

Outcomes of minimally invasive surgery for pulmonary metastasis: who benefits the most?

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Abstract

Introduction: Metastatic disease is one of the main causes of death and factors affecting overall survival. It is known that selected patients with pulmonary oligometastases whose primary tumor is under control and who have adequate respiratory capacity may benefit from metastasectomy by resecting all detected lesions.

Aim: To report our findings on the use of video-assisted thoracoscopic surgery (VATS) for pulmonary metastasectomy, with a focus on identifying suitable candidates.

Material and methods: Between August 2010 and 2023 a total of 532 pulmonary metastasectomy procedures were performed in our institution. Metastasectomy was performed with VATS for 281 of those patients.

Results: VATS metastasectomy was performed in 131 patients with a single lesion on preoperative imaging, while 110 patients underwent metastasectomy for multiple lesions. The rate was significantly ($p < 0.05$) lower in the group with multiple lesions removed during surgery (38 months) than in the group with only one lesion removed during surgery (60 months). The predicted survival time in the group with other tumor histology (79 months) was significantly ($p < 0.05$) higher than in the groups with tumor histology carcinoma (41.4 months) and sarcoma (55.5 months).

Conclusions: The best prognosis after metastasectomy is provided in cases with a single nodule. Grade is also an important prognostic factor affecting survival, particularly for grade 1 tumor. The histopathological type of the primary tumor is also a significant prognostic factor affecting survival after pulmonary metastasectomy in secondary pulmonary neoplasms, particularly for sarcoma and carcinoma.

Key words: minimally invasive thoracic surgery, pulmonary metastasectomy, video-assisted thoracic surgery.

Introduction

Malignant tumors are often treated by individual surgical resection, radiotherapy systematic oncologic medical treatment or a combination of these methods. Advancements in techniques and content have led to successful results in recent years. However, the risk of local recurrence and distant metastasis still persists. The presence of metastatic disease

evidently has an effect on treatment outcomes and overall survival of patients. The lungs are a common site for metastasis of certain systemic malignancies such as breast cancer, colorectal cancer, sarcoma, and head/neck squamous cell carcinomas. Due to this common clinical situation, there has been ongoing debate about the most effective approach and purpose of surgery for solitary lung metastasis in frequent clinical cases since the 1970s. Howev-

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er, there are no randomized prospective studies comparing surgical resection with other treatment methods. It is widely understood that some patients with a pulmonary metastasis, whose primary tumor shows no signs of activity (no local recurrence or any either metastatic site), can benefit from undergoing pulmonary metastasectomy [1]. The current surgical referral is based on a publication from the International Lung Metastasectomy Unit [2] where the 5-year follow-up after pulmonary metastasectomy survival rate was in the range 20–40% [3]. A general rule of thumb is to ensure that the disease is being managed at the local level and that there are no indications of its spread across the body.

As minimally invasive surgery is becoming more commonly employed, there is a debate concerning the uses of the minimally invasive approach, video-assisted thoracoscopic surgery (VATS) and the classical open (thoracotomy) approach for metastasectomy cases.

Open surgery via thoracotomy is recommended due to the advantage that the lung can be palpated manually by the surgeon, making it possible to detect additional lesions, undiagnosed by radiological imaging [4]. Due to the advances IT technology in the last decade, the need for this has gradually decreased. The potential benefits of VATS for postoperative pain management and respiratory functioning have been demonstrated. Additionally, studies have shown that VATS allows for re-metastasectomy with reduced morbidity and comparable outcomes to open surgery [5–9].

