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Long-term Pulmonary Function after Metastasectomy for Childhood Osteosarcoma. A Report from the St. Jude Lifetime Cohort Study

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Abstract

Background—Complete resection of lung metastases improves survival in patients with osteosarcoma. We evaluated the long-term effect of metastasectomy on pulmonary function of patients treated for osteosarcoma during childhood.

Methods—We reviewed the medical records of patients who had pulmonary function tests (PFTs) following metastasectomy for osteosarcoma. Patient, tumor, and treatment variables were abstracted along with PFTs. PFTs were recorded as a percentage of predicted value and were classified as abnormal for FVC <80%, FEV₁ <80%, TLC <75%, and DLCO_{corr} <75%.

Results—Twenty-one patients had PFTs performed during follow-up. Mean age at diagnosis of osteosarcoma was 13.2±4.7 years. Fifteen patients had a single thoracotomy, and 6 patients had 2 thoracotomies (range, 2–6). Eighty lesions were resected. Nine patients had 2 lesions resected and 12 patients had >2 lesions (range, 3–12) resected. Mean time from the last surgical procedure to measurement of PFTs was 20.3±9.0 years. TLC was abnormal for 28.6%, DLCO_{corr} for 47.4%, FVC for 40%, and FEV₁ for 47.6% of the cohort members. Individual PFTs were abnormal in 13.3% (TLC) to 46.7% (DLCO_{corr}) of patients who had one thoracotomy and in 50.0% (DLCO_{corr}) to 66.7% (FEV₁, TLC) of patients with two thoracotomies. The number of thoracotomies was associated with abnormal TLC (p=0.03).

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Discussion—Patients who underwent pulmonary metastasectomy for osteosarcoma as children often had abnormal PFTs on long-term follow up, but the reduction in lung volumes and DLCO_{corr} was relatively mild. Multiple thoracotomies predicted greater impairment of pulmonary function.

Background

Osteosarcoma is the most common primary bone tumor in children and adolescents ¹. The tumor originates in regions of rapid bone growth, most commonly the distal femur, proximal tibia, and proximal humerus. Approximately 15–20% of patients will have metastases at diagnosis ^{2,3}; 75% of these are in the lung ^{4,5}. Additionally, more than 30% of patients will develop metachronous lung metastases ^{5,6}. The best predictor of survival in patients with lung metastases from osteosarcoma is a complete metastasectomy ^{5,7–9}. Over the last few decades, with progress in staging, local control, and chemotherapeutic regimens, the prognosis for metastatic osteosarcoma has improved with 5-year disease-free survival rates now reaching 30–50% ^{1,3,10}. Thus, long-term survival following pulmonary metastasectomy for childhood osteosarcoma is achievable.

A few studies ^{11–14} have evaluated long-term pulmonary function following pulmonary resection (predominantly lobectomy) for benign childhood disease processes. These series demonstrated a mild decrement in lung volumes on long-term follow-up.

Multi-agent chemotherapy and multiple pulmonary metastasectomies are often required to render children with osteosarcoma disease-free. However, this treatment approach has the potential to impair pulmonary function, which may interfere with the ability of long-term survivors to participate in life activities at an optimal level.

The impact of metastasectomy on pulmonary function in long-term survivors of osteosarcoma has not been previously studied. The aim of this study was to describe pulmonary function following metastasectomy in long-term survivors of childhood osteosarcoma.

Methods

A cohort of patients (St. Jude Lifetime Cohort Study [SJLIFE]) was identified that fulfilled the following criteria: diagnosis of childhood malignancy treated at St. Jude Children's Research Hospital (SJCRH), survival 10 years from diagnosis, and current age 18 years. The detailed methods used for ascertainment, recruitment, and evaluation of the members of this cohort have been reported previously ¹⁵. This investigation was approved by the institutional review board at SJCRH, and all participants and/or their legal guardians provided informed consent.

