

**Aim of the study:** The resection of pulmonary metastases is a routine practice of thoracic surgery wards; however, clear protocols or prognostic factors defining the surgical treatment criteria are still not available. The aim of the study is to evaluate the prognostic factors associated with long-term survival in a group of patients who underwent resection of pulmonary metastases.

**Material and methods:** A retrospective analysis was conducted on a group of 250 patients admitted to the Wrocław Thoracic Surgery Centre for radical resection of pulmonary lesions in the years 1996–2010.

**Results:** The patients included in the study ( $n = 250$ ) underwent 339 thoracotomies in total. The overall five-year survival was 52.8%. The univariate data analysis showed that the survival rate was significantly better in patients subjected to more than one thoracotomy ( $p = 0.01674$ ). Among the other data, such as sex, tumour histology, disease-free interval (DFI)  $\leq 12$  and  $> 12$  months, DFI  $\leq 36$  and  $> 36$  months, age, number of tumours identified in CT and number of tumours subject to resection, operated side, resection type, radicality of resection, extent of lymphadenectomy, and adjuvant therapy, no statistical significance was observed in univariate and multivariate analysis ( $p > 0.05$ ).

**Conclusions:** Outcomes of re-metastectomy are satisfactory if patients meet the baseline criteria for surgical treatment. None of the evaluated factors potentially influencing the patient survival was demonstrated to have any prognostic value. Further research, including the biology of tumours with pulmonary metastases, is necessary to select the group of patients that will benefit most from surgical treatment.

**Key words:** pulmonary metastasectomy, prognostic factors, re-metastectomy, secondary lung tumours.

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# Evaluation of prognostic factors in the surgical treatment of pulmonary metastases

Konrad Pawełczyk, Marek Marciniak, Piotr Błasiak, Adam Rzechonek

Chair and Department of Thoracic Surgery, Wrocław Medical University, Wrocław, Poland

## Introduction

For the majority of primary tumours the lungs are the first organ affected by remote metastases. The results of numerous studies show that in some of the patients the surgical resection of isolated pulmonary metastases represents an important and effective element of therapy [1, 2]. The five-year survival rate in patients after the radical resection of metastases from the most frequent primary tumours is around 40% [3–5]. The recurrence of metastases to the lungs does not mean that the possibilities of surgery have been exhausted because the results of many studies indicate that they can be subject to another resection, which provides better outcomes than the systemic treatment alone [2, 5]. Although many authors from different centres have described their own experience, clear protocols or prognostic factors defining the surgical treatment criteria are still not available. The aim of the study is to evaluate the prognostic factors associated with long-term survival in a group of patients who underwent resection of pulmonary metastases.

## Material and methods

A retrospective analysis was conducted for a group of 250 patients previously treated for primary malignant solid tumours, admitted to the Wrocław Thoracic Surgery Centre for elective radical resection of pulmonary lesions in the years 1996–2010. Patients were eligible for the radical resection of pulmonary metastases if the following initial conditions were fulfilled: a) the lack of local recurrence within the primary lesion, b) the number and location of pulmonary lesions ensuring their total resection with clean resection margins maintained, c) the lack of lesions outside the lungs, d) the lack of other available methods ensuring the effective treatment of the disease, and e) respiratory efficiency and stabilised co-morbidities making the elective resection of the pulmonary parenchyma possible. The number of lesions in the lung was determined using computed tomography of the thorax, and disseminated malignancy was excluded, as required, on the basis of the imaging studies of the abdominal cavity and central nervous system, scintigraphy, and since 2007 also on the basis of positron-emission computed tomography (PET-CT). Patient data were analysed against medical records to determine the date of resection and the histology of the primary lesion, the date of the resection of metastases or their recurrences, the number of thoracotomies, the extent of pulmonary parenchyma resection, the extent of mediastinal lymphadenectomy, the adjuvant therapy, and the radicality of resection.

