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# Survival in Chondrosarcoma Patients Treated with Limb-Salvage Surgery and Limb Amputation

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## Abstract

Background: Chondrosarcoma is the third most common primary bone malignancy. For tumors located within the extremities, surgeons must choose between limb-salvage surgery (LSS) and limb amputation (LA) to achieve sufficient resection margins. The outcomes from these procedures in chondrosarcoma patients has limited descriptions in current literature. Aims and Objectives: To conduct a multivariate survival analysis of overall and malignancy-related outcomes in chondrosarcoma patients based off the use of LSS or LA. Study Design: Retrospective Cohort Study. Setting: A national cancer database analysis performed at UTMB Galveston. Materials and Methods: Initial cases of chondrosarcoma diagnosed between 2000-2010 from the National Cancer Institute's Surveillance, Epidemiology and End Results database were used for this study. Patients treated with LSS and LA were included. Demographic, tumor characteristic, treatment and survival data were extracted. Statistics: Descriptive statistics were calculated using Fisher exact test. All-cause and malignancy-related mortality were compared using Kaplan Meier analysis and multivariate cox regression. Adjusted covariates included: age, race, sex, ICD-O-3 histology, primary site, grade, summary stage, laterality, use of radiation/chemotherapy. Results: 550 cases with a mean follow up time of 93.14 months (+/- 55.02) were included. 104 patients received LA and 446 received LSS. Kaplan Meier analysis showed that overall ($p < .001$) and malignancy-related ($p = .003$) survival were poorer for LA patients. Upon multivariate cox regression, adjusted all-cause mortality risk was significantly higher for patients treated with amputation (HR, 1.672; $p = .004$) compared to limb-salvage surgery. However, adjusted malignancy-related mortality did not significantly differ between the two treatment groups ($p = .167$). Conclusions: Malignancy-related outcomes are equivocal for LSS and LA, however all-cause mortality is significantly worse for LA patients. Less functional debilitation from LSS may allow for a better quality of life and overall health compared to amputation explaining differences in all-cause mortality.

**Keywords:** Chondrosarcoma, Amputation, Survival, Limb, SEER, Oncology.

## INTRODUCTION

Chondrosarcoma (CHS) is the third most common primary bone cancer, often presenting during middle-to-late adulthood.[1] The commonality amongst its subtypes is the secretion of a cartilaginous matrix by the cells comprising the tumor.

There is a lack of insight on pathogenesis which poses a major challenge to the development of effective targeted therapy. Surgery has been established as the primary intervention to treat CHS, as the cancer exhibits poor responsiveness to radiation and chemotherapy.[2] Certain subtypes, including mesenchymal and dedifferentiated CHS are sometimes treated with adjuvant chemotherapy, however this remains controversial.[3]

For tumors within the limb, health-care providers must weigh between limb amputation (LA) or performing limb-salvage surgery (LSS) to achieve sufficient tumor resection. As treatment and imaging modalities have become increasingly advanced, the use of LSS has become increasingly feasible in the management of extremity bone sarcomas, while the use of amputation has declined.[4]

Differences between the efficacy of LSS and LA have been researched extensively for the management of osteosarcoma, however few studies have assessed long-term outcomes for the two procedures in CHS.

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As CHS is a unique primary bone malignancy, it is imperative to expand research efforts that analyze treatment outcomes for this disease; improved insight may directly influence clinical practices and subsequent outcomes. We conducted a retrospective survival analysis of patients with primary CHS that underwent LSS and LA between 2000-2010 using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database.

## MATERIALS AND METHODS

### Ethical Statement

The UTMB Institutional Review Board reviewed this project on December 6, 2018 and determined that this submission did not meet the definition of human subject research. Therefore, this study did not require IRB approval or oversight.

### Data Source

Data was extracted from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database. The SEER program has collected population-based tumor data and cancer statistics since 1973. The specific registry used was titled 'Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (1973-2015 varying)'.[5]

A total of 2,962 cases of CHS were identified between 2000-2010 using the SEER recommended AYA Site Recode/WHO 2008 code "4.2 Chondrosarcoma". Only first primary tumor patients (2,588/2,962) were included. Tumors within the limb (1,052/2,588) were identified using SEER primary site codes: C40.0 long bones: upper limb, scapula and associated joints; C40.1 short bones: upper limb, scapula and associated joints; C40.2 long bones of the lower limb and associated joints; C40.3 short bones of the lower limb and associated joints; C40.9 Bone of Limb, NOS. Pelvic chondrosarcomas were excluded from this study. Patients treated with the following surgical codes were included: "40 - amputation of limb", "41- partial amputation of limb", "42 – total amputation of limb" as LA (104/1,052), and "30 – radical excision or resection of lesion with limb salvage" as LSS (446/1,052).

