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Association between Patient Age and the Risk of Mortality Following Local Recurrence of a Sacral Chordoma

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Abstract

Background: Local recurrence (LR) of sacral chordoma is a difficult problem and the mortality risk associated with LR remains poorly described. The purpose of this study was to evaluate the risk of mortality in patients with LR and determine if patient age is associated with mortality.

Methods: 218 patients (144 male, 69 female; mean age 59± 15 years) with sacrococcygeal chordomas were reviewed. Cumulative incidence functions and competing risks for death due to disease and non-disease mortality were employed to analyze mortality trends following LR.

Results: The 10-year overall-survival (OS) was 55%. Patients with LR had 44% 10-year OS, similar to patients without (59%, $p=0.38$). The 10-year OS between those <55 compared to ≥ 55 years were similar (69% vs. 48%, $p=0.52$). The 10-year death due to disease was worse in patients with LR compared to those without (44% vs. 84%, $p<0.001$). In patients without LR, patients ≥ 55 years were 1.6-fold more likely to experience death due to other causes.

Conclusions: Patients with a LR are more likely to die due to disease. Advanced patient age was associated with higher all-cause mortality following resection of sacral chordoma. LR of chordoma was associated with increased disease-specific mortality, regardless of age.

Keywords

Sacral chordoma; mortality; local recurrence; patient age

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Introduction:

Chordomas are the most common primary bone tumor of the sacrum and often are classified as low to intermediate grade malignant lesions which are often very large and locally advanced at the time of diagnosis [1–4]. Since chordomas are relatively resistant to chemotherapy and low-dose radiotherapy [5–9], the mainstay of treatment has been en-bloc excision with wide margins [2–12], however this approach is often associated with significant morbidity for the patient [3,4,9,13–15]. Even with surgical treatment and the addition of radiotherapy, local tumor recurrence remains a common problem. [2–12] For example, in our recent multicenter study, 19% (36/193) of patients developed local recurrence following resection of sacral chordoma.[9] Previous studies examining prognostic factors for survival have focused on epidemiological data from large registries of patients with chordoma.[16–18] These previous series have all identified older patient age as a negative predictor of overall survival, however the use of these databases is limited since they often include chordomas from multiple anatomical sites, do not account for competing disease and non-disease causes of death, and do not contain data on local tumor recurrence. [16–18]

How best to manage local recurrence of sacral chordoma continues to be debated as repeat surgery or radiotherapy can each impart substantial patient morbidity. [19] Since previous series examining mortality of patients with chordoma lacked data on local recurrences, there is currently a paucity of information pertaining to the risk of mortality following a local tumor recurrence, which could potentially help guide appropriate treatment recommendations. The purpose of this study was to combine the prospectively collected data from four tertiary-care sarcoma centers to evaluate the association of patient age on mortality following local recurrence of a sacral chordoma.

Materials and Methods:

Two hundred eighteen patients who underwent resection of primary sacrococcygeal chordomas from 1990 to 2015 were analyzed from four tertiary sarcoma centers. There were 144 males and 74 females with a mean age of 59±15 years.

All patients were treated with an en-bloc resection. There were no planned intralesional debulking procedures. One hundred eight patients (50%) underwent high sacral (osteotomy at or above the S2 level) resection and 37 patients (17%) had microscopically positive margins at the time of resection. Eighty-eight patients (46%) received adjunctive radiotherapy: 30 (16%) received preoperative treatment only, 42 (22%) received pre- and postoperative therapy, and 16 (8%) received only postoperative radiation.

Patients were prospectively followed for recurrence with a combination of clinical examination and MRI of the pelvis in addition to a plain radiograph or CT scan of the chest every 3 to 4 months for the first 2 years, every 6 months for years 2 to 5, and then annually for years 5 to 10. A local recurrence was defined as the presence of chordoma within or contiguous to the previously excised tumor bed appearing 3 or more months following resection.

