Impact of limb salvage versus amputation on overall survival in patients with osteosarcoma of the extremities: an update in the modern era using the National Cancer Database

Daniel R. Evans
Duke University School of Medicine
Alexander Lazarides (alexander.lazarides@duke.edu)
Duke University Hospital
Julia D. Visgauss
Duke University Hospital
Jason A. Somarelli
Duke University Hospital
Dan G. Blazer III
Duke University Hospital
Brian E. Brigman
Duke University Hospital
William C. Eward
Duke University Hospital

Research article

Keywords: Limb salvage surgery; amputation; osteosarcoma; osteosarcoma of the extremities; overall survival

Posted Date: March 27th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-18262/v1

Version of Record: A version of this preprint was published on October 14th, 2020. See the published version at https://doi.org/10.1186/s12885-020-07502-z.

Abstract

Background: Historically, amputation was the primary surgical treatment for osteosarcoma of the extremities; however, with advancements in surgical techniques and chemotherapies limb salvage has replaced amputation as the dominant treatment paradigm. This study assessed the impact of the type of surgical resection on overall survival in the era of modern limb salvage.

Methods: Utilizing the largest registry of primary osteosarcoma, the National Cancer Database (NCDB), we retrospectively analyzed patients with high grade osteosarcoma of the extremities from 2004 through 2015. Unadjusted five-year overall survival between patients who received limb salvage and amputation was assessed utilizing Kaplan Meier curves. A multivariate Cox proportional hazard model and propensity matched analysis was used to determine the variables independently correlated with survival.

Results: From a total of 3,421 patients, 2,634 underwent limb salvage and 787 underwent amputation. After controlling for confounders, limb salvage was associated with a significant survival benefit over amputation (HR: 0.70; $p<0.001$). This survival benefit remained significant after propensity matched analysis of all significantly different independent variables (HR: 0.74; $p=0.001$). Chemotherapy and negative surgical margins were also independently associated with survival.

Conclusion: Limb salvage is associated with a significant survival benefit over amputation, even when controlling for potentially confounding variables and differences between cohorts.

Background

Osteosarcoma is an aggressive bone cancer and the most common primary malignancy of bone.[1–4] A cancer that was previously considered a death sentence, improvements in chemotherapeutic and surgical treatment have dramatically improved five year overall survival for non-metastatic osteosarcoma from 22% in 1950 to 70% presently.[4–6] The previous gold standard for surgical treatment was amputation; however, with advances in surgical procedures and chemotherapeutic agents, limb salvage has become a possibility.[5, 6] In 1984, the National Institute of Health deemed limb salvage an equal treatment option to amputation, leading to some debate as to which procedure was the more effective treatment.[7] Although limb salvage offers both cosmetic and functional advantages, no consensus exists on whether limb salvage results in clinical survival benefits.[6–8]

Efforts to establish the benefits of limb salvage over amputation have yielded conflicting results in relation to survival, functional recovery, and psychological effects.[6, 7] Due to the rarity of osteosarcoma, many of the studies are low quality, have had small sample sizes, assess different outcome variables, and have limited scopes, all of which have restricted our ability to perform effective meta-analyses. Existing meta-analyses[6, 9] that have been performed have found that limb salvage improved survival; however, all of these analyses remain limited by low study numbers and sample sizes, and there is a continued need for studies that leverage larger data sets.

The National Cancer Database (NCDB) is a clinical oncology database that captures 70% of all new cancer diagnoses in the United States.[10] While osteosarcoma is rare, this database provides an opportunity to better investigate this cancer with adequate sample size while better controlling for confounders by normalizing variables and outcomes across cohorts.[10] In the present study we used the National Cancer Database to determine if there is a difference in survival in patients that receive radical resection (i.e. limb salvage surgery) versus those that receive amputation for osteosarcoma. We hypothesized that patients undergoing limb salvage in the modern era would experience increased overall survival versus amputation even when controlling for potentially confounding variables.