### Covariates

Extracted cohort data included patient demographic, tumor characteristic, treatment and survival variables. Demographic variables included age, sex and race. Multiple tumor characteristic variables were extracted to account for CHS subtype variability including: ICD-O-3 histologic subtype, primary site, grade, summary stage and laterality. Treatment variables included radiation and chemotherapy use.

### Statistical Analysis

Patients were categorized based off surgery type (LSS or LA) for analysis. Fisher exact test was used to compare demographic, tumor characteristic and treatment data between the two groups. Overall survival (OS) and cause-specific survival (CSS) times were compared using univariate Kaplan Meier analysis. Multivariate cox-regression analysis was then performed to compare all-cause and malignancy-related mortality risk based off surgery type, with LSS patients serving as reference. Multivariate cox regression models adjusted for the following covariates: age, race, sex, histology, limb level, grade, summary stage, laterality, use of radiation and chemotherapy. A p-value < .05 was used to assess statistical significance for all tests. Two authors (AL, TA) independently conducted the statistical analysis to ensure the accuracy of calculations. Statistical analysis was conducted using the computational statistical software IBM SPSS (Statistical Package for the Social Sciences) Statistics version 25.

## RESULTS

### Cohort Description

A total of 550 patients met the inclusion criteria for this study. Average follow-up time for the cohort was 93.14 months (SD, 55.02) Of these cases, 18.9% (104/550) underwent LA, and 81.1% (446/550) underwent LSS. Patients were mostly 40 years old or older (73.6%), male (52.9%), with a white racial background (87.3%). Fisher test showed a statistically significant difference in primary site (p = .005), grade (p = .026) and summary stage (p < .001) between the two treatment groups. Age (p = .106), sex (p = .063), race (p = .446), laterality (p = .207), histology (p = .702), radiation use (p = .800) and chemotherapy use (p = .456) did not significantly differ between treatment groups. Group differences in primary site, grade and summary stage variables are shown in table 1.

**Table 1:** Primary Site, Tumor Grade, and Summary Stage Characteristics Based off Surgery Type

| | | Surgery Type | | | | |
|---|---|---|---|---|---|---|
| | | LSS | | LA | | Exact Test |
| | | N | % | N | % | *p* |
| Primary Site | Lower Limb | 293 | 65.7 | 76 | 73.1 | 0.005 |
| | Upper Limb | 152 | 34.1 | 25 | 24 | |
| | Bone of Limb - Unspecified | 1 | 0.2 | 3 | 2.9 | |
| Grade | Grade I | 146 | 32.7 | 20 | 19.2 | 0.026 |
| | Grade II | 157 | 35.2 | 41 | 39.4 | |
| | Grade III | 66 | 14.8 | 17 | 16.3 | |
| | Grade IV | 44 | 9.9 | 19 | 18.3 | |
| | Unknown | 33 | 7.4 | 7 | 6.7 | |
| Summary Stage | Local | 176 | 39.5 | 18 | 17.3 | < .001 |
| | Regional Extension | 93 | 20.9 | 34 | 32.7 | |
| | Distant | 24 | 5.4 | 11 | 10.6 | |
| | Unknown | 153 | 34.3 | 41 | 39.4 | |

Primary site (*p* = .005) differed significantly between surgical groups, with a greater proportion of upper limb cases treated with LSS. Grade (*p* = .026) also differed between the two groups with a greater proportion of low grade tumors treated with LSS and high grade (III and IV) treated with LA. Lastly, summary stage (*p* < .001) differed significantly between the two groups with a greater proportion of LSS cases being local lesions.

**Table 2:** Mean Survival Time Based off Surgery Type via Kaplan Meier Analysis

| | Surgery Type | Mean (months) | Standard Error | 95% Confidence Interval | | *p*-value |
|---|---|---|---|---|---|---|
| Overall Survival | LSS | 144.518 | 3.534 | 137.59 | 151.445 | < .001 |
| | LA | 107.278 | 7.95 | 91.697 | 122.86 | |
| | Overall | 137.685 | 3.301 | 131.216 | 144.155 | |
| Cause-Specific Survival | LSS | 153.244 | 3.383 | 146.613 | 159.876 | 0.003 |
| | LA | 128.245 | 8.118 | 112.333 | 144.156 | |
| | Overall | 148.972 | 3.167 | 142.764 | 155.18 | |

Overall mean survival times significantly differed based off surgery type, with LA patients experiencing roughly a 3-year shorter mean survival time (*p* < .001) compared to LSS patients. With regard to CSS, LA patients experienced a significantly lower mean survival time of roughly 2 years (*p* = .003) compared to LSS patients.

