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What Are Risk Factors for and Outcomes of Late Amputation After Treatment for Lower Extremity Sarcoma: A Childhood Cancer Survivor Study Report

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Abstract

Background Although pediatric lower extremity sarcoma once was routinely treated with amputation, multiagent chemotherapy as well as the evolution of tumor resection and reconstruction techniques have enabled the wide adoption of limb salvage surgery (LSS). Even though infection and tumor recurrence are established risk factors for early amputation (< 5 years) after LSS, the frequency of and factors associated with late amputation (≥ 5 years from diagnosis) in children with sarcomas are not known. Additionally, the resulting psychosocial and physical outcomes of these patients compared with those treated with primary amputation or LSS that was not complicated by subsequent amputation are not well studied. Studying these outcomes is critical to enhancing the quality of life of patients with sarcomas.

Questions/purposes (1) How have treatments changed over time in patients with lower extremity sarcoma who are included in the Childhood Cancer Survivor Study (CCSS), and did primary treatment with amputation or LSS affect overall survival at 25 years among patients who had survived at least 5 years from diagnosis? (2) What is the cumulative incidence of amputation after LSS for patients diagnosed with pediatric lower extremity sarcomas 25 years after diagnosis? (3) What are the factors associated with time to late amputation (≥ 5 years after diagnosis) in patients initially treated with LSS for lower extremity sarcomas in the CCSS? (4) What are the comparative social, physical, and emotional health-related quality of life (HRQOL) outcomes among patients with sarcoma treated with primary amputation, LSS without

amputation, or LSS complicated by late amputation, as assessed by CCSS follow-up questionnaires, the SF-36, and the Brief Symptom Inventory-18 at 20 years after cancer diagnosis?

Methods The CCSS is a long-term follow-up study that began in 1994 and is coordinated through St. Jude Children's Research Hospital. It is a retrospective study with longitudinal follow-up of more than 38,000 participants treated for childhood cancer when younger than 21 years at one of 31 collaborating institutions between 1970 and 1999 in the United States and Canada. Participants were eligible for enrollment in the CCSS after they had survived 5 years from diagnosis. Within the CCSS cohort, we included participants who had a diagnosis of lower extremity sarcoma treated with primary amputation (547 patients with a mean age at diagnosis of 13 ± 4 years) or primary LSS (510 patients with a mean age 14 ± 4 years). The LSS cohort was subdivided into LSS without amputation, defined as primary LSS without amputation at the time of latest follow-up; LSS with early amputation, defined as LSS complicated by amputation occurring less than 5 years from diagnosis; or LSS with late amputation, defined as primary LSS in study patients who subsequently underwent amputation 5 years or more from cancer diagnosis. The cumulative incidence of late amputation after primary LSS was estimated. Cox proportional hazards regression with time-varying covariates identified factors associated with late amputation. Modified Poisson regression models were used to compare psychosocial, physical, and HRQOL outcomes among patients treated with primary amputation, LSS without amputation, or LSS complicated by late amputation using validated surveys.

Results More study participants were treated with LSS than with primary amputation in more recent decades. The overall survival at 25 years in this population who survived 5 years from diagnosis was not different between those treated with primary amputation (87% [95% confidence interval [CI] 82% to 91%]) compared with LSS (88% [95% CI 85% to 91%]; p = 0.31). The cumulative incidence of amputation at 25 years after cancer diagnosis and primary LSS was 18% (95% CI 14% to 21%). With the numbers available, the cumulative incidence of late amputation was not different among study patients treated in the 1970s (27% [95% CI 15% to 38%]) versus the 1980s and 1990s (19% [95% CI 13% to 25%] and 15% [95% CI 10% to 19%], respectively; p = 0.15). After controlling for gender, medical and surgical treatment variables, cancer recurrence, and chronic health conditions, gender (hazard ratio [HR] 2.02 [95% CI 1.07 to 3.82]; p = 0.03) and history of prosthetic joint reconstruction (HR 2.58 [95% CI 1.37 to 4.84]; p = 0.003) were associated

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with an increased likelihood of late amputation. Study patients treated with a primary amputation (relative risk [RR] 2.04 [95% CI 1.15 to 3.64]) and LSS complicated by late amputation (relative risk [RR] 3.85 [95% CI 1.66 to 8.92]) were more likely to be unemployed or unable to attend school than patients treated with LSS without amputation to date. The CCSS cohort treated with primary amputation and those with LSS complicated by late amputation reported worse physical health scores than those without amputation to date, although mental and emotional health outcomes did not differ between the groups.

Conclusion There is a substantial risk of late amputation after LSS, and both primary and late amputation status are associated with decreased physical HRQOL outcomes. Children treated for sarcoma who survive into adulthood after primary amputation and those who undergo late amputation after LSS may benefit from interventions focused on improving physical function and reaching educational and employment milestones. Efforts to improve the physical function of people who have undergone amputation either through prosthetic design or integration into the residuum should be supported. Understanding factors associated with late amputation in the setting of more modern surgical approaches and implants will help surgeons more effectively manage patient expectations and adjust practice to mitigate these risks over the life of the patient.

Level of Evidence Level III, therapeutic study.

