1. Title

Risk factors for and outcomes of late amputation among survivors of childhood lower extremity sarcoma: a report from the childhood cancer survivor study

2. Working group and investigators

a. Chronic Disease (primary)
b. Epidemiology and Biostatistics (secondary)
c. Psychology (secondary)

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3. Background and rationale

There are approximately 600 – 700 new cases of malignant bone or joint tumors diagnosed in the United States in children younger than 20 years annually.[1] Though rare, these tumors still account for one of the most common cancer diagnoses in the pediatric population.[2] The most common of these primary bone tumors is osteosarcoma, which accounts for just over half of new diagnoses, followed by Ewing sarcoma. Historically, the surgical treatment for these primary bone malignancies was limb amputation. In the 1970s, Rosen et al. introduced preoperative chemotherapy protocols, which created time for a custom-fitted prosthesis to be fabricated so that the surgeons could try to save the patient's limb during tumor resection.[3] The development of multi-agent neoadjuvant chemotherapeutic regimens effectively changed the prognosis of bone sarcomas, improving overall survival rates to 60 – 70% for localized disease.[4-6] These developments, plus advances in surgical techniques and implants, changed the surgical paradigm to one focused on tumor extirpation with limb preservation. Limb-sparing surgery (LSS) became the standard of care by the 1990s, and is now the preferred surgical approach in 90% of cases.[7,8] Limb-sparing techniques do not compromise oncologic outcomes as multiple analyses demonstrated similar disease recurrence rates and equivalent overall survival between limb salvage and ampuation.[1,9]

Improved treatment models result in more patients surviving for a longer time, which emphasizes the need for ongoing surveillance and support for this population. Studies have shown that survivors of pediatric cancers face challenges in multiple domains as they age. Oeffinger, et al, demonstrated that pediatric cancer survivors, in general, had a 3-fold higher likelihood of having a chronic health condition compared to a sibling cohort.[10] More strikingly, survivors of bone tumors exhibited the highest risk of developing a severe or life-threatening condition. Nagarajan, et al, specifically followed the survivors of childhood osteosarcoma in the Childhood Cancer Survivor Study (CCSS) patient population. When compared to their sibling cohort, survivors had worse health outcomes across all studied domains – general health, mental health, and functional status. Survivors of osteosarcoma had higher risks of severe adverse health conditions even compared to other survivors of childhood cancer.[11] Survivors of adult lower extremity sarcoma are also known to have higher risks of inactivity in their adult lives and are less likely than the general population to regularly exercise.[12]

Multiple studies have evaluated whether primary amputation or limb salvage surgery impacts these long-term general and functional health limitations, with mixed conclusions depending on the study population and the analysis tool.[1,13-17] It does appear that amputees, particularly those at more proximal levels, have increased reliance on mobility aids and experience limitations in physical function. A recent study also demonstrated improved emotional health and improved quality of life scores across multiple domains for limb-salvage patients compared to amputees for nonmetastatic sarcomas.[18] Substantial and reproducible differences however, have not born out as clearly as was anticipated in the literature.

The enhanced survivorship in the pediatric tumor populations challenges the longevity of oncologic reconstructions. Limb-sparing surgery – facilitated by either metal endoprosthetic or allograft reconstruction – is fraught with complications.[1,19] To date, there is no consensus as to whether biologic or metallic implants result in superior outcomes over the short to medium term.[20,21] Common sources of reconstructive failure include tumor recurrence and infection. Other sources of failure are unique to the reconstructive method: nonunion and resorption can plague allografts while mechanical failures and loosening blight prosthetic implants.

A potentially devastating outcome of these complications is secondary (or late) amputation, which is amputation that occurs after initial treatment with limb-sparing surgical resection. The causes of amputation after initial LSS are varied. In the very short term – typically within 5 years from initial diagnosis – secondary amputations are most commonly due to tumor recurrence. Over the longer term, the causes of an amputation after initial LSS change. Complications associated with the surgery such as deep infection or prosthetic failures begin to be the driving factors behind limb loss. These amputations that occur many years after initial LSS are termed "late" amputations.