Methods

Study Cohort:

We retrospectively queried the NCDB for all osteosarcoma cases between 2004 and 2015. Cases met inclusion criteria if they had the following features: (1) undergone surgical resection or amputation for osteosarcoma; 2) osteosarcoma was the primary cancer; 3) the primary tumor site was in the extremities; 4) and had histological diagnosis with a histological grade of 3 or greater (*Figure 1)*.. Cases were excluded that had incomplete or missing treatment data. Patients were also excluded that did not undergo radical resection or amputation.

Variables:

The demographic factors we considered included age, sex, race, insurance status, Zip code income quartile, Zip code educational quartile, rural/urban, distance from hospital in miles, and year of diagnosis. Age was considered as both a continuous and categorical variable, which was split into three categories (<18, 18–40, >40). Race was classified as Caucasian, African-American, Latinx/Hispanic, Asian/Pacific Islander, and other. Insurance status was classified as uninsured, insured, Medicaid, and Medicare. Year of diagnosis was parsed into before 2006, 2006–2010, and 2011–2015. Clinicopathological factors included American Joint Commission on Cancer (AJCC) clinical stage at diagnosis, upper/lower extremity, long/short bone, tumor size (cm), metastases at diagnosis, comorbidities at diagnosis, adjuvant chemotherapy, chemotherapy/surgery treatment sequence, surgical margins, unplanned readmission after surgery, length of inpatient stay after surgery, days from diagnosis to surgery, and number of days from diagnosis to treatment commencing. The primary outcome of interest was overall survival (OS).

Statistical Analysis:

Utilizing site-specific surgical codes, patients were separated into the following two study arms: 1) those who received radical resection with limb salvage and 2) those who received amputation. The demographic and clinicopathologic characteristics of study arms were compared using a student's T-test for continuous variables and Chi^2 for categorical variables. Unadjusted overall survival (OS) was estimated using the Kaplan Meier method, with statistical comparisons based on the log-rank test.

Univariate analyses to test for statistically robust associations between OS and patient demographic, clinical, and treatment were assessed via Kaplan Meier; using the log rank test if categorical or a univariate Cox regression if continuous. A multivariate Cox proportional hazard model was then used to determine OS adjusted to control for significant differences between study groups and potential confounding. Demographic and clinicopathological variables of age, sex, insurance status, upper/lower limb location, AJCC stage, tumor size, metastases at diagnosis, comorbidities, surgical margins, and adjuvant chemotherapy were potential confounders and were controlled for in the multivariate Cox analysis and were used to create the matched propensity score analysis. To account for clinician selection bias between study arms a logit matched propensity score analysis was used to match the two study arms on all demographic and clinicopathological variables that were significantly different, with a caliper distance of less than 0.1 standard deviations. A Cox regression was then used to analyze the hazard ratio of the matched cohorts.

Ethical Approval:

Ethical approval was granted by the Duke IRB Pro00045337. Statistical analyses were conducted using STATA 15 and statistical significance was determined at a p-value < 0.05.

Results

Cohort Characteristics:

A total of 3,421 patients met the inclusion criteria. The patient cohort had a median age of 17 (IQR 13 – 30), and a majority (59.8%) of the patients were male. Average tumor size was 11.5 cm (11.1—11.8cm) with metastases present in 489 (14.3%) of the patients. Of the patients that met the inclusion criteria, 2,634 patients underwent a radical resection while 787 patients underwent an amputation.

There were significant demographic and clinicopathological differences between study arms. Demographically, patients that underwent amputation were significantly more likely to be older, male, uninsured, and live in lower income Zip codes (p</ = 0.004) (*Table 1)..* Clinicopathologically, patients that underwent amputation were significantly more likely to have an earlier year of diagnosis, later stage osteosarcoma, larger tumors, metastases and comorbidities at diagnosis, not receive adjuvant chemotherapy, and have negative surgical margins (p</ = 0.023) (*Table 2)..* The incidence of limb salvage vs amputation increased over the study period (*Figure 2)..*

Univariate Survival Analysis:

Unadjusted univariate Kaplan Meier and Cox analyses found a significant difference in OS between study arms (log rank p<0.001). The five-year overall survival rates were 67.8% and 53.7% for limb salvage and amputation, respectively. The unadjusted hazard ratio for amputation was 1.667 (p<0.001).

