



Long-Term Outcome of Patients Following Surgery for Metachronous Pulmonary Metastases of Highly Aggressive Non-Colorectal Cancers

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Abstract

Background: Most epithelial tumors metastasize to the lung. In 20% of cases no involvement of other organs can be detected. In patients with resectable colorectal lung metastases, the benefit of metastasectomy has been proven. No uniform guidelines exist, regarding entities such as hepatocellular carcinoma, pancreatic carcinoma or esophageal carcinoma. This study evaluated the long-term-outcome after resection of pulmonary metastases from highly aggressive, non-colorectal cancer entities.

Methods: 49 patients were included who underwent complete pulmonary resection for lung metastases at the University Medical Center Hamburg-Eppendorf from 2000 to 2009. Overall-survival rates were evaluated by Kaplan-Meier analysis.

Results: The median follow-up time was 96 months. The overall median survival after diagnosis of the primary tumor was 59.9 months (mean survival 86.3 months). The overall 3-, 5- and 10 year survival rate was 71.4% (35/49), 49% (24/49) and 26.5% (13/49). Median survival after metastasectomy was 22.6 months (mean 55 months). The 1-, 5- and 10- year survival rate after resection was 67.3% (33/49), 36.7% (18/49) and 14.3% (7/49). The disease-free survival was 63.3% (31/49), 34.7% (17/49) and 12.2% (6/49) after 1, 3 and 5 years, respectively.

Conclusions: Even in patients with highly aggressive, non-colorectal cancer, pulmonary metastasectomy can be performed with a low morbidity and mortality. It can improve overall survival and provide a chance of long oncological outcome in selected patients. However, the decision to perform a pulmonary metastasectomy in this setting requires a multidisciplinary setting.

Keywords: Pulmonary metastases; Lung resection

Introduction

The majority of epithelial tumors metastasize to the lung [1]. Although pulmonary metastases indicate an advanced disease with a limited life expectancy, improved surgical techniques and changes in perioperative management result in an improved long-term survival after lung resection [2]. Today, resection of metastases in the lung from a wide range of primary sites has become a routine part of the daily clinical practice of a thoracic surgeon. Even in patients with advanced co morbidities, surgical treatment can be performed with low morbidity and mortality rates [3]. Thus, the spectrum of indications for pulmonary metastasectomy has been expanded.

20% of patients with lung metastasis have no detectable involvement of other organs and complete removal of pulmonary metastases improves long-term survival with 5-year survival rates of 30%. Surgical treatment is the treatment of choice in well selected patients [2]. Several studies indicated that a small number of lesions, a long disease-free interval and no lymph node metastases improve oncological long-term outcome [4]. In these patients, the primary tumor should be under control, no other potentially curative treatment available and all metastases should be totally resectable. On the contrary, diffuse or unresectable metastases are usually treated with palliative chemotherapy. However, there are no prospective randomized trials proving the benefit of the surgical treatment in patients with pulmonary, non-colorectal metastases. Especially, guidelines are missing for the treatment of pulmonary metastases of highly aggressive tumor entities like pancreatic or esophageal cancer.

This study evaluated the long-term outcome of patients following resection of pulmonary

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Table 1: Entity of the primary tumor.

Histology	No.
head and neck (hypopharyngeal carcinoma (5)	14
laryngeal carcinoma (3) floor mouth carcinoma (2)	
maxillary sinus carcinoma (1), tonsil carcinoma (1))	
parotid gland carcinoma (1), differentiated thyroid cancer (1)	
germ cell testicular carcinoma	9
malignant melanoma	8
hepato-Pancreato-Biliary carcinoma	8
esophageal carcinoma	2
urothelial cell carcinoma	2
breast carcinoma	1
nephroblastoma	1
adrenal gland carcinoma	1
ovarian carcinoma	1
porocarcinoma shoulder	1
anal carcinoma	1

metastases of aggressive, non-colorectal carcinomas.