Few studies have been able to look at the long-term outcomes of oncologic reconstructions. Futani looked at both endoprosthetic and allograft reconstruction in a series of 33 young pediatric patients who survived beyond 5 years from distal femoral sarcoma. Revision surgery was necessary in 52% of the cohort and the late amputation rate was 15% at 12 years of follow up. Holm followed 50 patients having mega-endoprostheses for an average of 14 years and classified failures according to the Henderson classification, the most common of which was a structural failure.[22] Fifty-four percent of their cohort had a revision surgery, and 12% required a late amputation. The very-long term outcomes of these reconstructions are even more challenging to study in large numbers. Grimer was able to retrospectively review the outcomes of patients who underwent an endoprosthetic reconstruction for a primary bone tumor with a minimum follow up of 25 years. Patients had undergone an average of 2.7 subsequent operations. In the 30 – 40% of their cohort who suffered an infection, their reoperation rate was even higher. The risk of amputation was 16% at 30 years, with the most common indications for amputation being infection and, more rarely, tumor recurrence.[23] Jeys reviewed 1,261 patients treated at their center over a 30-year period and found that 10% of amputations occurred 5 or more years from initial LSS. The most common reasons for late amputation, again, were local recurrence and infection.[24] Finally, resection of soft tissue sarcomas of the extremity can also result in limb amputation because of the morbidity caused both by surgical and neoadjuvant treatment modalities or long-term vascular issues.[25-27] Though primary and late amputation rates are lower for soft tissue compared to bone sarcomas, these malignancies present a substantial threat to a patient's limb, particularly if major blood vessels or nerves are involved.

Although some studies have evaluated the risk of late amputation in mid- to long-term survivors of pediatric sarcoma, rarely have the outcomes of these patients been further assessed. A few studies have shown that secondary amputees suffer from more significant body image concerns[16] and slightly diminished functional scores.[28] On the other hand, arguments exist that a late amputation may provide a freedom from the burdensome complications of limb-salvage.[29] The small number of patients in these studies make it difficult to draw firm conclusions about their patients' outcomes, but these contributions do represent an important step in recognizing an otherwise under-studied population.

Overall, we know that survivors of bone tumors and other sarcomas represent a very high-risk group for poor health outcomes over the long term. We also know that since the 1980s, this group of patients has experienced an increased life expectancy after diagnosis. Limb-salvage is oncologically safe but can carry a high risk of postoperative complications.

Although the rate of late amputations for sarcoma patients after primary limb salvage approximates around 10-15% in published studies, the rate of and risk factors for late amputation over the very long term is insufficiently studied. Further, the quality of life and functional outcomes in these late amputees has not been reported beyond small nested case series. The proposed study will address these gaps in knowledge by investigating the rate of and risks factors for late amputations in

CCSS survivors initially treated with primary limb salvage surgery for lower extremity bone and soft tissue sarcomas with minimum 5 years survival after initial treatment. We will also report psychosocial and functional outcomes for survivors treated with successful primary limb salvage, primary amputation, and late amputation compared to the CCSS sibling cohort.

4. Specific aims/objectives/research hypotheses

Specific Aim 1
To identify the 30-year cumulative incidence of late amputation among lower extremity sarcoma survivors initially treated with limb salvage surgery

- *Aim 1a* – To identify the overall rate of "limb survival" after primary LSS

Hypothesis: The risk of late amputation in survivors beyond 5 years from sarcoma diagnosis will approximate 10-15%.

Specific Aim 2
To identify demographic and treatment-related risk factors for late amputation in survivors of lower extremity sarcoma treated with limb salvage surgery. These regression analyses can be incorporated into a risk prediction model for late amputation in LSS survivors who have survived 5 years from diagnosis without amputation.
Hypothesis: We anticipate risk factors for late amputation to be bone sarcoma diagnosis (versus soft tissue sarcoma diagnosis), younger age at diagnosis, having undergone multiple surgeries within 5 years of diagnosis, treatment with radiation to the extremity, and tumors located below the knee (compared to tumors in the thigh).

