


# Survival in adult osteosarcoma patients after resection of isolated pulmonary metastases — a single-center experience

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## Abstract

**Introduction.** Data on factors affecting disease recurrence and survival after pulmonary metastasectomy in adult osteosarcoma patients are still limited and inconclusive.

**Material and methods.** The study included 30 consecutive patients from a single institution who underwent resection of isolated osteosarcoma, with follow-up of pulmonary metastases over the period of 15 years between 1997 and 2012. Various perioperative variables were analyzed retrospectively to confirm the prognostic role of pulmonary surgery for overall and progression-free survival after metastasectomy. The multidisciplinary approach was implemented in qualification for repeated thoracic intervention.

**Results.** The overall 5-year survival rate (OS) after metastasectomy was 28% (median 27.5 months) and the 5-year progression-free survival rate (PFS) was 9% (median 6.33 months). Only radical pulmonary resection significantly influenced both OS (HR = 5.41; 95% CI 1.87–15.60,  $p = 0.002$ ) and PFS (HR = 5.17; 95% CI 1.70–15.68,  $p = 0.004$ ) after metastasectomy. The efficacy of thoracic surgery was independent of the patient's age, sex, number of operable lung metastases, bilateral presence of lung metastases, or time to the appearance of lung metastases after surgery for osteosarcoma. Five-year OS and PFS after radical and nonradical pulmonary metastasectomy were 35% vs. 0% ( $p = 0.002$ ) and 11% vs. 0% ( $p = 0.004$ ), respectively. In the observed group, 60 thoracotomies were performed; 3 or more procedures were needed in 8 (27%) patients.

**Conclusions.** Similar to the population of children and adolescents, radical pulmonary metastasectomy may be a curative treatment strategy in selected adult patients with metastatic osteosarcoma. Repeated procedures are necessary in many cases.

**Keywords:** osteosarcoma, pulmonary metastasectomy, adult patients, outcome

## Introduction

The lung is the most frequent site of metastases in osteosarcoma. Osteosarcoma lung metastases are detected during initial diagnosis or as a recurrence after radical multimodal treatment. Approximately 20% of osteosarcoma patients have metastatic disease at the

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time of initial diagnosis, and the majority of these are pulmonary metastases without other symptoms of cancer disease [1]. Additionally, 30–50% of patients after radical multimodal treatment may have disease recurrence with a high probability of isolated lung metastases [2]. Pulmonary metastases are the only location of osteosarcoma disease in about 50–80% of patients [1–4]. Long-term survival in these patients has improved with aggressive resection of pulmonary metastases with the use of combination chemotherapy [5]. Most previous studies concerned the pediatric and adolescent population due to the higher incidence of osteosarcoma in young patients, and their prognosis appears better [6]. Similarly, most articles on survival and prognostic factors after pulmonary metastasectomy refer to both osteosarcoma and soft tissue sarcoma together in adult patients although the biology, treatment, and prognosis of these two cancer types are different [6–8]. Important prognostic factors for survival after pulmonary metastasectomy include the disease-free interval, age, sex, number of lesions, time of occurrence of metastases (synchronous/metachronous), laterality of metastases, and completeness of resection [2, 4, 7–11].

The main objective of our study was to evaluate prognostic factors for survival in adult patients with osteosarcoma after pulmonary metastasectomy based on a single-center experience.

