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Prognostic Factors for Survival After Pulmonary Resection of Metastatic Renal Cell Carcinoma

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Background. **Pulmonary resection in metastatic renal cell carcinoma is an accepted method of treatment. The purpose of this study was to determine the clinical course, outcome, and prognostic factors after surgery.**

Methods. **Between 1985 and 1999, 191 patients (145 men, 46 women) with pulmonary metastases from a renal cell carcinoma underwent surgical resection. Inclusion criteria for the study were the absence of primary tumor recurrence and other extrapulmonary metastases. Complete resection (CR) was achieved in 149 patients.**

Results. **The overall 5-year survival rate was 36.9%. The 5-year survival rate after complete metastasectomy and incomplete resection was 41.5% and 22.1%, respectively. In patients with pulmonary or mediastinal lymph node metastases, we observed after complete resection a 5-year survival rate of 24.4%, whereas the rate was 42.1% in patients without lymph node involvement. A significantly longer survival was observed for patients with fewer than seven pulmonary metastases compared with patients with more than seven metastases (46.8% vs 14.5%). For surgically rendered complete resection (CR) patients with a disease-free interval of 0 to 23 months, the 5-year survival rate was 24.7% compared with 47% for those with more than a 23-month disease-free interval. By multivariate analyses, we showed that the number of pulmonary metastases, the involvement of lymph node metastases, and the length of the disease-free interval were all predictors of survival after complete resection.**

Conclusions. **We conclude that pulmonary resection in metastatic renal cell carcinoma is a safe and effective treatment that offers improved survival benefit. Prognosis-related criteria are identified that support patient selection for surgery.**

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The lungs are the second most frequent site for metastases and often the only location of metastatic disease in renal cell carcinoma. The first resection of a pulmonary metastasis, an en bloc resection of the chest wall and adjacent lung metastases, was performed by Weinlecher in 1882 [1]. The first report of pulmonary metastasectomy in renal cell carcinoma was by Barney and Churchill in 1938 [2]. Since then, many patients have undergone similar procedures.

Because of the likely presence of macroscopically undetectable tumor cells, the value of pulmonary metastasectomy as a therapeutic option is under strong discussion. In metastatic renal cell carcinoma, most conventional antineoplastic drugs or radiation therapy have yielded no or little efficacy. Immunotherapy has proved to be a new treatment in the therapy of advanced renal cell cancer, although prospective controlled clinical studies are pending [3–7]. So far, surgery remains the only effective treatment for patients with limited metastatic disease. The 5-year survival rate of patients with unresected metastatic renal cell cancer is only 2.7% [8].

This article focuses on the outcome, long-term results, and factors associated with prolonged survival in a relatively large series of patients who underwent pulmonary resection for metastatic renal cell carcinoma.

Material and Methods

From January 1985 to December 1999, 191 patients at our institution with metastatic renal cell carcinoma underwent resection of pulmonary metastases. In all patients, the primary tumor was treated by radical nephrectomy; TNM classification an extend of the tumor less than 4 and showed no extrapulmonary metastatic disease. Patients with a history of renal cell carcinoma and one or more pulmonary nodules were evaluated by physical examination, chest roentgenograms, chest computed tomography (CT) scans, ultrasound of the abdomen, and bone scans. In cases of uncertain clinical or radiologic findings, further examinations were performed to exclude extrapulmonary metastases.

All 191 patients were retrospectively analyzed for gender and age, disease-free interval, number and type of pulmonary resections, number of pulmonary metastases, completeness of resection, infiltration of pulmonary or mediastinal lymph nodes, 30-day mortality, and long-term survival. Table 1 is a summary of pertinent patient demographics. There were 145 male and 46 female patients with a mean age of 57.7 years (7 to 76 years) at the time of the first pulmonary resection.

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Table 1. Patient Demographics

Characteristic	
Age	
Mean (range)	57.7 (7–76) years
Gender	
Male	145
Female	46
Disease-free interval (months)	
0–6	50
6–12	11
12–24	30
> 24	100

These 191 patients received a total of 248 thoracic procedures. The surgical approach was chosen according to the location and number of pulmonary nodules. The resection of peripherally located nodules was performed by sternotomy as bilateral synchronous metastasectomy. The bilateral sequential approach was preferred when technically advanced procedures were anticipated. The type of lung resection for metastasectomy ranged from wedge resection in the majority of patients, to various types of anatomical lung resections in selected cases (Table 2). Systematic hilar and mediastinal lymph node dissection was carried out concurrently with all procedures. Two hundred seventeen thoracotomies were performed as initial surgical resection on patients known to have lung metastases of renal cell carcinoma (RCC), compared with 31 thoracotomies on patients with recurrent pulmonary metastases (Table 3). These 31 repeat resections were performed in 28 of the 191 patients who presented with recurrent pulmonary metastases after having had curative resection.

Statistical Analysis

The data were analyzed using the SPSS for Windows (SPSS Inc., Chicago, IL). Critical values of prognostic factors that differentiate between patient groups with good and poor prognoses were determined by the crit level procedure described by Abel associates [9]. The best cut-off value was defined as the value that best discriminated between good and poor prognosis. Probability of survival was then analyzed by the Kaplan-Meier method [10] using the date of pulmonary resection as the starting point. For patients who underwent bilateral sequential metastasectomy, the date of the second operation was used as the starting point. The significance of differences between subgroups was calculated using the log-rank test [11]. The relationship between single parameters in the test groups was calculated by using Fisher's exact test [12]. For the multivariate analysis of prognostic factors, the Cox-model [13] was used. Factors analyzed included age, gender, repeated surgery, curative resection, disease-free interval, number of metastases, and lymph node metastasis. Values of p less than 0.05 were considered statistically significant.

Table 2. Surgical Approach for Patients With First-Time Metastasectomy

Approach	Procedures (n)	Patients (n)
Bilateral/staged	52	26
Unilateral	83	83
Sternotomy	63	63
Clamshell	17	17
VATS	2	2
Total	217	191

VATS = video-assisted thoracic surgery.

Table 3. Types of Pulmonary Resection

	Procedures (n)	Percent
Wedge resection	138	55.6
Segmental resection	38	15.4
Lobectomy/bilobectomy	55	22.2
Pneumonectomy	11	4.4
Other	6	2.4
Total	248	100

Results

The 30-day mortality rate was 2.1% (4/191 patients). The causes of death were pulmonary embolism in 2 patients and postoperative hemorrhage in 1 patient. Another patient developed a spontaneous esophageal rupture on the 12th postoperative day and died 29 days after surgery of multi-organ failure.

The follow-up period ranged from 0.1 to 157.8 months, with a median of 21.4 months. Cumulative 5-year survival rate of all patients was 36.9%. Of the prognostic factors analyzed, age, gender, and repeated thoractomy did not influence survival. However, curative resection, disease-free interval, number of metastases, and lymph node metastases were found to be independent significant prognostic factors for survival after metastasectomy (Table 4).

Complete resection was achieved in 78% (n = 149) of all patients. Incomplete resections (R1 or R2 resections) were documented in 42 patients. The 5-year estimated survival rate in patients with incomplete resections was 22.1% as compared with 41.5% in patients with complete resections (p = 0.036%; Fig 1).

Pulmonary metastases were diagnosed synchronously

Table 4. Potential Prognostic Factors Tested for Multivariate Analysis

Prognostic Factor	p Value
Age	NS
Gender	NS
Redo surgery for recurrent disease	NS
Number of metastases	0.0002
Complete resection	0.049
Lymph node metastases	0.0038
Disease-free interval	0.012

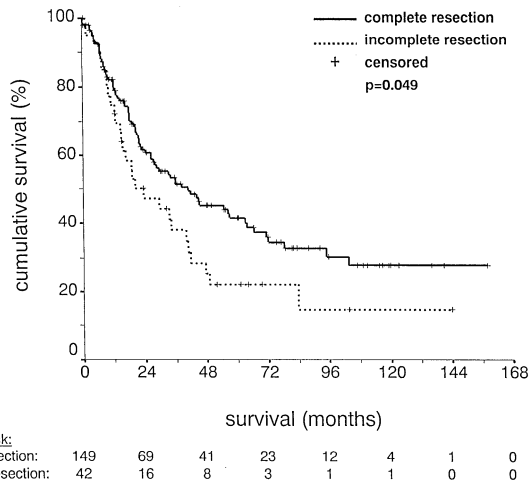

Fig 1. Probability of survival (death from any cause) of patients after pulmonary resection of metastatic renal cell carcinoma: complete resection (R0) versus incomplete resection (R1 or R2). Zero time on the abscissa *represents the date of pulmonary resection (*p = *0.049, log-rank test).*

in 50 patients. We found metachronous disease in 141 cases. The median survival time was 41.5 ± 6.2 months for metachronous disease versus 20.0 ± 5.2 months for synchronous disease. The survival time between these groups of patients with synchronous and metachronous metastases was significantly different ($p = 0.028$). The median disease-free interval (DFI) between nephrectomy and pulmonary resection was 25.3 months (range, 7.7 months before renal cell carcinoma was diagnosed to 119.7 months after nephrectomy). Five-year survival rate in patients with a disease-free interval greater than 23 months was 47.0% compared with 24.7% in patients less than or equal to 23 months ($p = 0.012$). Within the subgroup of patients who underwent complete resection of pulmonary metastases (n = 149), DFI was also a significant prognostic variable (Table 5).

The number of pulmonary metastases ranged from one to more than 30, with a median of four metastases. Complete resection was achieved in 85% of patients in the subgroup with less or equal seven metastases versus 58% in the subgroup with more than seven metastases. The largest number of metastases resected resulting in a complete resection was 29. The number of pulmonary metastases significantly influenced survival. A total of 28.1% of patients with more than seven pulmonary metastases, and 56.0% with fewer than seven pulmonary metastases were expected to survive 3 years or more after pulmonary metastasectomy ($p = 0.002$). The corresponding data (5–year survival rate) for the subgroup of patients after complete resection are shown in Table 5.

Pulmonary or mediastinal lymph node metastases were found in 57 patients, whereas 134 patients had no lymph node metastases. Analysis of the subgroups of patients with hilar versus mediastinal lymph node involvement revealed no significant differences in survival time ($p = 0,54$, after curative resection). The nodal status significantly influenced survival. The expected 3-year survival rate was 31.4% in patients with pulmonary or mediastinal lymph node metastases versus 55.4% in patients without lymph node involvement ($p = 0.0038$). Survival after complete resection was also influenced by the nodal status (Table 5). If one, two, or three of the above identified risk factors were combined, the discriminatory power of the different prognostic groups was highly significant (Fig 2).

In 28 patients, repeat thoracotomies (2–4) were performed for recurrent lung metastases after complete resection of pulmonary metastases. Repeat thoracotomy in recurrent lung metastases was not associated with an increase in morbidity or mortality. Five-year survival from the date of the first operation did not differ significantly from the survival observed in patients who had only one thoracotomy (Fig 3).

Comment

The present study was conducted to describe criteria for selecting patients with isolated pulmonary metastases in an attempt to identify patients who would benefit from surgical resection. In a multivariate analysis of a series of 248 thoracic surgical procedures in 191 patients, the results suggest that a complete surgical resection, disease-free interval, number of metastases, and the presence or absence of thoracic lymph node metastases are all independent significant prognostic factors for survival after metastasectomy.

Several studies concerning surgery for pulmonary metastases from renal carcinoma have been published, and the 5-year survival rates reported ranged from 21% to 60% [16–18]. In the present study, patients with complete resection of all pulmonary metastases had a 5-year survival probability of 41.5%. These data are comparable to survival data reported by Cerfolio and associates [17] (35.7%) from a series of 94 patients with pulmonary resection of metastatic renal cell carcinoma in which patients who had incomplete resection were excluded. Our study showed a 5-year survival rate of 22.1% in patients after incomplete surgical resection. Thus, pa-

Table 5. Survival of Patients Having Had Complete Resection of Pulmonary Metastases

	Metastasis ≤ 7	Metastasis > 7	LN positive	LN negative	DFI ≤ 23 months	DFI > 23 mo
Patients (n)	118	31	41	108	71	78
5-year survival (%)	46.8	14.5	24.4	42.1	24.7	47
p Value	0.0028		0.016		0.03	

DFI = disease-free interval; LN = lymph node.

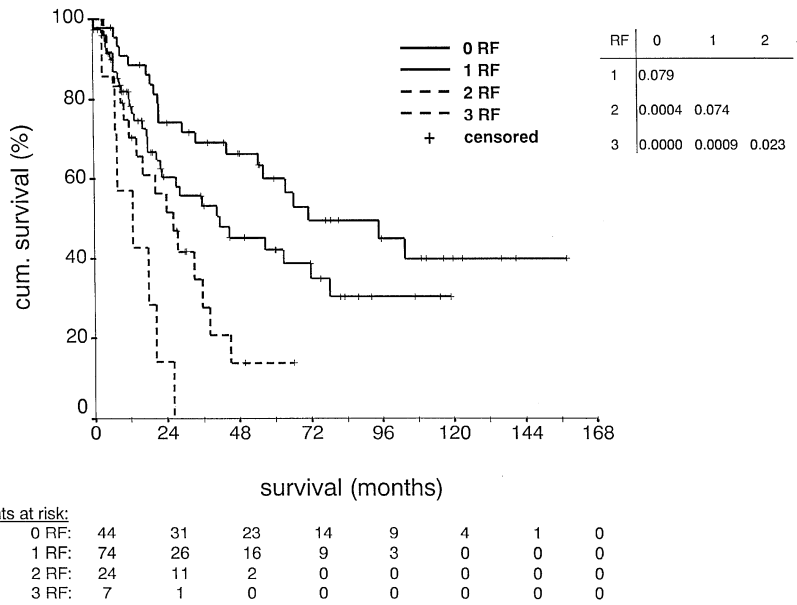

Fig 2. Survival curves after complete resection by the presence of one, two, or three of the following independent significant risk factors (RF) for survival that were identified by multivariate analysis: disease-free interval ≤23 months, number of metastases more than seven, and presence of lymph node metastasis. Zero time on the abscissa *represents the date of pulmonary resection (log-rank test).*

tients may benefit from incomplete resection because, even if they proved to be unresectable in entirety, they had a lesser tumor burden left behind.

Surgical procedures for resection in our study included unilateral thoracotomy, staged bilateral thoracotomy, and median sternotomy. The method chosen did not influence long-term survival if all metastases were resected. Median sternotomy was considered the procedure of choice for the initial exploration in the first half of the study interval. Recently, in the era of high-resolution CT, median sternotomy was reserved for patients with bilateral peripherally located nodules. However, we, among others [15], believe that open thoracotomy, with thorough palpation of the inflated and deflated lung, remains mandatory even in the light of modern CT sensitivity. The video-assisted approach (VATS) is only of diagnostic value.

In our study, lung resections were performed by removing pulmonary metastases with the most limited parenchymal resection, permitting a curative resection [14]. Surgical resection by means of wedge resection, segmentectomy, and, in selected cases, lobectomy or pneumonectomy was completed by a systematic interlobar, hilar, and mediastinal lymph node dissection. In our study, 57 patients were diagnosed with pulmonary or mediastinal lymph node metastases after performing lymph node dissection. In contrast to other authors [17], multivariate analysis of our data showed a statistically significant difference in survival between patients with lymph node involvement versus those without lymph node metastases. Thus, the suggestment that metastases induce metastases seems at present intriguing and provocative. However, with this finding, we may have demonstrated that a hilar and mediastinal lymph node dissection offers a further understanding of pulmonary metastases and remains a significant prognostic factor. This may have an impact on future adjuvant treatment strategies.

In addition to resectability and lymph node involvement, the multivariate analysis of our data identified two further favorable prognostic factors: DFI of 23 months or greater and number of metastases fewer than seven. With this finding, we in essence reconfirmed the data derived from the International Registry of Lung Metastases for the single primary tumor renal cell carcinoma [22]. Pastorino and collegues reviewed the long-term results after resection of pulmonary metastases from various primaries based on more than 5,000 patients collected from several institutions and found that DFIs of 36 months or greater and a solitary metastasis were associated with improved survival. In a smaller study from the National Institute of Cancer on 23 patients who underwent resection of pulmonary metastases from renal

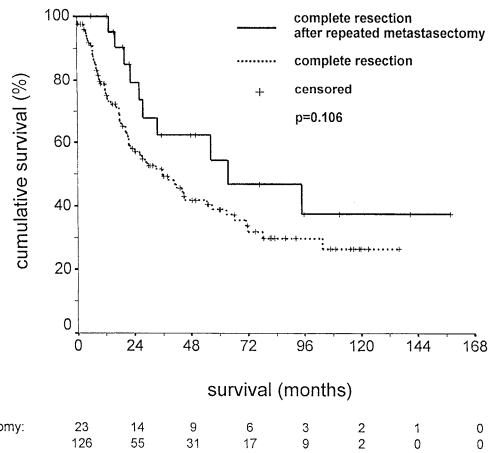

Fig 3. Probability of survival (death from any cause) of patients undergoing a single thoracotomy for renal cell carcinoma metastatic to the lung as compared with patients who underwent multiple thoracotomies for recurrent renal cell carcinoma to the lungs (survival starting at the first operation). Zero time on the abscissa *represents the date of the first thoracotomy (p = 0.11, log-rank test).*

cell carcinoma, postresection survival did not depend on the number of resected nodules or the DFI [18]. However, contrary to others [17, 20], these data show that a longer DFI is more favorable than a shorter one. In our study, patients with more than seven metastases had a significantly shorter 5-year survival rate. Although earlier studies [18, 19] demonstrated no difference in survival among patients with single versus multiple pulmonary metastases, we, like other authors [17, 20, 21], revealed the number of pulmonary metastases as a significant prognostic factor.

According to the system proposed by Pastorino and collegues [22], we grouped curative resected patients into prognostic categories including three values: DFI, number of metastases, and lymph node involvement. This model was used to construct a system of prognostic groupings that could take into account all the relevant prognostic factors simultaneously.

The presence of one, two, or three of these risk factors distinctly influenced survival. This grouping system may be helpful in selecting patients for resection of pulmonary metastases. Another interesting result from our data is the finding that survival of patients who underwent repeated thoracotomies for recurrent pulmonary metastases did not differ from survival after complete resection, suggesting repeated metastasectomy may set the clock back.

We conclude that resection of pulmonary metastases of renal cell carcinoma is a safe and effective treatment. Low mortality rate and, at present, the lack of established effective systemic chemotherapy justify an aggressive approach to surgical resection. Once metastases have been detected, resection should not be postponed. Good surgical candidates for pulmonary resection are those showing a long disease-free interval and a small number (fewer than seven) of pulmonary metastases. Five-year survival is influenced by resectability and metastatic pulmonary or mediastinal lymph node involvement. Repeat resection for recurrent lung metastases is warranted. Lifelong surveillance is necessary to detect recurrent disease. Yet, pulmonary resection of metastatic renal cell carcinoma is regarded as safe and effective, although factors that determine long-term survival are not completely understood.

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