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Location of pulmonary metastasis in pediatric osteosarcoma is predictive of outcome

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Abstract

Background: The 3-year survival after pulmonary metastasectomy for osteosarcoma (OS) is approximately 30%. Resection of metastatic disease can prolong life in pediatric patients with OS. Our objective is to assess the outcome of pediatric patients with pulmonary metastases located centrally as compared with peripheral lesions.

Methods: A retrospective review of patients 0 to 21 years old with a diagnosis of OS with pulmonary metastases on computed tomographic scan between 1985 and 2000 was completed. Demographics, metastasis location, survival, morbidity, and mortality were evaluated.

Results: Of 115 patients who had pulmonary metastasis secondary to OS, there were 96 wedge resections and 13 lobectomy/pneumonectomies in 84 patients. The morbidity of wedge resection was 9% and lobectomy/pneumonectomy was 8%. There were no deaths from surgery. The median survival for patients undergoing lobectomy compared with wedge resection was 0.61 and 1.14 years, respectively, but did not reach statistical significance. The median overall survival for the entire cohort was 0.75 years. The median overall survival after initial detection of metastatic disease was 1.06 years among the patients with peripheral disease, compared with 0.38 years in patients with central disease ($P = .008$).

Conclusion: Patients with central pulmonary metastases in OS have a very poor prognosis, even after operative treatment, compared with those with peripheral disease. Patients with central lesions may benefit from other nonsurgical treatment options.

Osteosarcoma is the most common bone tumor in children. The prognosis is based primarily on the development of metastasis, whether at presentation or at relapse. Patients with metastatic osteosarcoma to the lungs have a poor prognosis. Despite advances in chemotherapy, radiation therapy, and surgery, the 3-year survival of patients with metastatic osteosarcoma is 20% to 45% [1-4]. Surgical resection of pulmonary metastasis has been shown in numerous studies to prolong survival and is part of the standard surgical treatment of osteosarcoma [2,5-7]. It has also been shown that patients with pulmonary metastases do better than those with metastases in other sites. [8]. When

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planning a thoracic operation for metastatic osteosarcoma, the location of the lesion is important, and preoperative imaging is essential to the planning process. Although it has been shown that computed tomographic (CT) scans may underestimate the number of metastases, it remains the best diagnostic modality for evaluating metastases [9]. Some pulmonary lesions are located in the peripheral aspect of the lungs and when few in number are amenable to wedge resection, whereas others are located in the central portion of the lung close to the hilum and primary vascular and airway branches. Centrally located lesions may require anatomical resections such as a lobectomy instead of the more common wedge resections that are done for peripheral lesions. The prognostic significance of central vs peripheral pulmonary metastasis in osteosarcoma has not previously been evaluated and may support alternative nonsurgical therapies [10]. Our aim is to examine the outcome of patients with osteosarcoma with CT-identified central vs peripheral pulmonary metastasis who underwent surgical resection.

1. Materials and methods

Institutional review board approval was obtained for this retrospective review. Using our database of patients with metastatic osteosarcoma, we evaluated a cohort of patients diagnosed between January 1, 1985, and December 31, 2000. Patients younger than the age of 21 years were included if CT scans were available for review and clinical information was complete. Demographics, morbidity, mortality, survival, and disease status were examined. Operative notes were reviewed to determine the extent of resection and examine intraoperative morbidity.

Survival analysis was performed using the overall survival (OS), which was computed from the date of the first operation to the date of death or the date of last follow-up, whichever occurred first. The patients who were alive at the last follow-up date were censored. The Kaplan-Meier method was used to estimate the probability of the OS. The log-rank test and Cox proportional hazards regression analysis were used to determine the association of OS with the clinical factors and demographic parameters. The Wilcoxon rank sum test was used to compare the age between the central and peripheral procedure groups, and the Fisher's Exact test was used to determine demographic parameters between the central and peripheral procedure groups. All the analysis were performed using S-plus 7 (Insightful Corporate, Seattle, WA). Overall survival is defined by time from the first operation until death or the first identification of a central lesion until death.

For our study, we defined as central lesions those lesions that abut a first-degree bronchus or blood vessel, such that a resection of that lesion would require resection of that structure to assure adequate margins. Central lesions were determined by CT scan. Essential lesions were determined by CT scan as assessed by the authors. Because operative therapy is planned based on CT imaging, we used CT instead of operative findings as the definition. The coding of central vs peripheral lesions was done before statistical analysis; therefore, the coder was blinded to the patient outcome.

Many patients in this study had multiple thoracotomies. Our criteria for reoperation on metastatic lesions included no disease or controlled disease outside the lung or chest wall, the ability to achieve a complete resection of all metastasis without causing respiratory insufficiency or oxygen dependence based on preoperative spirometry testing, and performance status.

Multiple different combinations of chemotherapy and, rarely, radiation therapy were used but are not included in this report.

2. Results

The patient's ages ranged from 0 to 21 years. The median age was 14.1 years. The median follow-up was 9.72 years (95% confidence interval [CI], 6.54 to NA years), and the longest follow-up time was 14.89 years. There were 36 males (65.5%) and 19 females (34.5%) in the cohort. There were no significant differences in sex (P = .53), age (P = .57), or ethnicity (P = .63) between the group of patients with one or more central metastasis vs those with only peripheral metastasis. Table 1 shows other patient tumor characteristics.

Of the 115 patients who had pulmonary metastases secondary to osteosarcoma, we identified 84 that underwent surgical resection. Fifty-five of those patients had CT scans available for examination. This cohort underwent 118 total procedures: 96 wedge resections, 12 lobectomies, and one pneumonectomy. Ten patients had pulmonary metastasis at diagnosis. The remainder developed pulmonary metastasis after the initiation of therapy. (Patients who underwent biopsy alone were excluded.)

There were no surgical mortalities. The morbidity of wedge resection was 9% and lobectomy/pneumonectomy was 8%. Morbidity included fever of unknown origin, pneumothorax, hydropneumothorax, pneumonia, and prolonged air leak. One intended lobectomy had to be aborted secondary to intraoperative hemorrhage. There was no significant difference in surgical morbidity between the wedge resection and lobectomy group.

The log-rank test indicated that type of operation (wedge vs lobectomy) or the number of metastatic lesions was not a predictor of OS (Table 2). However, the central or peripheral locations of the lesions were significant predictors of survival (P = .008). The univariate Cox proportional hazards regression analysis indicates that the number of nodules (heart rate [HR], 1.1; P = .003), but not age (HR, 1.04; mp, 0.35), was significantly associated with survival (Table 2A). The multivariate analysis suggested that both location of the lesions and the number of nodules were significantly