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Surgery for Pulmonary Metastases: Long-Term Survival in 281 Patients

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Abstract

Background Despite weak evidence, pulmonary metastasectomy (PM) is widely performed with intent to improve patient survival. Our single-institution analysis aims to evaluate outcomes and to identify factors influencing survival of patients undergoing PM for metastases from wide range of primary tumors.
Materials and Methods All patients undergoing curative-intent PM between 2008 and 2018 were retrospectively analyzed. The impact of factors related to primary tumor, metastases, and associated therapy on overall survival (OS) was evaluated using univariable and multivariable Cox proportional hazard models. Cutoff values of continuous variables were determined by a receiver operating characteristic analysis.
Results In this study, 281 patients (178 male, median age 61 years) underwent PM. Two (0.7%) perioperative deaths and 23 (8.2%) major complications occurred. Median interval between the treatment of primary tumor and PM was 21 months. Median size of largest metastasis was 1.4 cm. After the median follow-up of 29 months, 134 patients (47.7%) had died. Five-year OS rate after first PM was 47.1%. Complete resection was achieved in 274 (97.5%) patients. Multivariable analysis identified genitourinary origin (hazard ratio [HR]: 0.30, 95% confidence interval [CI]: 0.15–0.60, $p = 0.0008$) as independent positive survival prognosticator; incomplete resection (HR: 3.53, 95% CI: 1.40–8.91, $p = 0.0077$) and age at PM of $\geq$66 years (HR: 1.97, 95% CI: 1.36–2.85, $p = 0.0003$) were negative prognosticators.
Conclusion The use of PM as a part of multimodal treatment is in selected population justified. Our analysis identified age, primary tumor origin, and completeness of resection as independent survival prognosticators.

Keywords
- lung metastases
- prognosis
- metastasectomy

Introduction

Pulmonary metastasectomy (PM) has been widely practiced over the past decades as an integral part of multimodal management of the wide range of tumors metastasizing to the lung. Due to associated low perioperative morbidity and good postoperative survival, despite weak evidence based mostly on retrospective single-center reviews, PM comprises even 15% of all lung resections performed in Europe.[1] To date, no randomized controlled trial has clarified whether those satisfactory outcomes result from more favorable course of a tumor disease in highly selected patient subgroup, applied systemic therapy or local treatment in the form of PM.

The aim of our single-institution study is to evaluate postoperative outcomes and to identify factors influencing survival of patients undergoing PM for metastases of various

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primary origin. This analysis is part of a series in which we have examined the survival after PM for metastatic colorectal cancer (CRC), sarcoma, and head and neck cancer before.[2–4]

Materials and Methods

All patients who underwent PM with curative intent at our tertiary care thoracic center from January 2008 to December 2018 were retrospectively analyzed. All patients met the following selection criteria for PM: controlled primary tumor site, no synchronous extrapulmonary metastases except for colorectal liver metastases, intent of complete resection (R0) of the lung lesions, and functional operability. Before the surgery was offered, all patients were presented at the multidisciplinary tumor conference, where the treatment options were discussed. Patients with initially unstable metastatic disease were classified for the induction chemotherapy and then reassessed based on the response evaluation criteria in solid tumors. Resectability of the lung metastases was assessed preoperatively by computed tomography (CT). A muscle-sparing lateral thoracotomy enabling a thorough palpation of the lung was the preferred approach in majority of patients. Single peripheral metastases were resected by a video-assisted thoracic surgery (VATS) approach; however, the decision was based on surgeon's preference. The video-assisted minithoracotomy was classified as an open technique. Completeness of the resection was defined by pathological examination. Patients were followed up with a CT scan 3 and 6 months after the first PM. If no recurrence occurred, follow-up intervals were prolonged to half-yearly and then yearly controls.

The following variables were analyzed: gender, age at PM, site of the primary, interval between completion of definitive treatment of the primary and PM (time to lung metastasis [TTLM]), number, size and distribution of the resected metastatic nodules, type and extent of PM, and administration of adjuvant therapy to the primary and/or prior to PM. As the thoracic lymph node dissection or sampling was not routinely performed, we could not evaluate the lymph node status as a prognostic survival factor. The study protocol was approved by the Institutional Ethics Committee (registration number 425_19 Bc). Individual patient consent for this retrospective observational study was not required.

Statistical Analysis

Overall survival (OS) after PM was estimated by the Kaplan–Meier's method from the date of the first PM until the date of death or the most recent follow-up. Bilateral-staged resections for synchronous metastases were performed 4 to 6 weeks apart and were counted as a single metastasectomy with the date of the first resection used for analysis. TTLM was calculated as the interval between resection or completion of definitive treatment of the primary and date of PM. The variables were assessed using the univariable Cox proportional hazard model, giving data as hazard ratio (HR) with a 95% confidence interval (CI). The continuous variables were split based on the cutoff values obtained by a receiver operating characteristic analysis. Independent prognostic significance of various clinicopathological factors was assessed using multivariable Cox proportional hazard regression model. The probability value (p) of less than 0.05 was considered statistically significant for both univariable and multivariable analyses. The software used for statistical analysis was STATISTICA 13.3 (StatSoft, Tulsa, Oklahoma, United States).

