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Effect of concurrent metastatic disease on survival in children and adolescents undergoing lung resection for metastatic osteosarcoma

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ABSTRACT

Purpose: To evaluate the impact of treated extra-pulmonary metastatic disease on overall (OS) and event-free survival (EFS) for pediatric osteosarcoma patients undergoing pulmonary metastatectomy.
Methods: We retrospectively reviewed pediatric patients who were treated for osteosarcoma at our institution from 2001 to 2011 and received pulmonary metastatectomy (n = 76). We compared OS and EFS between patients with metastases limited to the lungs (Group A, n = 58) to those with treated extra-pulmonary metastases (Group B, n = 18) at the time of first pulmonary metastatectomy.
Results: The estimated median OS and EFS from first pulmonary metastatectomy were 2.0 years (95% CI 1.5–2.8 years) and 5.5 months (95% CI 3.0–8.1 months), respectively. Median OS was significantly greater for Group A (2.6 years, 95% CI 1.9–3.8) compared to Group B (0.9 years, 95% CI 0.6–1.5) (log rank p = 0.0001). Median EFS was significantly greater for Group A (7.9 months, 95% CI 5.0–10.7) compared to Group B (1.6 months, 95% CI 0.8–2.7) (log rank p < 0.0001). Independent predictors of OS included extra-pulmonary metastatic disease at the time of first thoracotomy, bilateral pulmonary metastases, and >4 nodules resected at first thoracotomy (all p < 0.001).
Conclusions: Osteosarcoma patients with treated extra-pulmonary metastatic disease at the time of pulmonary metastatectomy have significantly worse survival compared to those with disease limited to the lungs.
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Osteosarcoma is the most prevalent primary bone cancer in children, with over half of the new cases occurring in children and adolescents under the age of 21 years [1]. The incidence of osteosarcoma in this age group is about 4.4 per million [2]. Among new osteosarcoma cases, 25% present with metastasis, 50% of which are in the lung [3]. In pediatric osteosarcoma patients with metastasis to the lung, the 5-year overall survival is approximately 30% compared to 70% for those patients without metastasis(es) [4].

In pediatric patients with pulmonary metastatic osteosarcoma, the mean survival after undergoing resection of the pulmonary metastasis is 34 months compared to 10 months in patients who did not have a surgical resection [5]. A number of factors affect overall survival for patients undergoing thoracotomy for resection of metastatic osteosarcoma including the number of nodules resected, bilateral versus unilateral disease, and location of the nodule within the lung (central versus peripheral) [6,7]. Although surgical resection has been shown to offer a survival advantage in patients with metastatic disease isolated to the lungs, it is unclear if it provides a similar advantage for patients with treated concurrent metastases outside the lung. The purpose of our study is to evaluate the impact of treated concurrent extra-pulmonary metastatic disease on the survival of pediatric patients undergoing thoracotomy for resection of metastatic osteosarcoma.

1. Materials and methods

We performed a retrospective case review and included all patients less than 21 years old who were treated for osteosarcoma between January 1, 2001 and December 31, 2011 at The University of Texas MD Anderson Children's Cancer Center and underwent one or more thoracotomy(ies). The electronic medical record was queried for the following data: patient demographics and baseline characteristics; dates of diagnosis, operations and relapse(s); location of the primary lesion, metastasis(es) and relapse(s); type of operation, margin status, histology and percent necrosis for the primary lesion and metastasis(es). Of the 308 patients initially identified, 232 patients were excluded for the following reasons: thoracotomy was not performed for metastatic pulmonary disease (n = 163), treatment records were incomplete and/or lacking sufficient information from outside records (n = 54), and pathology was benign after lung resection (n = 15) leaving 76 patients who met inclusion criteria and had sufficient data for analysis.

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Overall survival (OS) and event-free survival (EFS) were compared between patients with metastases limited to the lungs (Group A, n = 58) and patients who had treated extra-pulmonary metastases at the time of first pulmonary metastatectomy (Group B, n = 18). An event was defined as local recurrence at the primary tumor site, new metastases diagnosed by either marked progression on imaging or positive biopsy, progression of previously stable sites concerning for metastases on imaging, or death. A site was considered treated if complete surgical resection was performed with negative margins and/or a previously PET-avid metastasis was no longer PET-avid or biopsy negative after chemotherapy and/or radiation therapy.

Patient demographic and clinical characteristics were summarized using counts, percentages, means and standard deviations, and medians with minimum and maximum values. Variable associations with the study group were tested using the Fisher's exact test and Wilcoxon sign rank test as appropriate. Survival curves were prepared according to the Kaplan–Meier method and strata were compared using the log-rank test. Cox proportional hazards regression analysis was used to model survival. All tests were 2-tailed, and statistical significance was defined as a P value less than 0.05. Analyses were conducted using SAS® for Windows (release 9.1, SAS Institute, North Carolina).

2. Results

Seventy-six pediatric and adolescent patients underwent thoracotomy for metastatic osteosarcoma at our institution during the study period with sufficient data to include in the study (n = 76). The median age at diagnosis was 14.4 years (range 4–20 years). The median age at the time of first pulmonary metastatectomy was 15.5 years (range 6.0–22.6 years). Patient demographics and clinical characteristics are included in Table 1. Fifty-five deaths were observed. All deaths were related to metastatic disease. The 21 patients alive at the time of last follow-up were followed for a median of 6.3 years (range 1.7–12.3 years) after diagnosis. Fourteen were alive with no evidence of disease and 7 were alive with disease at the last follow-up.

Table 1
Patient demographics and clinical characteristics.