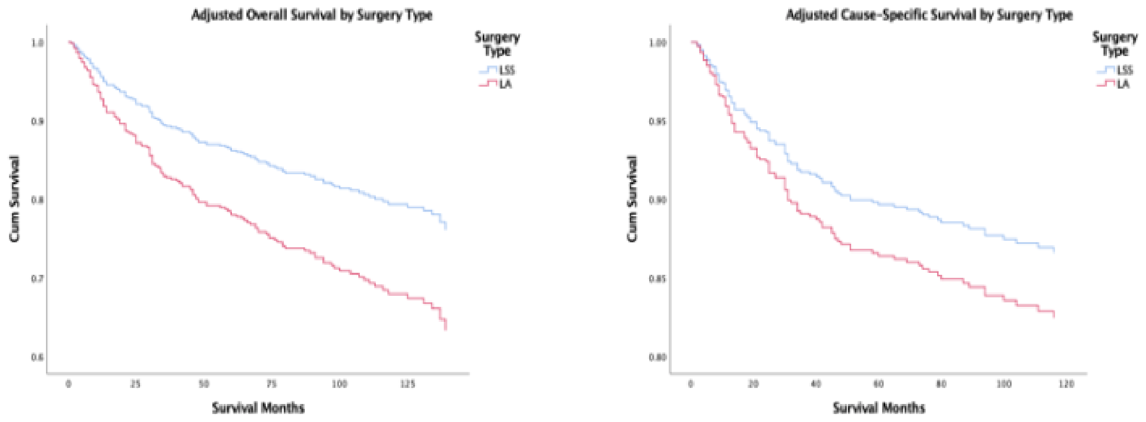


**Figure 1:** 10-Year Overall and Cause Specific Survival Curves Comparing Surgery Type

**Survival Analysis**

Kaplan Meier log-rank test showed that OS (p < .001) and CSS (p = .003) survival times differed significantly based off surgery type. These are displayed in table 2.

Upon adjustment for age, race, sex, ICD-O-3 histology, primary site, grade, summary stage, laterality, use of radiation and use of chemotherapy, all-cause mortality risk was significantly higher (HR, 1.672; 95% CI, 1.177, 2.374; p = .004) for patients treated with LA as compared to LSS via multivariate cox regression. However, malignancy-related mortality risk (HR, 1.341; 95% CI, .884, 2.032; p = .167) did not significantly differ between LA and LSS treatment groups. 10-year OS and CSS curves are depicted in figure 1.

**DISCUSSION**

Although a rich volume of literature exists on limb sarcomas and the comparative outcomes of LSS and LA, specific analyses of CHS surgical outcomes are scant and mostly limited to small sample studies. Such analysis of CHS often proves difficult, as the tumor grading and characterization for this group of malignancies limits grouped analysis. Our study utilized recommended tumor codes to identify CHS, and multiple controls for CHS variability to conduct a large and effective analysis of outcomes. Large cohort studies are beneficial in analyzing survival following these wide excision procedures that have gained favor in more recent years.

In our study, Kaplan-Meier analysis found that survival times differed between LSS and LA groups. However, multivariate cox regression showed that LA patients had a significantly higher overall mortality risk (p = .004), but no difference in disease-specific mortality risk (p = .167) compared to LSS patients. Because the disease-specific mortality risk did not differ upon covariate adjustment, the CSS differences from Kaplan-Meier analysis cannot be attributed solely to surgery type.

Our analysis suggests that LSS and LA techniques have similar efficacy in terms of malignancy-related survival. The reason for this may be that both procedures totally remove the tumor from the affected limb achieving similar resection margins. The surgeries differ, however, in that LSS will spare the limb, and LA will not. This may in part explain why there is a difference in all-cause mortality; the morbidities associated with limb loss may be more than those with limb preservation due to decreased functional outcomes post-operatively. While the literature regarding these procedures in CHS cases is limited, majority of studies strictly comparing the two procedures have shown increased or equivalent functional outcomes and patient satisfaction in those treated with LSS. [6-10] While these factors require further study, our study suggests that patients treated with limb removal via surgical amputation have poorer health overall, resulting in higher mortality risk from all-causes.

