Somato Publications ISSN: 2643-2692

International Journal of Orthopedics

Research Article

Evaluation of Pulmonary Metastases Resection in Patients with Osteosarcoma

Alcânia Walburga de Souza Pereira dos Reis[1,2*], Carla Donato Macedo[1,2], Vivian Tostes[2], Renato de Oliveira[2], Anderson de Oliveira[2], Maria Teresa de Seixas Alves[2,3], Bruna Fernanda Silva Cardoso[2], Henrique Manoel Lederman[2,4] and Antônio Sergio Petrilli[1,2]

[1]Pediatric Division, Universidade Federal de São Paulo, Brazil

[2]Institute of Pediatric Oncology, IOP, Universidade Federal de São Paulo, Brazil

[3]Pathology Department, Universidade Federal de São Paulo, Brazil

[4]Radiology Departament, Universidade Federal de São Paulo, Brazil

*Address for Correspondence: Alcânia Walburga de Souza Pereira dos Reis, Pediatric Division, Universidade Federal de São Paulo, Brazil, E-mail: alcania@gmail.com

Received: 11 September 2019; Accepted: 16 December 2019; Published: 18 December 2019

Citation of this article: Souza-Pereira-dos-Reis, AW., Donato Macedo, C., Tostes, V., de Oliveira, R., de Oliveira, A., de Seixas- Alves, MT., et al. (2019) Evaluation of Pulmonary Metastases Resection in Patients with Osteosarcoma. Int J Orth, 2(2): 70-77.

Abstract

Introduction: Osteosarcoma (OS) is the tumor malignant primary bone more common in childhood and in adolescence. The worst prognostic factor associated with the disease is the presence of metastasis at diagnosis. Among patients with metastatic disease, there is a tendency for a better response to treatment with cure through complete resection when there are only pulmonary and monumental lesions present.

Objectives: To evaluate the impact of pulmonary nodule resection in patients with suspected OS metastasis.

Methods: Bank review of 36 patient data with OS metastatic diagnosed in the period 2005-2015 in hospital on pediatric oncology in São Paulo, Brazil.

Results: Among the 36 patients included in the study, 19.4% were considered inoperable at diagnosis. Of the 29 patients operated, 9 (30%) patients had lesions false- positive. In the surgical procedure were resected 266 nodulos, with only 43.6% were diagnosed in the chest tomography showing that surgical resection was 3.4 times higher in the identification of nodulos in relation to the examination of image. Of the 29 operated patients, 14 patients had a single nodule (including nodulos smaller than 0.5 cm or larger than 1 cm) diagnosed with OS metastasis in 70% of them after the procedure. The survival rate overall in our population was of 52.3 months and, when excluded from the false positive, the average estimate of survival was 41 months. When we analyzed relapsed patients, almost 50% of those who could be approached three or more times had a higher overall survival rate than the group who could not be surgically approached.

Conclusions: This study showed that patients who completely resected their lung lesions had a significant impact on the overall survival rate in relation to those who did not operate.

Introduction

Metastatic disease and complications of metastatic disease treatment are the leading causes of mortality in children and adolescents with solid tumor including osteosarcoma (OS) in which about 20% of patients already have metastases at diagnosis, in general, pulmonary. The five-year survival rate increased from 40% to 76% in patients fewer than 15 years of age and from 56% to about 66% in adolescents aged between 15-19 [1,2]. This improvement is due to the adequate staging of these tumors, multidrug therapy, the refinement of imaging methods and the improvement of the more aggressive surgical approach [3-5]. In Brazil, Petrilli, et al. (2006) demonstrated that the survival rate and disease-free rate for 209 patients were of 50.1% and 39%, respectively.

Patients with metastatic OS at diagnosis comprise a heterogeneous group. Those with unilateral pulmonary metastasis may present up to 75% event-free survival, while those with multiple bone lesions have worse survival rates [2].