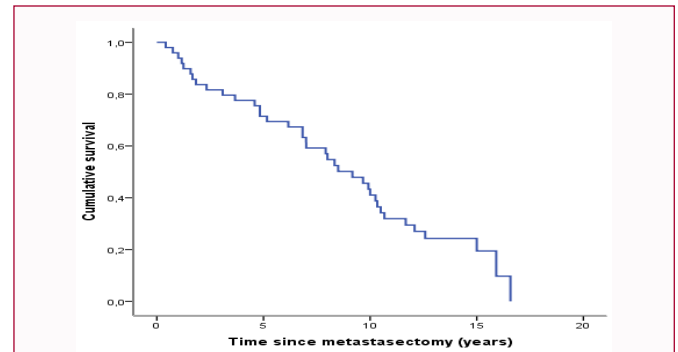
Patients and Methods

From 2000 to 2004, consecutively 49 patients with pulmonary metastases originate from other than colorectal or renal cell carcinomas with complete R0 resection at the University Medical Center Hamburg-Eppendorf were included. Informed consent was obtained from all patients. The study was approved by the medical ethics committee of the Chamber of Physicians of Hamburg. Data were collected retrospectively and followed up according to the national guidelines. Based on the primary tumor, the following data were collected: histology, date of diagnosis and surgical treatment, tumor-classification. Based on the pulmonary metastases the date of diagnosis and surgical treatment of metastases, surgical approach and procedure, number of radiographically detected and resected metastases, size of metastases, sequential and/or repeat metastasectomies incl. approach and procedure, recurrence other than pulmonary, perioperative therapy and the date of death were recorded.

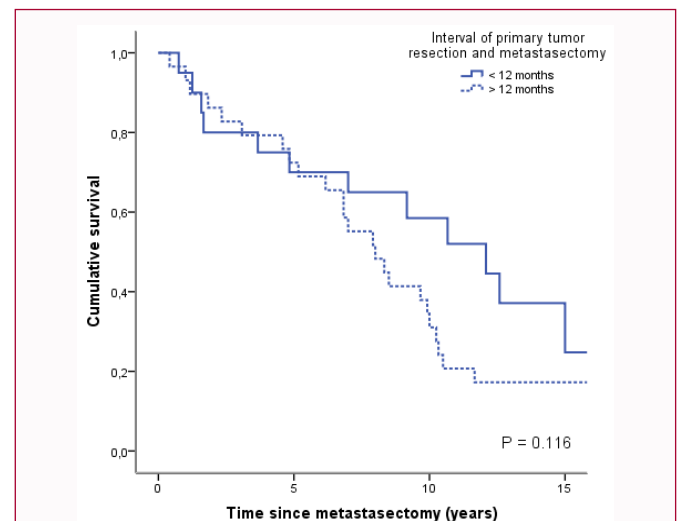
After primary tumor treatment, patients were evaluated at regular intervals with chest CT-scans, either at our centre or by associated oncologists. After the diagnosis of pulmonary metastases, patients were treated by surgical resection in the absence of contraindications. Operative approaches included lateral thoracotomy, sternotomy, mini-thoracotomy and video-assisted thoracoscopic surgery (VATS) depending on the number of metastases and the tumor location. Pulmonary resection was performed as wedge resection, lobectomy or bilobectomy. Patients, who developed pulmonary lesions during the follow up were treated with repeated lung resection.

Statistical analysis

Overall survival and three-, five- and ten-year survival was calculated from the date of diagnosis of the primary tumor. The time to death was modelled using the Kaplan Meier method. Deaths which resulted from the disease were treated as an endpoint for disease-specific survival; survival was treated as censored observations. Subgroup analyses were performed on disease-free interval, occurrence pattern, histology, surgical procedure, number and size

**Figure 1:** Cumulative survival after metastasectomy.**Table 2:** Mean survival after first metastasectomy.

Head and neck	24.5 months (4 patients were alive at time of last FUP)
Germ cell testicular metastases	49.5 months (5 patients were alive at time of last FUP)
Malignant melanoma	37.6 months (2 patients were alive at time of last FUP)
HCC-metastases	12.6 months
Pancreatic carcinoma	14.6 months
Urothelial cell carcinoma	5.9 months

**Figure 2:** Survival as a function of the time interval between primary tumor and pulmonary metastases.

of metastases. In all statistical analyses, p-value ≤ 0.05 was considered as significant.

Results

From 2000 to 2004, 49 patients, 34 (69%) male and 15 (31%) female, with a median age of 55 years (range 5 -78 years) received resection for pulmonary metastases from solid malignancies other than colorectal or renal cell carcinoma. The primary tumors were head and neck carcinoma (N=14), germ cell testicular carcinoma (N=9), malignant melanoma (N=8), hepatocellular carcinoma (N=5), pancreatic carcinoma (N=3), urothelial cell carcinoma (N=2), breast carcinoma (N=1), nephroblastoma (N=1), adrenal gland carcinoma (N=1), esophageal carcinoma (N=2), ovarian carcinoma (1), porocarcinoma shoulder (1), anal carcinoma (1), (Table 1).