Results

Overall, 281 patients (178 male) underwent curative-intent resections for pulmonary metastases. The clinical characteristics of the 281 patients are listed in ►**Table 1**. The median age for the patients at the time of first PM was 61 years

Table 1 Preoperative patient characteristics

Characteristics	$n = 281$
Age at PM (y), median (range)	61 (16–84)
Male gender, *n* (%)	178 (63.4)
Primary site, *n* (%)	
CRC	115 (40.9)
HNC	44 (15.7)
Sarcoma	40 (14.3)
GU	30 (10.7)
Melanoma	24 (8.6)
Germ cell	8 (2.8)
BRC	6 (2.1)
Other	14 (4.9)
TTLM (mo), median (range)	21 (0–290)
Onset of lung metastasis	
Metachronous	228 (81.1)
Synchronous	53 (18.9)
Number of lung metastasis, *n* (%)	
Solitary	160 (56.9)
2	47 (16.8)
≥3	74 (26.3)
Size of the largest lung lesion (cm), median (range)	1.4 (0.2–8.0)
Type of PM, *n* (%)	
VATS	54 (19.2)
Open	227 (80.8)
Extent of resection, *n* (%)	
Wedge resection	170 (60.5)
Segmentectomy	64 (22.8)
Lobectomy	44 (15.7)
Bilobectomy	2 (0.7)
Pneumonectomy	1 (0.3)
Complete (R0) resection, *n* (%)	274 (97.5)
LoHS (d), median (range)	6 (2–33)

Abbreviations: BRC, breast cancer; CRC, colorectal cancer; GU, genitourinary cancer; HNC, head and neck cancer; LoHS, length of hospital stay; PM, pulmonary metastasectomy; TTLM, time to lung metastasis; VATS, video-assisted thoracic surgery.

(range, 16–84 years). CRC was the most common primary (40.9%, $n = 115$), followed by head and neck cancer (15.7%, $n = 44$) and sarcoma (14.3%, $n = 40$). Median TTLM was 21 months (range, 0–290 months). Synchronous metastases with primary tumor were present in 53 (18.9%) patients. One hundred and eighty-eight (66.9%) patients had perioperative interval longer than 1 year and 40 (14.2%) patients had shorter perioperative interval (≤1 year).

The surgical approach consisted of muscle-sparing lateral thoracotomy (80.8%, $n = 227$) and VATS (19.2%, $n = 54$). At the time of first pulmonary resection, the majority (60.5%, $n = 170$) of patients had a wedge resection, followed by anatomical segmentectomy (22.8%, $n = 64$) and lobectomy (15.7%, $n = 44$). Complete (R0) resection was achieved in 274 (97.5%) patients. Majority of the patients underwent surgery for unilateral disease (77.9%, $n = 219$) and single pulmonary nodules (56.9%, $n = 160$). Seventy-four (26.3%) patients had three or more lung metastases (median 5; range, 3–23). The maximum number of resected metastatic lesions in one patient was 23.

Two (0.7%) perioperative deaths due to aspiration pneumonia, on the third and fourth postoperative days, occurred. Twenty-three (8.2%) patients had major (grade III/IV) complications, including six patients with hemothorax and four with bronchopleural fistula requiring rethoracotomy, four with pneumonia, three with impaired wound healing requiring surgical revision, two with empyema requiring decortication, two with postoperative atrial fibrillation, one with postoperative phrenic nerve paresis, and one with mesenteric ischemia requiring laparotomy. Median hospital stay after surgery was 6 days (range, 2–33 days).

A total of 166 patients (60.1%) had received chemotherapy as an adjuvant to the primary resection, and 53 (18.9%) patients underwent induction chemotherapy prior to PM.

After the median follow-up of 29 months (range, 0–143 months), 134 (47.7%) patients had died. The 5-year OS rate after the first PM was 47.1% (►**Fig. 1**). The OS rate after complete (R0) metastasectomy was 48.1% at 5 years versus 17.2% after incomplete (R1) resection. The univariable analysis disclosed that patients with the age of 66 years or more (area under the curve: 0.58, HR: 1.81, 95% CI: 1.28–2.56, $p = 0.0007$) had worse OS, whereas genitourinary (GU) origin of lung metastases (HR: 0.45, 95% CI: 0.23–0.88, $p = 0.02$) was associated with better survival after first PM (►**Table 2**). Multivariable analysis identified the GU primary (HR: 0.30, 95% CI: 0.15–0.60, $p = 0.0008$) as independent positive survival prognosticator and the age of ≥66 years (HR: 1.97, 95% CI: 1.36–2.85, $p = 0.0003$) and incomplete (R0) resection of pulmonary lesions (HR: 3.53, 95% CI: 1.40–8.91, $p = 0.0077$) as independent negative survival prognosticators (►**Table 3**). Gender, TTLM, chemotherapy, number, size and distribution of metastases, surgical approach (open vs. VATS) and resection extent did not significantly influence the long-term survival (►**Table 2**).