Introduction

Bone and soft tissue sarcomas represent 10% to 15% of childhood cancers [2, 20]. Historically, the surgical treatment for appendicular sarcomas was limb amputation. Beginning in the 1970s, neoadjuvant chemotherapy protocols substantially increased overall survival for patients with localized disease [12, 27, 34, 39]. These developments, in addition to advances in surgical techniques, imaging, and implant design, changed the surgical paradigm such that limb salvage surgery (LSS)—tumor resection with reconstruction of limb anatomy—could achieve comparable oncologic outcomes and became widely adopted by the 1990s [2, 3, 9, 25, 40, 41]. A fraction of patients today is treated with primary amputation when anatomically or functionally necessary [11, 42]. As more children who were treated for sarcomas achieve long-term survival, there is a need for ongoing clinical surveillance of treatment sequelae. Survivors of pediatric cancers face challenges in multiple domains as they age [4, 29], and children treated for sarcoma, specifically, have worse health outcomes than children treated for other cancers [24, 46].

Previous studies have evaluated whether primary amputation or LSS impacts long-term psychosocial and physical health outcomes, with mixed conclusions depending on the study population and the outcome measure used [25, 26, 32, 33, 35, 37, 43]. Durability of the oncologic reconstruction is also a challenge in children with sarcomas because children treated for sarcomas are likely to live for many years [13, 25, 31, 48]. Late amputation after failure of LSS is a potentially devastating outcome occurring years after the primary surgery. Although tumor recurrence and postoperative infection account for most amputations performed within 5 years after primary LSS, even long-term studies of LSS do not report specific medical and surgical cancer treatment exposures that may be associated with amputation 5 or more years from LSS using multivariable models [14, 19, 30]. Additionally, psychosocial outcome studies on this rare group of patients undergoing late amputation are limited [10, 37].

We therefore asked, (1) How have treatments changed over time in patients with lower extremity sarcoma who are included in the Childhood Cancer Survivor Study (CCSS), and did primary treatment with amputation or LSS affect overall survival at 25 years among patients who had survived at least 5 years from diagnosis? (2) What is the cumulative incidence of amputation after LSS for patients diagnosed with pediatric lower extremity sarcomas 25 years after diagnosis? (3) What are the factors associated with time to late amputation (≥ 5 years after diagnosis) in patients initially treated with LSS for lower extremity sarcomas in the CCSS? (4) What are the comparative social, physical, and emotional health-related quality of life (HRQOL) outcomes among patients with sarcoma treated with primary amputation, LSS without amputation, or LSS complicated by late amputation, as assessed by CCSS follow-up questionnaires, the SF-36, and the Brief Symptom Inventory-18 (BSI-18) at 20 years after cancer diagnosis?

Materials and Methods

Study Design and Setting

The CCSS is a long-term follow-up study that began in 1994 and is funded by the United States National Cancer Institute. Coordinated through St. Jude Children's Research Hospital in Memphis, TN, USA, it is a retrospective study with longitudinal follow-up of more than 38,000 5-year survivors of childhood cancer who were younger than 21 years at diagnosis and treated at one of 31 collaborating institutions from 1970 to 1999 in the United States and Canada. Cancer diagnosis and treatment data including chemotherapy, radiotherapy, and surgery were abstracted from medical records at treating institutions using standardized CCSS protocols. Study participants completed baseline surveys and follow-up questionnaires at published intervals. Detailed descriptions of the CCSS study design and cohort characteristics have been published [23, 38].

Participants

Participants in the CCSS with lower extremity bone sarcoma or soft tissue sarcoma were eligible for inclusion in this study. Lower extremity was defined as tumors at or distal to the hip according to ICD-9 diagnosis codes. Inclusion criteria for the study were treatment with either primary amputation or primary LSS within 1 year of diagnosis. Of 1301 patients with eligible diagnoses, 12% (155) were excluded because they were treated without surgery, 6% (83) were excluded because surgical treatment occurred more than 1 year from diagnosis, and 0.05% (6) were excluded because the date or age at surgical treatment was not available (treated as missing), leaving 1057 available for analysis. For HRQOL outcomes, analysis was restricted to the participants aged 25 years or older at the time of study follow-up. Of the eligible patients, 58% (587 of 1012) responded to the SF-36 (41% [241 of 587] primary LSS and 59% [346 of 587] primary amputation), and 53% (535 of 1012) responded to the BSI-18 (44% [234 of 535] LSS and 56% [301 of 535] primary amputation) survey instruments.

Description of Experiment, Treatment, or Surgery

Study patients were assigned to primary amputation—defined as amputation at any level as the index procedure for tumor control—or LSS treatment groups. The LSS cohort was subdivided into LSS with early amputation, defined as LSS complicated by amputation occurring < 5 years from diagnosis; LSS with late amputation, defined as patients undergoing primary LSS who subsequently underwent amputation ≥ 5 years from cancer diagnosis; and LSS without amputation, defined as study patients treated with primary LSS who had not undergone subsequent amputation at the time of last follow-up. For descriptive purposes, the demographics of early amputation survivors were collected, but these survivors were excluded from subsequent multivariable analyses to focus on factors associated with late amputations.