Each computed tomography was assessed with regard to the number of pulmonary lesions, their size, and side/sides affected by metastases. In the cases where metastases were present in both lungs the first thoracotomy was carried out on the side with a lesser or uncertain chance of radical treatment, resulting from a large number of lesions or their location in the lung

parenchyma. When intraoperatively complete resection with clear margins was not possible, only tumour biopsy was accomplished and the patients did not enter the study. In order to ensure the thorough and accurate palpation of pulmonary parenchyma to detect minor lesions, in each case thoracotomy was selected instead of minimally invasive procedures, i.e. video-assisted thoracoscopy. All tumours accessible through palpation were routinely removed from the parenchyma with a small (5–10 mm) margin of the healthy lung. In the case of a single lesion in the lung, the histopathological examination was conducted intraoperatively to exclude the primary pulmonary carcinoma. Patients with microscopically positive margins (R1) were referred to adjuvant therapy and were not reoperated. After the surgical treatment the patients had a clinical and radiological examination (X-ray, computed tomography) every three months for the first two years, then every six months until the fifth year after resection elapsed, and once a year afterwards. If another recurrence was detected, present exclusively in the pulmonary parenchyma, without any signs of dissemination and without any lesions outside the lungs, the patient was referred for another thoracotomy.

The type of lymphadenectomy varied: sampling was understood as the selective resection of enlarged medias-

tinal lymph nodes, suspected of metastatic disease, and systemic lymphadenectomy was understood as the en-bloc resection of all mediastinal lymph nodes.

The disease-free interval (DFI) was assessed, which was defined as the period between the treatment of the primary lesion and the detection of pulmonary metastases. The patients' overall survival was counted from the date of the first metastasectomy. The dates of patients' deaths were determined on the basis of the data obtained from the Information Office of the Citizen Service Department of the Ministry of Internal Affairs and Administration.

The statistical analysis was conducted by means of STATISTICA software, version 7.1, StatSoft, Inc. [2005]. Patient survival and survival without cancer recurrence were calculated by Kaplan-Meier method and compared using the log-rank test. A *p*-value < 0.05 was regarded as statistically significant.

## Results

Patient characteristics are presented in Table 1.

Patients included in the study (*n* = 250) underwent 339 thoracotomies in total. The mean follow-up time totalled 40.7 months and the median was 36 months (1–156). The overall five-year survival was 52.8% (median – 64 months)

**Table 1.** Patient characteristics

Variable	<i>n</i>	%
Age		
≤ 50 years	35	14
50–65 years	128	51.2
> 65 years	87	34.8
Sex		
F	135	54
M	115	46
Location of the primary tumour		
skin	9	3.6
head and neck	26	10.4
colon	65	26
uterus	30	12
soft tissues	10	4
kidney	46	18.4
urinary bladder	7	2.8
breast	42	16.8
prostate	8	3.2
other	7	2.8
Primary tumour histology		
squamous cell carcinoma	41	16.4
adenocarcinoma	94	37.6
melanoma	9	3.6
sarcoma	10	4
clear cell carcinoma	53	21.2
other	43	17.2
Number of tumours identified in CT		
≤ 2	223	89.2
> 2	27	10.8
Number of tumours subject to resection		
≤ 2	236	94.4
> 2	14	5.6

Variable	<i>n</i>	%
Operated side		
right	112	44.8
left	117	46.8
both	21	8.4
Resection type		
wedge resection	226	90.4
segmentectomy	9	3.6
lobectomy	15	6
Number of thoracotomies		
1	179	71.6
2	56	22.4
3	12	4.8
4	3	1.2
Radical resection		
yes	239	95.6
no	11	4.4
Type of lymphadenectomy		
no resection	195	78
sampling	36	14.4
systemic lymphadenectomy	14	5.6
Adjuvant chemotherapy		
yes	114	45.6
no	136	54.4
DFI (months)		
≤ 12	50	20
> 12	200	80
DFI (months)		
≤ 36	144	57.6
> 36	106	42.4