A computed tomography (CT) of the chest is useful in the initial staging and follow-up of the OS and is considered the "gold-standard" diagnostic method, although has limitations in sensitivity and specificity that are well established and must be used with caution for planning minimally aggressive surgery [6-8].

In 1970 all children and adolescents who had relapsed from OS, especially in the lungs, died within 5 years. Seventy-five to 85% of relapses are in lung, however, due to advances in imaging methods with more sensitive CT, and the aggressive surgical treatment, there was a change in the panorama of survival of this group of patients. Several studies about complete surgical resection of pulmonary metastasis have been reported in the literature with positive impact [9].

This study aims to evaluate the impact of complete resection of pulmonary metastases in the survival rate of patients with metastatic OS.

Material and Methods

We retrospectively analyzed the medical records and imaging exams of 36 patients admitted to the Pediatric Oncology Institute of the Child and Adolescent Cancer Support Group of the Universidade Federl de São Paulo (IOP / GRAACC / UNIFESP), from January 1st., 2005, to December 31, 2015, whose the result of primary tumor biopsy was compatible with OS and presentedpulmonary nodules with suspect of metastasis in chest CT performed at the diagnosis.

All patients diagnosed with metastatic OS diagnosed from 2005 to 2015 were included in the study. Patients who had pulmonary metastasis during the first treatment and those who underwent treatment in other institutions were excluded. The study was submitted and approved by Unifesp (0143/ 2016) and GRAACC (035/2015) Ethics Committee.

All patients were treated with the same protocol of the Latin Group Bone Tumor (LGBT) 2006. After ten weeks receiving chemotherapy with MAP scheme (cisplatin, doxorubicin and methotrexate), the local control surgery of the primary tumor site was performed. All patients in the study continued another MAP cycle associated with metronomic chemotherapy and were submitted to chest surgery. The treatment was completed with two more cycles of MA (methotrexate and doxorubicin), totaling 31 weeks of intravenous multidrug therapy. The metronomic chemotherapy was continued for another year and six months

The clinical characteristics of the 36 patients were analyzed regarding gender, age at diagnosis, primary tumor topography, primary tumor histology, degree of HUVOS of the surgical specimen. The pulmonary nodules were analyzed regarding the number and size (at diagnosis and pre-surgery) and histopathological characteristics after surgical resection.

Statistical analysis

Data were analyzed descriptively. Mean comparison between two groups was performed using Student's t-test for independent samples and normality was evaluated by the Kolmogorov-Smirnov test. For data with non-normal distribution, the Mann-Whitney test was used. For categorical variables, Fisher's exact test was performed. For comparison of the average number of nodules between two moments, the Wilcoxon's or Student's t tests were used according to the normality of the data.

The complete survival analysis evaluates the time until an event

occurs (in this case, death). They were analyzed separately for each predictor variable: age, number of nodules at diagnosis and in relapses, primary tumor site, HUVOS, surgical access, tomographic characteristic and pathological anatomy of the lung lesion. For categorical variables Kaplan-Meier survival analysis models was applied.