Variables, Outcome Measures, Data Sources, and Bias

Additional Clinical Variables

Additional covariates included gender, race, or ethnicity (according to participants' self-report), cancer diagnosis, age and year of diagnosis, and chronic health conditions. Information about chronic health conditions was obtained from organ-specific questions covering cardiovascular, endocrine, respiratory, gastrointestinal, renal, neurologic, immunologic, and hematologic systems. These conditions were graded for severity using the National Cancer Institute's Common Terminology for Adverse Events v4.3, including Grade 1 (mild or asymptomatic), Grade 2 (moderate), Grade 3 (severe and/or disabling), and Grade 4 (life-threatening) [29]. For the current analysis, we limited reporting to Grades 3 and 4 because all participants reported a Grade 1 to 2 condition, and prevalent amputation is a Grade 2 condition. ICD-9 procedure codes were used to determine whether a prosthetic joint reconstruction had been performed in association with LSS.

Outcomes

The main outcome of interest was a medical record or self-report of late amputation after primary LSS. Secondary outcomes including ability to work, attend school, drive, and manage routine needs of daily living, as well as impaired physical performance, were obtained from participants' responses to CCSS follow-up surveys (available at: https://ccss.stjude.org/tools-documents/questionnaires/baseline-and-follow-up-questionnaires.html). Physical performance was determined based on published methods [28]. Questions on physical limitation assessed the duration of such limitation (none, 3 months or less, or more than 3 months) based on six questions, where scores range from 6 (most physical limitation) to 18. Respondents with scores in the 10th percentile of a healthy control group (score ≤ 15) were defined as having a physical limitation. We evaluated HRQOL using the SF-36, which provides subscale scores for eight domains of HRQOL: mental health, physical health, emotional role function, physical role function, social health, pain, vitality and energy, and health perceptions. Raw scores from the SF-36 were converted to T scores (range 0 to 100) and dichotomized so that a score at or below 40 (1 SD below the population mean) was classified as a poor HRQOL outcome. We measured emotional distress with the BSI-18, a measure of depression, somatization, anxiety, and global mental health. Participants with T-scores of 63 or more on a particular scale were classified as having poor emotional health [28]. The median (range) follow-up time for survey data collection was 23 years (15 to 34) from the primary diagnosis. All-cause mortality for participants in the CCSS cohort was compared between the primary amputation and LSS groups. Vital status was determined up to 2017 using linkage with the National Death Index [6].

Ethical Approval

We obtained ethical approval for this study from our institutions.

Statistical Analysis

Demographic and treatment characteristics were organized around surgical treatment groups. The cumulative incidence of late amputation, with death as a competing risk, was calculated from the date of CCSS cohort entry to the last follow-up, amputation, or death. All amputations occurring within 5 years from diagnosis in the LSS cohort were included in the cumulative incidence estimation as prevalent procedures, starting at 5 years after cancer diagnosis.

We used a univariable Cox proportional hazards model to examine the impact of demographic and treatment variables, cancer recurrence, as well as Grades 3 and 4 chronic health conditions on the hazard ratio of late amputation after LSS (Supplementary Table 1; http://links.lww.com/CORR/A796). Cancer recurrence and Grades 3 and 4 chronic health conditions were treated as time-varying covariates. Factors from the univariable analysis with a p < 0.1 were included in a multivariable regression analysis. Because histologic diagnosis and treatment era were confounded by cancer treatments (Supplementary Table 2; http://links.lww.com/CORR/A797), models including these variables were run separately. The analysis was performed first with baseline covariates alone and then the time-varying covariates (cancer recurrence and chronic health conditions in this study) were added. The results were equivalent; thus, we report the results of the full model.

We estimated the overall survival rate using the Kaplan-Meier product-limit estimator and implemented using PROC LIFETEST (SAS Institute). We compared the restricted mean survival times (restricted at 20 years from CCSS cohort entry) between treatment groups by applying the generalized estimating equation approach to pseudo-values [22].

A modified Poisson regression approach [51] was used to estimate the relative risk of psychosocial, physical or functional, and HRQOL impairments (binary outcomes defined earlier) among treatment groups, adjusted for age at the time of evaluation. All analyses were conducted in SAS 9.4 (SAS Institute), R Studio (RStudio Inc), and GraphPad Prism 8.3.1 (GraphPad Software).

Results

Demographic, Treatment, and Survival Characteristics

Fifty-two percent (553 of 1057) of participants with lower extremity sarcoma were men, 73% (773 of 1057) were White, and 84% (888 of 1057) were diagnosed with osteosarcoma (Table 1). As expected, a greater percentage of study patients were treated with LSS than with primary amputation in more recent decades. Although 78% (222 of 284) of the study cohort from the 1970s were treated with

primary amputation, 72% (265 of 367) of the cohort from the 1990s were treated with primary LSS (Supplementary Table 3; http://links.lww.com/CORR/A798). When comparing by primary surgical treatment, there was no difference in the overall survival at 25 years in this population who had survived 5 years from diagnosis: 87% (95% confidence interval [CI] 82% to 91%) for primary amputation compared with 88% (95% CI 85% to 91%; p = 0.31) for LSS (Fig. 1).