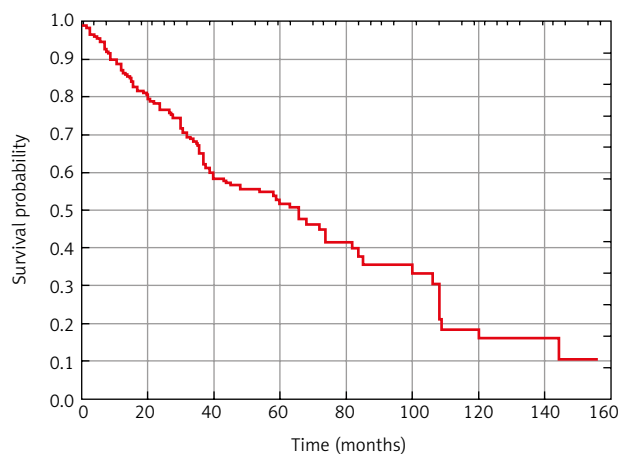


Fig. 1. Overall five-year survival for all patients

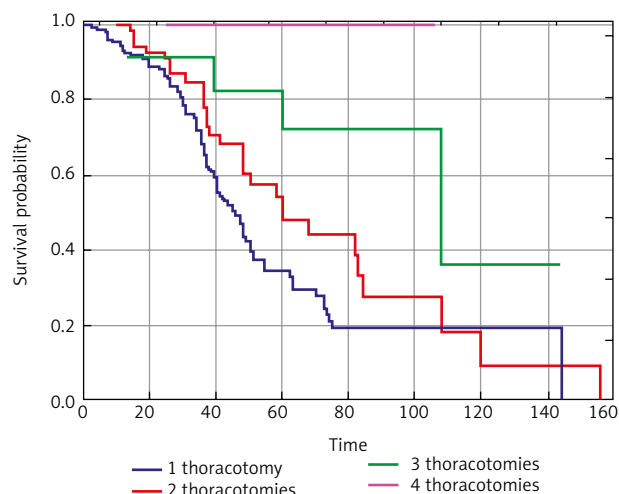


Fig. 2. Overall survival depending on the number of thoracotomies

Table 2. Multivariate analysis of prognostic factors

Variable	Relative risk	95% CI	<i>p</i> value
Sex	1.019843	0.694–1.498	0.9203
Age	0.897047	0.66–1.218	0.4872
Histology	1.028414	0.897–1.178	0.6877
DFI ≤ 12 / > 12 months	1.154973	0.698–1.909	0.5742
DFI ≤ 36 / > 36 months	0.909204	0.599–1.37	0.6544
Number of tumours identified in CT	1.164028	0.633–2.138	0.6244
Number of tumours resected	0.978883	0.434–2.207	0.9589
Operated side	0.997122	0.753–1.318	0.9838
Resection type	0.792723	0.515–1.218	0.289
Number of thoracotomies	0.893355	0.682–1.17	0.4127
Radicality of the resection (R0 vs R1)	0.649696	0.192–2.195	0.4875
Type of lymphadenectomy	0.890316	0.65–1.218	0.4685
Adjuvant chemotherapy	0.785815	0.542–1.138	0.2031

(Fig. 1). The thirty-day mortality rate was 0.4% (1/250), and the postoperative morbidity rate was 14.5% (49/339).

Nodal involvement according to the histologic type was: four in kidney cancer patients, seven in colorectal cancer patients, four in breast cancer patients, three in head/neck cancer patients, and five in the other primary tumours.

Patients with positive margins and non-radical resection R1 ( $n = 11$ , 4.4%) were referred to adjuvant chemotherapy; there were no R2 resections. Patients with bilateral tumours ( $n = 21$ ) had planned the surgery at the moment of the first diagnosis, and the thoracotomies were performed subsequently, usually with a three-week interval. In seven patients (7/223, 3.1%) with one or two tumours identified in CT, more changes were resected, but only in two cases (0.9%) we found additional metastasis. In the group of patients with more than two tumours identified

in preoperative CT scan ( $n = 27$ , 10.8%) no more than two metastases were found. In this group, seven cases (25.9%) had fewer pathologically confirmed metastases than was suspected regarding preoperative CT imaging.