## Material and methods

From January 1997 to December 2012, 176 adult patients (over 18 years old) with high-grade osteosarcoma were diagnosed and treated at the Maria Skłodowska-Curie Institute, Oncology Centre (now Maria Skłodowska-Curie National Research Institute of Oncology) in Warsaw. Twenty-two (12.5%) patients had metastases at presentation, 154 (87.5%) had localized disease. Among patients with tumors localized after radical multidisciplinary treatment, 53 (34.4%) had metastatic disease, and 42 (79.2%) of them had metastases located only in the lung. Twenty-four (57%) of them underwent pulmonary metastasectomy, and 18 (43%) were considered unresectable due to the high probability of incomplete resection or fast progression during chemotherapy before planned metastasectomy. Among 22 patients with synchronous metastases, 6 had isolated resectable pulmonary metastases. Thus, we identified 30 consecutive adult patients with synchronous (6 patients) or metachronous (24 patients) pulmonary osteosarcoma metastases who underwent at least one pulmonary metastasectomy between 1997 and 2012. All patients had isolated pulmonary metastases without evidence of extrapulmonary disease at the time of pulmonary resection. Patients with synchronous pulmonary metastases underwent radical multimodal

treatment of the primary tumor including surgery and standard perioperative chemotherapy before metastasectomy. Patients with metachronous metastases underwent multiagent chemotherapy (including mainly etoposide and ifosfamide as second-line systemic therapy in our institution) before metastasectomy. All patients qualified for metastasectomy had no progression of the disease after preoperative chemotherapy. Computed tomography (CT) scans were performed at least 4 weeks before surgery. The indications for pulmonary metastasectomy included primary tumor control, lack of other metastatic sites outside the lungs, and sufficient pulmonary reserve to avoid pulmonary failure after complete surgical resection of metastases. All lung resections were performed by thoracotomy, also in bilateral lesions. Mediastinal lymphadenectomy or sampling during lung metastasectomy was performed in all patients. Palpation of the lung tissue was carried out to detect metastases that were not identified earlier on CT scans. Follow-up after radical pulmonary resection included alternating chest radiographs and CT scans performed every 6 weeks in the first year, every 3 months in the second and third year, and every 6 months thereafter. Complete staging based on chest CT and bone scans was repeated if lung disease relapse was suspected. The next pulmonary metastasectomy was attempted in most patients with isolated pulmonary metastases after disease recurrence. The collection of follow-up data was completed in June 2020. The study was carried out according to the principles recommended by the bioethics commission at the Maria Skłodowska-Curie National Research Institute of Oncology in Warsaw. All patients signed informed consent.

The prognostic variables were extracted from medical records and included age at the time of the first metastasectomy, sex, number of lung metastases (as confirmed by pathologists), laterality of metastases, disease-free interval (DFI; calculated as the time from primary radical resection of osteosarcoma to initial diagnosis of pulmonary metastases) and how radical metastasectomy was. Complete resection was defined as the lack of tumor cells in the surgical margins of the resected lung examined macroscopically and histologically and surgical removal of all visible and palpable nodules. All bilateral procedures (including staged bilateral thoracotomies) that occurred within 6 weeks of each other were considered a single intervention in the analysis.

Overall survival (OS) was calculated as the time from the date of initial pulmonary metastasectomy to the date of death (complete) or the last follow-up (censored data). Progression-free survival (PFS) was calculated as the time from the date of initial pulmonary metastasectomy to the date of disease recurrence (complete) or the last follow-up (censored).

The Kaplan-Meier methods, log-rank test, and Cox's proportional hazards model were used to determine prognostic factors for both OS and PFS.

## Results

In the group of 30 adult patients after pulmonary metastasectomy for osteosarcoma, there were 20 (66.7%) men and 10 (33.3%) women. At the onset of lung involvement, the median age was 26 years (range 19-56). The disease-free interval (DFI) rate ranged from 0 months to 11 years, including 6 (20%) patients with a simultaneous diagnosis of the primary tumor and pulmonary metastasis. The lung was the first site of osteosarcoma recurrence after radical multimodal treatment of the primary site in 17 (57%) patients. In 7 (23%) patients locoregional recurrence was observed first and radically treated before detection of lung metastases. In 16 (53%) patients, lung metastases were found to be bilateral. Population characteristics are listed in Table 1.