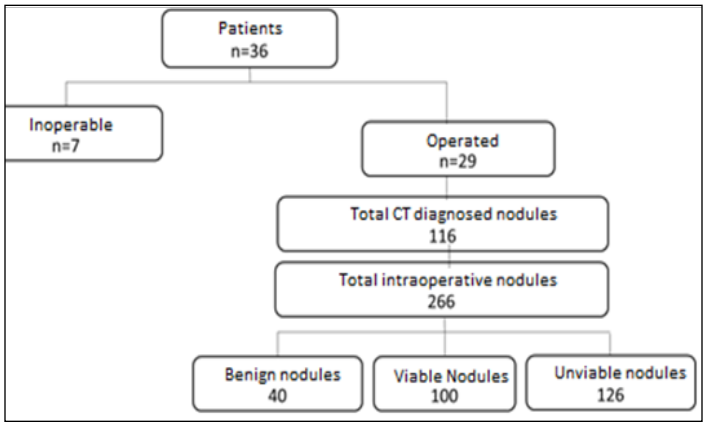
Results

From 2005 to 2015, 159 cases of OS were diagnosed at the IOP / GRAACC / UNIFESP, and 36 patients (22%) had probably or possibly metastatic pulmonary nodules at diagnosis. Consequently, data from 36 patients suspected of pulmonary metastasis were analyzed, whose mean age at diagnosis was 16.3 ± 5.3 years (minimum of 7 and maximum of 26 years) (Table 1).

Of the 36 patients included in the study, seven were considered inoperable. The remaining 29 patients underwent pulmonary nodule resection surgery. Manual exploration and subsequent segment resection were performed, with complete resection of 266 nodules in 29 patients. Of these, 226 (84.9%) nodules were classified as OS metastasis, 100 (37.6%) considered as viable nodules and 126 (47.3%) as non-viable nodules. Eight nodules were also removed in two patients who did not have nodules after chemotherapy on control CT whose pathological findings identified 100% of the nodules as OS metastases. The number of nodules by surgical resection using the palpation method was 3.4 times higher than the number described on chest CT. Of the 29 patients, 31% had false positive nodules, totaling 40 (15%) of the resected nodules (Figure 1).

Fourteen patients had a single pulmonary nodule at the initial diagnostic evaluation by chest CT, and 11 patients (78.5%) had

Figure 1: Study population flowchart and number of nodulos.



CT: Computed tomography.

Table 1: Clinical and demographic characteristics of 36 patients with suspected metastatic OS at diagnosis (%).

	n (%)
Gender	
Male	19 (52.8)
Female	17 (47.2)
Race	
White	19 (52.8)
Non-White	17 (42.7)
Age at diagnosis (years) *	16.3 ± 5.3
Primary tumor site	
Femur	18 (50.0)
Tibia	6 (16.7)
Fibula	1 (2.8)
Humerus	5 (13.9)
Pelvis	2 (5.6)
Jaw	1 (2.8)
Polyostotic	3 (8.3)
Histology - Osteoblastic	20 (55.6)
Histology - Non-Osteoblastic	16 (44.4)
Primary tumor HUVOS **	
1	14 (50.0)
2	5 (17.9)
3	3 (10.7)
4	6 (21.4)
Not analyzed	8 (22.2)
Pulmonary nodule as suspected single metastatic site	27 (75.0)
Classification of nodules at diagnosis	
1 to 3 nodules and at least 1 nodule ≥ 0.5 cm	22 (61.1)
≥ 4 nodules	14 (38.9)
Inoperable for pulmonary nodules	7 (19.4)

Note: * Mean ± Standard Deviation, ** Data available from 28 patients.

nodules smaller than 1 cm and six (42.8%) patients had nodules upto 0.5 cm (Figure 2).

Nine patients have false positive results. Fivepatients presented femur as the primary site, seven had one to three nodules in chest CT at the diagnosis, six had at least one nodule greater than 0.5 cm larger diameter and four patients were good responders to chemotherapy.

However, it was observed that in the group of false positive patients, 31.8% had few nodules, approximately 60% presented small

nodules with at least one 0.5 cm nodule and almost 50% had HUVOS between 3 and 4. However, truly metastatic patients (68.2%) had truly few nodules, almost 90% lump size of up to 0.5cm and about 84.2% presented HUVOS 1 and 2.

Also, the groups with the best survival curves were those with femur as primary site, HUVOS 3-4 and osteoblastic histological subtype (Table 3).