Characteristic	No. of patients	Group A (n = 58)	Group B (n = 18)	P
Age at diagnosis (years) median (minimum–maximum)	14.4 (4.5–20.1)	14.4 (4.5–19.8)	14.6 (4.8–20.1)	0.9367
Sex				1.0000
Male	40 (52.6%)	31 (53.4%)	9 (50.0%)	
Female	36 (47.4%)	27 (46.6%)	9 (50.0%)	
Race				0.6011
Non-Hispanic White	45 (59.2%)	33 (56.9%)	12 (66.7%)	
Hispanic	20 (26.3%)	17 (29.3%)	3 (16.7%)	
Non-Hispanic Black	9 (11.8%)	6 (10.3%)	3 (16.7%)	
Asian	2 (2.6%)	2 (3.4%)	0 (0.0%)	
Primary tumor location				0.1959
Femur	51 (67.1%)	38 (65.5%)	13 (72.2%)	
Humerus	13 (17.1%)	10 (17.2%)	3 (16.7%)	
Tibia	8 (10.5%)	8 (13.8%)	0 (0.0%)	
Pelvis	3 (4.0%)	2 (3.4%)	1 (5.6%)	
Other	1 (1.3%)	0 (0.0%)	1 (5.6%)	
Histology				0.6650
Chondroblastic	19 (25.0%)	15 (25.9%)	4 (22.2%)	
Osteoblastic	26 (34.2%)	17 (29.3%)	9 (50.0%)	
Fibroblastic	6 (7.9%)	6 (10.3%)	0 (0.0%)	
Telangiectatic	3 (4.0%)	3 (5.2%)	0 (0.0%)	
Other	9 (4.0%)	8 (13.8%)	1 (5.6%)	
Unknown	13 (17.1%)	9 (15.5%)	4 (22.2%)	
Number of nodules resected at first surgery				0.1108
1	17 (22.7%)	15 (26.3%)	2 (11.1%)	
2–3	29 (38.7%)	24 (42.1%)	5 (27.8%)	
4 or more	29 (38.7%)	18 (31.6%)	11 (61.1%)	
Extrapulmonary site				
Axillary skeleton			10 (55.65)	
Appendicular skeleton			4 (22.2%)	
Lymph nodes			4 (22.2%)	

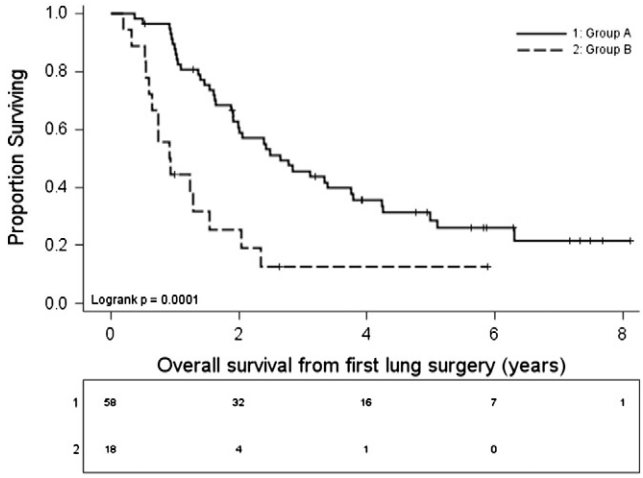

Fig. 1. Kaplan–Meier plot of overall survival from first thoracotomy stratified by study group. Group A: metastases limited to the lungs at first thoracotomy. Group B: pulmonary and treated extra-pulmonary metastases at first thoracotomy.

For the study population, the estimated median overall survival from diagnosis was 3.8 years (95% CI 3.1–5.0 years). At the time of diagnosis, 23 (30%) of the patients had metastatic disease limited to the lungs, 5 (7%) had extra-pulmonary metastatic disease and 51 (67%) had no evidence of metastases. The median overall survival from diagnosis was 5.0 years (95% CI 3.8–6.0 years) for those who presented without metastasis compared to 2.6 years (95% CI 1.6–3.4 years) for those who presented with metastasis(es) limited to the lungs and 1.5 years (95% CI 1.1–2.3 years) for patients who presented with both pulmonary and extra-pulmonary metastases at the time of diagnosis ($P < 0.0001$).

At the time of first thoracotomy, 58 (76%) patients had metastatic disease limited to the lungs (Group A) and 18 (24%) had concurrent treated extrapulmonary metastases (Group B). Overall survival from the first thoracotomy was significantly better for patients in Group A (median 2.6 years, 95% CI 1.9–3.8 years) versus patients in Group B (median 0.9 years, 95% CI 0.6–1.5 years) (log rank $P < .001$) (Fig. 1). Univariate models of overall survival from first thoracotomy completion are included in Table 2, and a multivariate model is shown in Table 3.

During follow-up after the first thoracotomy, an event was observed in 66 patients. The median event-free survival was 5.5 months (95% CI 3.0–8.1 months). The 9 patients who had not progressed after the first thoracotomy were followed for a median of 47.3 months (range 11.9–86.1 months). Group B had a significantly poorer event-free survival

Table 2
Univariate models of overall survival from completion of first thoracotomy for resection of lung metastasis(es).

Independent Variable	HR	95% CI		P
Study Group B vs A	3.106	1.684	5.728	<0.001
Age at thoracotomy (per year increase)	1.033	0.956	1.116	0.409
2–3 nodules resected vs 1 nodule	2.031	0.855	4.820	0.108
≥4 nodules resected vs 1 nodule	4.582	1.977	10.621	<0.001
≥98% necrosis of primary tumor vs < 98%	0.499	0.196	1.273	0.146
Positive vs negative margins	0.803	0.357	1.808	0.596
Uncertain vs negative margins	1.148	0.362	3.640	0.815
Central vs peripheral pulmonary nodules	1.317	0.642	2.698	0.453

HR = hazard ratio.
CI = confidence interval.