The cumulative doses for 32 specific chemotherapeutic agents (5-azacytidine, bleomycin, busulfan, carboplatin, carmustine, cisplatin, cyclophosphamide [intravenously [IV] or orally], cytarabine [IV, intramuscularly, intrathecally, subcutaneously], dacarbazine, dactinomycin, daunorubicin, dexamethasone, doxorubicin, etoposide [IV, orally], fludarabine, fluorouracil, hydroxyurea, idarubicin, ifosfamide, L-asparaginase, lomustine,

melphalan, methotrexate [IV, intramuscularly, intrathecally], nitrogen mustard, prednisone, procarbazine, teniposide, thioguanine, thiotepa, tretinoin, vinblastine, vincristine), surgical procedures, and radiation treatment fields, dose, and energy source were abstracted from the medical records according to a protocol similar to that used in the Childhood Cancer Survivor Study (CCSS) ¹⁶.

Participants underwent a risk-based assessment as suggested by the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer (COG Guidelines) ¹⁷.

The Institutional Review Board (IRB) approved a retrospective review for patients diagnosed with osteosarcoma who were eligible for the SJLIFE study who had undergone pulmonary metastasectomy for osteosarcoma.

Spirometry measured forced vital capacity (FVC) ¹⁸, forced expiratory volume in 1 second (FEV₁) ¹⁸, and single breath diffusion capacity for carbon monoxide corrected for hemoglobin (DLCO_{corr}) ¹⁹. Total lung capacity (TLC) ²⁰ was determined by body plethysmography. All tests were performed according to the American Thoracic Society standard and expressed as percent of predicted using race, age, and sex appropriate equations. PFTs were classified as abnormal for FVC <80%, FEV₁ <80%, TLC <75%, and DLCO_{corr} <75%. For patients who had more than one measurement of PFTs, the most recent values were recorded. Obstructive lung disease (FEV₁/FVC < 0.70) was evaluated using the GOLD criteria ²¹. Restrictive lung disease (TLC < 75% predicted) was evaluated using the Guides to the Evaluation of Permanent Impairment ²².

Statistical Methods

Fisher's exact test was used to examine the association between the number of thoracotomies and abnormal values of PFTs, and between the number of lesions resected and abnormal values of PFTs. Data were analyzed with SAS version 9.2 (SAS Institute, Cary, NC).

Results

Of 26 patients who underwent pulmonary metastasectomy for osteosarcoma from 1968 to 1998 and who were alive and eligible for SJLIFE, 21 patients had PFTs performed during follow-up, 16 during their SJLIFE on campus evaluation and five at an earlier time but after one or more thoracotomies. The mean age at diagnosis was 13.2±4.7 years and the mean age at PFT evaluation was 34.9 ± 10.9 years. The most recent PFT was performed 20.3 ±9.0 years after the final thoracotomy, except for one patient whose PFTs were performed after the second and prior to the third thoracotomy. Most patients were male (n=14) and Caucasian (n=16). All primary tumors were located in the extremities (femur=12, tibia/fibula=7, humerus=2) (see Table 1). All patients received multi-agent chemotherapy. Six patients received bleomycin with a mean dose of 107 mg/m² (range, 45–140 mg/m²). No patients received carmustine (BCNU) or chest radiation therapy. Four of the five who did not return for PFTs were males, all were Caucasian and all had primary tumors of the lower extremity (femur – 4, tibia – 1). One died due to a widely metastatic second malignant

neoplasm (leiomyosarcoma), one died from a medication overdose, two have participated in SJLIFE as Survey Only¹⁵ and one has not yet been contacted regarding SJLIFE participation.

Fifteen patients had a single and 6 patients had 2 thoracotomies (range, 2–6). Eighty lesions were resected. Lesions were located in the right middle lobe (n=11), right lower lobe (n=11), right upper lobe (n=10), left lower lobe (n=9), left upper lobe (n=5), and lingula (n=2). Nine patients had 2 metastases resected and 12 patients had >2 metastases (range, 3–12) resected. One patient underwent a middle lobectomy and subsequently a left upper lobectomy (TLC - 71% of predicted at follow-up). One additional patient required a left pneumonectomy (TLC - 66% of predicted at follow-up). All other pulmonary resections consisted of wedge resections. Few patients were smokers; one patient had a 17 pack-year history and an additional three patients were self-described “social smokers.”