On univariate analysis improved survival after limb salvage was significantly associated with patients that were younger, female, insured, with lower AJCC stage, smaller tumor size, no metastases, no comorbidities, had received chemotherapy, had negative surgical margins and a shorter time from diagnosis to treatment commencing (p</ = 0.040). Improved survival after amputation was significantly associated with patients who were younger, from a higher income zip code, insured, had a lower AJCC stage, osteosarcoma of the short bones or the lower limb, smaller tumor size, no metastases, no comorbidities, received chemotherapy, and a shorter time from diagnosis to surgical treatment (p</ = 0.038).

Multivariate Survival Analysis:

When controlling for potentially confounding variables, a multivariate Cox analyses found a significant difference in OS between study arms favoring limb salvage, with a hazard ratio of 1.41 (p<0.001) for amputation, indicating a detriment on survival. This survival benefit persisted even when controlling for metastases at diagnosis and differences in treatment and tumor characteristics between patients. Across all patients, when controlling for confounding variables, improved overall survival was associated with patients that were younger (p<0.001), female (p = 0.003), received adjuvant chemotherapy (p = 0.003), had a lower AJCC stage (p<0.001), smaller tumor size (p<0.001), negative surgical margins (p = 0.001), and had no metastases at diagnosis (p<0.001).

Propensity Score Matched Survival Analysis:

An analysis was performed controlling for the likelihood of patients to receive certain treatments based on their specific demographics and tumor characteristics. A matched propensity score analysis demonstrated improved survival with limb salvage, having a five-year overall survival treatment benefit of 10.7% (5.4—16.0%; p < 0.001) (*Figure 3)*.. Cox regressions adjusted by linear matched propensity score also revealed similar results with a hazard ratio of 1.35 (p < 0.001) for amputation. Within the propensity score matched cohort improved survival was significantly associated with patients that were younger, lower AJCC stage, had osteosarcoma of the short bones or the lower limb, smaller tumor size, no metastases, and received adjuvant chemotherapy (p</ = 0.001) (*Table 3)*..

Discussion

The advent of multi-agent chemotherapy revolutionized the care of osteosarcoma patients and made limb salvage a possibility. However, there exists no data on the current state of amputation vs. limb salvage and its impact on survival. Our study provides a modern update to the question of the impact of amputation vs. limb salvage on overall survival in patients with high grade osteosarcoma. We found that limb sparing resection rather than amputation was found to be significantly associated with improved five-year overall survival in univariate, multivariate, and matched propensity core adjusted multivariate

analyses. On matched propensity score adjusted multivariate analyses receiving limb sparing resection rather than amputation was associated with significantly improved five-year overall survival, with a treatment benefit of 10.9%.

Historically, limb salvage surgery with chemotherapy was viewed as an equivalent surgical option to amputation with regards to overall survival. A seminal study by Rougraff et al. investigated 227 patients with nonmetastatic high grade osteosarcoma in a multicenter retrospective review [11]. They found that, compared with amputation, limb salvage resulted in higher rates of reoperation and a higher functional outcome without affecting long-term survival. These findings were supported by a study from Bacci et al. investigating 560 patients with osteosarcoma of the extremities and found no difference in survival between patients treated with limb salvage vs. amputation, finding instead that response to chemotherapy and surgical margins were a much better predictor of local recurrence and overall survival [12]. They concluded that limb salvage is safe at institutions where patients will undergo margin negative surgery with appropriate adjuvant therapies.

