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- A** Study Design
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## Lung surgery for metastatic epithelial tumours

### Chirurgiczne leczenie przerzutów nowotworów nabłonkowych do płuc

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#### Summary

**Introduction:**

The aim of this study is to evaluate outcomes following the surgical treatment of pulmonary metastases in patients with different types of epithelial cancers, as well as to identify prognostic factors after metastasectomy.

**Material/Methods:**

We retrospectively reviewed data for 61 patients who underwent 76 curative resections of pulmonary metastases from epithelial tumours during 1997-2002 at our department. Potential prognostic factors affecting survival after lung metastasectomy were analysed: disease-free interval (DFI), gender, age, the size and number of metastases, mono- or bilateral tumour, number of operations and the extent of pulmonary resection.

**Results:**

The median survival was 36 months. Three factors were identified as prognostic for survival after metastasectomy: DFI<24 (p=0.0045), unilateral pulmonary metastases (p=0.0062) and no more than one operation (p=0.0065).

**Conclusions:**

We concluded that: i) Resection of epithelial pulmonary metastases may offer a significant survival benefit for selected patients. ii) Good surgical candidates for pulmonary resection are those with a disease-free interval greater than 24 months. iii) The total number of thoracotomies, and metastases confined to one lung are factors defining patients who experience a better outcome after surgery. iv) Lung metastasectomy by conventional surgery is a safe procedure with low perioperative morbidity and mortality rates.

**Keywords:**

lung metastases • epithelial cancers • surgical treatment

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## INTRODUCTION

The capability to disseminate, giving rise to local or distant metastases, is the main characteristic of malignant tumours. After the liver, the lung is the organ most commonly affected by metastases. However, less than 20% of patients with solid tumours may have metastases exclusively in the lung, with no detectable involvement of other organs [4]. The prognosis is typically poor and only a few patients survive more than one year after diagnosis [9,26]. In all patients for whom there are no other therapeutic options, in whom the primary disease is controlled, and who do not present contraindications, pulmonary metastasectomy should be proposed. As the safety of the operation has improved over time, indications have been extended more widely; however, a substantial proportion of pulmonary metastases tend to be part of systemic disease, so criteria for the resection of pulmonary metastases have yet to be established.

The goal of this study is to evaluate outcomes following the surgical treatment of pulmonary metastases in patients with different types of epithelial cancers, as well as to identify prognostic factors after metastasectomy.

## MATERIAL AND METHODS

From 1997 to 2003 in the Second Department of Oncological Surgery of Great Poland Cancer Centre, 61 patients underwent 76 curative resections of pulmonary metastases from epithelial cancers. The criteria for selection of patients were as follows: primary tumour is controlled, no disease is evident outside the lung, computed tomography (CT) scan shows that complete resection is possible, and patients are a low operative risk. Lung metastases were detected by routine X-ray films along with computed tomography. To eliminate the diagnostic errors in 38 cases we performed under computed tomography control fine needle biopsy, so final histological patterns of primary tumour and lung metastases were the same. Extrapulmonary spread was determined by physical examination, abdominal ultrasound and bone radionuclide scanning. Posterolateral thoracotomy was performed in all cases. Twelve patients were operated on again due to other side metastases. All patients were observed subsequently on an outpatient basis and underwent a metastatic and local recurrence work-up. All patients were retrospectively analysed for gender, age, primary site, type of resection, number of operations, mono- or bilateral tumour, and number and size of metastases. We assessed disease-free interval (DFI), i.e. the time between primary breast cancer surgery and the diagnosis of lung metastases, the overall survival and disease-free survival after lung metastasectomy. Disease-free survival was defined as the duration from resection of the primary tumour to the initial diagnosis of the metastatic tumour.

We used the Shapiro-Wilk test to estimate departures from normality. The comparative analysis of frequen-

cies was compared with the  $\chi^2$  square test with Pearson's modifications for categorical variables and Fisher's exact test for small samples. The Mann-Whitney *U*-test served as the nonparametric method. Survival probability was estimated using the Kaplan-Meier method. Subsequently data of statistical significance were correlated with survival time. The statistical significance of prognostic factors for survival time in univariate analysis was assessed by the log-rank test. Prognostic factors were matched in a multivariate analysis, using Cox regression models. A probability value of  $p < 0.05$  was considered statistically significant for all procedures. The statistical analysis was performed using Statistica for Windows version 6.0.