Cumulative Incidence of Amputation After LSS

The cumulative incidence of amputation at 25 years from diagnosis in the primary LSS cohort was 18% (95% CI 14% to 21%) (Fig. 2A). With the numbers available, there was no difference in the 25-year cumulative incidence of amputation among patients treated with LSS in the 1970s (27% [95% CI 15% to 38%]) versus those in the 1980s (19% [95% CI 13% to 25%]) and 1990s (15% [95% CI 10% to 19%]; p = 0.15) (Fig. 2B).

Factors Associated with Late Amputation (≥ 5 Years After Diagnosis)

After controlling for variables associated with late amputation including gender, chemotherapy exposure, prosthetic joint reconstruction, and chronic health conditions, being a man (hazard ratio [HR] 2.02 [95% CI 1.07 to 3.82]; p = 0.03) and history of prosthetic joint reconstruction (HR 2.58 [95% CI 1.37 to 4.84]; p = 0.003) were associated with an increased likelihood of late amputation (Table 2). With the data available, treatment in the 1970s compared with treatment in the 1990s (HR 2.33 [95% CI 0.99 to 5.45]; p = 0.05) was not associated with an increased likelihood of late amputation (Supplementary Table 4; http://links.lww.com/CORR/A799) and neither was primary histologic diagnosis (Supplementary Table 5; http://links.lww.com/CORR/A800).

Social, Physical, and Emotional HRQOL Outcomes

Participants treated with primary amputation and those who underwent late amputation after LSS fared worse than those without amputation after LSS on nearly all physical function metrics in CCSS surveys (Table 3). Specifically, after controlling for age, we found that participants with primary amputation (relative risk [RR] 2.76 [95% CI 1.29 to 5.89]; p = 0.009) and late amputation (RR 4.45 [95% CI 1.44 to 13.70]; p = 0.009) were more likely to need help with routine needs than were participants without amputation after LSS. Patients treated with primary amputation or LSS with late amputation were also more likely to be

Table 1. Demographic and treatment characteristics of lower extremity sarcoma survivors treated with primary amputation or LSS

Characteristics	Primary amputation (n = 547)	Primary LSS (n = 510)
Women	45 (244)	51 (260)
Race[a]		
White, non-Hispanic	75 (409)	71 (364)
Black, non-Hispanic	7 (41)	6 (31)
Asian/Pacific Islander	1 (8)	3 (17)
Other	16 (89)	19 (98)
Age at diagnosis in years		
< 10	22 (123)	14 (70)
10-14	41 (227)	42 (213)
15+	36 (197)	45 (227)
Age at last follow-up or death in years	42 ± 11	37 ± 10
Decade of diagnosis		
1970s	41 (222)	12 (62)
1980s	41 (223)	36 (183)
1990s	19 (102)	52 (265)
Diagnosis		
Ewing sarcoma	9 (48)	17 (85)
Osteosarcoma	89 (488)	78 (400)
Soft tissue sarcoma	2 (10)	4 (20)
Other bone tumors	0.2 (1)	1 (5)
Chronic medical condition		
Any Grade 3-4[b]	25 (136)	26 (130)
Treatment		
Surgery only	15 (84)	8 (42)
Surgery + chemotherapy	82 (448)	80 (408)
Surgery + leg RT	0.5 (3)	0.2 (1)
Surgery + chemotherapy + leg RT	2 (12)	12 (59)
Prosthetic joint reconstruction	2 (10)	25 (126)
Chemotherapy exposure		
Any	85 (467)	93 (476)
Anthracycline	82 (446)	88 (451)
Alkylating agent	61 (332)	72 (368)
Platinum	39 (215)	58 (298)
Vinca alkaloid	42 (230)	38 (194)
Antimetabolite	65 (358)	67 (340)
Topoisomerase inhibitor or antitumor antibiotic	83 (456)	92 (471)
Cancer recurrence	21 (115)	12 (63)

Data presented as % (n) or mean ± SD.
[a]Race according to study participants' self-report.
[b]National Cancer Institute's Common Terminology for Adverse Events v4.3, including Grade 1 (mild or asymptomatic), Grade 2 (moderate), Grade 3 (severe and/or disabling), and Grade 4 (life-threatening); leg RT = external beam radiation, specifically the operative extremity.

unable to work or attend school (RR 2.04 [95% CI 1.15 to 3.64]; $p = 0.02$ and RR 3.85 [95% CI 1.66 to 8.92]; $p = 0.002$, respectively).