FVC was abnormal for 40%, FEV₁ for 47.6%, TLC for 28.6%, and DLCO_{corr} for 47.4% of cohort members. The mean percent of predicted for FVC was 76.7% (standard deviation (SD), 18.8%), FEV₁ 74.8% (SD, 19.7%), TLC 84.4% (SD, 21.8%), and DLCO_{corr} 76.7% (20.4%). The proportions of patients with 1, 2, 3, or 4 abnormal PFTs were 21.1%, 5.3%, 10.5%, and 21.1% respectively.

Patients with multiple thoracotomies had a higher percentage of abnormal values for TLC, FVC, and FEV₁, but these differences did not achieve statistical significance except TLC (Table 3). Individual PFTs were abnormal in 13.3% (TLC) to 46.7% (DLCO_{corr}) of patients who had one thoracotomy and in 50.0% (DLCO_{corr}) to 66.7% (FEV₁, TLC) of patients with 2 thoracotomies. There was a significant association between an increasing number of thoracotomies and abnormal TLC ($p = 0.03$, Fisher’s exact test).

Individual PFTs were abnormal in 11.1% (TLC) to 66.7% (DLCO_{corr}) of patients who had 2 lesions resected, compared to 30.0% (DLCO_{corr}) to 50.0% (FEV₁) of patients with >2 lesions resected (Table 4). There was no statistically significant association between an increasing number of lesions and abnormal values for any of the PFTs.

No patient had evidence of obstructive lung disease (FEV₁/FVC < 0.70). Six (28.6%) patients had evidence of restrictive lung disease (TLC < 75% predicted).

Individual PFTs were abnormal in 16.7% (TLC) to 50% (FVC, FEV₁, DLCO_{corr}) of patients who had received bleomycin, compared to 33.3% (TLC) to 50% (FEV₁) of patients who had not received bleomycin (Table 5). None of these differences were statistically significant. One of six patients who received bleomycin had evidence of mild interstitial lung disease on chest radiograph, and the other five patients had no evidence of interstitial disease.

After excluding the three patients with anatomic pulmonary resections (n=3), 18 patients with PFTs remained. Fourteen had a single thoracotomy and 4 patients had 2 thoracotomies (range, 2–6). Seven patients had 2 lesions resected and 11 patients had >2 lesions (range, 3–12) resected. FVC was abnormal for 33.3%, FEV₁ for 38.9%, TLC for 22.2%, and DLCO_{corr} for 41.2%. The mean percent of predicted for FVC was 78.7% (SD, 17.8%), FEV₁ 78.2% (SD, 18.6%), TLC 85% (SD, 22.4%), and DLCO_{corr} 79.2% (SD,

19.6%). The proportions of patients with 1, 2, 3, or 4 abnormal PFTs were 23.5%, 5.9%, 5.9%, and 17.7% respectively. No patients had evidence of obstructive lung disease ($FEV_1/FVC < 0.70$). Four (22.2%) patients had evidence of restrictive lung disease ($TLC < 75\%$ predicted).

Discussion

At least 50% of children with osteosarcoma will develop pulmonary metastases at some point in their disease course⁴⁻⁶. Long-term survival is achievable with multi-agent chemotherapy and pulmonary metastasectomy^{10,23}, but its impact on pulmonary function has not been previously studied. Based on data suggesting pulmonary dysfunction following thoracotomy with resection of lung tissue in non-cancer populations, we hypothesized that long-term survivors of pulmonary metastasectomy would have a similar risk. In this, the first report of long-term pulmonary function in patients who underwent pulmonary metastasectomy for osteosarcoma in childhood, we demonstrate a substantial proportion have deficits in pulmonary function.