Statistical Methods

Survival estimates were calculated using the cumulative incidence method, accounting for additive causes such as death due to disease and death due to other causes when analyzing overall survival and patient subsets. We employed competing risks as the method of analysis in our multivariable model, where death from other causes was considered as a competing risk to death due to disease (i.e. chordoma). Cox Proportional hazards analyses for specific causes of death (i.e. due to disease, due to other causes), employing a reference age of 55 years (HR: 1.00) for comparisons of hazards ratios for death and survival was performed. All tests were two-sided. P-values < 0.05 were considered statistically significant. Analyses were performed using R 3.4.3 (R Core Team, Vienna, Austria).

Results:

Survival:

During postoperative follow-up, 41 patients died due to disease, 45 died from other causes, and 132 were alive at the time of final follow-up (mean 7±5 years for surviving patients). The overall 2-, 5-, and 10-year survival was 88%, 73%, and 55% respectively.

During the course of follow-up, 41 patients (19%) experienced a local recurrence. The mean time to local recurrence was 3 years (range, 6 months-12 years). Patients with local recurrence had 90% 2-year, 73% 5-year, and 44% 10-year overall survival, which was statistically similar to that of patients who did not experience local recurrence (88%, 74%, and 59% respectively, p = 0.38). When examining disease specific mortality (Figure 1), all patients with a local recurrence who died, died due to metastatic disease. This imparted a worse disease specific mortality in patients with local recurrence where the 10-year disease specific survival was 44% compared to 84% (p<0.001) in those without a local recurrence.

Patient Age and Mortality:

All patients who developed local recurrence and died, died due to their disease. For patients with local recurrence, age less than 55 years conferred similar (p = 0.52, Figure 2A and 3A) overall mortality rates (2 Years: 7%, 5 Years: 29%, 10 Years: 69%) compared to patients ≥ 55 years (2 Years: 11%, 5 Years: 27%, 10 Years: 48%). Amongst patients without local recurrence, those under 55 years of age also had similar risk of death due to disease compared to patients ≥ 55 years (12% versus 11% at 10 years, p = 0.82; Figure 2B). In contrast, most deaths in patients without LR were due to other causes, and a greater than linear increase in death due to other causes was seen with increasing patient age (Figure 2B, 3B). Patients ≥55 were observed to be 1.6-fold more likely to experience death due to other causes (34% at 10 years) than patients under 55 (21% at 10 years, p = 0.01).

Discussion:

Even with the addition of adjuvant therapies, local recurrence remains a major clinical problem following surgical resection of sacral chordoma. The results of the current series indicate that local recurrence is associated with a worse disease specific survival, however when examining the age of patient there was no difference in disease specific survival.

However, older patients with chordoma are more likely to die from other factors rather than their disease.

Previous series examining the Unites States Surveillance, Epidemiology and End Results (SEER) database have shown older patient age to be independently associated with overall mortality in patients with sacral chordoma.[16–18] It was theorized that advanced patient age was associated with a more aggressive form of chordoma, in addition to the lower physiological reserve of older patients, which accounted for their increased mortality.[16–18] Although these series provide information from large patient databases, they lack a critical data point in oncological outcome, namely local recurrence. When examining patients with or without a local tumor recurrence, advanced patient age was not associated with an increased risk of disease-related death in the current series. However, older patient age was associated with an increased risk of all-cause mortality, and this was largely accounted for by non-oncologic deaths.

Other studies found that local tumor recurrence was associated with poor survival in patients with sacral chordoma.[2,9] In the current series, all deaths in patients with local recurrence were disease related, and their disease-related mortality was higher than in patients without local relapse. However, when using a competing risk analysis, there was no difference in the risk of death due to chordoma in patients who had or did not have a local recurrence based on age. This data is potentially useful in recommending treatment options for patients with a local recurrence, since the results of this study indicated that patients over the age of 55 are more likely to die of causes other than their locally recurrent chordoma. For these patients there should be consideration for less invasive treatments such as proton therapy, which has 5-year local control rates of 78% in patients with recurrent disease,[20] carbon ion radiation or newer molecular targeted therapies [21].