Specific Aim 3
To compare psychosocial, general health, and functional outcomes amongst survivors who underwent LSS with and without late amputation vs. survivors who underwent primary amputation. The CCSS sibling cohort will serve as a reference group.
Hypothesis: We suspect the long-term functional, general health, and socioeconomic outcomes for survivors treated with LSS without late amputation will be subtly superior to those treated with primary amputation. We also suspect that the overall outcomes of survivors who underwent a late amputation will be the worst of all groups studied. We anticipate the overall outcomes across all domains for survivors in each category to be inferior to the CCSS sibling cohort.

Specific Aim 4
To compare late all-cause mortality rates and standardized mortality ratios (SMR) for survivors of lower extremity sarcoma treated with primary amputation and primary limb salvage who did and did not undergo late amputation. Mortality statistics for the general US population will serve as a comparison.

- *Aim 4a* – To identify all-cause mortality rates in survivors stratified by decade of treatment

Hypothesis: The late all-cause mortality for survivors treated with primary LSS and primary amputation will be similar, and both will be greater than the general US population over the duration of follow up. Late all-cause mortality for survivors undergoing late amputation will be the highest of the studied groups but may not reach statistical significance. Given the survivor bias of the CCSS cohort, we cannot use these statistics to support index surgical treatment decisions, but I think it still carries relevance for mortality due to causes unrelated to sarcoma (example: late amputees having a higher 30 year SMR because of medical complications related to poor limb function).

5. Analysis Framework

a. *Subject population*

Inclusion criteria –. We will include all childhood cancer survivors of lower extremity bone or soft tissue sarcomas who completed the baseline survey (original and expansion cohorts) and siblings who participated in the CCSS original and expanded cohorts. Lower extremity tumors will include tumors of bone - osteosarcoma, Ewing sarcoma or primitive neuroectodermal tumor, chondrosarcoma, fibrosarcoma, and malignant fibrous histiocytoma (aka undifferentiated pleomorphic sarcoma) – as well as soft tissue sarcomas – rhabdomyosarcoma, liposarcoma, synovial sarcoma, leiomyosarcoma, fibrosarcoma, and malignant fibrous histiocytoma (aka undifferentiated pleomorphic sarcoma). The primary amputation patient cohort are survivors treated with amputation at any level as part of their index surgery for tumor resection. The limb salvage surgery cohort is defined as patients treated with surgical resection of extremity sarcoma without performing an amputation at any level during this index procedure. The late amputation patient cohort is defined as any survivor treated with LSS who eventually underwent a limb amputation at any level >5 years after their index procedure. Survivors treated with primary LSS who had an amputation <5 years from initial treatment should be noted and graphically represented but then excluded from analysis of risk factors for late amputation.
Amputation will be an outcome in some specific aims and an exposure in others. Thus, to more clearly define study populations:

- For specific aim 1, all patients who initially underwent limb salvage surgery will be included as the subject population with amputation being an outcome variable.
- For specific aim 2, the study population will be survivors initially treated with LSS who eventually underwent a late amputation.
- For specific aims 3 and 4, the study populations are survivors treated with primary amputation at index surgery, survivors treated with LSS with no late amputation, and survivors treated with LSS who also underwent late amputation.

Exclusion criteria – Any patient not treated with definitive LSS or primary amputation for tumor (so surgical biopsy only patients are excluded). Failure to complete LTFU surveys.

b. *Outcomes of interest*

The primary outcome of interest will be late amputation after primary LSS, defined as self-report of any amputation of the affected limb >5 years after initial cancer diagnosis and treatment. The prevalence ratio of survivors treated with primary LSS who had an amputation <5 years from initial treatment should be calculated, but then these patients are excluded from the study analysis of risk factors for late amputation.

- Amputation of extremity or digit (B.I1, BE.I1, FU4 J1, FU5 J1)
- Include each reported amputation from the 'free-text' section
- Prevalent cases – or amputations that occurred within 5 years of diagnosis – are not the focus of subsequent analyses but should, nonetheless, be counted. Cumulative incidence curves can be created with prevalent cases noted on the Y axis at time = 0 (which is 5 years post-cancer diagnosis by CCSS convention).