Several components of treatment regimens for childhood malignancies can produce pulmonary toxicity. Bleomycin therapy has been associated with pulmonary fibrosis which is dose-related²⁴. Kharasch et al. performed PFTs at various times points following the initiation of therapy in 35 children with osteosarcoma who received multi-agent chemotherapy including bleomycin (cumulative dose, 120 to 150 mg/m²). In the first few months, decrements in FEV_1 , TLC , and $DLCO_{corr}$ were seen. PFTs performed more than 2 years after therapy did not differ from PFTs done at diagnosis²⁵. In our cohort, six patients received bleomycin (90 to 140 U/m²), but there was no difference in the prevalence of decreased FVC, FEV_1 , TLC , and $DLCO_{corr}$ between those in the present study who had and had not received treatment that included bleomycin. None of the patients in the current series received radiation therapy involving the lungs. Thus, the present cohort of patients had few confounding treatment factors, making thoracotomy and metastasectomy the predominant treatment variables.

Previous studies have evaluated pulmonary function in children who underwent pulmonary resection for congenital lobar emphysema and other benign lung diseases. These studies suggested that pulmonary resections during childhood resulted in mild decrements in pulmonary function but were limited by small sample size and evaluations of clinically heterogeneous cohorts¹¹⁻¹⁴. In addition only the study by McBride *et al.* evaluated pulmonary function in patients many years (median of 15 years) after undergoing lobectomy during infancy. Even though these patients had on average 22% of their total lung tissue by predicted weight removed, vital capacity (VC) was normal in 13 of 15 patients and TLC was normal in 14 of 14 patients. FEV_1 was below normal in 14 of 15 patients, with a mean predicted value of 73%, whereas the mean values for both VC (94%) and TLC (93%) were normal¹¹.

In our cohort, the PFTs were performed in adults a mean of 20 years after the last pulmonary metastasectomy. Depending upon the specific test considered, 28.6% (TLC) to 47.7% (FEV_1) of the results were abnormal. Among the patients who had 2 thoracotomies,

abnormal PFT results were identified in 50.0% (DLCO_{corr}) to 66.7% (FEV₁, TLC) of patients. Although multiple thoracotomies were associated with more frequent impairment of pulmonary function, the reduction in lung volumes was mild and the reduction in lung diffusing capacity was consistent with the reduction in lung volume.

This study reports long-term follow-up of pulmonary function of 21 long-term survivors of childhood osteosarcoma. The patients received multi-agent chemotherapy, which could complicate the interpretation of the results. However, only a few patients received bleomycin and none was administered carmustine or chest irradiation. Some evidence suggests that even adults experience lung growth²⁶. Perhaps the multi-agent chemotherapy administered to this patient population impairs lung recovery or growth. Additionally, it is possible that other environmental exposures or life styles choices over the intervening years impacted pulmonary function.

Children with osteosarcoma who undergo pulmonary metastasectomy can achieve long-term survival. Long-term follow-up reveals that they have mildly impaired pulmonary function when compared to the normal subjects. It is imperative that these patients be spared additional pulmonary toxic therapies when possible and be counseled about environmental exposures, such as smoking, that might cause a further decrement in pulmonary function.

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Table 1

Demographics

	Patients with PFTs	Patients without PFTs
Mean Age at Diagnosis (years)	13.22 (SD=4.71)	14.45 (SD=2.23)
Mean Age at PFTs (years)	34.90 (SD=10.91)	
Sex		
Male	14 (66.7%)	4 (80.0%)
Female	7 (33.3%)	1 (20.0%)
Race/Ethnicity		
Caucasian	16 (76.2%)	5 (100%)
African American	5 (23.8%)	0 (0%)
Primary Tumor Site		
Femur	12 (57.1%)	4 (80.0%)
Tibia/Fibula	7 (33.3%)	1 (20.0%)
Humerus	2 (9.6%)	0 (0%)