The results of the current series should be taken in light of certain limitations. Due to the retrospective nature of the study there were limits to the data we were able to collect and this placed constraints on the analysis. In addition this series only included patients treated surgically, and as such we are unable to comment on the outcomes of patients who were deemed not to be surgical candidates or chose non-operative treatment. Although this study included a large number of patients with primary chordoma of the sacrum, the sample size remains small and as such there is the potential that with a larger patient population the results of the series may differ. Patients in the current study were treated at multiple institutions, and as such there was no standardized treatment. This may also limit the generalizability of the results.

This study shows that advanced patient age was associated with higher all-cause mortality in patients with sacral chordoma. In addition when using a cumulative incidence model, although local tumor recurrence was associated with increased disease-specific mortality this did not vary according to patient age. Patient treatment decisions should be individualized, however for older patients consideration for less morbid therapies should be considered, in light of their increased non-disease related mortality.

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Synopsis:

Following resection of a sacral chordoma, patients older than 55 years of age, without a local tumor recurrence are more likely to die of something other than their disease. However in patients with a tumor recurrence, local recurrence was associated with increased disease specific mortality irrespective of patient age.

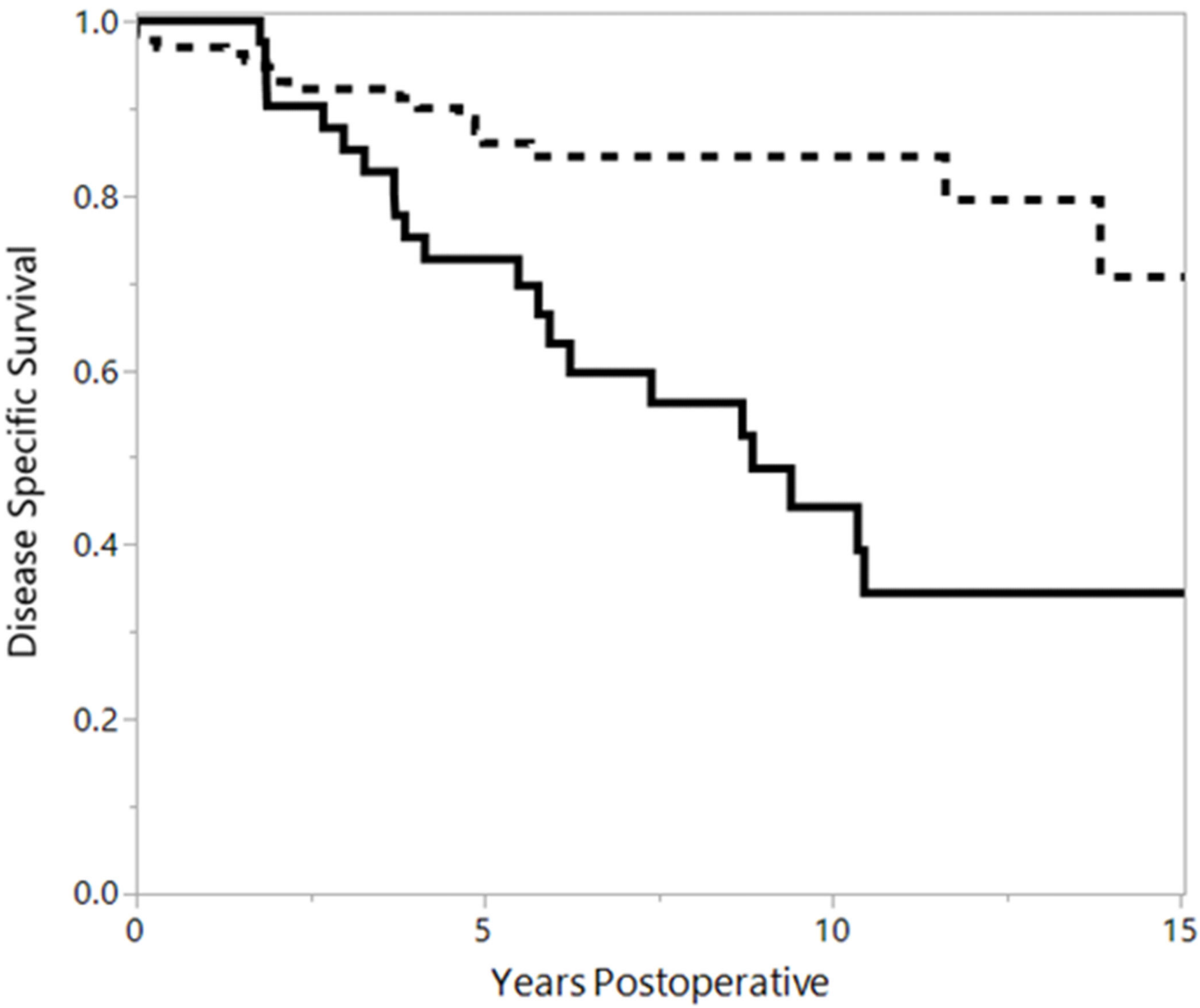

Figure 1:

In patients undergoing en-bloc sacrectomy for chordoma patients with local recurrence (solid) had worse 10-year disease specific survival compare to those without (dash) local recurrence (44% vs. 84%, p<0.001).

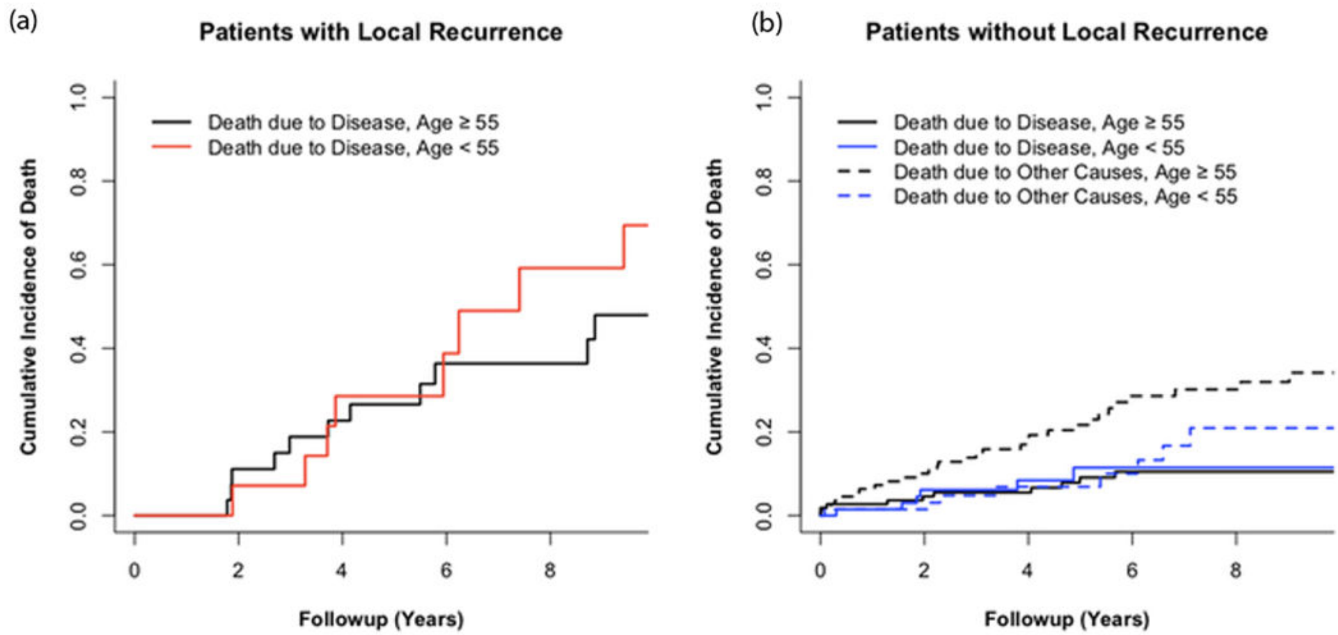

Figure 2:

Cumulative incidence of death due to disease and death due to other causes by patient age for A) Patients with local recurrence, and B) Patients without local recurrence.

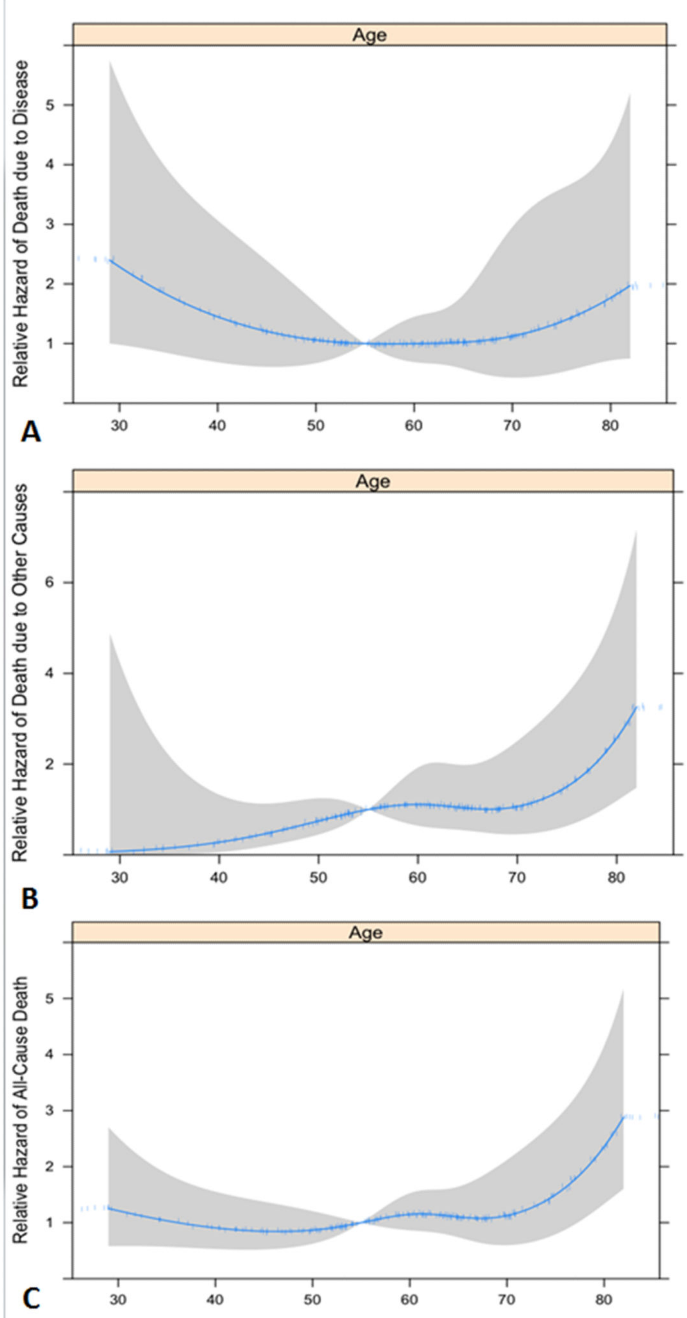

Figure 3:
Smoothed splines for the relative hazard of specific causes of death, namely A) Death due to Disease, B) Death due to Other Causes, and C) All-Cause Death, employing a reference age of 55 years.