Secondary outcomes include health-related quality of life, socioeconomic, psychosocial, and physical/functional outcomes, as well as late all-cause mortality – defined as mortality >5 years after initial cancer diagnosis – among survivors who underwent primary amputation or LSS with and without late amputation as treatment for their cancer.

- Health-related quality of life (HRQOL), as assessed by Short Form 36 (SF-36), and Brief Symptom Inventory (BSI) surveys. The relationship between late amputation and HRQOL will be evaluated using data collected from the most recent surveys completed.
    - HRQOL: based on answers to LTFU 2014 #O1-O6. Categorical (ordinal) data.
- Socioeconomic outcomes (education, employment status, income, health insurance status, marital status, etc.) based on LTFU 2014 #A4-A10, excluding #A8, and #M1-3. Categorical data. (M1-3 may be nominal data).
- Psychosocial: BSI results are based on Baseline #J16-37 (excluding J25 and J28), Baseline Expansion #K1-K20, and LTFU 2014 #L1-L20; #G1-20; #P1. Categorical data and binary (Depression vs. no depression; anxiety vs. no anxiety; etc)
- Functional status and activity status classified based on answers to questions adapted from the National Health Interview Survey and the Behavioral Risk Factor Surveillance System Survey Questionnaire. LTFU 2014 #N15-29. Numerical (discrete) and binary data.
- All-cause mortality rates can be calculated as described in the *Statistical methods* section, below

c. *Exploratory variables*

- Demographic variables
    - Age (continuous and categorical; Baseline #A1; ExpBaseline #A1)
    - Sex (categorical; Baseline #A2; ExpBaseline #A2)
    - Race/ethnicity (categorical; Baseline #A4; ExpBaseline #A5)
- Chronic conditions

- Common Terminology Criteria for Adverse Events[10]
  - No condition
  - Grade 1 condition (mild)
  - Grade 2 (moderate)
  - Grade 3 (severe)
  - Grade 4 (life-threatening or disabling)
  - Grade 5 (fatal)

- Cancer variables
  - Initial diagnosis (osteosarcoma, Ewing sarcoma, soft tissue sarcoma, other)
  - Tumor location (above knee / below knee)
  - Local tumor recurrence (Baseline & ExBaseline #K1 and K4, LTFU 2014 #S1 and S5)
  - Distant metastasis (binary)
- Treatment variables
  - Decade of diagnosis (1970-1979, 1980-1989, 1990-1999)
  - Surgery variables
    - Initial surgery (categorical: biopsy only/none, primary amputation, LSS)
      - Exclude survivors who did not undergo surgery and those who only underwent surgical biopsy
      - Primary amputation is an amputation at any level as part of the index surgery for tumor resection
      - Limb salvage surgery is defined as surgical resection of extremity sarcoma without performing an amputation at any level during this index procedure
    - Number of limb operations within 5 years of diagnosis (1, 2-4, ≥5)
      - Exclusive of biopsies
    - Joint replacement as treatment for initial surgery (Baseline & ExpBaseline #I5, LTFU 2014 #J5)
  - Any chemotherapy (binary) – (LTFU #T2)
    - Vinca alkyloid (binary)
    - Platinum agent (binary)
    - Alkylating agent (binary)
    - Antracycline (binary)
    - Antimetabolite (binary)
    - Topoisomerase inhibitor (binary)
  - Any limb-directed radiation therapy (binary) (LTFU 2014 #T1 – need to confirm follow up response is to ipsilateral lower extremity)
    - Radiation data to limbs is located in the body region dosimetry file

d. *Statistical methods*

We will first tabulate the number of survivors who underwent a late amputation after primary LSS for pediatric lower extremity sarcoma. We will then compare descriptive statistics for demographic and clinical variables amongst survivors that underwent successful primary LSS, primary amputation, and late amputation. We will also include the CCSS sibling cohort for relevant demographic variables. Chronic medical conditions will be assessed using the Common Terminology for Adverse Events. To compare categorical data, we will use the chi-square test (Table 1).