According to the Cox model, patients with pulmonary metastasis have an 8.08 times higher risk of death than patients without this condition. Although such results were not statistically significant, patients with only pulmonary metastasis showed an overall 48-month survival rate of 55.6% (± 10.7), which is higher than those with combined bone and lung or lymph node metastasis 30% (± 23.9) (Table 3). In addition, via Kaplan Meier model, a mean survival time of 52.3 months (38.7 - 65.9; 95% CI) and 41.0 months (26.9 - 55.0; 95% CI), respectively to the total and excluding the cases of false positives (Table 4).

In almost half of the cases in our study where detected two to four relapses in 48 months. In those that presented only one recurrence, the survival incidence at 48 months was 19% (Table 5).

Discussion

Chest CT is the gold standard test to identify lung nodules. However, this test presented limitations in daily clinical practice with the possibility of underestimating the number of lung metastatic lesions in 40 to 50% of the cases and not distinguishing malignant and benign disease, including the differential diagnosis with anthracose, fibroma, benign calcification, tuberculosis or even normal lung tissue [12]. Fernandez-Pineda, et al. [13] showed that of

Figure 2: Single node flowchart.

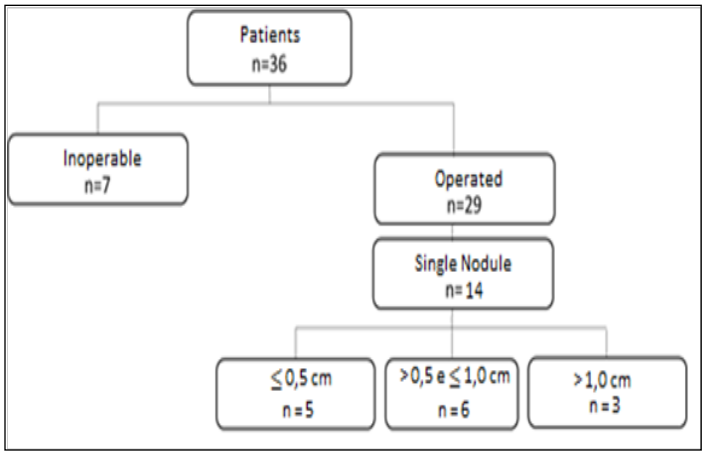


Table 2: Characteristics of patients with OS metastasis and false positives.

		Yes*		Not*		Total	P
	no	%	no	%	no	%	
Primary location	9	31	20	69	29	100	1,000
Femur	5	31.3	11	68.8	16	100	
Other	4	30.8	9	69.2	13	100	
Classification of nodulos at diagnosis	9	31	20	69	29	100	1,000
1 to 3 nodulos	7	31.8	15	68.2	22	100	
≥ 4 nodulos	2	28.6	5	71.4	7	100	
Classification of pre - thoratocomy nodulos	9	31	20	69	29	100	0.233
1 to 3 nodulos and all ≤ 0.5cm	1	11.1	8	88.9	9	100	
1 to 3 nodulos and at least 1 nodule> 0.5cm	6	46.2	7	53.8	13	100	
≥ 4 nodulos	2	28.6	5	71.4	7	100	
Primary tumor HUVOS *	7	25	21	75	28	100	0.188
1-2	3	15.8	16	84.2	19	100	
3-4	4	44.5	5	55.5	9	100	

* YES: Metastatic, No: False positive

Table 3: Results of Kaplan-Meier survival analysis by population characteristics.