A recent study that was published by Traven et al [13] indicated that, in a propensity matched analysis, amputation was associated with significantly worse survival compared to limb salvage surgery, with a hazard ratio of 1.7 for amputation. Their study similarly utilized advanced statistics to help control for factors that are possible confounders, specifically the propensity to receive certain treatments based on tumor and patient characteristics. Additionally, the SEER database allows for investigation of disease specific survival, an important consideration that is not available in the NCDB. However, there are a number of limitations with this study and many questions remain unanswered. The SEER database only captures 30% of new cancer diagnoses, a factor that raises the concern that this study does not represent the population as a whole. The final study cohort of limb salvage and amputation patients included only 2,820 patients. In contrast, the NCDB captures over 70% of new cancer diagnoses annually with strict follow-up requirements. Additionally, information about treatment specifics, an important consideration for patients with osteosarcoma, is limited in the SEER database. Finally, and perhaps most importantly, the SEER database includes data ranging from 1975- 2016; nearly 60% were inadequately staged and had a grade of “unknown.” Without proper exclusion, this introduces a significant confounding variable, as it stands to reason that the state of cancer care, supportive measures and technical skill has improved between 1975 and 2016. Taken together, these limitations indicate additional studies are required to understand the modern impact of limb salvage surgery versus amputation on survival.

The most important finding in our study of 3,421 patients with high grade osteosarcoma was that amputation was approximately 1.4 times more likely to result in mortality than limb salvage in our propensity matched analysis. These findings are similar to those of Traven et al [13]. Importantly, our study represents the most modern cohort to date, capturing patients from 2004 to 2015. While consistent with the results of Traven et al. these findings differ from the findings of many of the early studies investigating limb salvage and amputation, which demonstrated no difference in survival between the two groups [11, 12]. While it is notable that limb salvage carries a survival benefit, it is important to note that these findings do not imply causation and that there may be factors attributable to this survival

benefit, particularly as patients undergoing amputation are likely to be sicker and have larger tumors, factors that certainly impact survival. This also begs to the question of how to contextualize this information into modern clinical practice. We suggest that, when possible, limb salvage remains the gold standard of care for patients undergoing management for osteosarcoma of the extremities and does not appear to have a detrimental association with survival. Amputation should be chosen if patient and clinical factors make a favorable outcome with LSS unlikely; the mainstay of all conversations around the surgical management of osteosarcoma should involve a patient centered approach discussing the risks and benefits of each surgical option as well as expected functional outcomes and possible complications. As a part of this conversation, physicians may include that modern limb salvage techniques may be associated with improved survival overall.

In addition to corroborating the potential clinical benefit of limb salvage our study also confirms the importance of chemotherapy, which was found to be a protective factor in a multivariate analysis. Conversely, positive margin status was found to be a negative predictor of outcome in a multivariate analysis. The importance of good chemotherapeutic response and margin-negative surgery in the treatment of high-grade osteosarcoma has been well established in the literature [12, 14, 15]. We also found that low tumor grade and lower AJCC staging was also prognostic for improved overall survival. These factors have similarly been previously demonstrated as important prognostic factors for survival in osteosarcoma [16, 17]. Interestingly, female gender was similarly found to a favorable prognostic factor, results which are in concordance with prior studies.[18, 19] Taken as a whole, these findings affirm the importance of these factors in the management and treatment of high-grade osteosarcoma.

While this study provides important support as to the modern state of limb salvage surgery versus amputation, it is not without its own limitations. Importantly, this is a retrospective database review. The quality of the database is only as strong as the quality of the data entry. It should be noted that the NCDB employs advanced quality screening metrics and mandates that contributing centers maintain at least 70% follow-up. Nonetheless, it is possible the data is inputted inaccurately. Additionally, the retrospective nature of this database cannot imply causation and is inherently subject to selection bias and possible confounding biases not otherwise addressed in this study. This is notable limitation as there are limits to the granularity of the data available in the NCDB. It stands to reason that there are tumor and patient specifics that contribute to the decision for amputation vs. LSS that simply cannot be captured by the basic socioeconomic and tumor/ treatment variables noted in this database. For instance, it stands to reason that patients with extensive neurovascular involvement, poor chemotherapeutic response or for whom life expectancy is not expected to be very long may be precluded from receiving LSS. Despite this, we made every limitation to control for the variables available and provide the most robust data analysis possible using propensity matched methods. Another limitation of the NCDB is that it does not include data about local recurrence or disease-specific survival. This is an important consideration when discussing amputation vs. local recurrence and must be acknowledged, particularly as multiple prior studies have suggested an increased risk of local recurrence with limb salvage [11, 20–22]. Finally, the NCDB lacks specifics regarding resections, such as neurovascular involvement or response to chemotherapy; these may be important considerations in the decision-making towards limb salvage.