In our opinion, resection for isolated lung metastases is the most reliable method for diagnosis. To maximize the chances of survival, resection using video-assisted thoracic surgery VATS is recommended. Here we report our findings on the use of minimally invasive surgery (VATS) for pulmonary metastasectomy, with a particular focus on identifying the most suitable candidates for the surgery. Our inclusion criteria were as follows: the primary tumor should be treated with no signs of local recurrence (viable tissue) and isolated organ (lung) metastasis. According to the standard procedure with all lung surgery patients, adequate respiratory capacity measures are mandatory. Our exclusion criteria were as follows: insufficient respiratory function, multi-organ metastasis, local recurrence, potential other high medical risks due to which the patient is unwilling to undergo surgery. We have considered the

use of VATS due to its less invasive nature and the potential for better pain management. Conducting a study to verify the positive outcomes of surgery in this specific patient population, while considering relevant confounders, might aid in the process of selecting patients.

Aim

Our aim is to report our findings on the use of VATS for pulmonary metastasectomy, with a focus on identifying suitable candidates.

Material and methods

Patients

Between August 2010 and 2023 a total of 532 pulmonary metastasectomy procedures were performed in our institution. Metastasectomy was performed with VATS for 281 of those patients. The pathology results showed that 40 patients had a primary tumor and benign lesions, so they were not included (Figure 1). A total of 241 patients who met the inclusion criteria made up the study group and their data were reviewed retrospectively.

All patients discussed at the oncology council underwent positron emission tomography/computed tomography (PET-CT) scanning to confirm the presence of lung metastasis without any additional metastases outside the thoracic region, and it was determined that the primary tumor was under control. Pre-operative respiratory function tests showed the available lung function for pulmonary resection including lobectomy. If the patient had a suspected lesion for primarily lung cancer, preoperative diagnosis by fine needle aspiration was planned.

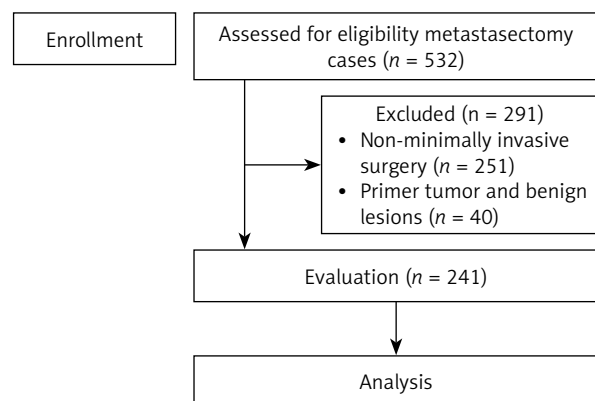


Figure 1. Consort diagram

All patients underwent a multidetector thin-section thorax CT scan days before surgery (1–7 days). All imaging analyses were supervised by both a senior radiologist and surgeons.

Surgical procedure

Patients were placed in a lateral decubitus position after double lumen intubation. Depending on the preference of the surgical groups, one or two incision ports were placed in the intercostal spaces in the 5th and 7th intercostal spaces. By using surgical instruments, a general view was achieved. In addition to focusing on the specific lesion identified through CT findings, a broader examination was also conducted. Once the lesions had been clearly identified, the lung was then grasped at the site of the lesion and a compressive clamp was placed below the lung lesion along the anticipated surgical margin line. Once the surgical margin distance appeared to be acceptable (2–3 cm), a parenchymal endostapler was placed and wedge resection was completed. The integrity of the stapler line and margin was evaluated, and the stapling process was continued below the parenchymal resection line.

The most commonly used tissue preservation method is wedge resection. However, it is necessary to ensure that the surgical margins are safe and clean while preserving the parenchyma for additional surgery, therefore potentially accepting the possibility of lobectomy. This may be disadvantageous in terms of providing the patient with more cardiopulmonary reserve to withstand subsequent treatments in case of the recurrence of the disease and preserving the patient's quality of life. When conversion to open surgery is necessary, it should be carried out without hesitation.

Statistical analysis

Mean, standard deviation, median, lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. Cox regression (univariate-multivariate) and Kaplan-Meier curves were used for the purpose of survival analysis. The SPSS 28.0 program was used in the analyses.