In terms of surgical management of CHS, NCCN guidelines suggest wide excision achieved by either LSS or LA. [11] Generally, LA is reserved for cases in which LSS is contraindicated. [12] A study evaluating CHS patients found no difference between limb-preserving surgery and amputation in either overall or cause-specific survival. [13] However, this study did not restrict its sample to cases within the limb. Our study offers unique insight regarding surgical protocols and their outcomes related to limb tumors specifically, rather than grouping analysis with tumor sites such as the pelvis. Nearly all other studies comparing these two procedures are not specific to CHS, but rather group different neoplasms in their analysis. Many of these studies showed no difference in overall or disease-free survival between LSS and LA. [9,14,15] In other studies, non-CHS sarcomas were treated with the use of adjuvant therapy in conjunction with LSS in order to optimize long-term survival. [12,16] Chondrosarcoma is unique, as previously mentioned, in that it is largely resistant to chemoradiation. Therefore, it is difficult to extrapolate outcomes to CHS cases specifically given its distinct treatment considerations.

To our knowledge, this study is one of the largest to compare long-term outcomes of LSS and LA in CHS patients. It aligns with the current notion that LSS is the preferred technique whenever possible for wide-based tumor resection. Providing CHS specific data is critical to verify current practice and guidelines with the goal of optimizing patient outcomes. Our study offers prognostic insight to health-care providers and patients in regard to long-term implications of these surgical procedures.

In conducting our analysis, we encountered some limitations. First, whereas a randomized control study is often the preferred design to compare two treatment methodologies, our study utilizes a retrospective approach. However, our retrospective approach offers valuable insight by maximizing sample size and cohort comparability in our analysis. Second, we extracted our sample from a database, which limited us to the variables and outputs provided by the registry. As a result, we were unable to distinguish exact primary sites within the limb, specific measurements of amputation extent or functional measurements of patients following treatment. We controlled for this however, by grouping tumors as upper or lower limb and using the most specific site codes available to select cases. Specific functional measurements are not reported in the SEER database and therefore could not be assessed; however, this warrants future research that assesses differences in long-term functional outcomes between the two procedures in CHS patients. Third, the AYA/WHO 2008 definition of CHS included multiple histologies which can differ in behavior, response to treatment and aggressiveness. In this study, histologic subtypes did not statistically differ between the two groups, and were controlled for along with grade, summary stage, primary site, and use of adjuvant therapy to account for any variability. Lastly, outputs were missing or unknown for certain variables. This did not impact the majority of variables with the exception of tumor summary stage. In order to mediate this, these outputs were placed in one group for descriptive tests and also adjusted for along with the tumor characteristic factors previously mentioned. The grouping of none and unknown status for adjuvant therapy in SEER should not compromise the utility of our analysis due to low responsiveness in CHS, and because any differences were also adjusted for during calculation.

## CONCLUSION

In patients with CHS of the limb, those who undergo LA possess an increased all-cause mortality risk compared to those who undergo LSS, however, the choice of LSS or LA does not affect malignancy-related mortality risk. Either procedure is therefore effective at adequately resecting the tumor and the intervention does not independently influence cancer-related prognosis. However, a limb salvage approach may allow for better functional preservation, patient perception and quality of life compared to amputation; leading to better overall health and subsequent survival from other diseases. These findings are important clinically as they improve prognostic insight and health risk assessment for Chondrosarcoma patients following these major surgical procedures. Future research should explore further the functional outcomes and morbidities related amputation that contribute to poorer overall survival in these patients.

### Contribution to Existing Knowledge

It is current knowledge that malignancies of the limb, particularly osteosarcoma, can be effectively managed with limb-salvage surgery instead of amputation if sufficient resection margins are possible, however limited studies have described comparative outcomes in chondrosarcoma patients. This study adds to the current knowledge by demonstrating that both procedures are also equally effective for resection of chondrosarcomas, but that the overall health of amputees may be poorer in the long run compared to patients with a preserved limb. Our findings uncover that amputees may have additional challenges and potentially unmet care needs leading to poorer overall health outcomes compared to patients with a salvaged limb.

### Conflicts of Interest

Disclosures: The authors of this study have no conflicts of interest to disclose.

### Author Contribution

1. Talha Ayaz, BS – This author contributed to the original conception and design of the study and contributed to data extraction, statistical analysis/interpretation and manuscript drafting. Approved final version to be published.

2. Adil Shahzad Ahmed, MD - This author contributed by helping refine the study methodology, conducting literature review and revising the manuscript critically using intellectual content. Approved final version to be published.

3. Asad Loya, BS - This author contributed to the study by assisting with data extraction and performing statistical analysis. Approved final version to be published.

4. Vinod Kumar Panchbhavi, MD, FACS - This author served as the senior author for the study and assisted in all aspects of the project ranging from project conception, study methodology development, interpretation of data and providing oversight on the drafting of a manuscript. Approved final version to be published.


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