After 30 initial thoracotomies, 6 (20%) patients underwent non-radical resection. In those patients, small lesions caused by disease dissemination that had not been visualized on the preoperative CT scans were detected during thoracotomy. A non-radical wedge resection was performed to confirm metastatic disease. All of the patients with non-radical operations died within 2 years due to progression despite intensive chemotherapy.

Twenty-four (80%) patients were qualified for radical resection based on macroscopic and microscopic examinations. However, in 19 patients one or more wedge resections were performed, and in 4 cases, lobectomy and pneumonectomy were performed in one subject. No metastases involving the hilar or mediastinal lymph nodes were found. The mean number of metastatic nodules resected was 4.9 (range: from 1 to 18 nodules).

The median follow-up time was 29 months (range: 5–209 months). Among 24 patients after radical resection, 3 (12.5%) patients were alive without recurrence after initial thoracotomy, 21 (87.5%) had disease progression: 17 (81%) patients had isolated pulmonary metastases, 11 (64.7%) underwent next pulmonary metastasectomy, and 8 (33%) were operated at least 3 times (range: 3–9) due to isolated pulmonary recurrence. The patient after 9 procedures was still alive without progression with overall survival of 90 months.

In the analyzed group of 30 patients, we performed 60 thoracotomies without postoperative death (Tab. 2).

The median OS rate after pulmonary metastasectomy in the entire group was 27.5 months, and the 5-year OS rate was 28%. Patients after radical resection had median OS of 33.5 months and a 5-year

**Table 1.** Characteristics of 30 patients with osteosarcoma requiring thoracic surgery for lung metastases

<b>Age [years]</b>	
Median	26
Quartiles	24–36
Min.–max.	19–56
<b>Sex</b>	
Female	10 (33.3%)
Male	20 (66.7%)
<b>Lung metastases</b>	
Synchronous	6 (20.0%)
Metachronous	24 (80.0%)
<b>Lung metastases</b>	
Unilateral	14 (46.7%)
Bilateral	16 (53.3%)
<b>Time to lung metastases occurrence after surgery due to osteosarcoma [months]</b>	
Median	14.5
Quartiles	5.8–23.3
Min.–max.	0–133.5
<b>Number of operable lung metastases</b>	
One	10 (33.3%)
Two or three or four	9 (30.0%)
Five and more	11 (36.7%)
<b>Radical pulmonary metastasectomy</b>	
Yes	24 (80.0%)
No	6 (20.0%)
<b>Disease progression</b>	
Yes	27 (90.0%)
No	3 (10.0%)
<b>Death</b>	
Yes	21 (70.0%)
No	9 (30.0%)

**Table 2.** Outcomes of 60 thoracotomies in 30 patients

Status	Number of patients	Number of thoracotomies				
		1	2	3	4	5 9
No evidence of disease	7	3		1		2 1
Alive with disease	2	1		1		
Died due to disease	21	15	3	2	1	