Results

Of 241 patients, 133 (55.2%) were male and 108 (44.8%) were female (Table I). The median patient

age was 56 (5–79) years. Metastasectomy via VATS was performed in 131 patients with a single lesion while 110 patients underwent metastasectomy for multiple lesions. The histopathological distribution of the primary tumor and other clinical characteristics of the patients are shown in Table I.

In the final pathology, it was found that 147 (61.0%) patients had single lesions, whereas 94 (39.0%) patients had numerous lesions. The median number of lesions found on preoperative thorax CT scans was 1 (1–23) and the median number of excised lesions was 1 (1–13). When the number of preoperative CT lesions and the number of surgically removed lesions were examined, it was observed that there was no significant difference ($p > 0.001$). There was a significant correlation between the number of lesions excised by VATS metastasectomy and the number of lesions reported on preoperative images ($n = 418/455$) (Spearman's correlation coefficient 0.83; $p < 0.001$) (Figure 2).

The following factors were considered and calculated: age, gender, primary malignancy site, procedure side, treated lobe, preoperative chemotherapy and/or radiotherapy, surgical procedure, lymph node excision and presence of metastasis, occurrence of complications, number of metastasectomies, time between metastasectomies, number of operations, postoperative length of stay (Table II).

In the univariate model, age, gender, primary malignancy site, procedure side, procedure lobe, preoperative chemotherapy and/or radiotherapy, surgical procedure, lymph node excision, lymph node metastasis, complications, number of metastasectomies, time between metastasectomies, number of operations and postoperative length of stay were not observed to have a significant effect on survival time ($p > 0.05$) (Table III).

In the univariate model, it was observed that tumor histology, number of preoperative CT lesions, and number of excised lesions had a significant effect on survival time after surgery ($p < 0.05$) (Table III).

In the multivariate model, it was observed that the number of lesions removed had a significant independent effect on survival time ($p < 0.05$) (Table III).

The predicted survival time in the group with preoperative CT lesion count > 1 (41 months) was significantly ($p < 0.05$) lower than the group with preoperative CT lesion count 1 (60 months) (Tables IV, V). Survival rates according to preoperative lesion numbers are shown in Table V and Figure 3.

Table I. Clinical characteristics of overall patients

Parameter	Minimum	Maximum	Median	Mean \pm SD or n %
Age	5.0	79.0	56.0	50.2 \pm 17.2
Sex:				
Female				133 55.2%
Male				108 44.8%
Primary malignancy area:				
Colorectal carcinoma				77 32.0%
Bone				53 22.0%
Soft tissue				24 10.0%
Head, neck				18 7.5%
Gynecologic				15 6.2%
Breast				12 5.0%
Malign melanoma				11 4.6%
Renal				8 3.3%
Stomach				5 .1%
Thyroid				4 1.7%
Kidney				3 1.2%
Lymphoma				3 1.2%
Testis				3 1.2%
Bladder				2 0.8%
Pancreas				2 0.8%
Esophagus				1 0.4%
Side:				
Right				128 53.1%
Left				109 45.2%
Bilateral				4 1.7%
Lobe:				
Upper lobe				90 37.3%
Middle lobe				6 2.5%
Lower lobe				91 37.8%
Upper + middle lobe				3 1.2%
Upper + middle lobe				34 14.1%
Middle + lower lobe				7 2.9%
Upper + middle + lower lobe				9 3.7%
No lobe information				1 0.4%
Preop. chemotherapy and/or radiotherapy:				
Received				66 27.4%
No				175 72.6%
Pathology:				
Adenocarcinoma				91 37.8%
Osteosarcoma				45 18.7%

Table I. Cont.

