Journal of Pediatric Surgery (2006) **41**, 194–199

ELSEVIER

Journal of Pediatric Surgery

www.elsevier.com/locate/jpedsurg

Long-term survival after aggressive resection of pulmonary metastases among children and adolescents with osteosarcoma☆

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Index words:
Osteosarcoma;
Thoracotomy;
Pulmonary metastases;
Pediatric

Abstract

Purpose: Although survival without resection of pulmonary metastases from osteosarcoma is unlikely, not all surgeons agree on an aggressive surgical approach. We have taken an approach to attempt surgical resection if at all feasible regardless of number of metastases and disease-free interval (DFI). This study presents information on long-term follow-up after this aggressive approach to resection.

Methods: A single-institution retrospective cohort study of osteosarcoma patients younger than 21 years with pulmonary metastases, limited to the contemporary chemotherapeutic period (1980-2000), was conducted.

Results: In 137 patients, synchronous (23.4%) or metachronous (76.6%) pulmonary nodules were identified. The median follow-up was 2.0 years (5 days to 20.1 years) for all patients. Overall survival among patients who had pulmonary nodules was 40.2% and 22.6% at 3 and 5 years, respectively. Ninety-nine patients underwent attempted pulmonary metastasectomy (mean survival, 33.6 months; 95% confidence interval, 25.1-42.1) and 38 patients did not (mean survival, 10.1 months; 95% confidence interval, 6.5-13.6; $P < .001$, t test). Characteristics that were associated with an increased likelihood of 5-year overall survival after pulmonary resection were primary tumor necrosis greater than 98% after neoadjuvant chemotherapy ($P < .05$) and DFI before developing lung metastases more than 1 year ($P < .001$). No statistically significant difference in overall survival or disease-free survival was found based on the number of pulmonary metastases resected. Characteristics including primary tumor size, site, or extension; chemotherapy; early vs late metastases; unilateral vs bilateral metastases; and resection margins did not significantly affect survival.

Conclusions: Most patient and tumor characteristics commonly used by surgeons to determine utility of resection of pulmonary metastases among patients with osteosarcoma are not associated with outcome.

Presented at the 36th Annual Meeting of the American Pediatric Surgical Association, Phoenix, AZ, May 29-June 1, 2005.

☆ This study was supported in part by grants K23HD001473 and K24RR17050 from the National Institutes of Health, Bethesda, Md.

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0022-3468/$ – see front matter
doi:10.1016/j.jpedsurg.2005.10.089

Biology of the particular tumor (response to preoperative chemotherapy, measured by tumor necrosis percentage, and DFI), as opposed to tumor burden, appears to influence survival more significantly. We would advocate considering repeat pulmonary resection for patients with recurrent metastases from osteosarcoma.

Although the prognosis for patients with osteosarcoma has improved significantly over the last 3 decades [1-3], those who develop metastatic disease to the lung continue to pose a particularly difficult challenge. Of all patients diagnosed with osteosarcoma, 10% to 20% will have clinically detectable pulmonary metastases at presentation [1,4-6] and 40% to 55% of the remaining patients will develop pulmonary disease over time [5,7-9]. Although the 5-year survival has reached 40% to 70% for all osteosarcoma patients [1,2,10], only 20% to 40% of those found to have pulmonary metastases will survive 5 years [4,5,9,11,12].

Surgical resection has been consistently shown to prolong survival among patients with pulmonary metastases [3,13-15]. The indications for pulmonary metastasectomy have evolved, secondary to clarification of prognostic factors and optimization of surgical technique. Prognostic factors associated with improved survival after resection of pulmonary metastasis are still unclear [9,16].

This study is a retrospective review of our experience with pediatric osteosarcoma patients whose lung metastases were managed via an aggressive surgical approach. The primary objective was to identify patient and tumor characteristics that are associated with improved survival.

1. Materials and methods

After obtaining institutional review board approval, a comprehensive search of the Tumor Registry database at the University of Texas MD Anderson Cancer Center was used to identify patients younger than 21 years with osteosarcoma metastatic to the lung. Patients with primary tumors of the head and neck, radiotherapy-induced osteosarcoma, or initial diagnosis and majority of treatment (defined as preoperative through postoperative chemotherapy) at outside institutions were excluded. Patients diagnosed between January 1, 1980, and December 31, 2000, were included and follow-up data were obtained through December 2003.

Over the course of the study period, we have been aggressive with respect to our surgical approach to pulmonary metastases secondary to osteosarcoma. Our indications for pulmonary resection have included control of the primary tumor and sufficient pulmonary reserve to withstand complete resection, regardless of volume or location of pulmonary disease.

We collected patient data including demographics, disease history, primary tumor characteristics, treatment strategy (including surgery, chemotherapy, and/or radiotherapy), follow-up (including disease recurrence / progression), surgical complications, and length of survival.

The primary outcome measures were overall survival and disease-free survival. Characteristics evaluated included primary tumor size/site/extension/necrosis, disease-free interval (DFI), number of pulmonary metastases resected, timing of pulmonary metastases, location of pulmonary metastases, completeness/margins of resection, pleural disruption, and chemotherapy. Comparison of various characteristics between groups was made using t tests (means) or χ^2 tests (proportions/categorical variables). Survival curves were generated using the Kaplan-Meier actuarial survival method and statistical significance was derived from log-rank testing.

For this analysis, we defined overall survival as the time from pathological diagnosis until death, censoring, or last follow-up. Disease-free survival was defined as survival with no detectable disease after pulmonary resection. Disease-free interval was defined as the time from resection of the primary tumor until the development of metastatic disease or local recurrence.

2. Results

There were 272 patients with osteosarcoma of the trunk or extremities who were younger than 21 years and who had medical records available for review. Of these, 137 developed or presented with radiographically evident (on lung tomograms, chest x-ray, or computed tomographic scan) pulmonary nodules. These 137 patients formed the initial study cohort.

The median follow-up for the initial cohort was 2.5 years (5 days to 20.1 years). Overall survival at 3 and 5 years was 40.2% and 22.6%, respectively. Patient and tumor characteristics of the initial study cohort can be found in Table 1.

Of the 137 patients with suspected pulmonary metastatic disease, 99 (72.3%) underwent an operation (unilateral thoracotomy, bilateral [staged or simultaneous] thoracotomies, or median sternotomy) to render them disease-free, whereas 38 (27.7%) did not undergo surgical therapy. Six patients had benign or non–osteosarcoma pulmonary disease. The 93 patients (mean age, 13.9 $\pm$ 4.2 years) who underwent surgical resection of pulmonary metastasis from osteosarcoma formed the final study cohort.

The patients who underwent pulmonary metastases resection had a mean survival of 33.6 months (95% confidence interval, 25.1-42.1), whereas the 38 patients who did