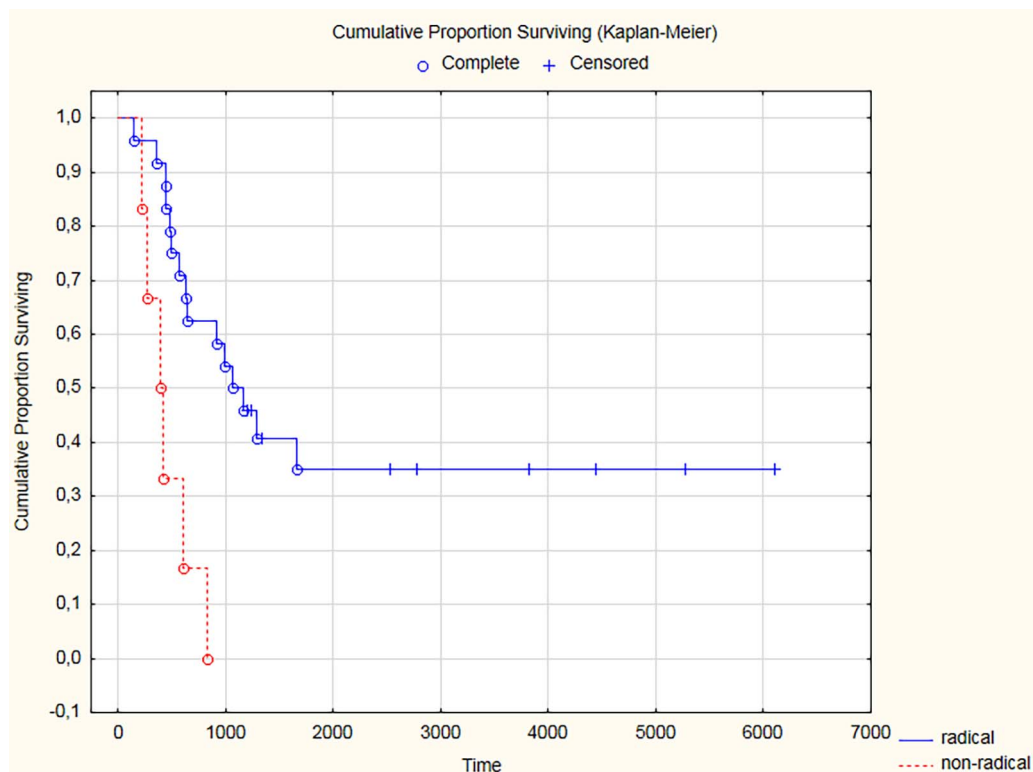
OS rate of 35%. Patients after nonradical resection had a significantly worse prognosis: median OS was 13.3 months, and the 5-year OS rate was 0%. (Tab. 3, Fig. 1).

In the univariate analysis, only radical pulmonary resection was a significantly important factor that influenced OS (Tab. 4). Multivariate analysis confirmed the independent importance of radical pulmonary resection for OS.

**Table 3.** Survival estimates in relation to thoracic surgery

	<b>2-year</b>		<b>5-year</b>		<b>p-value</b>
	Rate	SE	Rate	SE	
<b>Progression-free survival (PFS)</b>					
<b>All patients</b>	0.13	0.06	0.09	0.06	
<b>Radical pulmonary metastasectomy</b>					
No	0	0	0	0	p = 0.004
vs.					
Yes	0.17	0.08	0.11	0.07	
<b>Overall survival (OS)</b>					
<b>All patients</b>	0.53	0.09	0.28	0.09	
<b>Radical pulmonary metastasectomy</b>					
No	0.17	0.15	0	0	p = 0.002
vs.					
Yes	0.63	0.1	0.35	0.1	

SE — survival estimate



**Figure 1.** Survival estimates in relation to thoracic surgery

Median PFS in the entire group was 6.33 months, and the 5-year PFS rate was 9%. Patients after microscopically radical resection had a median PFS rate of 8.1 months and a 5-year PFS rate of 11%, which was a significantly better outcome compared to patients after non-radical resection: 3.3 months and 0%, respectively (Tab. 3).

Similarly, in the univariate and multivariate analysis, only radical pulmonary resection was significantly associated with longer PFS (Tab. 5).

## Discussion

Pulmonary metastasectomy has become the standard therapy for various metastatic malignancies in the lungs, including osteosarcomas. Therefore, we decided to report our institutional experience in pulmonary metastasectomy in the population of adult patients with osteosarcoma and to evaluate its role in extending OS and PFS. This was a retrospective study of adult patients who underwent pulmonary metastasectomy for synchronous and metachronous isolated

**Table 4.** Analysis of the clinically important factors that influenced overall survival (OS) in osteosarcoma patients after thoracic surgery for lung metastases