Parameter	Minimum	Maximum	Median	Mean ± SD or n %
Squamous cell carcinoma				13 5.4%
Breast carcinoma				12 5.0%
Malign melanoma				11 4.6%
Synovial sarcoma				11 4.6%
Ewing sarcoma				10 4.1%
Clear cell carcinoma				8 3.3%
Chondrosarcoma				5 2.1%
Leiomyosarcoma				5 2.1%
Spindle cell malignant mesenchymal tumor				4 1.7%
Lymphoma				3 1.2%
Rhabdomyosarcoma				3 1.2%
Adenoid cystic carcinoma				2 0.8%
Fibrosarcoma				1 0.4%
Germ cell tumor				2 0.8%
Papiller carcinoma				2 0.8%
Adeno squamous carcinoma				1 0.4%
Gastrointestinal stromal tumor				1 0.4%
Glomus tumor				1 0.4%
Hurthle cell carcinoma				1 0.4%
Insular carcinoma				1 0.4%
Choriocarcinoma				1 0.4%
Nasopharyngeal carcinoma				1 0.4%
Neuroendocrine tumor				1 0.4%
Renal cell carcinoma				2 0.8%
Sarcoma				1 0.4%
Sarcomatoid squamous cell carcinoma				1 0.4%
Sex cord stromal tumor				1 0.4%
Tumor histology:				
Sarcoma				86 35.7%
Carcinoma				149 61.8%
Other				6 2.5%
Grade:				
I				39 30.0%
II				27 20.8%
III				63 48.5%
IV				1 0.8%

The predicted survival time in the group with the number of excised lesions > 1 (38 months) was significantly ($p < 0.05$) lower than in the group with the number of excised lesions > 1 (60 months) (Tables VI, VII). Survival rates according to the number of lesions excised are shown in the Table VII and Figure 4.

The survival rate was significantly ($p < 0.05$) lower in the group with multiple lesions removed during surgery (38 months) than in the group with only one lesion removed during surgery (60 months) (Tables VIII, IX).

Survival rates according to the lesions removed in surgery are shown in Table IX and Figure 5.

There was no significant ($p > 0.05$) difference between the predicted survival time of the group with tumor histology as carcinoma (41.4 months) and the groups with tumor histology as sarcoma (55.5 months). The predicted survival time in the group with other tumor histology (79 months) was significantly ($p < 0.05$) higher than in the groups with tumor histology carcinoma (41.4 months) and sarcoma (55.5 months) (Table X). Kaplan-Meier analysis did identify any differences for these variables.

Survival rates according to the tumor histology are shown in Tables X, XI and Figure 6.

The difference was not significant when the grades were analyzed one by one, but it was significant when they were divided into two groups (grade I and grades II, III, IV). The survival time (80.1 months) in the grade II/III/IV group was significantly ($p < 0.05$) shorter than the grade I group. The results are shown in Tables XII, XIII (in Table XII, the total time is different from the other results because the analysis was performed only in the grade group) and Figure 7.

Discussion

Although the primary malignant tumor is treated locally with surgery and radiotherapy, treatment practices for systemic metastases continue to be a topic of debate. Lung metastases of primary malignant tumors require exceptional evaluation among systemic metastases. It has been reported that the number of nodules detected in secondary pulmonary neoplasms, particularly in thorax CT, is 50% lower than the number of nodules detected during surgery [10, 11]. In our study, the median number of lesions found on preoperative thorax CT scans was 1 (between 1 and 23) and the median number of