We will then perform multivariable analyses to identify risk factors for late amputation from the demographic and clinical treatment variables available. As mentioned above, these variables can include age, sex, race, chronic health condition status, and cancer and treatment variables as above (Table 2). Adjusted rate ratios of late amputation in survivors who underwent LSS overall and by cancer diagnosis or tumor location relative to siblings will be calculated after controlling for basic demographic variables (Table 3).

Cumulative incidence curves demonstrating the 30-year rate of late amputation over the course of the follow up period will be constructed comparing survivors and siblings (Figure 1). Prevalent cases – or amputations that occurred within 5 years of diagnosis – are not the focus of statistical analyses but should, nonetheless, be noted. Cumulative incidence curves can be created with prevalent cases noted on the Y axis at time = 0 (which is 5 years post-cancer diagnosis by CCSS convention). The overall rate of "limb survival" in this cohort after primary LSS (or those who had not undergone late amputation after LSS by the date of last follow up) can be represented graphically using the Kaplan-Meier method (Figure 2). Lines for the total cohort, as well as curves stratified by decade of diagnosis can be represented on the same graph for comparison.

We will then compare the health, socio-economic, and functional outcomes of survivors who underwent primary amputation versus successful primary LSS versus late amputation. These groups will be compared to the CCSS sibling cohort (Table 4a and 4b). Multiple domains of health status are captured in the baseline, expansion, and long-term follow up questionnaires. Using the SF-36 and the BSI-18 instruments, psychosocial impairment can be compared amongst the aforementioned groups. Psychosocial outcomes can be dichotomized into impaired vs. not impaired using thresholds set at the population norm highest 10^{th} percentile (T-score ≥63) values for the BSI-18 and the lowest 16^{th} percentile (T-score <40) for the SF-36. Multivariable logistic regressions are used to estimate the association between late amputation and psychosocial impairment. Accounting for repeated measures is the most challenging with clinical relevance existing for measures taken both immediately pre- and then status post a late amputation. The most straightforward path to take regarding data collection will be to collect data based upon the most recent survey completed. Socio-economic outcomes such as marital and employments status, education attained, income, and health insurance are similarly captured. Odds ratios will be calculated for each outcome measure with the sibling cohort to serve as the reference.

We will then explore the mortality outcomes in survivors having undergone successful LSS versus primary amputation versus late amputation. Deaths and causes will be determined using the National Death Index. Standardized mortality ratios for all-cause mortality will be calculated for each group using age-sex-calendar-year specific US mortality rates. Deaths due to sarcoma recurrence or metastasis will also be specified (Table 5). The Kaplan-Meier method will be used to depict overall survival curves (Figure 3). The first graph will detail overall survival of survivors treated with primary limb-sparing surgery (inclusive of the late amputation cohort) versus primary amputation (Figure 3a). The second graph will detail overall survival curves for survivors treated with successful limb-sparing surgery, with primary amputation, and those who underwent late amputation (Figure 3b).

6. Sample Tables/Figures:

Table 1: Demographic characteristics of lower extremity sarcoma survivors treated with limb-sparing surgery, primary amputation, or late amputation and their siblings

	LSS (n = ***)		Primary amp (n= ***)		LSS with late amp (n= **)		Siblings (n=***)		Amp <5yrs# (n=***)		p-value
	n	%	n	%	n	%	n	%	n	%	
Sex											
Male											
Female											
Race											
White											
Non-white											
Age at Dx											
<4											
5-9											
10-14											
15+											
Age at last follow up											
Mean											
Range											
History of smoking											
Yes											
No											
Chronic medical condition											
None											
Grade 1-2											
Grade ≥ 3											
≥2 of any grade											
Year of Dx											
1970s											