## RESULTS

Between January 1997 and December 2002, 49 patients (80.33%) were found to be affected by unilateral and 12 patients (19.67%) by bilateral metastases and were submitted to 76 operations for lung metastasectomy. Mean age was 55.3 years (standard deviation 11, range 33-77 years). The cohort consisted of 35 females and 26 males. The maximum tumour size ranged from 10 to 60 mm with median 26.4 mm. Characteristics of the 61 patients are listed in Table 1.

There were no differences according to tumour type. Patients with breast cancer were younger with longer average DFI compared to patients with metastases from other primaries, but these differences are not significant.

The median survival for 61 patients with pulmonary metastatic lesions after metastasectomy was 36 months (lower quartile 15.38). The survival curve for patients after metastasectomy is shown in Figure 1.

Disease-free interval (DFI), the average time interval between primary tumour surgery and the diagnosis of lung metastases, was 24.9 months (range: 0-102 months). We divided our group of patients into groups with  $DFI < 12$ ,  $DFI < 24$  and  $DFI < 36$  months. There was a statistically significant difference in survival time, with better prognosis for patients with  $DFI < 24$  (Fig. 2, log-rank test:  $p = 0.0045$ ) and respectively for patients with  $DFI < 36$  months (log-rank test:  $p = 0.0029$ ). There was no significant difference in the group of patients with  $DFI < 12$  months ( $p = 0.1117$ ).

Disease-free survival was 24.6% at 3 years and 6.5% at 5 years. Mean disease-free survival was 31.58 months. Six patients are currently alive without evidence of disease, and two patients are alive with disease (breast cancer). Twenty-eight patients died.

All patients underwent potentially curative resections, 33 with solitary metastasis, 12 with two, 5 with three, 3 with five, 1 with six, 1 with nine and 1 with twelve metastases.

**Table 1.** Patient characteristics

Variable	No. of patients (%)
Sex	
Male	26 (57.4%)
Female	35 (42.6%)
Primary site	
Breast cancer	33 (54.1%)
Colorectal cancer	14 (22.9%)
Kidney cancer	12 (19.6%)
Pancreatic cancer	1 (1.7%)
Skin cancer	1 (1.7%)
Type of resection	
Lobectomy	24 (31.1%)
Segmentectomy	25 (32.5%)
Wedge resections	28 (36.4%)
Number of operations	
1	49 (80.3%)
More	12 (19.7%)
Tumour laterality	
Monolateral	49 (80.3%)
Bilateral	12 (19.7%)
Number of metastases	
Solitary	33 (54.1%)
2	12 (19.7%)
3	5 (8.2%)
>3	11 (18.0%)
DFI	
<36 months	44 (72.1%)
>36 months	17 (27.9%)

There was no better survival for patients with 1 metastasis versus more (log-rank test:  $p=0.1477$ ). The patients were divided into a group with unilateral pulmonary metastases and a group with bilateral metastases. There was a significant difference between these two groups (log rank test:  $p=0.00654$ ) (Fig. 3).

As for the size of metastatic tumour, there was no significant difference in survival between patients with tumours with minimal diameter or larger than 3 cm and patients with smaller tumours (log-rank test:  $p=0.4090$ ).

The operations performed included 25 segmentectomies, 24 lobectomies and 27 wedge resections. Twelve patients were operated upon more than once. Patients who underwent multiple operations tended to show worse prognosis (log-rank test:  $p=0.00617$ ) (Fig. 4). In addition, analysis of the survival rates for patients after different types of pulmonary resection showed no significant differences.

**Table 2.** Potential prognostic factors

Factors	univariate analysis, p-value	multivariate analysis, p-value
Age	0.3950	
Sex	0.9156	
Histology of primary tumour	0.3950	
Type of lung resection		
Lobectomy	0.7232	
Segmentectomy	0.1497	
Wedge resection	0.2402	
systemic treatment	0.2222	
Single/multiple metastases	0.1477	
Single/multiple operations	0.0062	0.7416
Unilateral/bilateral metastases	0.0065	0.6017
Size <3 cm	0.4090	
Size <2 cm	0.0773	
Size <1 cm	0.3066	
DFI <12 months	0.1116	
DFI >24 months	0.0045	0.6571
DFI >36 months	0.0029	0.1033

Complications, occurring in 10 patients (16.4% of patients and 13.2% of procedures) included 1 case of pulmonary embolism, 5 cases of pneumonia, and 4 cases of pneumothorax. There was one case of postoperative death (1.63% of patients and 1.31% of procedures) due to pulmonary embolism on the first day after the operation. We did not operate on patients in the event of complications. All complications were treated non-invasively except one case of pneumothorax where extension drainage was needed.