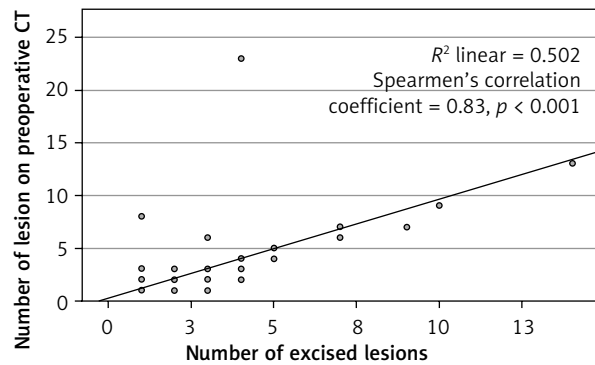


Figure 2. Number of lesion on preoperative CT – excised lesions scatter plot

excised lesions was 1 (between 1 and 13). There was a significant correlation between the number of lesions excised by metastasectomies via VATS and the number of lesions reported on preoperative images ($n = 418/455$) (Spearman's correlation coefficient 0.83; $p < 0.001$). It is thought that the reason is the use of newly developed technological devices with thin incisions and three-dimensional imaging in axial, coronal and sagittal planes. Additionally, this approach will prevent unnecessary re-metastasectomy. While performing surgery, it is essential to preserve the intact parenchyma as much as possible, and to ensure that the surgical margins are safe and free from tumors. In cases where the parenchyma is preserved but the surgical margins are not tumor-negative, a metastasectomy will not contribute to survival [12, 13]. For this reason, anatomic resection was performed in cases where it was considered that tumor-negative surgical margins would not be possible with other types of resection (lobectomy) in centrally located lesions. Anatomic resection was performed in 12 (4.97%) cases due to multiple metastases and these rates are corroborated by the literature [14].

In our study, the mean follow-up time was calculated as 58.6 months and the cumulative 5-year survival rate was found to be 43.8%, similar to the rates reported in the literature [10, 12–14]. This is especially related to the high accuracy rate of nodules detected by new technology imaging methods and the excision of additional nodules that we detect preoperatively. Recurrences may occur after metastasectomy, especially in sarcomas and melanomas. In these cases, if metastasectomy criteria are applicable, re-metastasectomies may even be performed on the same side. In our study, re-metastasectomy was performed in 42 (17.4%) cases and contributed

Table II. Results

Parameter	Minimum	Maximum	Median	Mean ± SD or n %
Lymph node excision	(-)			197 81.7%
	(+)			44 18.3%
Lymph node met.	(-)			43 97.7%
	(+)			1 2.3%
Preop. CT lesion count:	1.0	23.0	1.0	1.9 ± 2.0
	Count = 1			137 56.8%
	Count > 1			104 43.2%
Number of lesions excised:	1.0	14.0	1.0	1.7 ± 1.5
	Count = 1			153 63.5%
	Count > 1			88 36.5%
Complication:	(-)			217 90.0%
	(+)			24 10.0%
Expansion defect				8 3.3%
Prolonged air leak				6 2.5%
Fever				3 1.2%
Hypoxia, desaturation				1 0.4%
Pneumoderma				2 0.8%
Palpitation				1 0.4%
Self-slipping of the drain				1 0.4%
Decubitus ulcer				1 0.4%
Delirium, dementia				1 0.4%
Number of metastasectomy:	I			179 74.3%
	II			43 17.8%
	III			13 5.4%
	IV			3 1.2%
	V			1 0.4%
	VI			1 0.4%
	VII			1 0.4%
Interval between metastasectomies [months]	0.0	74.0	16.5	19.5 ± 19.0
Surgery:	Single			147 61.0%
	Multiple			94 39.0%
Number of lesions removed in surgery:	Single			153 63.5%
	Multiple			88 36.5%
Postoperative hospitalization period [days]	1.0	13.0	2.0	3.0 ± 1.7
Tracking period [months]	1.0	158.0	34.0	39.3 ± 27.8
Survival:	(-)			123 51.0%
	(+)			118 49.0%