The univariate data analysis showed that the survival rate was significantly better in patients subjected to more than one thoracotomy,  $p = 0.01674$  (Fig. 2).

Univariate and multivariate analyses demonstrated no prognostic significance of the other data, such as sex, tumour histology, DFI ≤ 12 months and > 12 months and DFI ≤ 36 months and > 36 months, age (ranges ≤ 50 years, 50–65 years and > 65 years), number of tumours identified in CT and number of tumours subject to resection, operated side, resection type, radicality of resection, extent of mediastinal lymphadenectomy, and adjuvant therapy ( $p > 0.05$ ) (Fig. 3) (Table 2).

## Discussion

The resection of pulmonary metastases from the primary sites located in the whole organism is a routine practice of numerous thoracic surgery wards. It results not only from the pressure exerted by oncologists and patients, but also predominantly from the relatively good outcomes in many groups of around 40–50% of the overall five-year survival [1, 2]. Unfavourable prognostic factors most frequently referred to in the literature include multiple metastases, a short disease-free interval, non-radical resection, metastases to mediastinal and hilar lymph nodes, and the advanced stage of the primary lesion [6–9]. The majority of the studies involved small groups of patients. The results of our study show that repeated resections do not necessarily imply a poor prognosis ( $p = 0.0167$ ). In a carefully selected group the patients undergoing subsequent resections of metastases have good outcomes, provided that they meet the baseline criteria for surgical treatment. Other factors, listed in the literature as those that may have a potential prognostic impact, were not observed to have any significant influence on the patients' survival in the univariate and multivariate analysis. The favourable prognostic factor that is mentioned most often