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
<b>Age</b>						
Older than median ( $\geq 27$ y) vs. younger ( $\leq 26$ y)	0.57	0.23–1.38	p = 0.21	0.43	0.16–1.13	p = 0.08
<b>Sex</b>						
Female vs. male	0.65	0.25–1.70	p = 0.38	0.64	0.19–2.15	p = 0.47
<b>Time to lung metastasis occurrence after surgery for osteosarcoma [months]</b>						
$\leq 12$ m vs. $> 12$ m	1.72	0.72–4.12	p = 0.22	1.44	0.48–4.31	p = 0.52
<b>Lung metastases</b>						
Bilateral vs. unilateral	1.39	0.59–3.29	p = 0.45	0.59	0.16–2.24	p = 0.44
<b>Number of operable lung metastases</b>						
More than one vs. one	1.21	0.49–3.01	p = 0.68	1.19	0.33–4.29	p = 0.79
<b>Radical pulmonary metastasectomy</b>						
No vs. yes	5.41	1.87–15.60	p = 0.002	10.09	2.32–43.91	p = 0.002

CI — confidence interval; HR — hazard ratio

**Table 5.** Analysis of the clinically important factors that influenced progression-free survival (PFS) in osteosarcoma patients after thoracic surgery for lung metastases

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
<b>Age</b>						
Older than median ( $\geq 27$ y) vs. younger ( $\leq 26$ y)	0.47	0.21–1.06	p = 0.07	0.60	0.23–1.52	p = 0.28
<b>Sex</b>						
Female vs. male	1.03	0.44–2.40	p = 0.94	1.46	0.52–4.15	p = 0.48
<b>Time to lung metastasis occurrence after surgery for osteosarcoma [months]</b>						
$\leq 12$ m vs. $> 12$ m	1.50	0.69–3.26	p = 0.31	1.59	0.64–3.95	p = 0.32
<b>Lung metastases</b>						
Bilateral vs. unilateral	1.31	0.61–2.82	p = 0.49	0.51	0.18–1.46	p = 0.21
<b>Number of operable lung metastases</b>						
More than one vs. one	1.67	0.72–3.89	p = 0.23	1.86	0.61–5.65	p = 0.27
<b>Radical pulmonary metastasectomy</b>						
No vs. yes	5.17	1.70–15.68	p = 0.004	6.28	1.71–23.04	p = 0.006

CI — confidence interval; HR — hazard ratio

pulmonary osteosarcoma metastases. To our knowledge, this is one of the largest series in the adult population after pulmonary metastasectomy for osteosarcoma reported by individual institutions.

The median age of our patients at the onset of lung involvement was 26 years (range 19–56). Aljubranet et al. [12] reported a series of 85 adult and adolescent patients after pulmonary metastases. The median age of their patients was 29 years (range 14–77), and 71 (83.5%) of them were  $< 18$  years old. Only 47 (55.35%) of all patients underwent pulmonary metastasectomy. Furthermore, there were 35 (74.5%) complete pulmonary resections. Our rate for complete resections was similar (80%). The most frequent reasons for aborting complete surgery were small metastatic deposits in the lungs found during thoracotomy. This underlines the need for careful

palpation of the lung during thoracotomy. Due to the high risk of micro-nodular dissemination in patients with metastatic pulmonary osteosarcoma, it seems that video-thoracoscopic surgery should be carefully considered only in patients with a single metastasis. The complete resection rate is variable in the literature, ranging between 65% and 91.5% [3, 13–16]. In our study, only radical resection was a significantly important predictor of long-term OS and PFS after pulmonary metastasectomy. The completeness of resection has been reported to be a better prognostic factor for overall survival in many studies including pediatric populations [1, 3, 7, 14, 16–18], but only two reports [3, 7] confirm this result for progression-free survival in metastatic osteosarcoma patients. Salah et al. noted this association in 14 of 32 patients with metastatic lung osteosarcoma [3]. Kempf-Bielack

et al. [7] reported on a larger group, but their study was not restricted only to lung metastases and the adult population.