Table III. Factors effecting the survival

Parameter	Univariate model			Multivariate model		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	0.995	0.985–1.005	0.348			
Sex	1.023	0.711–1.474	0.901			
Primary malignancy area	0.969	0.916–1.024	0.267			
Side	1.079	0.758–1.536	0.673			
Lobe	0.992	0.894–1.100	0.876			
Preop. chemotherapy and/or radiotherapy	0.687	0.465–1.015	0.060			
Surgical procedure	1.079	0.744–1.564	0.689			
Tumor histology	0.629	0.450–0.880	0.007			
Lymph node excision	1.318	0.864–2.009	0.200			
Lymph node met.	5.353	0.658–43.551	0.117			
Number of preop. CT lesion	1.627	1.133–2.337	0.008			
Number of excised lesion	1.757	1.217–2.536	0.003			
Complication	1.307	0.734–2.327	0.363			
Number of metastasectomy	1.105	0.910–1.343	0.313			
Interval between metastasectomies [months]	0.990	0.947–1.036	0.679			
Surgery (one/multi)	1.237	0.858–1.784	0.255			
Number of lesions removed in surgery	1.757	1.217–2.536	0.003	1.757	1.217–2.536	0.003

Table IV. Effect of number of preoperative ct lesions on survival

Parameter	Survival time [months]	95% CI	P-value
Preop. CT	Lesion number = 1	60.0	0.007
	Lesion number > 1	41.0	
Total	53.0	45.6–60.4	

Kaplan Meier (Log Rank).

Table V. Cumulative survival rate

Year	Cumulative survival rate		
	Total	Preop. CT lesion number	
		1	> 1
1	95.7%	96.2%	95.1%
2	77.0%	83.4%	68.8%
3	63.6%	69.2%	56.5%
4	54.0%	60.9%	44.7%
5	41.0%	50.1%	29.1%
10	29.4%	34.2%	22.8%

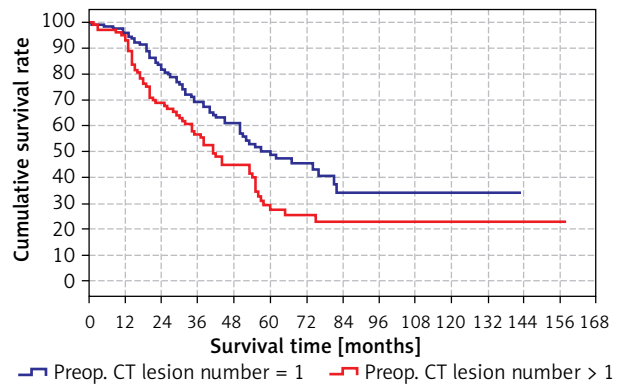


Figure 3. Survival according to the number of pre-operative CT lesions

Table VI. Survival of one or more excised lesions

Variable		Survival time [months]	95% CI	P-value
Excised	Lesion number = 1	60.0	46.9–73.1	0.002
	Lesion number > 1	38.0	29.1–46.9	
Total		53.0	45.6–60.4	

Kaplan Meier (log rank).

Table VII. Cumulative survival rate

Year	Cumulative survival rate		
	Total	Number of lesions excised	
		1	> 1
1	95.7%	95.2%	96.5%
2	77.0%	83.3%	66.4%
3	63.6%	69.8%	53.2%
4	54.0%	61.5%	40.5%
5	41.0%	49.9%	24.5%
10	29.4%	33.7%	21.6%

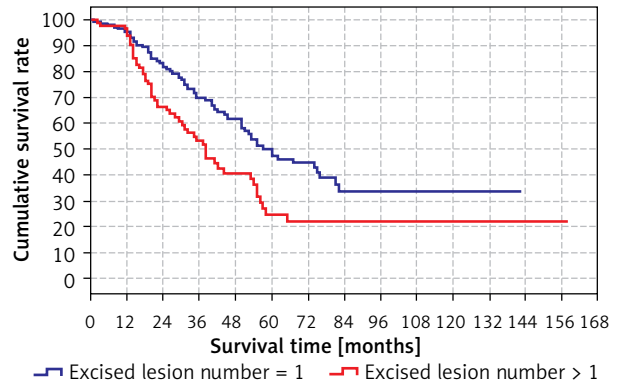


Figure 4. Survival rates according to lesions removed in surgery

Table VIII. Survival according to single and multiple lesions

Variable		Survival time [months]	95% CI	P-value
Number of excised lesion	One	60.0	46.9–73.1	0.002
	Multiple	38.0	29.1–46.9	
Total		53.0	45.6–60.4	

Kaplan Meier (log rank).

