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Adverse impact of regional lymph node involvement in osteosarcoma

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Abstract ***Background:*** Metastatic dissemination in osteosarcoma occurs haematogenously, though regional lymph node involvement is rarely reported. We investigated incidence, patient characteristics and survival for patients with osteosarcoma and regional lymph node involvement at diagnosis.

Methods: We identified 2748 cases of high-grade osteosarcoma with available information regarding regional lymph node involvement in the Surveillance Epidemiology and End Results database from 1973 to 2009. Demographics were compared using chi-squared tests or *t*-tests. Overall survival was estimated using Kaplan–Meier method and compared with log-rank tests. Multivariate analysis of overall survival was performed using Cox proportional hazards methods.

Results: There were 74 patients (2.7%) with regional lymph node involvement at diagnosis of whom 19 (0.7%) were pathologically confirmed. Patients with regional node involvement were more likely to have extraskeletal tumours, distant metastases, tumours arising outside the lower extremity ($p < 0.0001$ for all comparisons) and larger tumours ($p = 0.033$). Five-year overall survival in those with and without regional node involvement was 10.9% (95% confidence interval (CI) 4.6–20.4) and 54.3% (95% CI 52.2–56.4; $p < 0.0001$). In multivariate analysis, regional node involvement remained predictive of inferior survival after controlling for differences in metastatic status, age, tumour site and extraskeletal origin (hazard ratio 2.05, 95% CI 1.57–2.67; $p < 0.0001$). Similar survival results were found when the analysis was restricted to patients with pathologically confirmed positive or negative regional lymph nodes.

Conclusion: This analysis confirms that regional node involvement is a significant adverse prognostic factor that is independent of metastatic status, extraskeletal origin, age and tumour site.

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1. Introduction

Osteosarcoma is a primary malignant bone tumour that affects both adults and children.[1] The peak incidence is in adolescence and in the United States the annual reported incidence rate is approximately 8.7 cases per million children and adolescents younger than 20 years.[2] Metastatic dissemination in osteosarcoma usually occurs haematogenously, with lung and bones the most common metastatic sites. [2]

Regional lymph node involvement is thought to be rare with reported incidence rates varying from <1% to 10%.[3–6] In one series, Tobias and colleagues reported an incidence of regional lymph node involvement of 2.3% in their patients (4/176). Overall survival was poor for these patients, with median survival of only 8.5 months after diagnosis, which was similar to patients with distant metastatic disease in their series.[4] The Cooperative Osteosarcoma Study Group (COSS) reported an incidence of lymph node involvement of 0.8% (15/1702).[6]

Given the paucity of data describing these patients, we completed a population-based analysis of this rare subgroup of patients with osteosarcoma and regional lymph node metastasis. We provide a description of the incidence, patient characteristics and overall survival for this unique group of patients.

2. Methods

2.1. Patients

This is a cohort study evaluating patients with osteosarcoma with and without regional lymph node involvement. Data are derived from the publicly available US National Cancer Institute's SEER (Surveillance Epidemiology and End Results) database, which provides a large cohort of both children and adults with osteosarcoma. This database comprises patient information from multiple regions around the United States representing approximately 28% of the US population. Cancer data are collected from health providers, pathology reports, laboratories, autopsy reports and death certificates. Data are then subjected to edits and investigations to ensure quality data. Patient data have already been stored on the database allowing access to patient demographics, tumour details and survival data for the current analysis.

Patients of all ages with histologically confirmed high-grade osteosarcoma were included. All ages were included to allow a description of patients with regional node involvement across the age spectrum for osteosarcoma. Given their low metastatic potential, we did not include patients with low-grade osteosarcoma such as parosteal and intraosseous osteosarcoma. From the years 1973 to 2009, the SEER database included 4178 cases of high-grade osteosarcoma. We excluded patients without available data on regional lymph node status ($n = 1430$). The group of excluded patients had similar age, size, tumour site and overall survival compared to patients in the analytic cohort (data not shown). The analytic cohort therefore included the remaining 2748 patients. Patients with known metastatic or distant nodal involvement in addition to regional nodal involvement were included but a separate analysis of overall survival was performed in patients with both regional node involvement and distant metastatic disease and those with only regional node involvement (see Section 3).

2.2. Predictor variable

We evaluated patient characteristics and outcomes according to presence or absence of regional lymph node involvement at the time of diagnosis. Involved regional lymph nodes were defined based upon the SEER registry definition, a malignant neoplasm that extends beyond the limits of the organ and involves regional or neighbouring lymph node chain by way of the lymphatic system. Regional nodes were considered to be involved based upon positive evidence of involvement in any of the following SEER data fields: evidence of disease (EOD) 2, 4 and 10 coding systems, regional node data field, collaborative staging (CS) lymph node status and American Joint Committee on Cancer Stage (AJCCS). CS and EOD are specific to patients diagnosed within a particular time frame: EOD 2, 1973–1982; EOD 4, 1983–1987; EOD 10, 1988–2008; CS, 2004–present. AJCCS data are available for patients diagnosed from 2004 and later while the regional node data field is available for patients diagnosed from 1988 and later. These fields were based upon data from imaging, physical examination and pathology findings. Only one data field (regional node data field) relied exclusively upon pathologic confirmation of regional node involvement and was used in a sub-analysis. Some patients had data available in multiple fields and each field was compared to the others to allow for internal consistency.

2.3. Outcome variables

Patient characteristics and overall survival were evaluated based on regional lymph node status. Variables of interest included age at diagnosis (continuous variable and also dichotomised at age 18 years), year of diagnosis (in 10-year blocks), sex, race, histologic subtype, tissue of origin (osseous versus extraosseus), primary tumour site, and tumour size (dichotomised at 10 cm). We also evaluated tumour stage, defined as either localised or metastatic. Patients whose only site of disease outside