24 (49%) patients presented with unilateral and 25 (51%) with bilateral metastases. The surgical approach was lateral thoracotomy (N

= 30), sternotomy (N = 16) and VATS (N = 2) and mini thoracotomy (N = 1). The resection was performed as a wedge resection (N = 45), lobectomy (N = 3) and bilobectomy (N = 1). Six patients underwent sequential resection due to initially bilateral metastases. 11 patients had a repeated resection after pulmonary tumor recurrence.

18 patients had a relapse of the primary tumor. Four of them had a malignant melanoma, four a germ cell testicular carcinoma, three a hepatocellular carcinoma, one pancreatic carcinoma, one urothelial cell carcinoma, one ovarian carcinoma, two esophageal carcinoma, one hypopharyngeal carcinoma and one differentiated thyroid cancer. Median interval from diagnosis of primary tumor to the diagnosis of lung metastases was 21 months (range 0-160 months). The overall median survival after diagnosis of the primary tumor was 59.9 months (mean survival 86.3 months). The overall 3-year actuarial survival rate was 71.4% (35/49), the five-year survival rate of 49.0% (24/49) and then 10-year survival rate after diagnosis of the primary tumor was 26.5% (13/49). The cumulative survival is shown in (Figure 1).

Median survival after metastasectomy was 22.6 months (mean 55 months). The 1-year survival rate after resection was 67.3% (33/49), 3-year survival rate after resection was 42.9% (21/49), the 5-year survival rate was 36.7 % (18/49) and the 10-year survival rate after first metastasectomy was 14.3% (7/49). The disease-free survival was 63.3% (31/49), 34.7% (17/49) and 12.2% (6/49) after 1, 3 and 5 years, respectively. The mean survival rates related to the different tumor entities are shown in (Table 2). Kaplan-Meier Survival Analysis revealed no significant differences in histology, bilateral or unilateral lung metastases, number or size of resected metastases or surgical procedure (data not shown). Time interval between diagnosis of the primary tumor and pulmonary metastases more than 12 months showed longer overall survival in comparison to a time interval smaller than 12 months (Figure 2). The follow up was calculated from the first pulmonary metastasectomy, the median follow-up was 82 months.

For the 12 patients who were alive at the time of last follow-up, the median post-metastasis follow-up was 57.5 months. The primary malignancy of these patients was testicular carcinoma (N = 5), malignant melanoma (N = 2), hypopharyngeal carcinoma (N = 2), maxillary sinus carcinoma (N = 1), poro-carcinoma (N = 1) and thyroid gland carcinoma (N = 1). 8 of these 12 patients had no evidence of tumor recurrence at the last follow-up.

Discussion

Metastases cause 90% of cancer deaths. Only a few patients with metastases survive more than one year after diagnosis [2]. In patients presenting with diffuse or unresectable metastases, palliative chemotherapy is usually the standard treatment. Accepted criterias for resection are technical feasibility, controlled primary tumor site, adequate cardiopulmonary function and complete removal of metastases. Unresectable primary tumor and predicted incomplete metastasectomy are contraindications to pulmonary metastasectomy [4-6].

Standard treatment for isolated pulmonary metastases arising from colorectal carcinoma is the surgical removal [7], but only a few reports have addressed the value of surgical resection of pulmonary metastases from other solid tumors. This study describes the clinical courses of 49 patients operated on pulmonary metastases arising from 20 different solid tumor entities.

In addition to the stage of disease, histology and tumor biology are the major prognostic predictors and define the surgical approach [3].

Patients suffering from head and neck cancer have a poor outcome. Head and neck cancers often metastasize to distant organs and most commonly to the lung [8,9]. Studies showed that pulmonary metastasectomy improves survival of patients with squamous cell carcinoma of the head and neck. Five-year survival rates are up to 40% in the literature [10,11]. Shiono et al. [12] reviewed retrospectively 114 patients who were operated on pulmonary metastases. The median survival time was 26 months, which is comparable to our data (mean survival 24.5 months). Wedman et al. [8] demonstrated the benefit of the surgical approach by reporting a 5-year survival rate of 59% compared to 4% in the non-metastasectomy group. But for other histological types of head and neck cancers like thyroid cancer and adenoid cystic carcinoma is less clear [9]. Winter et al. [13] described a significant better outcome in patients who underwent pulmonary metastasectomy when compared to chemotherapy regimes. Therefore, Younes et al. [14] and Kaifi et al. [4] postulated that all patients with head and neck cancers with no extrapulmonary metastasis should undergo pulmonary resection to achieve long-term survival.