Table IX. Cumulative survival rate

Year	Cumulative survival rate		
	Total	Lesion removed in surgery	
		One	Multiple
1	95.7%	95.2%	96.5%
2	77.0%	83.3%	66.4%
3	63.6%	69.8%	53.2%
4	54.0%	61.5%	40.5%
5	41.0%	49.9%	24.5%
10	29.4%	33.7%	21.6%

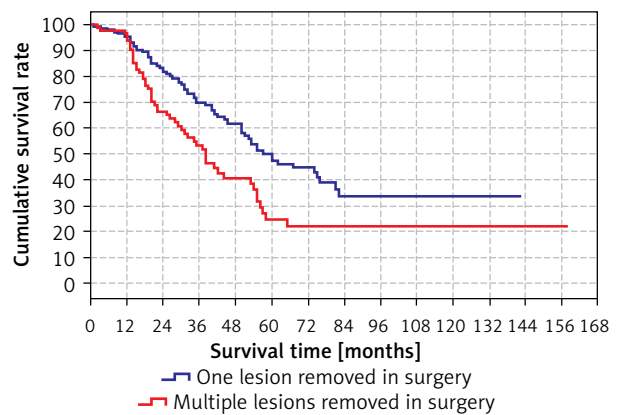


Figure 5. Survival according to single and multiple lesions

Table X. Survival by histology

Tumor histology	Survival time [months]	P-value
Carcinoma	41.4	0.011
Sarcoma	55.5	

Kaplan Meier (log rank).

Table XI. Cumulative survival rate

Yea	Cumulative survival rate			
	Total	Tumor histology		
		Sarcoma	Carcinoma	Other
1	95.7%	96.4%	95.2%	100.0%
2	77.0%	75.5%	76.9%	100.0%
3	63.6%	59.9%	64.2%	100.0%
4	54.0%	42.2%	59.0%	100.0%
5	41.0%	28.3%	45.5%	100.0%
10	29.4%	28.3%	29.8%	100.0%

to survival times by an average of 45 months. Studies on typical open surgical procedures have indicated a 5-year survival rate of 54% and a recurrence rate of 30%. It is noteworthy that the recurrences we reported were most common in the contralateral lung and that ipsilateral recurrences could be operated on with VATS in the majority of cases; this adds some weight to the notion that most patients with solitary metastases will have a high propor-

Table XII. Survival rate by grade

Variable	Survial rate [months]	95% CI	P-value
Grade	I	103.1	82.1–124.0
	II–III–IV	80.1	65.0–95.3
Total	89.3	75.8–102.7	

Kaplan Meier (log rank).

Table XIII. Cumulative survival rate

Year	Cumulative survial rate		
	Total	Grade I	Grade II–III–IV
1	98.4%	97.1%	98.9%
2	85.3%	93.4%	82.4%
3	70.8%	80.0%	67.7%
4	58.9%	75.0%	53.8%
5	47.1%	67.5%	40.8%
10	43.4%	67.5%	35.8%

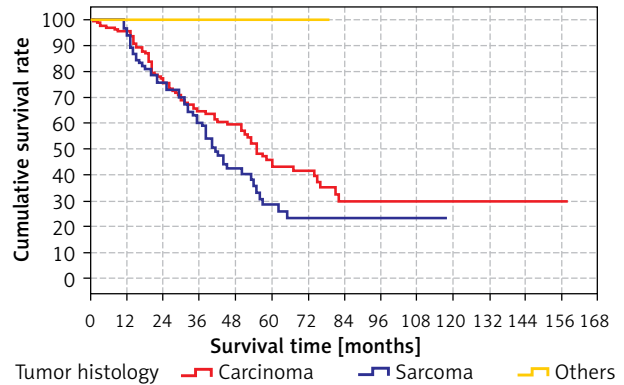


Figure 6. Cumulative survival rate according to tumor histology

tion of lung tissue and will benefit from a minimally invasive surgical approach [15]. The predicted survival time in the group with other tumor histology (79 months) was significantly ($p < 0.05$) higher than in the groups with tumor histology carcinoma (41.4 months) and sarcoma (55.5 months). Our survival rates in cases are higher than those in the literature [16]. Imaging methods allow detailed imaging of the lung parenchyma since it is located within a limited area in the rib cage, thus facilitating early detection of metastases.