Nonetheless, we feel that this study is an important update as to the current state of surgical intervention for osteosarcoma; multivariate and propensity score matched statistics were used help control for the retrospective nature of the study and potentially confounding variables to better identify the true impact of limb salvage on overall survival vs. amputation.

Conclusions

Using the largest modern patient cohort to date, this study suggests that patients with high grade osteosarcoma undergoing limb salvage surgery may demonstrate improved survival as compared to amputation, even when controlling for confounding variables and propensity to receive certain treatments. This study also confirms the importance of chemotherapy and negative surgical margins in the treatment of osteosarcoma. Further investigation is necessary to help inform proper decision- making so surgeons can ensure appropriate utilization of limb salvage surgery.

Declarations

Abbreviations

NCDB: National Cancer Database; SEER: National Cancer Institute's Surveillance, Epidemiology and End Results; OS: Overall Survival; AJCC: American Joint Commission on Cancer

Ethics approval

Our study received Institutional Review Board approval (Pro00045337) from our institution.

Consent to participate

No consent to participate was necessary. This study was deemed exempt as above

Availability of data and material

The data and materials supporting our findings is maintained by the national cancer database; the data is stored securely, but is publicly accessible by any group affiliated with a Fellow of the American College of Surgeons applying and wishing to gain access. More information may be found at: http://ncdbpuf.facs.org/.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was obtained for this study.

Authors' contributions

DE and AL identified the question, were responsible for study design and manuscript preparation. DE performed statistical analyses. JV, JS, DB, BB, WE provided study oversight and helped to draft/ revise the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The data used in this study are derived from a de-identified National Cancer Data Base file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigators.

References

1.Mirabello, L., R. J. Troisi, and S. A. Savage, *International osteosarcoma incidence patterns in children and adolescents, middle ages and elderly persons.* International journal of cancer, 2009. *125(*1): p. 229–234.

2.Ottaviani, G. and N. Jaffe, *The epidemiology of osteosarcoma,* in *Pediatric and adolescent osteosarcoma.* 2009, Springer. p. 3–13.

3.Howlader N, N. A., Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). *SEER Cancer Statistics Review, 1975–2016.* 2019, National Cancer Institute. Bethesda, MD.

4.Misaghi, A., et al., *Osteosarcoma: a comprehensive review.* SICOT-J, 2018. *4:* p. 12–12.

5.Li, X., et al., *Impact of close surgical margin on local recurrence and survival in osteosarcoma.* International orthopaedics, 2012. *36(*1): p. 131–137.

6.Li, X., et al., *A comparative study between limb-salvage and amputation for treating osteosarcoma.* Journal of bone oncology, 2016. *5(*1): p. 15–21.

7.Veth, R., et al., *Limb salvage in musculoskeletal oncology.* The Lancet Oncology, 2003. *4(*6): p. 343–350.

8.Mei, J., et al., *Functional outcomes and quality of life in patients with osteosarcoma treated with amputation versus limb-salvage surgery: a systematic review and meta-analysis.* Arch Orthop Trauma Surg, 2014. *134(*11): p. 1507–16.

9.He, X., et al., *A meta-analysis of randomized control trials of surgical methods with osteosarcoma outcomes.* Journal of orthopaedic surgery and research, 2017. *12(*1): p. 5.

10.Bilimoria, K. Y., et al., *The National Cancer Data Base: a powerful initiative to improve cancer care in the United States.* Annals of surgical oncology, 2008. *15(*3): p. 683–690.

11.Rougraff, B. T., et al., *Limb salvage compared with amputation for osteosarcoma of the distal end of the femur. A long-term oncological, functional, and quality-of-life study.* J Bone Joint Surg Am, 1994. *76(*5): p. 649–56.

12.Bacci, G., et al., *Osteosarcoma of the limb. Amputation or limb salvage in patients treated by neoadjuvant chemotherapy.* J Bone Joint Surg Br, 2002. *84(*1): p. 88–92.