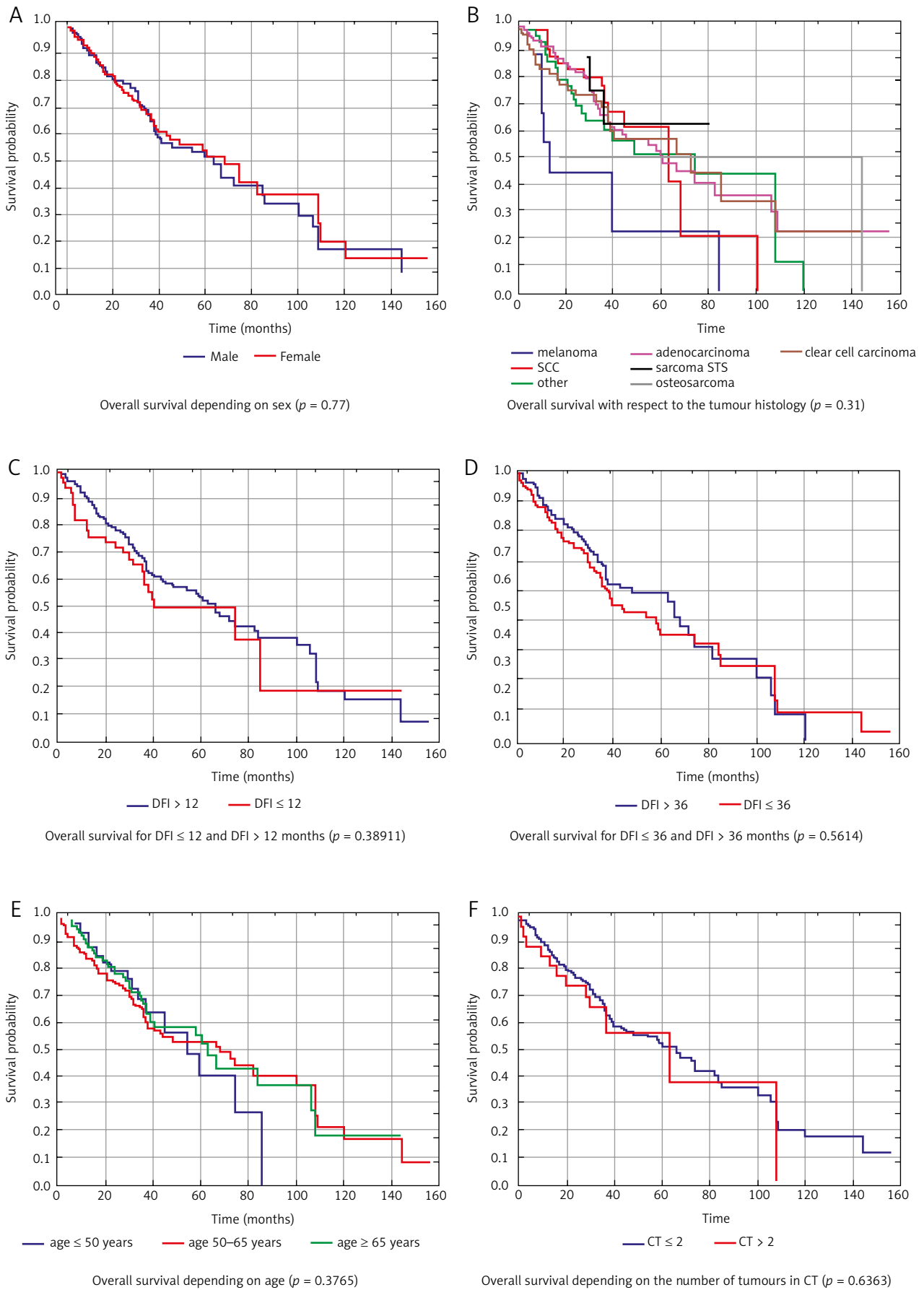
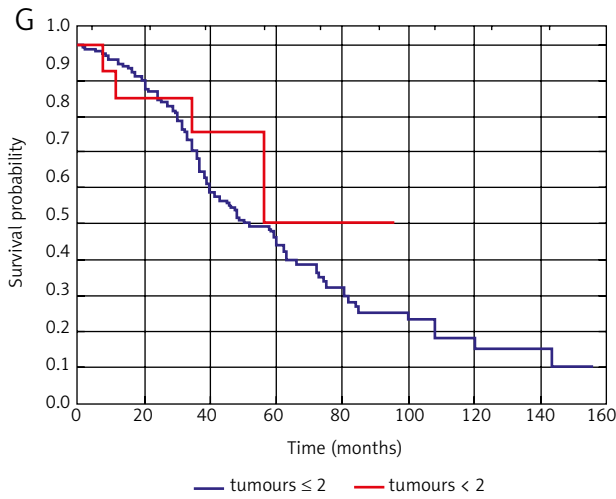
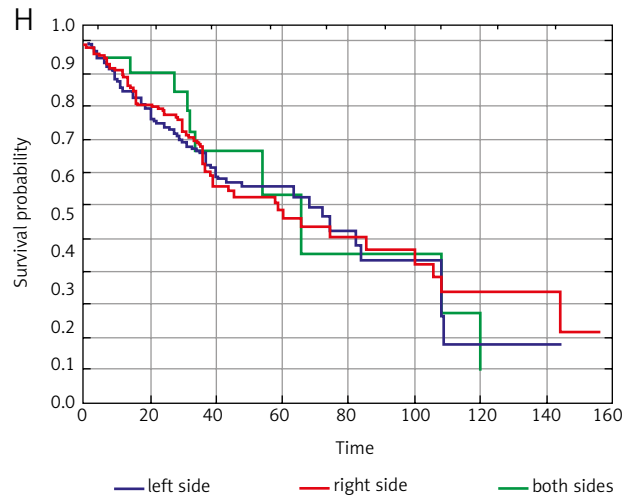