1980s	
1990s	
Diagnosis	
Osteosarcoma	
Ewing Sarcoma	
Soft tissue sarcoma	
Other	
Cancer site	
Above knee	
Below knee	
Cancer recurrence	
Yes	
No	
Treatment	
Surgery only	
Chemo + Surgery	
Surgery + XRT	
Chemo + XRT+ Surgery	
Missing	
Chemotherapy exposure	
None	
Any	
Anthracycline	
Alklating agent	
Platinum	
Vinca alkyloid	
Antimetabolite	
Topoisomerase inhibitor	

#Represents the patients who underwent initial LSS but then underwent amputation within 5 years

Table 2: Risk factors for late amputation after primary limb salvage surgery. Initial Limb-sparing surgery cohort, n = ***

	RR	CI	p-value
Sex			
Male	1.0		
Female			

Race	
White	1.0
Non-white	
History of smoking	
Yes	
No	1.0
Chronic medical condition	
None	1.0
Grade 1-2	
Grade ≥ 3	
≥2 of any grade	
Year of Dx	
1970s	1.0
1980s	
1990s	
Age at Dx	
<10	1.0
≥ 10	
Diagnosis	
Osteosarcoma	1.0
Ewing Sarcoma	
Soft tissue sarcoma	
Other	
Cancer site	
Above knee	1.0
Below knee	
Cancer recurrence	
Yes	
No	1.0
Treatment	
Surgery only	1.0
Chemo + Surgery	
Surgery + XRT	
Chemo + XRT+ Surgery	
Surgeries within 5 years	
One	1.0
Two - four	
≥Five	
Joint replacement as primary treatment	
Yes	
No	1.0
Chemotherapy exposure	
None	1.0

Any	
Anthracycline	
Alklating agent	
Platinum	
Vinca alkyloid	
Antimetabolite	
Topoisomerase inhibitor	

Table 3: Adjusted rate ratios of late amputation in survivors who underwent LSS overall and by cancer diagnosis or tumor location relative to siblings

	Adjusted rate ratio* (95% confidence interval)
Siblings	
All survivors	
Survivors by primary cancer diagnosis	
Osteosarcoma	
Ewing sarcoma	
Soft tissue sarcoma	
Other	
Survivors by tumor location	
Above knee	
Above knee	

Table 4: Measures of adverse health status and socio-economic outcomes of sarcoma survivors treated with limb-sparing surgery (LSS), primary amputation, or late amputation compared to CCSS siblings

4a.Adverse Health Status

	LSS, *n (%)*		**Primary Amp, n (%)**		**LSS with Late Amp, *n (%)***		**Siblings, *n (%)***	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Any domain								1.0
Activity Limitation								1.0
Functional Status								1.0
General Health								1.0
Mental Health								1.0
Pain								1.0
Depression								1.0
Anxiety								1.0

4b. Socio-economic outcomes

	LSS, *n (%)*		Primary Amp, n (%)		LSS with Late Amp, *n (%)*		Siblings, *n (%)*	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Marital Status								
Never married								1.0
Still married								1.0
No longer married								1.0
Education								
Below high school								1.0
High school graduate								1.0
College graduate								1.0
Employment								
Unemployed								1.0
Employed								1.0
Income (household)								
<$60,000								1.0
$60,000 - $100,000								1.0
>$1000,000								1.0
Health insurance								
None								1.0
Public								1.0
Private								1.0

Table 5: All-cause and cause-specific Standardized Mortality Ratios (SMR) for survivors of extremity sarcomas

	Limb-sparing surgery			Primary Amputation			Late Amputation		
	# Death	SMR	95% CI	# Death	SMR	95% CI	# Death	SMR	95% CI
All-cause									
Sarcoma recurrence/ progression									
Health-related									

Figure 1: 30-year cumulative incidence of late amputation among LSS survivors and siblings.

Figure 2: Kaplan-Meier survival curve showing the probability of limb survival after LSS for lower extremity sarcoma by decade of diagnosis.

Figure 3a: Kaplan-Meier survival curve showing the overall survival of survivors initially treated with primary limb-sparing surgery (including late amputation) versus primary amputation.

Figure 3b: Kaplan-Meier survival curve showing the overall survival of survivor cohorts treated with successful limb-sparing surgery, with primary amputation, and those having undergone late amputation.

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