13.Traven, S. A., et al., *A propensity-score matched analysis of limb salvage vs amputation for osteosarcoma.* J Surg Oncol, 2019.

14.Reddy, K. I., et al., *Does amputation offer any survival benefit over limb salvage in osteosarcoma patients with poor chemonecrosis and close margins?* Bone Joint J, 2015. *97-B(*1): p. 115–20.

15.Bertrand, T. E., et al., *Do Surgical Margins Affect Local Recurrence and Survival in Extremity, Nonmetastatic, High-grade Osteosarcoma?* Clin Orthop Relat Res, 2016. *474(*3): p. 677–83.

16.Petrilli, A. S., et al., *Increased survival, limb preservation, and prognostic factors for osteosarcoma.* Cancer, 1991. *68(*4): p. 733–7.

17.Bramer, J. A., et al., *Prognostic factors in localized extremity osteosarcoma: a systematic review.* Eur J Surg Oncol, 2009. *35(*10): p. 1030–6.

18.Smeland, S., et al., *Scandinavian Sarcoma Group Osteosarcoma Study SSG VIII: prognostic factors for outcome and the role of replacement salvage chemotherapy for poor histological responders.* Eur J Cancer, 2003. *39(*4): p. 488–94.

19.Whelan, J. S., et al., *Survival from high-grade localised extremity osteosarcoma: combined results and prognostic factors from three European Osteosarcoma Intergroup randomised controlled trials.* Ann Oncol, 2012. *23(*6): p. 1607–16.

20.Han, G., et al., *Amputation Versus Limb-Salvage Surgery in Patients with Osteosarcoma: A Meta-analysis.* World J Surg, 2016. *40(*8): p. 2016–27.

21.Tsuchiya, H. and K. Tomita, *Prognosis of osteosarcoma treated by limb-salvage surgery: the ten-year intergroup study in Japan.* Jpn J Clin Oncol, 1992. *22(*5): p. 347–53.

22.Springfield, D. S., et al., *Surgical treatment for osteosarcoma.* J Bone Joint Surg Am, 1988. *70(*8): p. 1124–30.

Tables

Due to technical limitations, Tables 1 - 3 are only available for download from the Supplementary Files section.