Table 2

Characteristics of study subjects

Patient	Age at diagnosis	Sex	Location of primary tumor	Cumulative drug dose (mg/m ²)			Chest radiation dose (cGy)	Number of thoracotomies	Total number of lesions removed	Pulmonary function test (% predicted)			
				Bleomycin	Doxorubicin	BCNU				TLC	DLCO	FVC	FEV ₁
1	10.4	M	Tibia	0	0	0	0	1 ^a	2	105%	69%	76%	65%
2	15.4	M	Femur	0	424	0	0	1	2				
3	11.0	M	Femur	0	500	0	0	1	1				
4	17.5	M	Fibula	0	226	0	0	2 ^b	2	66%	42%	41%	37%
5	15.9	M	Femur	0	352	0	0	1	1				
6	18.8	M	Femur	0	448	0	0	1	1	79%	71%	80%	82%
7	16.3	M	Tibia	0	390	0	0	1	1				
8	11.0	M	Femur	0	0	0	0	5	8	71%			61%
9	3.3	F	Femur	0	225	0	0	5	12	47%		32%	33%
10	17.9	M	Femur	119	425	0	0	1	2	82%	67%	81%	84%
11	9.4	M	Femur	0	225	0	0	6 ^{c,d}	9	73%	72%	67%	60%
12	12.9	F	Femur	90	380	0	0	1	4	80%	77%	76%	78%
13	10.8	M	Femur	114	380	0	0	1	1	80%	67%	72%	74%
14	15.3	F	Humerus	45	290	0	0	1	3	80%	80%	89%	96%
15	14.1	M	Femur	135	330	0	0	1	8	97%	87%	97%	98%
16	18.8	M	Tibia	140	380	0	0	1	3	57%	48%	57%	48%
17	14.9	F	Femur	0	390	0	0	1	2	89%	64%	81%	82%
18	10.3	F	Femur	0	399	0	0	1	2	107%	78%	95%	85%
19	18.1	M	Femur	0	533	0	0	1	5	58%	61%	53%	56%
20	6.4	M	Fibula	0	372	0	0	2	5	150%	132%	108%	101%
21	4.8	M	Humerus	0	349	0	0	1	1	89%	76%	81%	78%
22	19.9	M	Tibia	0	392	0	0	2	3	87%	88%	85%	84%
23	15.6	M	Femur	0	561	0	0	1	3	82%	77%	85%	84%

Patient	Age at diagnosis	Sex	Location of primary tumor	Cumulative drug dose (mg/m ²)				Chest radiation dose (cGy)	Number of thoracotomies	Total number of lesions removed	Pulmonary function test (% predicted)				
				Bleomycin	Doxorubicin	BCNU					TLC	DLCO	FVC	FEV ₁	
24	13.4	F	Fibula	0	432	0		0	1	3	106%	88%	91%	104%	
25	13.5	F	Femur	0	363	0		0	1	7					
26	13.8	F	Tibia	0	464	0		0	1	1	87%	113%	87%	80%	

^aRight lower lobectomy;

^bLeft pneumonectomy;

^cRight middle lobectomy;

^dLeft upper lobectomy

Table 3

PFTs with respect to the number of thoracotomies (1 versus 2)

PFT	1 thoracotomy	2 thoracotomies	p-value (fisher's exact test)
Abnormal FVC	5/15 (33.3%)	3/5 (60.0%)	0.347
Abnormal FEV ₁	6/15 (40.0%)	4/6 (66.7%)	0.362
Abnormal TLC	2/15 (13.3%)	4/6 (66.7%)	0.031
Abnormal DLCO _{corr}	7/15 (46.7%)	2/4 (50.0%)	1.00

Table 4

PFTs with respect to the number of resected lesions (≤ 2 versus >2)

PFT	2 resected lesions	>2 resected lesions	p-value (Fisher's exact test)
Abnormal FVC	3/9 (33.3%)	5/11 (45.5%)	0.670
Abnormal FEV ₁	4/9 (44.4%)	6/12 (50%)	1.000
Abnormal TLC	1/9 (11.1%)	5/12 (41.7%)	0.178
Abnormal DLCO _{corr}	6/9 (66.7%)	3/10 (30%)	0.179

Table 5

PFTs with respect to treatment that did or did not include bleomycin

PFT	No bleomycin	Bleomycin	p-value (Fisher's exact test)
Abnormal FVC	5/14 (35.7%)	3/6 (50.0%)	0.642
Abnormal FEV ₁	7/15 (50.0%)	3/6 (50.0%)	1.00
Abnormal TLC	7/15 (33.3%)	1/6 (16.7%)	0.623
Abnormal DLCO _{corr}	6/13 (46.2%)	3/6 (50%)	1.00