Study patients generally reported no differences in mental and emotional health outcomes on the SF-36 and BSI-18, regardless of surgical treatment group (Table 4).
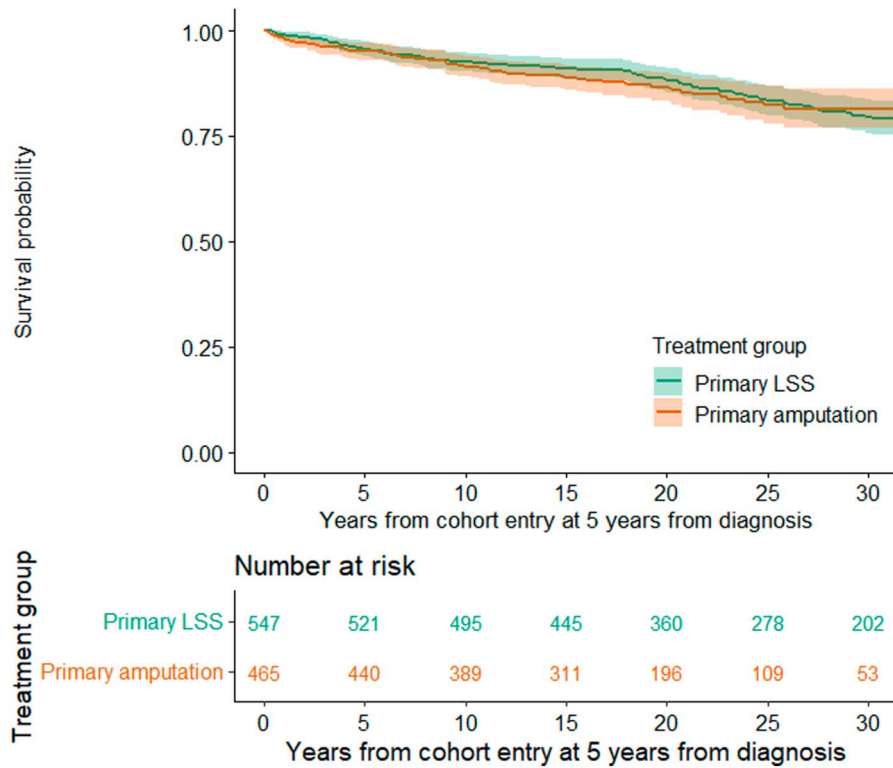
Fig. 1 This graph shows the overall survival rate among 5-year survivors of lower extremity sarcoma by primary surgical treatment approach.

However, those treated with primary amputation and those with LSS complicated by late amputation reported worse physical health scores than those without amputation after LSS. Specifically, participants with primary amputation and those experiencing late amputation after LSS were more likely to report impaired physical functioning (RR 1.34 [95% CI 1.04 to 1.72]; p = 0.02 and RR 2.46 [95% CI 1.66 to 3.63]; p < 0.001, respectively) and worse bodily
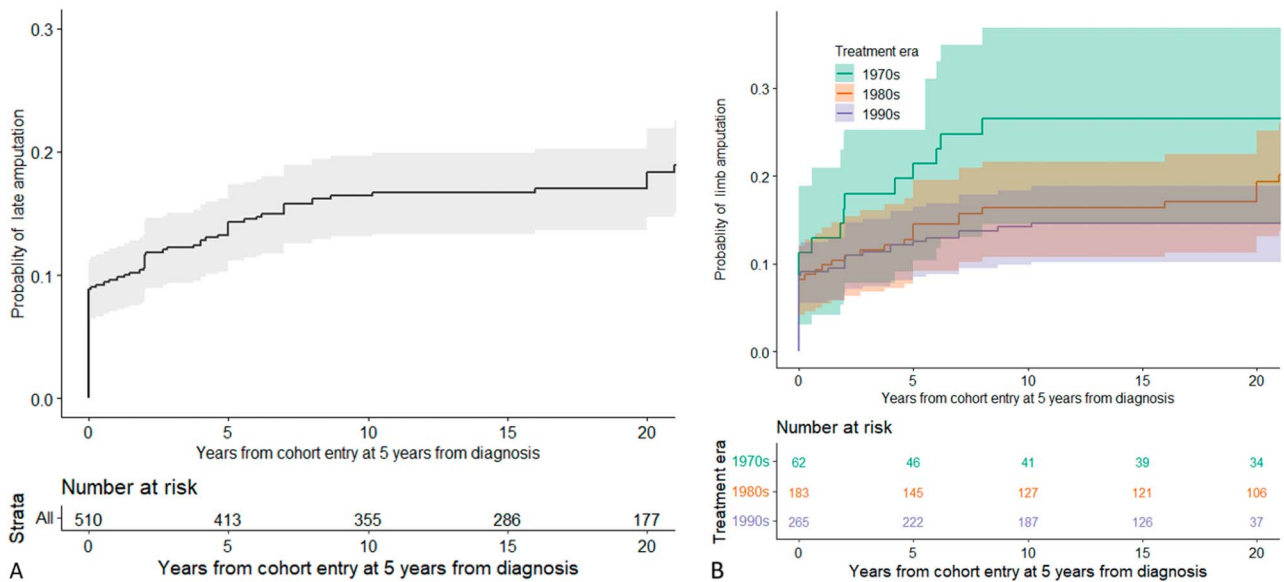

Fig. 2 A-B These graphs show the cumulative incidence of amputation among cohort participants treated with LSS (**A**) overall and (**B**) by decade of diagnosis.