	Accumulated% of Survival				
	6 Months	12 Months	24 Months	48 Months	P
Total (n = 36)	86.2 ± 6.4	75.7 ± 8.0	60.9 ± 9.3	51.5 ± 9.9	-
Tumor site (n = 36)					0.28
Femur	93.8 ± 6.1	80.8 ± 10.0	59.8 ± 12.8	59.8± 12.8	
Other	76.9 ± 11.7	69.2 ± 12.8	61.5 ± 13.5	41± 14.9	
Huvos (n = 28)					0.019
1-2	88.2 ± 7.8	70.6 ± 11.1	52.3 ± 12.3	37.3± 12.5	
3-4	88.9 ± 10.5	88.9 ± 10.5	88.9 ± 10.5	88.9± 10.5	
Pathological anatomy (n = 29)					0.016
Osteosarcoma Metastasis	80.0 ± 8.9	64.6 ± 10.8	47.9 ± 11.6	35.9± 11.4	
Non - Osteosarcoma Metastasis	100	100	88.9 ± 10.5	88.9± 10.5	
Primary tumor histology (n = 36)					0.056
Osteoblast	93.8 ± 6.1	93.8 ± 6.1	81.3 ± 9.8	65± 12.9	
Non osteoblastic	76.9 ± 11.7	52.7 ± 14.1	35.2 ± 13.9	0± 0.0	
Target location at diagnosis (n =29)					0.298
Lung	83.3 ± 7.6	75.0 ± 8.8	61.2 ± 10.2	55.6± 10.7	
Lung and Others	100	80.0 ± 17.9	60.0 ± 21.9	30± 23.9	

133 patients with OS, 18 (13.5%) had benign pulmonary lesions and 16 had a single nodule. Pastorino, et al. [26] demonstrated that of 3498 (67%) patients, 86% were completely resected and 14% were inoperable; 51% of patients had a single radiation injury and 49% multiple injuries. The probability of incomplete response was higher in patients with multiple injuries (23% vs 9%). Tomography underestimated 16% to 39% of cases. This underscores the importance of surgical resection in all patients with suspected pulmonary metastasis at diagnosis, as patients with OS and pulmonary metastasis will be healed only if all lesions are removed. In the present study, patients with OS and lung metastasis have 8.08 more chances of death than patients without metastases.

In a study by Kayton, et al. [12], 329 nodules were resected and 36.5% were benign. In a study by Heaton, et al. [14], from 835 resected nodulos, 33.1% were benign. Our study is pioneer in the Brazilian population and demonstrated similar results to other countries.

Since 1979, the best imaging exam to identify possible lung metastases has been CT, and over the years it has become helical CT, which identifies lesions of less than six millimeters in up to 60% of cases with 80% sensitivity in all types of pulmonary metastasis [15]. Kayton, et al. [12] showed a false positive rate of about 40% and have also demonstrated that CT may underestimate the number of nodules when dry, since thatin 19 thoracotomies were found more nodules on CT, from a total of 54.

When we analyzed patients with disease (pulmonary metastasis of OS), including those inoperable, the 48-month survival rate was 31.9%. Patients with metastatic OS usually over the years do not improve in survival rates and their exclusion in many clinical trials may validatethe decreased exposure of these patients to more aggressive approaches and more recent treatments [9]. When the false positive cases were excluded, the estimated average survival was 41 months.

The present study brings relevant data to the national literature that will contribute to metastatic OS studies, since demographic data such as gender, primary site, primary tumor histological type and degree of chemotherapy response (HUVOS) were similar to those reported in the literature, both in terms of frequency and overall survival rate, except race – white race was more frequent in our study.

Table 4: Estimate of the average survival time (months) estimated by the Kaplan-Meier model.

	Average	EP	CI (95%)
All patients (N = 36)	52.3	6.9	38.7 - 65.9
1 to 3 nodulos and all nodulos ≤ 0.5	59.3	13.1	33.6 - 85.0
1 to 3 nodules and at least 1 nodule> 0.5	59.3	10.8	38.2 - 80.5
4 or more nodules	73	13.7	46.1 - 99.9
Inoperable	9.9	2.1	5.8 - 13.9
All patients except inoperable patients with 4 or more nodules(N = 27)	41	7.2	26.9 - 55.0
1 to 3 nodulos and all nodulos ≤ 0.5	54	13.6	27.3 - 80.7
1 to 3 nodules and at least 1 nodule> 0.5	45.6	12.7	20.7 - 70.4
4 or more nodules	53.6	13.9	26.3 - 80.9
Inoperable	9.9	2.1	5.8 - 13.9

Table 5: Results of Kaplan-Meier survival analysis by number of relapses including all nodulectomy patients (n = 29).