Figures

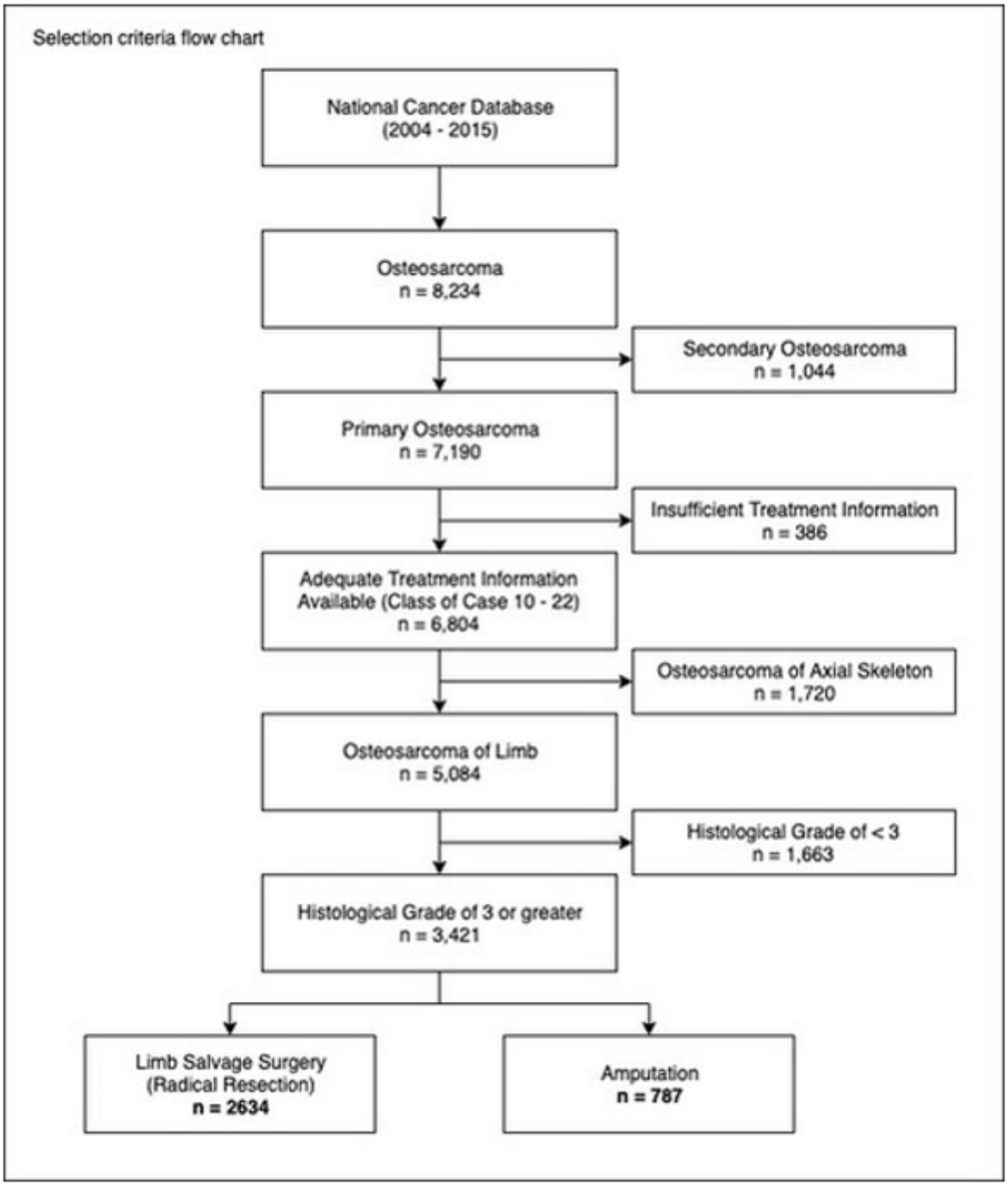

Figure 1

Flow chart demonstrating the selection criteria for patients included in this study