Table 2. Multivariable analysis of risk factors for late amputation after initial LSS (model includes treatment modalities chemotherapy and radiation)

Variable	HR (95% CI)	p value
Men (vs women)	2.02 (1.07-3.82)	0.03
Alkylating agent exposure (vs no exposure)	2.14 (0.86-5.30)	0.10
Vinca alkaloid exposure (vs no exposure)	1.76 (0.93-3.35)	0.08
Prosthetic joint reconstruction (vs no reconstruction)	2.58 (1.37-4.84)	0.003
Cancer recurrence (vs no recurrence)	0.92 (0.42-2.01)	0.83
Grades 3-4 chronic health condition (vs Grades 1-2)[a]	1.71 (0.72-4.06)	0.22

[a]National Cancer Institute's Common Terminology for Adverse Events v4.3, including Grade 1 (mild or asymptomatic), Grade 2 (moderate), Grade 3 (severe and/or disabling), and Grade 4 (life-threatening); all study participants reported a Grade 1 to Grade 2 chronic health condition.

pain scores (RR 1.50 [95% CI 1.10 to 2.06]; p = 0.01 and RR 2.33 [95% CI 1.27 to 4.26]; p = 0.006, respectively) than those without amputation after LSS.

Discussion

The advent of preoperative chemotherapy protocols, in addition to advances in surgical techniques, imaging, and implant design, ushered in the wide adoption of LSS instead of amputation for most primary pediatric lower extremity sarcomas [2, 3, 8, 9, 12, 25, 27, 40, 41]. As more children with these diagnoses achieve long-term survival,

there is a need for ongoing clinical surveillance of treatment-related sequelae. Previous studies have evaluated whether primary amputation or LSS impacts long-term psychosocial and physical health outcomes, with mixed conclusions depending on the study population and the outcome measure used [25, 26, 32, 33, 35, 37, 43]. Additionally, even long-term studies of LSS do not report on patient or clinical variables associated with late amputation after limb salvage and infrequently on the outcomes of this rare group of patients undergoing late amputation [10, 14, 19, 30, 37]. Using the CCSS cohort (individuals who had survived 5 years from cancer diagnosis at enrollment), we found that the cumulative incidence of

Table 3. Physical and social outcomes for cohort participants treated with primary amputation and LSS complicated by late amputation assessed by CCSS follow-up surveys

Outcome	Modified Poisson regression adjusted for age at physical function		
	Yes	RR (95% CI)	p value[a]
Limited physical performance			
LSS with late amputation	74 (14 of 19)	1.81 (1.29-2.52)	0.001
Primary amputation	47 (189 of 403)	1.1 (0.89-1.37)	0.37
Help needed for routine needs			
LSS with late amputation	24 (4 of 17)	4.45 (1.44-13.7)	0.009
Primary amputation	15 (57 of 372)	2.76 (1.29-5.89)	0.009
Cannot work or attend school			
LSS with late amputation	35 (6 of 17)	3.85 (1.66-8.92)	0.002
Primary amputation	20 (73 of 372)	2.04 (1.15-3.64)	0.02
Driver's license (older than 16 years of age)			
LSS with late amputation	19 (3 of 16)	2.59 (0.82-8.21)	0.11
Primary amputation	9 (32 of 367)	1.55 (0.70-3.43)	0.28

Data presented as % (n).
[a]The reference group is the LSS group without amputation to date for all comparisons.

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Table 4. HRQOL and psychosocial outcomes based on the Medical Outcomes SF-36 and BSI-18 for cohort participants treated with primary amputation and LSS complicated by late amputation adjusted for age at evaluation

Outcomes	Poor outcome	RR (95%CI)	p value[b]
HR-QOL[a]			
Physical health			
Physical functioning			
LSS with late amputation	71 (12 of 17)	2.46 (1.66-3.63)	< 0.001
Primary amputation	38 (132 of 346)	1.34 (1.04-1.72)	0.02
Physical role			
LSS with late amputation	47 (8 of 17)	1.87 (1.06-3.30)	0.03
Primary amputation	22 (75 of 346)	0.87 (0.64-1.19)	0.38
Bodily pain			
LSS with late amputation	47 (8 of 17)	2.33 (1.27-4.26)	0.006
Primary amputation	30 (104 of 346)	1.50 (1.10-2.06)	0.01
General health			
LSS with late amputation	47 (8 of 17)	1.98 (1.10-3.56)	0.02
Primary amputation	23 (71 of 303)	1.00 (0.72-1.38)	0.99
Mental health SF-36			
Vitality			
LSS with late amputation	35 (6 of 17)	1.59 (0.78-3.24)	0.20
Primary amputation	25 (76 of 303)	1.15 (0.83-1.59)	0.41
Social functioning			
LSS with late amputation	24 (4 of 17)	1.39 (0.56-3.47)	0.48
Primary amputation	17 (60 of 346)	1.03 (0.71-1.49)	0.89
Role-emotional			
LSS with late amputation	12 (2 of 17)	0.68 (0.18-2.62)	0.58
Primary amputation	22 (76 of 346)	1.28 (0.90-1.82)	0.17
Mental health			
LSS with late amputation	35 (6 of 17)	2.20 (1.07-4.52)	0.03
Primary amputation	22 (67 of 303)	1.39 (0.95-2.01)	0.087
BSI-18[c]			
Depression			
LSS with late amputation	19 (3 of 16)	0.95 (0.86-1.06)	0.39
Primary amputation	15 (45 of 300)	0.97 (0.94-1.00)	0.08
Anxiety			
LSS with late amputation	0 (0 of 16)	NA	NA
Primary amputation	9 (28 of 300)	0.99 (0.96-1.01)	0.37
Somatic			
LSS with late amputation	19 (3 of 16)	0.96 (0.86-1.07)	0.43
Primary amputation	14 (42 of 300)	0.98 (0.95-1.01)	0.20

Data presented as % (n).
[a]SF-36: Raw scores were converted to T scores (range 0 to 100) and dichotomized so that a score at or below 40 (1 SD below the population mean) was classified as a poor HRQOL outcome.
[b]The reference group is the LSS group without amputation to date for all comparisons.
[c]BSI-18: Participants with T-scores of 63 or more on a particular scale were classified as having poor emotional health.

amputation after LSS was 17.9% at 25 years from cancer diagnosis. We identified gender (men) and prosthetic joint reconstruction procedures as independently associated with an increased likelihood of late amputation. Lastly, we established that study participants treated with primary amputation for tumor control and those who undergo late

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amputation after LSS are less likely to attend school or be employed than those without amputation after LSS, and they also report greater degrees of physical impairments (but not mental or emotional) across multiple patient outcome metrics.

Limitations

Our study has several limitations. Given the 25 years of follow-up, it was not possible for us to report on comparable long-term outcomes for current state-of-the-art LSS procedures. Our results are generated from a cohort of patients with sarcoma diagnosed between 1970 to 1999, and surgical techniques, endoprosthetic implant design, and manufacturing have evolved over this period. However, in many respects, the clinical experience of patients with sarcoma and the risks both for late amputation and poor health outcomes remain unchanged. Improved metallurgy has not eliminated the extensive surgical exposures needed to resect sarcoma nor has it perfected the fixation of implant to host bone [17]. Prosthetic socket design has not changed in decades, so patients undergoing amputation today for sarcoma treatment face similar functional challenges as those in our study [7, 15, 18]. Finally, although neoadjuvant chemotherapy was a critical advance at its inception, the drug regimens in use today are very similar to the treatment exposures in our cohort. We also lacked information on the specific method of reconstruction employed for a given patient or the cause of an amputation after LSS. We were unable to capture surgical site infection as a dependent variable because it is not included in CCSS follow-up questionnaires. Nonetheless, establishing a cumulative incidence of late amputation after LSS in a large cohort with long-term follow-up and factors associated with late amputation is an important step forward for our understanding of the limitations of limb salvage.

We also could not reliably specify transtibial versus transfemoral status. However, we know that patients who have undergone transtibial amputation experience similar degrees of socket-related issues and dissatisfaction as patients whose amputations were at the transfemoral level [16], and physical activity outcomes in the CCSS cohort are not different based upon transfemoral versus transtibial amputation status [46]. Additionally, follow-up survey data rely on accurate self-report. Further, additional study follow-up may see patients currently in the LSS without amputation cohort convert to the late amputation cohort. Our data are limited by the last health outcomes assessment. It is worth noting that we are likely underestimating the effect size of a truly successful primary limb salvage because, if a patient who underwent LSS has a future amputation—which our data suggest is associated with a decline in quality of life—that will likely reduce the size of the beneficial effect we are currently attributing to long-term limb salvage. Lastly, although this is one of the largest cohorts assembled to study late amputation, our ability to examine the association of some rarer treatment factors with late amputation was still limited. Future studies on factors associated with late amputation will require multi-institutional collaborations to assemble the study cohort size needed to draw additional conclusions.

Demographic, Treatment, and Survival Characteristics

Our cohort included study participants with a diagnosis between 1970 and 1999 and reflects the evolution in sarcoma care during that period [2]. Although most participants (78%) in the 1970s were treated with amputation for tumor control, 72% of participants with a diagnosis in the 1990s were treated with LSS. We affirmed that in children who survived 5 years from sarcoma diagnosis, the index surgical procedure was not associated with any difference in long-term survival. Similar oncologic outcomes, including overall survival after LSS or amputation for lower extremity sarcoma, had been shown in studies of patients with a new diagnosis of sarcoma and intermediate-term (5 to 10 years) follow-up [40, 41]. Our study cannot be a direct extension of these, since CCSS eligibility criteria includes 5-year survival from the date of cancer diagnosis, so future studies designed to compare overall and disease-specific survival between LSS and primary amputation beyond 10 years should include all patients from the time of diagnosis followed longitudinally.

Cumulative Incidence of Amputation After LSS

Our finding of an 18% incidence of amputation at 25 years from diagnosis among children treated for sarcoma with LSS supports findings from previous studies using smaller, selected populations. Holm et al. [19] reported an amputation proportion of 12% at 14 years after tumor resection in 50 patients undergoing endoprosthetic reconstructions. Futani et al. [13] reported specifically on the clinical outcome of LSS for 35 patients younger than 11 years of age who had a diagnosis of distal femur sarcoma and were followed for more than 10 years. Among patients who survived a minimum of 5 years from diagnosis, five amputations (four for LSS complications, one for sarcoma skip metastasis) were performed (14%). Our findings extend these studies using a considerably larger cohort and longer duration of follow-up, affirming a substantial risk for late amputation even after initial salvage from tumor. This emphasizes the need for lifelong mitigation strategies to reduce reconstruction complications. A study of similar

size and follow-up with more detail on specific surgical reconstructions and the complications directly leading to loss of limb will better inform what those mitigation strategies should be.

Factors Associated with Late Amputation (≥ 5 Years After Diagnosis)

We found that being a man (compared with being a woman) and undergoing prosthetic joint reconstruction were independently associated with time to late amputation after LSS. The etiology of the elevated risk associated with gender likely is multifactorial and may include factors such as higher BMI or activity levels [46] that place more demand over time on oncologic reconstructions. It should be noted that given the wide confidence interval that approaches 1 for this result, the actual effect size of gender on late amputation may be small or negligible. In light of that, we recommend that surgeons not consider gender as a factor strongly associated with this endpoint. This finding would benefit from further study of LSS complications controlling for factors such as BMI and physical activity.

Limb salvage for lower extremity sarcoma often includes knee or hip reconstruction. Endoprosthetic joint reconstruction has advantages such as immediate weight-bearing, modularity, and inherent joint stability [48], but these implants are prone to multiple mechanisms of failure, including infection and aseptic loosening [17]. A recent meta-analysis calculated that the mean time to infectious complications was 2 years and for aseptic loosening it was 7 years [44]; thus, children will be adolescents or young adults by the time of their first revision procedure, and multiple revision procedures increase the likelihood that a patient will eventually undergo amputation. In a study of 230 endoprosthetic reconstructions with 30-year follow-up, patients underwent an average of 2.7 reoperations, culminating in a 16% risk of late amputation [14]. Identifying prosthetic joint reconstruction as a factor associated with late amputation again identifies a group who need lifelong clinical surveillance to identify and address reconstruction complications. Understanding what specific complications increase the risk of late limb loss will inform improvements in implant design, manufacturing, fixation, and resistance to infection.

Social, Physical, and Emotional HRQOL Outcomes

We found that primary and late amputation status is associated with an increased likelihood of impaired physical function and diminished educational attainment compared with LSS without amputation using CCSS follow-up survey metrics and the physical health component of the SF-36. Overall, children with central nervous system tumors, lymphoma, or bone or soft tissue sarcomas have the lowest mean HRQOL scores compared with children treated for other cancers and compared with sibling controls without cancer [49]. The largest effect sizes with respect to impaired physical functioning have been demonstrated in children treated for sarcoma compared with siblings without cancer [50]. Our results suggest that a disproportionate burden of the poor physical outcomes in these studies is borne by children treated with primary amputation for sarcoma and those who underwent late amputation after LSS. Patients treated with primary amputation have, after all, been reported to have worse physical function than those undergoing LSS [1], in support of our finding.

Patients treated for sarcoma, specifically bone tumors, have demonstrated more psychological distress, including anxiety, somatization, and lower mental health scores on the SF-36 subscales, than controls [49, 50]. In contrast to our physical health and functional outcomes, we did not find that these mental and emotional health outcomes depended on the type or outcome of surgical treatment. We did, however, note increased bodily pain scores among respondents with a primary or late amputation. A recent assessment of longitudinal pain symptoms and pain interference in children treated for various cancers identified that amputation increased the risk of severe recurrent pain [21], supporting our findings. Our findings suggest that interventions focused specifically on functional improvement for oncologic patients with amputation and on amputation pain mitigation can help close the gap in health outcomes compared with children treated with limb salvage for sarcoma who survive into adulthood without late amputation. Specific functional interventions may include prosthetic design, rehabilitation protocols, or osseointegration, which has been shown to substantially improve the function of patients with transfemoral and transtibial amputations [36]. In addition to medical therapy, amputation pain can be addressed intraoperatively with targeted muscle reinnervation [45] or postoperatively with physical therapy of the healthy and phantom limb [47].

Our finding that study participants who underwent primary amputation and those who underwent late amputation were less likely to attend school or work compared with participants who did not have an amputation after LSS is worth emphasizing. A smaller, single-institution study of 38 patients younger than 20 years with osteosarcoma found that patients with amputation were less likely than patients without amputation to have a graduate degree (16% versus 42%) [32]. It is necessary to study why this disparity exists and to what degree this is due to school or workplace factors versus physical disability stemming from the amputation itself. Vocational rehabilitation should be a part of recovery for all patients who undergo an amputation [5].

Conclusion

There is a substantial risk of late amputation after LSS, and both primary and late amputation status are associated with decreased physical HRQOL outcomes. Children treated for sarcoma who survive into adulthood after primary amputation and those who undergo late amputation after LSS will benefit from interventions focused on improving physical function and reaching educational and employment milestones. Efforts to improve the physical function of people who have undergone amputation either through prosthetic design or integration into the residuum should be supported. Understanding factors associated with late amputation in the setting of more modern surgical approaches and implants will help surgeons more effectively manage patient expectations and adjust practice to mitigate these risks over the life of the patient.

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