Accumulated% of Survival					
	6 Months	12 Months	24 Months	48 Months	P
Number of Relapses					0.208
0	87.5 ± 8.3	81.3 ± 9.8	67.0 ± 12.2	67.0 ± 12.2	
1	85.7 ± 13.2	57.1 ± 18.7	57.1 ± 18.7	19.0 ± 16.8	
4-Feb	83.3 ± 15.2	83.3 ± 15.2	50.0 ± 20.4	50.0 ± 20.4	

Note: Survival probability estimate ± Standard error, P - Descriptive level of Log Rank test (Mantel-Cox)

In the present study, all patients with lung nodules were considered metastatic at diagnosis, representing 22% of OS patients. In the literature, metastatic disease is described in 18% to 20% of OS patients at diagnosis [16,17]. Bacci, et al. [18] showed that 61% to 75% had only pulmonary metastasis and Harting, et al. [19] found that the lung may be the site of metastasis in up to 85% of OS patients, similar to our study.

Bielack, et al. [20] also described that the presence of metastasis at diagnosis has been considered a worse prognostic factor, demonstrating that patients with isolated pulmonary metastasis have a better prognosis and survival rates, similar to our study. Kim, et al. [21] evaluated 126 patients with OS and found overall survival at 3, 5 and 10 years of 38.5%, 31% and 25.3%, respectively. Moreover, these authors described that perform the resection of lung nodules ($p < 0.001$), single only metastasis ($p = 0.007$), response to chemotherapy ($p = 0.022$) and the absence of recurrence ($p = 0.049$) had a positive impact on patient survival.

Regarding pulmonary relapses, it is already described in the literature that 75% - 85% of patients with OS relapse in the lung with approximately 25% five-year survival when thoracotomy was performed [12,22-24]. Several studies have shown that resection of pulmonary metastases improves survival rates for OS [12,21,25] patients and that combined therapy with surgery and multidrug therapy results in survival rates of 65-70% [20,21]. Pastorino, et al. [26] suggest that several surgical resections for pulmonary nodule removal may be necessary to achieve definitive healing and that repeated retrieve surgery may be safe and effective in the long term. In the present study, of 36 patients, 36.1% had some pulmonary recurrence. In addition, the survival rate in those who underwent between four and five multidrug-associated thoracotomies achieved a 48-month survival rate of 100%. On the other hand, those patients who did not achieve complete resection in the second and third thoracotomies had survival rates between 19% and 25%.

We recognize some limitations of the study. First, although the small number of patients limits some analyzes, it is a rare disease representing about 6% of malignant neoplasms in the pediatric age group, whose case series and reliable data on the disease are not always easily accessible. Second, although it is a retrospective study, patients were followed for 10 years undergoing the same protocol of chemotherapy. Chest CT scans were performed by the same CT scanner and wereblind reviewed by a single radiologist with extensive experience in pediatric oncology for anatomopathological outcome. Surgical procedures (pulmonary and orthopedic) were performed by the same teams in all cases, showing standardization in the sample. Finally, due to its retrospective nature, we cannot rule out the influence of other factors on patient survival.

Thus, we demonstrated that pulmonary surgical resection has an impact on this select group of patients, data never before evaluatedin the Brazilian population.Besides that, patients with OS pulmonary metastasis have 8.08 times higher risk of death when compared to those who do not. Consequently, we confirmed that complete resection of these lesions improves the survival and cure rate of the disease and that all groups of patients with pulmonary metastasis benefits from the surgical procedure. The chest CT presented some limitations and cannot diagnose and identify accurately all suspicious lesions. However, new treatment protocols for OS in an attempt to improve the curves of survival must develop new strategies to reduce false positives and increase the sensitivity of diagnosis.

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