The results of univariate and multivariate analysis of overall and disease-free survival for clinico-pathological variables are reported in Table 2.

In the present study, three factors were identified as prognostic factors for survival after metastasectomy: (i) DFI >24 ( $p=0.0045$ ), (ii) unilateral pulmonary metastases ( $p=0.0062$ ), (iii) multiple operations ( $p=0.0065$ ).

No other factors, such as sex, age, type of lung resection, histology of primary tumour, type of lung resection, systemic treatment, single/multiple metastases, size up to 1, 2 or 3 cm of metastases, or DFI <12 months, when analysed in univariate analysis, were demonstrated to significantly influence long-term prognosis. All significant clinico-pathological features described above were subjected to multivariate analysis. In multivariate analysis,

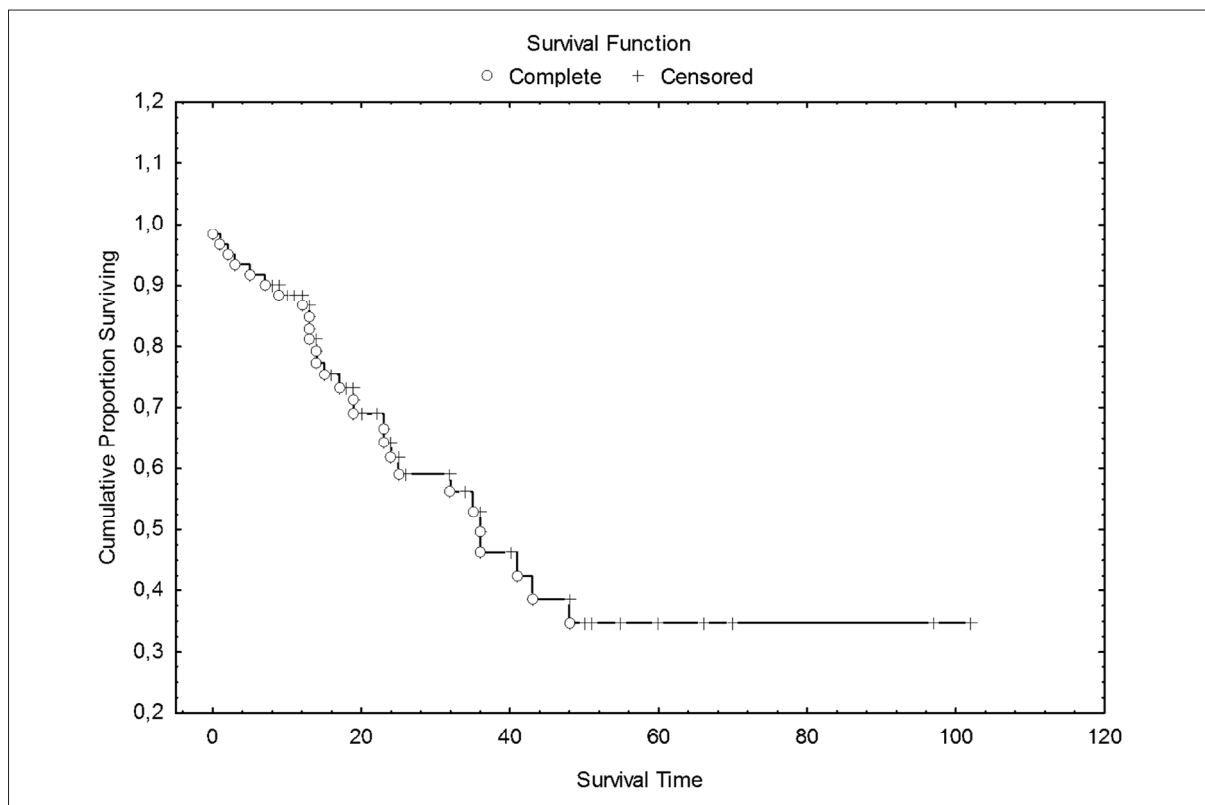


Fig. 1. Graph of survival times vs. the cumulative proportion surviving, according to the Kaplan-Meier method, for 61 patients after lung metastases from epithelial tumour metastasectomy

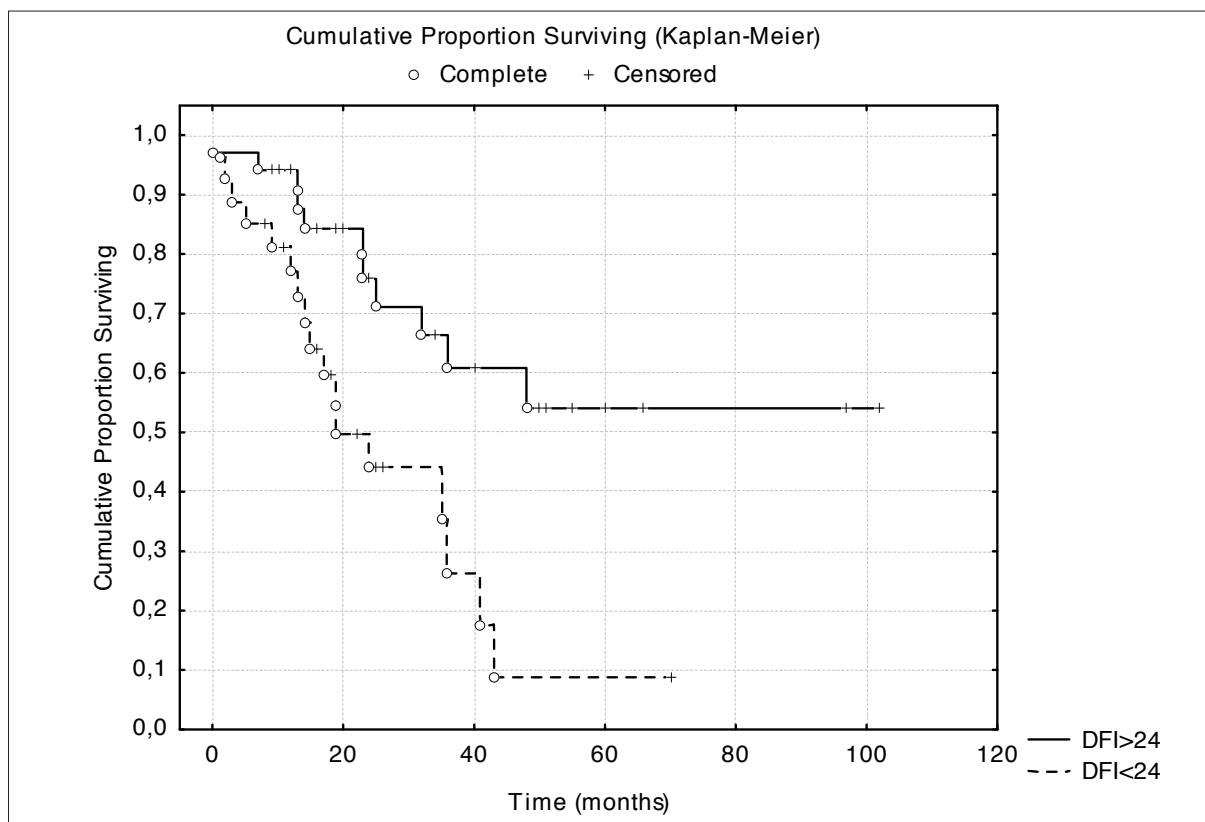


Fig. 2. Survival for patients with DFI > 24 months compared with DFI < 24 months

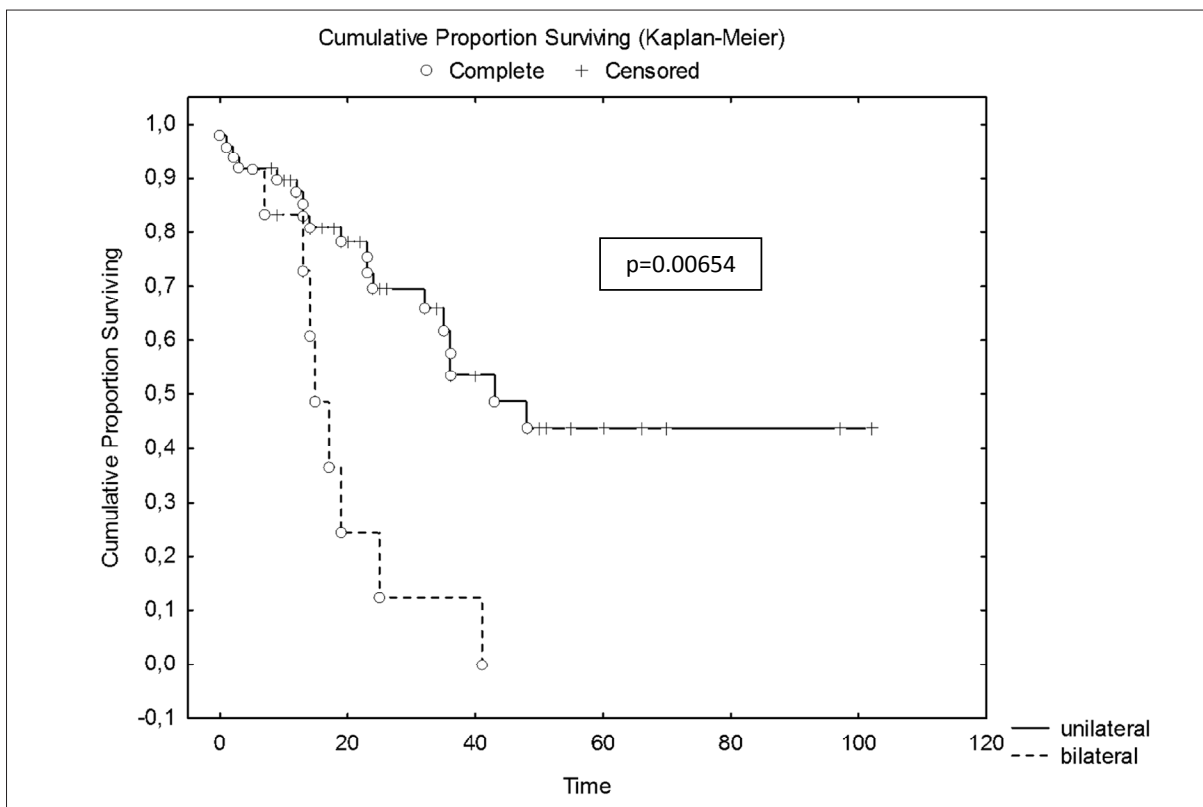


Fig. 3. Survival for patients with unilateral and bilateral pulmonary metastases

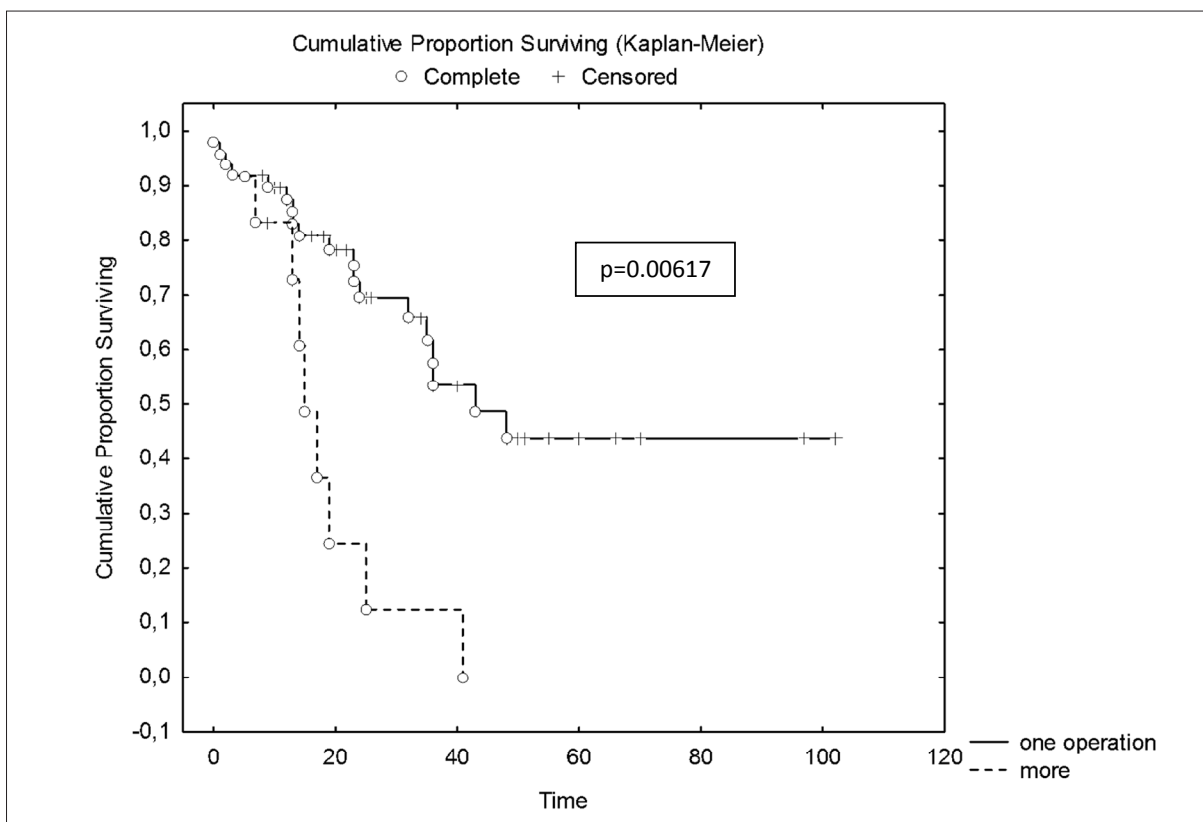


Fig. 4. Survival for patients who underwent multiple operations

sis there was no significant influence on long-term prognosis.

## DISCUSSION

During the last 30 years, surgical resection has become a widely accepted treatment for pulmonary metastases. Thormford et al. [23] first reported the indications for pulmonary metastasectomy in 1965. Resection of pulmonary metastases has been recognized as the only curative therapy, as no curative chemotherapy is available for metastatic colorectal adenocarcinoma. The role of lung metastasectomy will continue to evolve with the improvements in systemic treatment. These patients have had chemotherapy in the course of their metastatic disease in a consistent way as part of the treatment protocol for lung metastases in combination with surgery. In some cases lung resection is carried out to effectively prolong life expectancy, in other cases to provide adjuvant treatment after curative resection.

The International Group for the Study of Lung Metastases in 1997 reached the conclusion that there were three important prognostic factors: the disease-free interval (worse prognosis for a patient with DFI<36 months), single or multiple metastases, and resectability [18]. According to Mc Cormack the criteria for pulmonary resections are: the patient's ability to tolerate the operation, absence of extrapulmonary metastases, locoregional extent of the disease with primary tumour control, and the extent of pulmonary resection (resectability) [13]. Several authors consider that the presence of extrapulmonary metastatic disease is not a contraindication for pulmonary resection, as long as both are completely resectable [10]. We used similar criteria, and all our patients satisfied the required selection criteria: the primary tumour is controlled, no disease is evident outside the lung, computed tomography scan shows that complete resection is possible, and patients are a good operative risk. There were no patients with extrapulmonary metastatic disease.

Most of the metastatic nodules could be removed by wedge resection; this applied to 27 patients in our group, while in 25 patients segmentectomy and in 24 lobectomy was performed because of either the size or intrapulmonary location of the metastatic tumour. Lobectomy is only indicated when it is not possible to perform metastasectomy due to complete resection, large or centrally located lesions, or multiple lesions in a single lobe. This is in accordance with the data in the literature [1].

The perspectives for a better cure for lung metastases rely on the effectiveness of systemic therapies in preventing their appearance. In our experience, 41 patients were treated with curative purposes with radical resection of pulmonary metastases, and these patients have had chemotherapy in the course of their metastatic disease or lung resection provided adjuvant treatment after curative resection. In the other 20 cases, lung

resection was carried out to prolong life expectancy as the only curative therapy, as no curative chemotherapy was available. In our group, adjuvant chemotherapy did not significantly influence the survival prognosis.

It is generally accepted that without surgery the mean survival of patients with pulmonary metastases from colorectal carcinoma is 10 months, with 5-year survival below 5%, whereas surgical treatment has achieved survival rates of 21%-43% at 5 years [1]. The five-year survival for metastatic disease to the lung from breast cancer is thought to be very low. In the study by Staren et al., mean 5-year survival of the non-invasively treated group was only 11%, as compared to the surgical group, whose mean 5-year survival was 36% [22]. Other reports of surgical control of the disease for a prolonged period of time have been provided by McDonald et al. (37.8% mean 5-year survival), Kelm et al. (35%), Simpson et al. (62%) and Friedel et al. (38%) [5,8,14,21]. Our results with median survival time of 35.87 months and 35% at 5-year survival add further weight to the argument that surgical resection of lung metastases from epithelial cancers leads to a significant improvement in survival.

In the present study, two factors were identified as prognostic factors for survival after metastasectomy: DFI<24 and unilateral pulmonary metastases. The significantly favourable outcome of the patients indicates that such patients are the most promising candidates for pulmonary resection. The third factor connected with post-operative prognosis was no more than one lung operation. In our study we observed that the significantly favourable outcome of the patients satisfying these factors indicates better prognosis.

Disease-free interval seems to be a favourable prognostic factor, which is supported by many authors [13,18]. According to Friedel et al. and Pastorino and the International Registry of Lung Metastases, based on risk factors a disease-free interval of >36 months showed 5-year survival of 50%, with the best prognosis in this group of patients [13,18]. In our studies, patients with a disease-free interval of >36 months showed 5-year survival of 45%, with a significant improvement in survival. There were no significant differences in survival rates between patients with synchronous metastases (DFI<12 months) and patients with metachronous disease. This factor was significant in other studies [3,17,25].

Metastasectomy for patients with unilateral metastases had better prognosis. In addition, patients with bilateral lesions had poor survival rates [3,26]. Univariate analysis in this study suggested a significant influence on survival of patients presenting unilateral disease.

In the literature, one of the most common prognostic factors is the number of pulmonary metastases. Many authors have reported that significantly longer survival was observed for patients with colorectal carcinoma with a single metastasis [6,19,24,27]. In our series, the

number of pulmonary lesions did not appear as a prognostic factor. The Danish Colorectal Cancer Group investigated occurrence of synchronous colorectal cancer metastases confined to the lungs, risk factors for these patients and their impact on survival. Patients subjected to pulmonary metastasectomy, resection of primary tumour and chemotherapy had a superior overall survival compared with non-treated patients [16].

Type of surgical resection and the total number of thoracotomies failed to influence the outcome of the patients. As reported, repeated resection may be beneficial in patients with relapses that are confined to the lung [25]. In our series, patients affected by unilateral pulmonary metastases who underwent a single operation had a better prognosis than patients with multiple operations.

Various prognostic factors have been suggested in previous articles. As indicated by other authors, sex, age, and size up to 1, 2 or 3 cm of metastases did not influence prognosis [7,19]. This is consistent with the current study. There is also a group of patients with a single lung tumour who do not have metastases to another organ but have a second independent primary lung cancer. The authors performed computed tomography fine needle biopsy control in the preoperative examination. This avoids incorrect qualifications for metastasectomy [11]. Although multiple serum-based tumour markers have

been described for lung cancer, the available markers are of no value in clinical differential diagnosis [12].

Lung metastasectomy by conventional surgery is a safe procedure with low perioperative morbidity and mortality rates. Most authors have reported morbidity and mortality rates between 0% and 30% and between 0% and 7% respectively [2,15,20]. In our series, morbidity and mortality were the same as previously described.

We conclude that: i) Resection of epithelial pulmonary metastases may offer a significant survival benefit for selected patients; ii) Good surgical candidates for pulmonary resection are those with a disease-free interval greater than 24 months; iii) In the present study the total number of thoracotomies and metastases confined to one lung are factors defining patients who experience a better outcome after surgery; iv) Common risk factors such as sex, age, type of lung resection, systemic treatment, single/multiple metastases, size up to 1, 2 or 3 cm of metastases, and DFI<12 months did not show a significant difference for survival in our series of 61 patients; v) Lung metastasectomy by conventional surgery is a safe procedure with low perioperative morbidity and mortality rates.

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The authors have no potential conflicts of interest to declare.