In the sarcoma group, the 5-year survival was 35% and the overall survival of metastasectomy was calculated as 37.42 months. Nevala *et al.* reported the 22-month overall survival after pulmonary me-

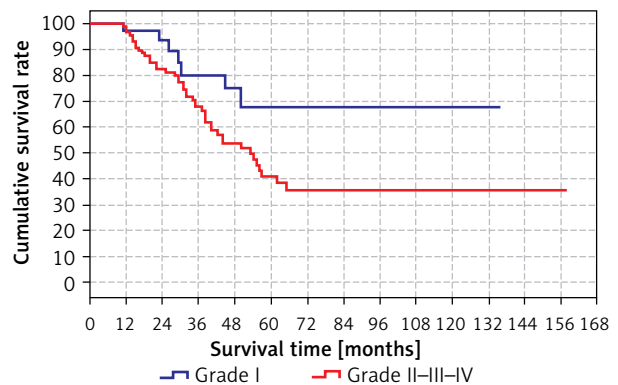


Figure 7. Survival according to grades

tastasectomy for sarcomas, and a higher survival rate was found in our study [17]. In our study, re metastasectomies were performed mostly in the osteosarcoma group. The synovial sarcoma group had the highest number of lesions excised at one time, with 14 lesions.

Since not all metastatic nodules may be detected radiologically, intraoperative lung inspection and evaluation should be carried out carefully. The presence of additional nodules should be investigated by digital and instrument-based inspection. In this regard, the main factors determining survival are thought to be tumor histopathology and the extent of the disease. Surgical approaches to pulmonary metastasectomy should be determined according to the number and location of the nodules. Since it is essential to remove all nodules, two-session interventions may be performed if necessary. Nodules whose presence is revealed radiologically should also be revealed during the operation; otherwise, they cannot be detected radiologically.

Conclusions

Metastases are a sign of rapid disease progression along with uncontrolled tumor growth [18]. However, isolated lung metastases follow favorable tumor biology. These patients are more suitable for local and local-systemic treatment applications than cases with multiple organ metastases. In all branches of expertise related to malignancy, imaging methods to evaluate the lungs should be used in cases with primary controlled tumors, and when the possibility of isolated pulmonary metastasis is detected, the opinion of the thoracic surgeon should be obtained and cases that meet the metastasectomy criteria should be referred to surgery. We have found that utilization of VATS in metastasectomies is safe and yields a similar survival rate. Since it is essential to remove all nodules, two-session interventions can be performed if necessary; VATS provides an advantage in this case. Nodules that are detected radiologically should also be revealed during the operation. Additionally, keeping in mind that there may be nodules that cannot be detected radiologically, careful detection should be performed and all detected nodules should be removed. The best prognosis after metastasectomy is provided in cases with a single nodule. Grade is also an important prognostic factor affecting survival, particularly for grade 1 tumor. In

secondary pulmonary neoplasms, gender does not affect the contribution of metastasectomy to survival. The histopathological type of the primary tumor is also a significant prognostic factor affecting survival after pulmonary metastasectomy in secondary pulmonary neoplasms, particularly for sarcoma and carcinoma.

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Ethical approval

This study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). The institutional review board of the Medical School of Istanbul University-Cerrahpaşa gave ethical approval for this study. Data supporting this study are included within the article and/or supporting materials.

Conflict of interest

The authors declare no conflict of interest.

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