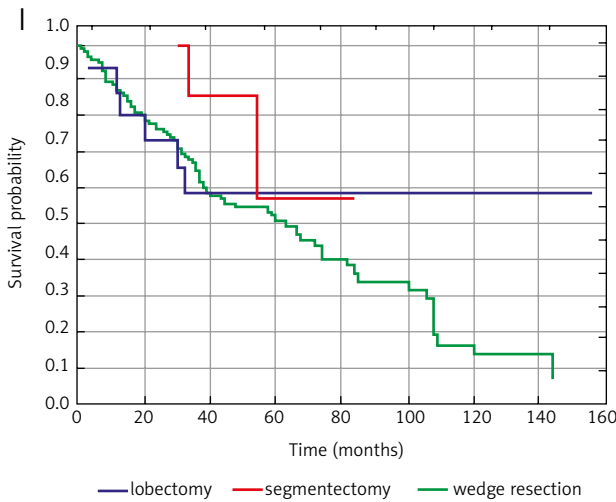
Fig. 3. Overall survival depending on the subjected variables (continued on the next page)



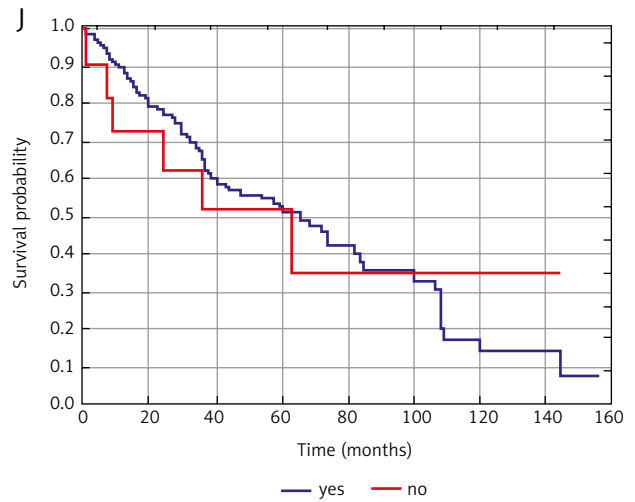
Overall survival with respect to the number of tumours subject to resection ( $p = 0.38864$ )



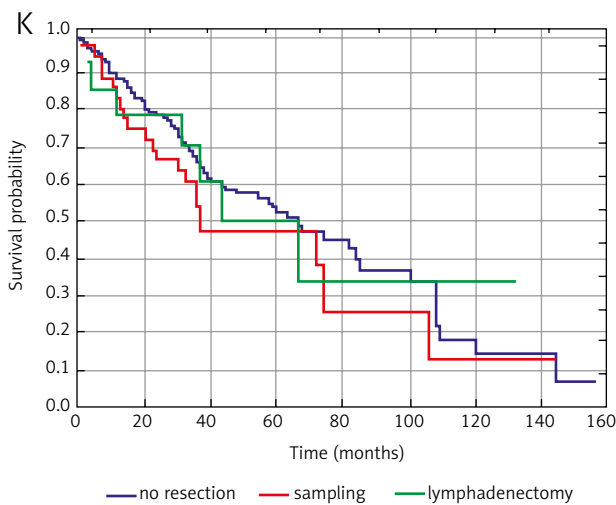
Overall survival depending on the operated side ( $p = 0.63267$ )



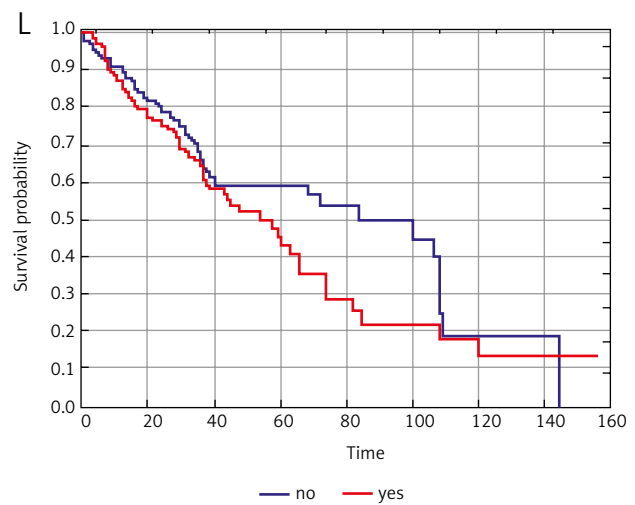
Overall survival depending on the type of resection ( $p = 0.23377$ )