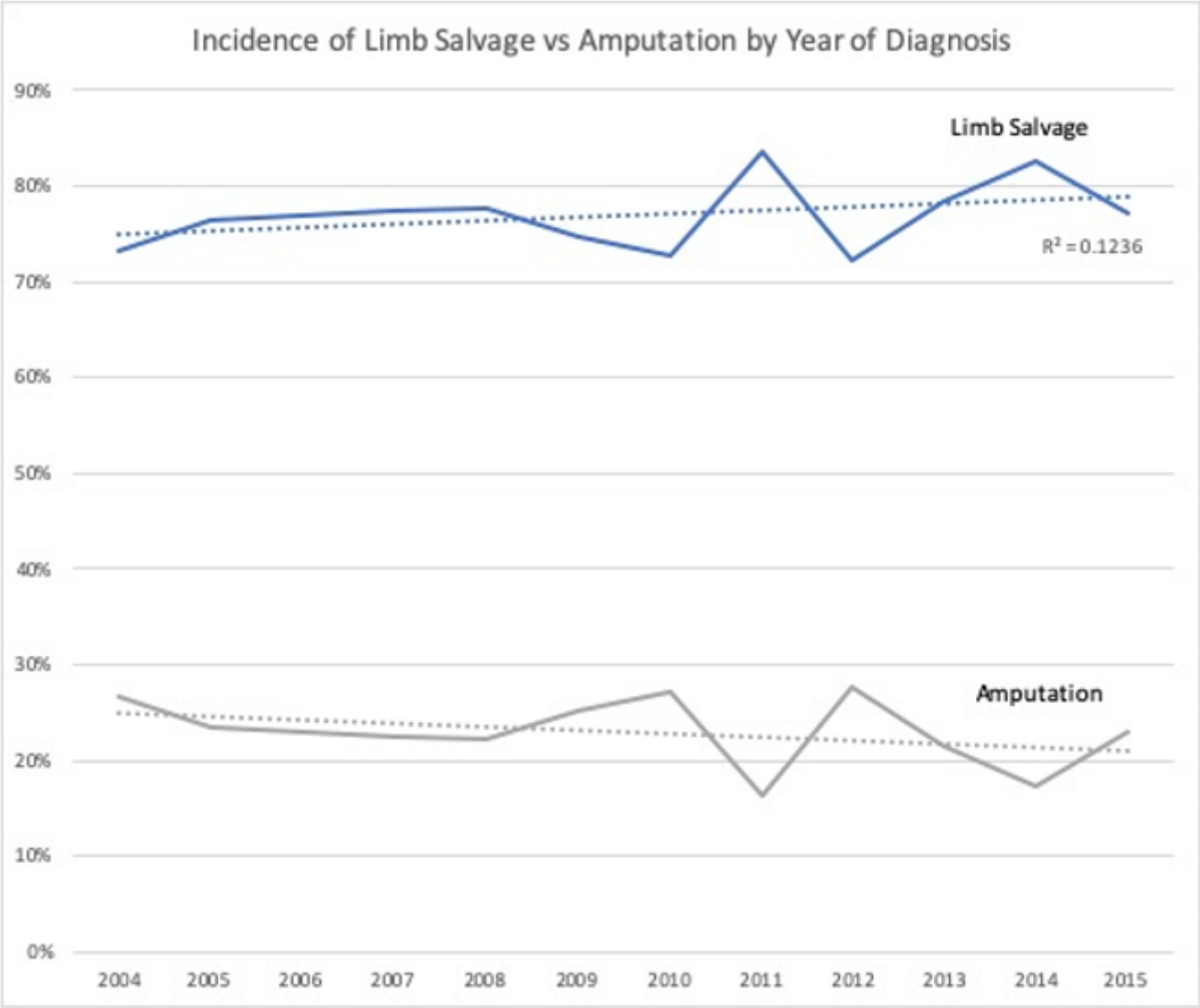

Figure 2

Incidence of limb salvage vs amputation over the study period

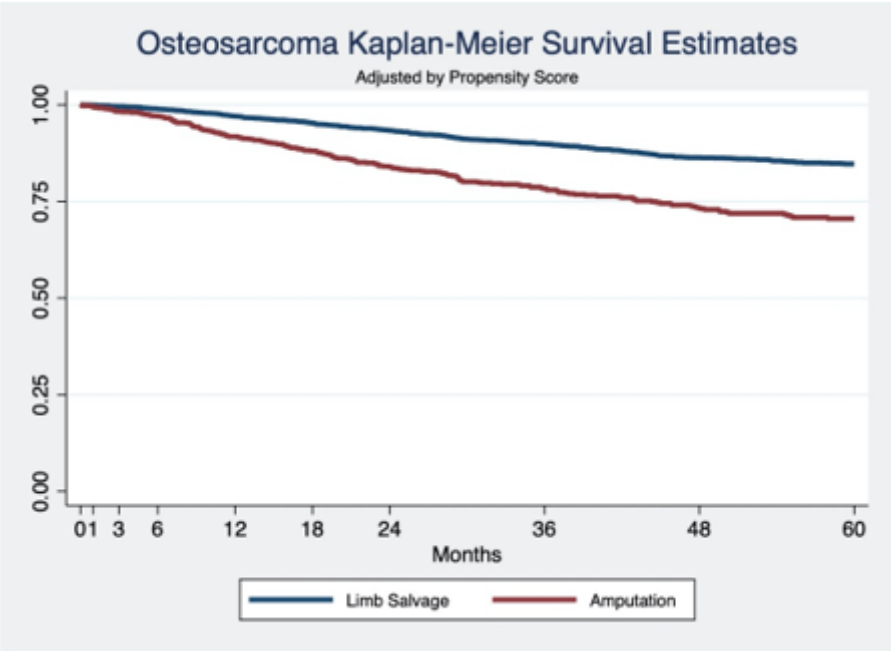

Figure 3

Kaplan Meier survival for limb salvage vs. amputation adjusted for propensity score cohort matched analysis

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx