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Outcome after Pulmonary Metastasectomy

Analysis of 5 Years Consecutive Surgical Resections 2002–2006

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Introduction: In this study, we analyze the results of management of pulmonary metastases in 5 years consecutive operations at our institution. We aim to define the patients who are most likely to benefit from surgery by investigating long-term survival and prognostic factors associated with prolonged survival.

Methods: The data on all consecutive patients between 2002 and 2006 were reviewed retrospectively. One hundred seventy-eight patients underwent 256 surgical resections for suspected pulmonary metastases from different primary malignancies. Prognostic factors analyzed included age, sex, surgical approach, surgical resection, number of metastases, distribution of metastases, disease-free interval, presence of synchronous metastases, recurrence of disease, prior liver resection (colorectal cancer), and tumor histology (sarcomas).

Results: Complete resection was achieved in 248 cases (96.8%). The mean follow-up was 61.6 months. Five-year survival with respect to primary malignancy was colorectal carcinoma (50.3%), sarcoma (21.7%), malignant melanoma (25.0%), renal cell carcinoma (51.4%), and miscellaneous malignancies (50.0%). Of the prognostic factors analyzed by univariate analysis, none was found to be significant in all the different groups of cancers.

Conclusions: Pulmonary metastasectomy is a safe and effective treatment that may be associated with prolonged survival in highly selected patients. Low morbidity and mortality rates in contrast with the lack of any other effective treatment justify the aggressive approach of surgery. Thoracoscopic resection is a valid option in selected patients. In case of recurrence of pulmonary disease and if the patient fulfils the initial criteria for pulmonary metastasectomy, repeat surgery should be performed. Solid prognostic factors still need to be established.

Key Words: Lung, Metastases/metastasectomy, Thoracoscopy/VATS, Thoracotomy.

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Metastatic spread of malignant disease remains one of the major obstacles when treating patients with cancer. The lungs are the most common organ to which cancer metastasizes, and approximately 30% of all patients with cancer will develop lung metastases at some point.[1] Pulmonary metastasectomy has been performed for decades, and numerous retrospective series have demonstrated long-term survival superior to conventional oncological treatment. Many prognostic factors have been analyzed and the ones that primarily emerge are as follows: number of pulmonary metastases, disease-free interval (DFI), radical surgery, and for colorectal cancer, level of preoperative carcinoembryonic antigen.

Today, despite the lack of randomized studies, pulmonary metastasectomy is considered an accepted therapeutic option in selected patients as a treatment of proved value. With the advancements in anesthetical and surgical techniques, the safety of surgery has improved and the indications for surgery have been extended more widely. More and more patients are now being referred to thoracic departments for pulmonary metastasectomy. In a recent survey by Internullo et al.,[2] among the members of the European Society of Thoracic Surgeon, lung metastasectomy represented up to 10% of clinical volume, and the need for solid prognostic factors remains strong and has yet to be established.

In this study, we analyze the results of management of pulmonary metastases in 5 years consecutive and recent operations at our institution. We aim to define those patients who are most likely to benefit from surgical treatment by investigating outcome, long-term survival, and prognostic factors associated with prolonged survival.

MATERIALS AND METHODS

Between January 2002 and December 2006, 307 operations for suspected pulmonary metastases were performed at our institution. The operative data were entered into the Patient Analysis & Tracking System, version 1108-UK16. When these data and patient charts were reviewed retrospectively, one operation was performed because of pain and another because of continuous air leakage. These two operations were therefore excluded. Two patient charts accounting for two operations could not be located and were thus also excluded. Of the remaining 303 operations, 47 were solely for diagnostic purpose and therefore not with curative intent. Thus, these were excluded. Therefore, a total of 256 pulmonary resections with curative intent were included in this study.

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The patients eligible for curative surgery were to meet the following standard criteria[1]: primary tumor was controlled,[2] no extra-thoracic lesions were detected (with the exception of hepatic lesions in which it was possible to completely remove both hepatic and pulmonary metastases),[3] the metastases were technically resectable, and[4] the general and functional risks were tolerable.

Preoperative diagnostic assessment to exclude extra-thoracic disease and to assess patient risks included chest x-ray, chest and abdominal computed tomographic (CT) scan, and cardiac and pulmonary function tests (spirometry, electrocardiogram and/or pulmonary perfusion scintigram, echocardiogram, and positron emission tomography/CT). In some patients, bronchomediastinoscopy was performed to exclude malignant disease in the hilar and/or mediastinal lymph nodes if suspected by CT. Lymph node dissection was not systematic and only performed with the detection of malignancy suspect lymph nodes during surgery.

The medical charts for all patients were reviewed for age, gender, primary tumor, date of primary tumor operation, date of pulmonary resection, surgical approach, type of resection, location and number of metastases, DFI, 30-day mortality and morbidity, and duration of survival. DFI was defined as the time from the date of primary tumor surgery till the date of pulmonary metastasectomy. Survival was calculated from the time of pulmonary metastasectomy to death or the date of last follow-up. All available survival data were updated in January 2010 for a minimum follow-up of 36 months. Survival status of the patients was obtained from the Danish National Registry.

Data on preoperative level of carcinoembryonic antigen were only available in a few patients and therefore not analyzed. Moreover, data on neoadjuvant and adjuvant chemotherapy/radiotherapy were not readily available for analysis.

In total, 256 thoracic procedures with curative intent were performed in 178 patients. The surgical approach was chosen according to the location and number of metastases. One hundred forty-three thoracotomies and 60 video-assisted thoracoscopic surgery (VATS) were performed. In 53 patients, the operation was initiated as VATS but was converted to thoracotomy because of inability to achieve radical resection thoracoscopically. The type of pulmonary resection ranged from predominantly wedge resection to extra-pleural pneumonectomy in one patient.

Table 1 is a summary of surgical approach and types of resection.

TABLE 1. The Surgical Approaches for All Resections, Surgical Approaches At the First Operation, Surgical Approach When Staged Surgery, and Number and Type of Resection for All the Surgeries

	No. (%)
Surgical approach total	
VATS	60 (23%)
VATS/thoracotomy	53 (21%)
Thoracotomy	143 (56%)
Surgical approach at first operation	
VATS	24 (19%)
VATS/thoracotomy	21 (16%)
Thoracotomy	53 (42%)
Staged bilateral surgery	29 (23%)
Surgical approach when staged surgery	
Bilateral VATS	3 (10%)
VATS/thoracotomy	6 (21%)
Bilateral thoracotomy	20 (69%)
Type of surgical resection	
Wedge	210 (82%)
Segmental	6 (2.5%)
Thoracic wall resection	9 (3.5%)
Lobectomy	21 (8.5%)
Pneumonectomy	2 (0.5%)
Extra pleural pneumonectomy	1 (0.5%)
No resection	7 (2.5%)

VATS, video-assisted thoracoscopic surgery.

Statistical Analysis

The data were analyzed using the SPSS for Windows software (Statistical Package for Social Science, SPSS Inc, version 15.0). Probability of survival was analyzed according to the Kaplan-Meier method using the date of pulmonary resection as the starting point. For patients who underwent staged bilateral surgery, the date of the first operation was used as starting point. The significance of differences between variables was analyzed using the log-rank test. A p value of 0.05 or less was considered significant.

Factors analyzed included age (</>60 years), sex, surgical approach (VATS versus thoracotomy), surgical resection (wedge resection versus all other), number of metastases, distribution of metastases (unilateral versus bilateral), DFI, presence of synchronous metastases, recurrence of pulmonary disease, prior liver resection (colorectal cancer only), and tumor histology (sarcomas only). In Table 2 the results are summarized.

RESULTS

The 30-day mortality was 1.9% (5/256). One patient with hepatocellular carcinoma with benign histology from the resected lung lesion was discharged to another ward and died 4 days after. Of the patients with radical metastasectomy, three patients died due to the following complications: fatal stroke, perforated ulcer, and sepsis/respiratory failure. One patient was discharged to the oncological department and died 12 days after his third surgery in which radical resection could not be achieved.

Postoperative complications occurred after 6.6% (17/256) of the procedures and included seven infections, two pneumonias, two atrial fibrillations, two empyemas, one pneumothorax, one persistent air leak, one stroke, and one perforated ulcer.

Twenty-six (10.1%) operations revealed benign histology of the resected lesion. Twenty-five (9.8%) operations revealed a primary lung cancer, and these patients were either perioperatively treated with lobectomy or entered the formal

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TABLE 2. Estimated 5-yr and Median Survival for Each Group of Cancers

	Primary Cancer				
Factors Analyzed	**Colorectal**	**Sarcoma**	**Melanoma**	**Renal Cell Carcinoma**	**Miscellaneous Cancers**
No. of patients	53	32	16	10	16
5-yr estimated survival (%)	50.3	21.7	25.0	51.4	50.0
Median survival (mo)	33.5	25.5	10.2	43.4	39.9
Age ≤60 yr	$p = 0.23$	$p = 0.43$	$p = 0.52$	$p = 0.42$	$p = 0.32$
Gender	$p = 0.61$	$p = 0.31$	$p = 0,45$	$p = 0.85$	$p = 0.35$
Surgical approach	$p = 0.54$	$p = 0.82$	$p = 0.92$	$p = 0.66$	$p = 0.46$
Surgical resection	$p = 0.07$	$p = 0.98$	$p = 0.22$	$p = 0.18$	$p = 0.12$
Metastases					
1 vs. more	$p = 0.40$	$p = 0.67$	$p = 0.07$	$p = 0.06$	$p = 0.56$
2 vs. 3 or more	$p = 0.40$	$p = 0.08$	$\mathbf{p = 0.04}$	$p = 0.17$	$p = 0.77$
3 vs. 4 or more	$p = 0.11$	$p = 0.11$	$p = 0.12$	$p = 0.39$	$p = 0.39$
4 vs. 5	NP	$p = 0.12$	NP	NP	NP
Unilateral vs. staged bilateral surgery	$p = 0.61$	$p = 0.25$	$p = 0.24$	$p = 0.11$	$p = 0.12$
DFI					
<12 mo	$p = 0.76$	$p = 0.09$	$p = 0.41$	$\mathbf{p = 0.04}$	$\mathbf{p = 0.03}$
<24 mo	$p = 0.72$	$p = 0.23$	$p = 0.96$	$p = 0.20$	$p = 0.26$
<36 mo	$p = 0.65$	$p = 0.46$	$p = 0.63$	$p = 0.20$	$p = 0.62$
Synchronous metastases	$p = 0.42$	$p = 0.85$	$p = 0.57$	$p = 0.58$	NP
Repeat surgery	$p = 0.30$	$p = 0.37$	$p = 0.50$	$p = 0.55$	$p = 0.40$
Liver metastases	$p = 0.001$	NT	NT	NT	NT

p value for each prognostic factor analyzed is shown.
DFI, disease-free interval; NP, no patients; NT, not tested.

TABLE 3. Patient Demographics

Age, mean (range) yr	57 (16–82)
Sex	
Male	61 (48%)
Female	66 (52%)
Primary tumor	No. of patients (%)
Colorectal	53 (43)
Sarcoma	32 (24)
Melanoma	16 (13)
Renal cell	10 (7)
Miscellaneous	16 (13)

diagnostic protocol for lung cancer. A total of 127 patients with a total of 205 procedures were therefore included as having performed radical surgery for pulmonary metastases. Table 3 is a summary of patient demographics of the patients with pulmonary metastasectomy.

Exact calculation of DFI was possible in 11 patients. In most patient charts ($N = 64$), the time of primary surgery was only noted with month and year of surgery, e.g., March 2002. In these cases, the date of surgery was set to the 15th. In the remaining cases ($N = 52$), only the year of primary surgery was known, and in this study, the date was set to the 1st of June.

Ninety-eight patients had unilateral surgery and 29 patients had bilateral metastases and therefore staged bilateral surgery as their initial surgery. In all, 24 of 127 patients developed recurrent pulmonary disease. In these patients, 49 repeat resections were performed ranging from one to six operations.

Completeness of resection was not achieved in eight (3.1%) patients. Of these, six patients were diagnosed inoperable perioperatively, and two patients had microscopically nonradical surgery and could not tolerate further surgery. Three patients were lost to follow-up. The mean follow-up was 61.6 ± SD 18.1 months.

Colorectal Cancer

Fifty-three patients were resected because of colorectal metastases, and the median survival was 33.5 months and the estimated 5-year survival was 50.3% (Figure 1). Of the prognostic factors analyzed, age, sex, type of resection, type of surgical approach, the number of metastases, or the presence of synchronous metastases none significantly influenced survival. The median DFI between resection of the primary tumor and lung resection was 13.1 months (range 0–139 months). No cutoff value of DFI was significant. Forty-one patients presented with unilateral disease and 12 patients with bilateral disease and thus staged bilateral surgery was performed. No significant difference in survival was found ($p = 0.61$).

In seven patients, recurrence of pulmonary metastases resulted in repeat resections (one to three operations) after the initial complete resection of lung metastases. Repeat resection was not associated with an increase in morbidity or mortality or with a significant difference in survival ($p = 0.30$).

Seven patients had liver resection performed because of hepatic metastatic disease before lung metastasectomy. For patients with liver metastases, the median survival and 5-year

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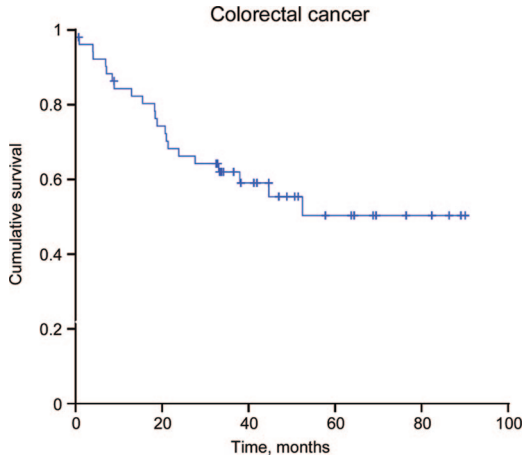

FIGURE 1. The estimated 5-year survival after pulmonary metastasectomy for patients with colorectal metastases.

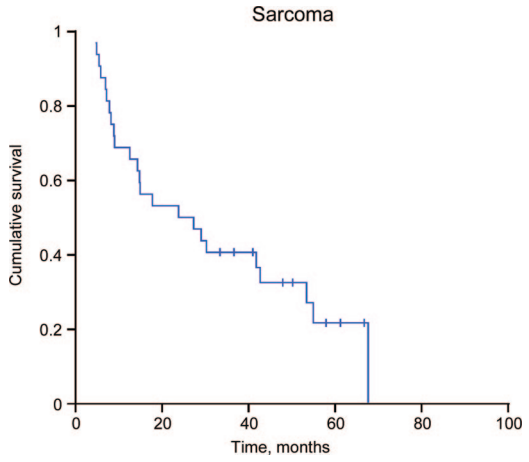

FIGURE 2. The estimated 5-year survival after pulmonary metastasectomy for patients with sarcoma metastases.

estimated survival were 15.4 months and 0% and for patients without liver metastases 28.6 months and 61.7%, respectively. The difference in survival between these groups was found to be significant ($p = 0.001$).

In two patients, radical surgery could not be achieved. They died 18 and 27 months after attempted pulmonary metastasectomy, respectively.

Sarcoma

Thirty-two patients were resected because of sarcoma metastases, and the median survival was 25.5 months and the estimated 5-year survival was 21.7% (Figure 2). The group was composed of a heterogeneous group of sarcomas such as osteogenic, Ewing sarcoma, chondrosarcoma, liposarcoma, synovialsarcoma, and others. Of the prognostic factors analyzed, age, sex, type of resection, type of surgical approach, tumor histology, presence of synchronous metastases, or number of metastases, none significantly influenced survival. The median DFI between resection of the primary tumor and lung resection was 21.4 months (range 0–317 months). No cutoff value of DFI was significant.

Twenty-three patients presented with unilateral disease and nine patients had bilateral disease and therefore staged surgery. No statistical difference in survival was found ($p = 0.25$).

In all, 10 of 32 patients (31%) had repeat surgery for recurrence of lung metastases after the initial complete resection of pulmonary metastases. Number of repeat surgery ranged from one to six operations after initial radical surgery. Repeat resection was not associated with an increase in morbidity or mortality or with a significant difference in survival ($p = 0.37$).

Three patients did not have radical surgery. All were diagnosed inoperable perioperatively because of extensive tumor growth. They died after attempted surgery after 4, 5, and 8 months, respectively.

Melanoma, Renal Cell Carcinoma, and Miscellaneous Cancers

Sixteen patients were resected because of metastatic melanoma, and the median survival was 10.2 months and the estimated 5-year survival was 25.0% (Figure 3). Ten patients were resected because of renal cell carcinoma metastases, and the median survival was 43.4 months and the estimated 5-year survival was 51.4% (Figure 4). Sixteen patients had pulmonary metastasectomy because of miscellaneous primary tumors (Table 4). For this heterogeneous group, the median survival was 39.9 months and the estimated 5-year survival was 50.0%.

Of the prognostic factors analyzed, age, sex, presence of synchronous metastases, laterality, type of resection, type of surgical approach, and repeat resection did not significantly influence survival.

For malignant melanoma, the number of pulmonary metastases was found to be a significant prognostic factor. The cutoff value that significantly differentiated between good and poor prognosis was found to be two or less metastases with a median and 5-year survival of 17.9 months and 40.0% and 7.3 months and 0% for three or more metastases ($p = 0.04$). No other differences in number of metastases

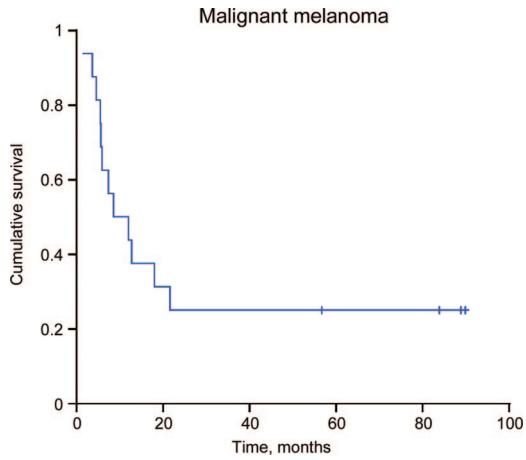

FIGURE 3. The estimated 5-year survival after pulmonary metastasectomy for patients with malignant melanoma metastases.

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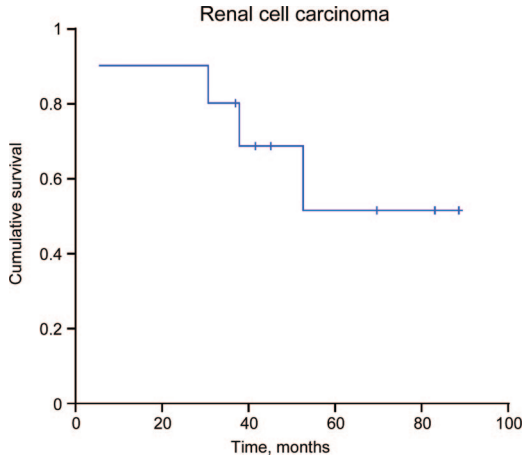

FIGURE 4. The estimated 5-year survival after pulmonary metastasectomy for patients with renal cell carcinoma metastases.

TABLE 4. Numbers of Different Tumors in the Miscellaneous Cancers Group

Miscellaneous Cancers	
Primary Tumor	**No. of Cases**
Testis	4
Thyroid	4
Parotis	2
Tonsil	1
Uterus	1
Adrenocortical	1
Ovarian	1
Esophagus	1
Bladder	1

were found to be significant. In the renal cell carcinoma or miscellaneous group, the number of metastases was not significant.

The DFI was a significant prognostic factor in both the renal cell carcinoma and the miscellaneous cancers group. For renal cell carcinoma, the median DFI between resection of the primary tumor and lung resection was 15 months (range 0–215 months). A DFI of less than 12 months resulted in median survival and 5-year estimated survival of 30.6 months and 33.3% in contrast to median survival and 5-year estimated survival of 55.4 and 75.0% ($p = 0.04$) for a DFI more than 12 months. For miscellaneous primary tumors, the median DFI between resection of the primary tumor and lung resection was 31.3 months (range 11–198 months). A DFI of less than 12 months resulted in median survival and 5-year estimated survival of 2.7 months and 0% in contrast to median survival and 5-year estimated survival of 48.3 and 44.4% ($p = 0.03$) for a DFI >12 months. In both groups, further statistical analysis of DFI could not demonstrate other cutoff values of significance. However, one must bear in mind that the number of patients in these groups is very small so statistical analysis must be interpreted with caution.

DISCUSSION

During the last decades, pulmonary metastasectomy has become an increasingly used therapy for various metastatic malignancies to the lungs with metastasectomy from colorectal carcinomas and sarcomas being the most common. However, pulmonary metastases from a wide range of tumors are being referred for treatment. The search for solid prognostic factors is ongoing and needed. We therefore decided to retrospectively analyze a recent cohort of 5 years consecutive pulmonary metastasectomies at our institution to identify patients who would benefit from surgical resection.

Approximately 10 to 20% of patients with colorectal cancer will develop pulmonary metastatic disease.[3] Isolated pulmonary metastases without extra-thoracic disease is, however, rare and accounts for as little as 2% of patients with metastatic colorectal carcinoma.[4] For pulmonary metastases of colorectal origin, several studies have reported 5-year survival rates ranging from 27 to 61%.[5] In our study, the data for survival were consistent with these previous studies with an overall estimated survival of 50.3%. Age and sex were not significant prognostic factors.

More than half of the patients presented with single lesions (30/53). Previous studies have demonstrated that the number of metastases significantly influences survival.[6] Usually, in terms of patients with a single lesion have the best prognosis or the fewer metastases the better. Phannschmidt and colleagues reported that patients with up to four metastases demonstrated a better survival than patients with more than four metastases. Koga et al.[7] found the cutoff value to be 3 or less metastases.

In our study, we could not find a cutoff value for the number of lesions that significantly influenced survival. Neither could we demonstrate prognostic significance between patients with unilateral or bilateral disease. However, in our study, the maximum number of colorectal metastases removed during a single surgery was three metastases, and most of the patients presented with one or two metastases. A bias to consider in this study is that perhaps only patients in good preoperative condition and few metastases (<3) are being referred to surgery, and we therefore only operate on patients with a good prognosis. Even so, no difference in survival was found between patients with one or two lesions.

Previous studies have demonstrated the DFI to be a significant prognostic factor in terms of the longer the DFI, the better survival.[8] The presence of synchronous metastases as a prognostic factor with an adverse effect on survival has also been reported.[9] In our study, the DFI did not influence survival, nor did the presence of synchronous metastases.

Approximately 15% of patients resected for colorectal carcinomas can be expected to have hepatic metastases at the time of exploration.[10] As many as 50% will eventually develop liver metastases and liver resection, for metastatic disease is an established treatment. Several studies have reported no significant adverse effect on survival when performing pulmonary metastasectomy in the presence of previously complete liver resection.[5,8] In our study, we found the presence of previously treated hepatic metastases to be an ominous prognostic factor ($p = 0.001$).

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An interesting observation when looking at the Kaplan-Meier plot is that the survival curve seems to flatten out indicating that long-term survival is possible.

Patients with sarcoma are particularly prone to develop pulmonary metastases. In osteosarcoma, 10 to 20% of patients will have detectable pulmonary lesions at initial diagnosis, and up to 70% of patients will develop metachronous pulmonary metastases.[11] Pulmonary metastases in soft tissue sarcoma are less frequent and develop in approximately 20% of patients.[12]

For pulmonary metastases from sarcomas, previous studies have demonstrated 5-year survival rates between 15 and 37%.[13,14] Our survival data with an estimated 5-year survival of 21.7% were consistent with these previous studies. Age, sex, surgical approach, type of resection, or the presence of synchronous metastases did not influence survival significantly. Previously published significant prognostic factors include number of metastases, laterality, and DFI. None of these could be confirmed in our study.

Several studies have shown that the complete resection of pulmonary metastases from sarcomas is a significant prognostic factor.[15] In our study, three patients had only explorative surgery because of widespread tumor growth detected perioperatively. Incomplete resection had a very bad prognosis, and all three patients died within 9 months after surgery.

Surgical treatment of lung metastases from melanoma is controversial as the expected outcome is much poorer than for other primary tumors. Malignant melanomas' ability to widespread dissemination causes the number of patients eligible for pulmonary metastasectomy to be very small as patients with isolated pulmonary metastases are a very small proportion of patients with disseminated malignant melanoma. Once malignant melanoma has spread to a distant site, the median survival is 8 months and 5-year survival is less than 5%.[16] Previous studies with pulmonary metastasectomy from malignant melanoma have demonstrated 5-year survival rates of up to 33%[17] and thus far superior to medical treatment alone. Our survival data with an estimated 5-year survival of 25.0% were consistent with these previous studies. The presence of single metastasis and complete resection are the most often published significant prognostic factors. We also found the number metastases to be significant. Two metastases or fewer were significantly associated with prolonged survival. In the International Registry of Lung Metastases,[6] a DFI of more than 36 months was also found to be significant but this could not be confirmed in our study. None of the other analyzed factors in our study were significant. However, the number of patients in the melanoma group in our study is small ($N = 16$) so the statistical analysis must be interpreted cautiously.

Approximately 25 to 30% of patients with renal cell carcinoma will have metastatic disease at diagnosis and a further 30% of patients will eventually develop metastases with the lungs being the most common organ.[18] Previous studies have demonstrated 5-year survival rates of up to 40% after pulmonary metastasectomy from renal cell carcinoma.[19] Our results are consistent with these findings. Previously investigated significant prognostic factors that influence survival include complete resection, number of metastases, DFI, and lymph node status.[19] In our analysis, only a DFI less than 12 months was confirmed as a significant prognostic factor with adverse effect on survival. However, because of the small number of patients ($N = 10$), the statistical analysis must be interpreted cautiously.

The subgroup with miscellaneous primary tumors represents such a heterogeneous group of cancers (Table 4) from which no conclusion can be drawn from this group. However, emphasis must be put on that every patient is examined carefully for the eligibility for potential pulmonary metastasectomy.

The surgical approach in pulmonary metastasectomy remains a controversial issue. Open surgery through lateral thoracotomy, median sternotomy, or even clamshell incision enables the surgeon to perform bimanual palpation of the whole lung and thereby potentially detect lesions missed by preoperative imaging. Several studies have shown the inadequacy of preoperative CT scan, even with high-resolution helical scanners, to detect all pulmonary lesions found during surgery.[20]

VATS is a less invasive procedure resulting in less surgical trauma and postoperative morbidity.[21] In the case of repeat surgery for recurrence of pulmonary disease, it does not complicate a potential reoperation by thoracotomy. The disadvantage is the lack of tactile sensation and the risk of missing lesions that could possibly have been detected with conventional thoracotomy and bimanual palpation.

However, with the improvement in radiology and surgical techniques, several more recent studies have now been published investigating the VATS approach in pulmonary metastasectomy and demonstrating survival rates equivalent to open surgery.[22,23] These studies only investigated patients with small (<3 cm) and few (<2) metastases.

At our institution, the current approach is to perform thoracoscopy in patients with few lesions (<2) located in the periphery of the lung. In the case of inability to achieve certain R0 resection, the procedure is converted to open surgery. The remaining patients will have conventional open surgery performed.

In our study, no significant difference in survival was observed between patients who had thoracoscopy or thoracotomy performed, regardless of primary tumor (colorectal, $p = 0.54$; sarcoma, $p = 0.82$; melanoma, $p = 0.92$; or renal cell carcinoma, $p = 0.66$). Hence, our current practice seems justified.

Twenty-four (18.9%) patients developed recurrence of pulmonary metastases and 49 repeat surgeries were performed ranging from one to six operations in a single patient. Sarcoma patients (10/32) were the most likely to develop recurrence followed by renal cell carcinoma (2/10) and colorectal (7/53) patients. All but one patient developed recurrence in a different lobe from where the previous resection was performed. The one patient with six repeat resections had osteosarcoma as the primary malignancy, and in two of these resections, recurrence of disease developed in a lobe where a previous resection had been performed.

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The estimated 5-year survival of patients who underwent repeated surgery for recurrent pulmonary metastases did not differ significantly from those who only had single/staged surgery (colorectal $p = 0.30$; sarcoma, $p = 0.37$; melanoma, $p = 0.50$; or renal cell carcinoma, $p = 0.55$). This indicates that as long as a patient can fulfill the initial criteria for pulmonary metastasectomy, repeat surgery is not an ominous prognostic factor and surgery should be attempted. Aggressive follow-up after pulmonary metastasectomy must be conducted.

Initially, 32 patients had thoracoscopy performed, 24 had thoracoscopy converted to thoracotomy performed, and 71 had thoracotomy performed. In the thoracoscopy, group 6 patients developed recurrence (18.7%), and in the combined group of thoracoscopy converted to thoracotomy and only thoracotomy, 18 patients developed recurrence (18.9%). Hence, no difference in recurrence between the two groups could be demonstrated.

Regarding survival, when the six patients with thoracoscopy were analyzed against the other patients with recurrence where thoracotomy was performed, no significant difference in survival could be demonstrated ($p = 0.34$).

In addition, the thoracoscopic approach seems justified in appropriately selected patients. The question of lymph node sampling and/or involvement remains controversial. The performance of lymph node dissection during pulmonary metastasectomy is infrequent and varies between institutions, including our own. Of all the patients in The International Registry of Lung Metastases, only 4.6% of patients underwent lymph node dissection. In a recent survey by Internullo et al., among the members of European Society of Thoracic Surgeons, 55% perform mediastinal lymph node sampling, whereas 33% perform no nodal sampling at all. The rate of lymph node involvement varies between primary tumors. Phannschmidt and colleagues performed systemic lymph node dissection in concurrence with pulmonary metastasectomy in 245 patients with metastases from colorectal carcinoma, renal cell carcinoma, and sarcoma. Nodal involvement was more frequent in renal cell carcinoma (42.4%) and colorectal carcinoma (31.3%) than sarcomas (20.3%). Several studies have found the presence of positive intrathoracic lymph nodes, an ominous prognostic factor. Ercan and colleagues found a 3-year survival of 69% for patients without lymph node involvement versus 38% in patients with positive lymph nodes. Saito and colleagues reported a 5-year survival of 53.6 for patients without hilar or mediastinal node involvement versus 6.2% at 4 years for patients with positive nodes.

It remains unclear whether the removal of these lymph nodes confers a survival benefit or merely allow for a more accurate postoperative staging and guidance for additional oncological treatment. The above-mentioned authors proposed the latter.

CONCLUSION

Patients with untreated metastatic disease have a 5-year survival rate of less than 5 to 10%, and for a patient with isolated metastatic disease of the lungs, pulmonary metastasectomy is often the best hope for cure. It is a safe and effective treatment that leads to possible cure in selected patients. Regardless of primary tumor, completeness of resection is the key to improved survival. Low morbidity and mortality rates in contrast with the lack of any other effective systemic oncological treatment justify the aggressive approach of surgery. Thoracoscopic resection is a valid option in selected patients with few, peripherally located metastases. In case of recurrence of pulmonary disease and if the patient fulfils the initial criteria for pulmonary metastasectomy, repeat surgery should be performed. Aggressive postoperative follow-up is warranted. The patients should be treated in close collaboration between the medical oncologist, diagnostic radiologist, and thoracic surgeon.

However, despite numerous studies and decades of metastasectomies, the lack of randomized studies continues to make the effect of pulmonary metastasectomy questionable. Most studies have been retrospective and the biases are many: possibly only patients in good physical condition are referred, possibly only patients with slow-growing tumors are referred (time-length bias), or possibly earlier detection through more aggressive follow-up leads to earlier surgery with a seemingly longer survival. Most reports recommend pulmonary metastasectomy for a properly selected group of patients. However, the case-mix from which patients are selected for surgery is rarely described.

Whether the survival of these patients is based on selection rather than surgery is still not clear. As argued by Treasure,[24] among others it remains "a common practice based on weak evidence."

Furthermore, prognostic factors that determine which patients benefit from surgery are still not clearly established. To determine how to select surgical candidates for pulmonary metastasectomy, more precisely further analysis of prognostic factors is evident, and the need for a prospective, randomized, multicenter study is clear. The recently opened PulMiCC trial[25] may provide some answers.

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