The number of resected nodules and DFI have been often identified by many previous studies as important independent risk factors for long survival after lung metastasectomy in osteosarcoma patients [3, 7, 12, 13, 19]. Some studies have reported only the number of nodules as a statistically significant risk factor for OS, while DFI had no importance [14, 16, 18]. In contrast, Harting has reported the importance of DFI, and the number of pulmonary metastases was also insignificant [15]. Laterality of metastases has been identified as an independent risk factor only in a few studies [3, 18]. All of these reports included pediatric patients. Our study found that the above-described factors are nonsignificant for OS and PFS.

In our study, the 5-year survival rate was 28% in all groups, 35% in radically resected patients, and 0% in patients with unexpected nodule dissemination during thoracotomy. This result is similar to previous studies, including pediatric cases [1, 3, 7, 13–17, 19], and confirms the important and independent role of radical surgery in treating pulmonary metastases. A few reports described a survival rate of 5% in nonradical metastasectomy patients or between 10–16% in patients without metastatic surgery [12, 18, 20]. Furthermore, national or international registries have recorded 5-year survival for all patients with metastatic osteosarcoma at 19–24% [3, 19, 21], but it is worth emphasizing that aggressive radical surgery offers a higher probability of longer survival in carefully selected patients with pulmonary metastases. However, no randomized controlled trials have compared pulmonary metastasectomy with other treatment modalities [16, 21].

In our group of 30 patients after initial resection, 11 (37%) needed a repeated metastasectomy due to isolated recurrence of pulmonary osteosarcoma. In addition, 8 (27%) patients had 3 or more thoracotomies, and 4 patients were alive and disease-free at the last follow-up. It emphasizes the important role of repeated pulmonary metastasectomy in selected patients as a curative treatment. This phenomenon has been observed in many other studies, but complete surgery is still crucial as the treatment strategy for recurrent disease [3, 4, 14–16, 18–20, 22]. The next problem is maintaining a satisfactory quality of life with good cardiopulmonary exercise capacity after repeated thoracic surgery. A specialized multidisciplinary team is needed for patient care.

We are aware of several limitations to our study. The results should be interpreted with caution due to the retrospective design of the study and the relatively small number of patients. However, the limitations mentioned above result from the small incidence of

osteosarcoma, especially in the adult population. Our well-defined patient cohort represented a relatively satisfactory study group. Additionally, chemotherapeutic regimens and surgical strategies have evolved substantially and rapidly over the last 20 years and treatment decisions are individualized according to tumor biology and unique patient characteristics in many tumor types, but not in osteosarcoma.

## Conclusions

Pulmonary metastasectomy may be a curative treatment strategy in selected adult patients with isolated pulmonary metastases of osteosarcoma, similar to the populations of children and adolescents. The possibility of radical resection seems to be the most important indication for pulmonary metastasectomy and repeat surgery. These procedures require careful collaboration of the multidisciplinary team and offer a satisfactory probability of longer survival with a good cardiopulmonary exercise capacity.

## Article Information and Declarations

### Data availability statement

All analyzed data is included in this article. Further inquiries may be directed to the corresponding author.

### Ethics statement

The study was conducted according to the criteria set by the declaration of Helsinki. Due to the retrospective nature of the study, local Bioethics Committee approval was not necessary.

### Author contributions

M.G.: study concepts and design, data acquisition, analysis and interpretation, quality control of data, literature review, manuscript preparation, manuscript editing, manuscript review; S.S.: statistical analysis, manuscript editing, manuscript review; O.G.: data acquisition, literature review, manuscript editing; I.Ł.: data acquisition, quality control data; Ł.T.: data acquisition; M.Ż.: data acquisition; P.R.: data acquisition, manuscript review.

All authors approved the final version of the manuscript.

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### Conflict of interest

The authors declare they have no conflict of interest.

### Supplementary material

None.

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