The lung is the most common site of metastasis in patients with germ cell tumors. The surgical treatment of pulmonary metastases in germ cell testicular cancer patients is due to the high efficacy of anticancer chemotherapy confined to residual tumors. Metastasectomy enables detection of viable tumor cells which indicate direct further chemotherapy. This multimodal treatment regime can achieve 5-year survival rates of up to 82% [10] and even repeated resections are indicated [15]. We analysed the course of disease of 9 patients, of which five patients survived with no signs of relapse, mean survival after first metastasectomy was 49.5 months. These results support the observation that a substantial number can be successfully salvaged. Xia et al. [16] showed that surgical resection of all residual masses is indicated in patients with metastatic germ cell tumors of the lung and mediastinum.

In 40% of patients with malignant melanoma, pulmonary metastasis is the first sign of metastatic disease [17]. Pulmonary metastases from malignant melanoma are associated with poor survival due to the propensity to metastasize systemically to other sites in addition to the lung. The 5-year survival rate of patients with pulmonary metastases is 4% [18]. The resection of isolated pulmonary metastases can achieve 5-year survival rates of up to 27% [19,20]. In our study, two of eight patients were alive, one had recurrent pulmonary metastases, and the other patient had no signs of relapse. The mean survival after first metastasectomy was 37.6 months. In accordance to our results, Petersen et al. [21] support the role of surgery for select subset of patients with isolated pulmonary metastasis. Main prognostic factor for improved survival are complete resection, long duration for formation of metastases, less than two nodules and tumor negative thoracic lymph nodes [18].

The lungs are the most common extrahepatic metastatic site [22]. Only few data are available about lung metastasectomy for hepatocellular carcinoma [23,24]. Zhang et al. [25] analyzed one hundred and five patients with lung metastases from HCC retrospectively. The mean and median survival times were 8.7 and 5.9 months after lung metastases. The poor prognosis of this entity is confirmed by our results, the mean survival was 12.6 months. Patients with pancreatic cancer have a very limited life-expectancy.

Median survival is 8 to 12 months for patients with locally advanced unresectable disease and only 3 to 6 months for those who present with metastases. The 3 patients that have been analysed in this study had a mean survival of 14.6 months. However, due to the small number of patients a valid conclusion cannot be made. A report of the International Registry of Lung Metastases from 1997 evaluated the long-term survival after pulmonary metastasectomy in more than 5000 patients [3]. 5- and 10-year survival rates were 36% and 26%, respectively, which is comparable to our series with a five-year actuarial survival rate of 39,6% (19/48). Factors associated with a better prognosis are a longer disease-free interval between treatment of the primary tumor and diagnosis of pulmonary metastases, complete resection of the metastases and the presence of a single or limited number of metastases. While our retrospective analysis confirmed the better prognosis for patients in whom the metastases occur late (< 12 vs. > 12 months; Figure 2). No difference could be seen depending on the number of metastases.

In our study, 18 of 49 (37%) patients had a relapse after initial metastasectomy. The most frequent site of relapse following pulmonary resection is the lung [26,27]. Following potentially curative metastasectomy, additional lesions are identified in 50 percent of cases due to the subsequent growth of previously undetectable lesions. Among the patients who underwent repeated metastasectomy, the 5- and 10-year survival rates were 44% and 29%, respectively. Repeat resection after several metastasectomies can significantly improve overall survival. Kandioler et al. [28] analyzed 35 patients with recurrent pulmonary metastases. The authors could show that patients with a long disease-interval between resection for the primary tumor and the first pulmonary metastasectomy have a significantly better 5-year survival rate. These results are in accordance to other studies analysing the value of repeat pulmonary metastasectomies [29,30]. In contrast, the median survival among patients who were not resected following relapse in one series was 8 months [31].

Conclusion

Radical tumor resection continues to be the most effective therapy in patients with malignant tumors. In order to restrict surgery to those patients who are most likely to benefit in terms of symptom palliation or prolonging survival the decision to perform a pulmonary metastasectomy requires a multidisciplinary approach. In patients with limited pulmonary metastatic disease, pulmonary metastasectomy is a well accepted treatment with low morbidity and mortality rates. This treatment approach can improve overall survival and provide a chance of cure in selected patients which would probably not be possible by systemic therapy alone. Although the study population is limited and the tumor entities are heterogeneous with different tumor biology, this report may contribute to the discussion on the implication of pulmonary metastasectomy in patients suffering from aggressive, non-colorectal cancer entities.

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