function/health status. For example, some studies have not found an association between age and MSTS (1987) or TESS, but have found an association between motor nerve resection and more impairments and activity limitations.^{19,25,35,36,38}

Participation restrictions, as measured by RNL, are an important aspect of patient-reported quality of life that have been underinvestigated in ESTS.^{39,41} The only significant determinant of postoperative RNL score in this study was preoperative RNL score. Schreiber et al. similarly found the number of preexisting comorbid conditions to be the only significant correlate of postoperative RNL score in a retrospective study of 100 ESTS patients.³⁹ These findings suggest that other, unmeasured factors are influencing postoperative participation restrictions. Indeed, studies in other populations have suggested that social support, socioeconomic status, cognition, and emotional well-being are important determinants of participation outcome.^{41–45} These factors need to be explored in future studies of ESTS.

A secondary outcome of this study was postoperative complications. Patients receiving flap reconstruction had more complications than patients treated with primary closure in this study (41% of 56 versus 31% of 191). Although not statistically significant, this 10% difference in complications has clinical significance for patients with ESTS. Lohman et al. and Cannon et al. similarly found an approximately 10% higher incidence of complications in patients receiving soft tissue reconstruction.^{16,46} Two other studies reported equivalent rates of complications in patients treated with reconstruction and primary closure.^{17,47} However, both of these studies included patients receiving skin grafts and/or complex primary closures in their reconstruction group. Not only are these procedures less morbid, but patients receiving skin grafts and complex

primary closures are likely to have less adverse tumor and treatment characteristics than patients requiring flaps. Yet another study reported fewer complications in patients receiving flaps versus primary closure, but the very small sample sizes in this comparison limit interpretation of this finding.⁴⁸

An important question is whether the increased complications in patients receiving soft tissue reconstruction in this study is due to additional flap-related morbidity or due to other characteristics of patients receiving flaps for limb salvage. In support of the latter, patients receiving flap reconstruction had a number of identified risk factors for increased complications in ESTS, including large tumor size, preoperative irradiation, and bone resection.^{17,46,48–51} Furthermore, soft tissue reconstruction was not an independent predictor of complications in multivariate logistic regression analyses. This finding agrees with that of O'Sullivan et al., although these authors did include skin grafting as part of their reconstruction group.¹⁷ Importantly, neither this study nor that of O'Sullivan et al. had sufficient numbers of subjects to evaluate the impact of soft tissue reconstruction on complications in logistic regression analyses while accounting for all potentially important confounders, and so these results must be viewed as preliminary and interpreted with caution.¹⁷

The main limitations of this study lie in its generalizability and retrospective design. The patients in this study were treated at the two largest specialty adult sarcoma centers in Canada (Montreal and Toronto). Given that care for individuals with sarcoma in Canada is routinely provided in a tertiary oncology setting, the patients seen at the sarcoma centers in this study should represent those presenting to centers across Canada. However, the centers in Toronto and Montreal that contributed to the study database have similar treatment protocols wherein chemotherapy is not routine care for individuals with ESTS. Considering the potential impact of chemotherapy on function, health status, and complications in ESTS, the findings of this study may not be generalizable to ESTS patients treated routinely with (neo)adjuvant chemotherapy. Selection bias related to exposure group classification is also a concern in this study, as highlighted by the significant differences in baseline characteristics between study groups. However, in using multivariate regression analyses to adjust for important confounders, identified a priori from the literature and clinical expertise, and in large part measured prospectively, best efforts were made to minimize treatment selection bias in these analyses.

In conclusion, this study provides new and important information for the multidisciplinary sarcoma team to improve patient education and better manage patients' expectations regarding their recovery. First, patients who require reconstructive surgery for limb preservation can

achieve good functional outcomes. Based on the results of this study, surgeons can expect that patients with reconstructed extremities may have more impairments and activity limitations relative to patients treated with simple wound closure techniques following tumor ablation. However, this may not translate into worse participation or health status outcomes. Third, reconstructive approaches centered mainly on muscle-bearing flaps do not adversely affect 1–2-year function or health status outcomes relative to primary wound closure techniques. This is an important point considering recent trends towards use of more technically challenging, free perforator flaps for extremity reconstruction. Furthermore, while complication rates may be higher in patients requiring reconstructive surgery, surgical flaps themselves do not appear to either increase or decrease wound complications in this population. However, prospective studies are warranted to better assess the risk–benefit profile of soft tissue reconstruction in regard to postoperative complications, considering that this and prior studies have been underpowered to thoroughly evaluate this association. Taken together, the findings of this study reinforce the value of flap reconstruction in the management of extremity soft tissue sarcoma, both to achieve limb preservation and to reduce the morbidity of limb-salvage procedures in difficult cases.

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