Overall survival depending on the radicality of resection ( $p = 0.9281$ )



Overall survival for lymphadenectomy ( $p = 0.23377$ )



Overall survival for adjuvant chemotherapy ( $p = 0.15270$ )

**Fig. 3.** Overall survival depending on the subjected variables

is the radical resection of lesions, leaving the margins free from malignant infiltration, which is not always possible when the number of tumours removed from the lung is high [1, 4, 10–12]. In the studied group the radical resection was performed in 95.6% of patients, which, however, did not lead to significantly better outcomes of treatment.

No significant benefit was demonstrated with regard to survival taking into account the number of removed lesions ( $p = 0.6363$ ). This might be attributed to the fact that the surgery takes place when the disease is in its generalised stage (remote metastases to the lungs). Metastasectomy consists of the removal of localised lesions identified during the follow-up imaging studies (eradication of residual foci). Therefore, during the preoperative patient assessment considerable emphasis is placed on the possibility of performing radical resection (Ro) or a small number of lesions (a higher number of metastases makes it technically difficult to remove them entirely from the pulmonary parenchyma). However, it is necessary to keep in mind the generalised stage of the disease and the lack of technical possibilities of imaging the presence of micro-metastases or malignant cells circulating in the organism. Quite often, despite the accurate palpation of the pulmonary parenchyma, it is difficult to localise small lesions, identified or not in the preoperative imaging studies. From a practical point of view, even with very careful palpation during open thoracotomy, 2–3 mm intrapulmonary changes that are described on CT scans are sometimes impossible to detect. Among others, for this reason, VATS procedures are admissible in pulmonary metastasectomy and are used in our department at the present time. A small number of additional metastases (0.9%) found during open thoracotomy in patients with one or two tumours identified in preoperative CT also justify VATS resections. On the other hand, patients who underwent a resection of lung metastases should be monitored closely with repeated chest CT. A growing tumour that was overlooked or not found during first surgery would be detected and resected in the next step. A proportion of patients undergo repeated metastasectomies (in the studied group – 22.4%), which confirms the thesis that the precise assessment of the advancement of the disease and its extent before the planned resection is not possible. However, the repeated metastasectomies are justified as long as the patient meets the eligibility criteria for surgical resection. Therefore, systematic and thorough follow-up after the surgery is justified [2]. In the majority of available publications [4, 13], and similarly in our patient group, the prognostic value of mediastinal lymphadenectomy has not been demonstrated (no resection vs. sampling of lymph nodes vs. systemic mediastinal lymphadenectomy), as it is the case with primary non-small cell lung cancer. In connection with the baseline stage of cancer some of the patients receive systemic adjuvant therapy – chemotherapy (in our patient group – 45.6%). In our study the application of adjuvant chemotherapy did not translate into a significantly longer patient survival. Some of the studies indicate the benefits of systemic treatment (longer DFI) after the resection of metastases from colon cancer [14, 15].

Taking account of current oncological knowledge, it is difficult to work out an ideal method for the treatment of patients with detected pulmonary metastases. It is well known that the available methods for assessing the preoperative stage of the disease, including PET-CT imaging, are insufficient. None of the evaluated factors potentially influencing patient survival was demonstrated to have any prognostic value. Perhaps the choice between surgery and another form of treatment should be also influenced by factors related to the biology and behaviour of the primary tumour, and it should not rely only on a purely technical possibility of resection while maintaining the margins free from malignant infiltration. Therefore, surgical resection should only be one of the elements to be considered in the management of patients with pulmonary metastases. Further research, including the biology of tumours with pulmonary metastases, is necessary to select the group of patients that will benefit most from surgical treatment.

*The authors declare no conflict of interest.*

#### References

- Pastorino U, Buyse M, Frierder G. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. The International Registry of Lung Metastases. *J Thorac Cardiovasc Surg* 1997; 113: 37-49.
- Hornbech K, Ravn J, Steinbrüchel DA. Outcome after pulmonary metastasectomy: analysis of 5 years consecutive surgical resections 2002-2006. *J Thorac Oncol* 2011; 6: 1733-40.
- Younes RN, Fares AL, Gross JL. Pulmonary metastasectomy: a multivariate analysis of 440 patients undergoing complete resection. *Interact Cardiovasc Thorac Surg* 2011; 14: 156-61.
- Casiraghi M, De Pas T, Maisonneuve P, et al. A 10-year single-center experience on 708 lung metastasectomies: the evidence of the "international registry of lung metastases". *J Thorac Oncol* 2011; 6: 1373-8.
- Chen F, Sakai H, Miyahara R, Bando T, Okubo K, Date H. Repeat resection of pulmonary metastasis is beneficial for patients with colorectal carcinoma. *World J Surg* 2010; 34: 2373-8.
- Koga R, Yamamoto J, Saiura A, Yamaguchi T, Hata E, Sakamoto M. Surgical resection of pulmonary metastases from colorectal cancer: Four favourable prognostic factors. *Jpn J Clin Oncol* 2006; 36: 643-8.
- Rena O, Papalia E, Oliaro A, Filosso P, Ruffini E, Maggi G, Casadio C. Pulmonary metastases from epithelial tumours: late results of surgical treatment. *Eur J Cardiothorac Surg* 2006; 30: 217-22.
- Melloni G, Doglioni C, Bandiera A, Carretta A, Ciriaco P, Arrigoni G, Zannini P. Prognostic factors and analysis of microsatellite instability in resected pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg* 2006; 81: 2008-13.
- Poncelet AJ, Lurquin A, Weynand B, et al. Prognostic factors for long-term survival in patients with thoracic metastatic disease: a 10-year experience. *Eur J Cardiothorac Surg* 2007; 31: 173-80.
- Shiono S, Kawamura M, Sato T, et al. Pulmonary metastasectomy for pulmonary metastases of head and neck squamous cell carcinomas. *Ann Thorac Surg* 2009; 88: 856-60.
- Kanzaki R, Higashiyama M, Fujiwara A, Tokunaga T, Maeda J, Okami J, Nishimura K, Kodama K. Long-term results of surgical resection for pulmonary metastasis from renal cell carcinoma: a 25-year single-institution experience. *Eur J Cardiothorac Surg* 2011; 39: 167-72.
- García Franco CE, Torre W, Tamura A, Guillén-Grima F, San-Julian M, Martín-Algarra S, Pardo FJ. Long-term results after resection for bone sarcoma pulmonary metastases. *Eur J Cardiothorac Surg* 2010; 37: 1205-8.

13. Kudelin N, Bölükbas S, Eberlein M, Schirren J. Metastasectomy with standardized lymph node dissection for metastatic renal cell carcinoma: an 11-year single-center experience. *Ann Thorac Surg* 2013; 96: 265-70.
14. Brandi G, Derenzini E, Falcone A, et al. Adjuvant systemic chemotherapy after putative curative resection of colorectal liver and lung metastases. *Clin Colorectal Cancer* 2013; 12: 188-94.
15. Kumar R, Price TJ, Beeke C. Colorectal Cancer Survival: An analysis of patients with metastatic disease synchronous and metachronous with the primary tumor. *Clin Colorectal Cancer* 2013; 13: S1533.

**Address for correspondence****Konrad Pawełczyk**

Chair and Department of Thoracic Surgery  
Wrocław Medical University  
Grabiszyńska 105  
53-439 Wrocław, Poland  
e-mail: kopaw@wp.pl

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