Discussion

Twenty to 54% of all metastatic lesions are being found in the lung, making this organ the second most frequent metastatic target in the human body.[5] Since in 1995, Hellman and Weichselbaum proposed the concept of the oligometastatic state (≤5 metastases) between limited local disease and disseminated cancer, it has been even more widely believed that PM, as a form of local treatment, could improve patient survival.[6] In 2006, Niibe and Hayakawa defined oligorecurrence as a stable primary tumor site with one to several distant metastases/recurrences in one to several organs.[7] Based on the oligorecurrence criteria, PM has become a worldwide standard curative-intent local treatment in the

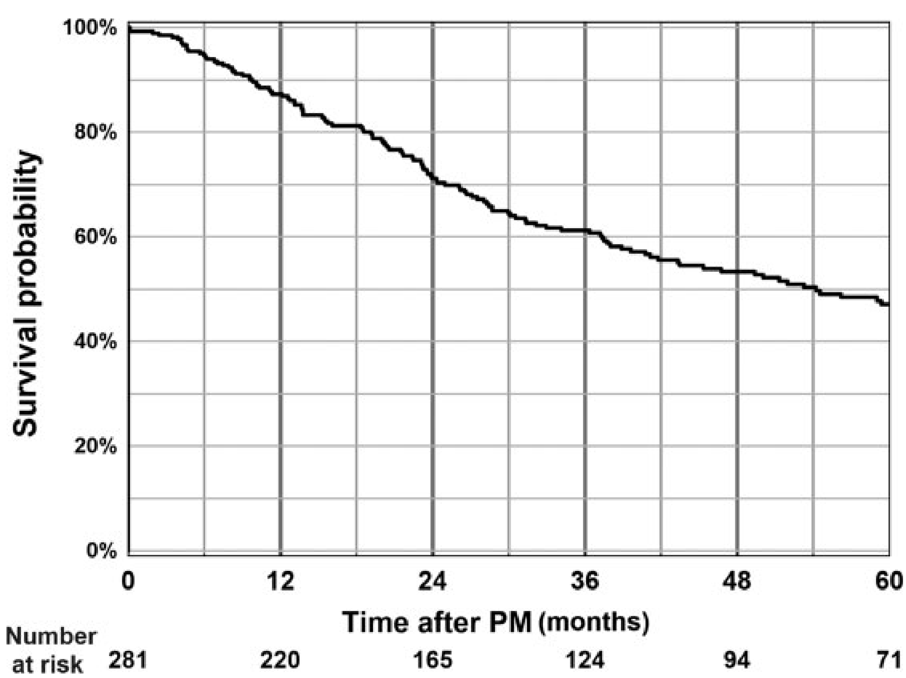

Fig. 1 Overall survival of 281 patients after first pulmonary metastasectomy (PM).

Table 2 Univariable analysis of factors influencing patient survival after pulmonary metastasectomy

Factor	Groups	*N* (%)	5-y OS (%)	Univariable HR (95% CI)	*p*-Value
Age at PM (y)	< 66	184 (65.5)	54.8	1.81 (1.28–2.56)	**0.0007**
	≥ 66	97 (34.5)	33.6		
Gender	Male	178 (63.3)	48.1	1.07 (0.75–1.52)	0.71
	Female	103 (36.7)	45.7		
Primary site	GU	30 (10.7)	69.7	0.45 (0.23–0.88)	**0.02**
	Non-GU	251 (89.3)	44.4		
TTLM (mo)	< 12	90 (32.0)	51.6	1.19 (0.81–1.75)	0.36
	≥ 12	191 (68.0)	45.5		
Adjuvant therapy to primary	Yes	166 (60.1)	47.8	1.01 (0.71–1.44)	0.96
	No	110 (39.9)	48.1		
Induction therapy to metastases	Yes	53 (18.9)	46.3	1.03 (0.68–1.58)	0.88
	No	228 (81.1)	47.5		
Onset of lung metastasis	Synchronous	228 (81.1)	45.5	0.74 (0.46–1.19)	0.21
	Metachronous	53 (18.9)	55.9		
Number of lung metastases	Single	160 (56.9)	51.0	1.26 (0.89–1.77)	0.19
	≥ 2	121 (43.1)	42.9		
Size of largest lung lesion (cm)	< 1.9	193 (68.7)	51.1	1.39 (0.98–1.98)	0.06
	≥ 1.9	88 (31.3)	39.3		
Distribution of lung metastases	Unilateral	219 (77.9)	44.7	0.73 (0.47–1.12)	0.14
	Bilateral	62 (22.1)	55.7		
Type of PM	Open	227 (80.8)	45.1	0.69 (0.42–1.13)	0.14
	VATS	54 (19.2)	57.8		
Extent of PM	Wedge	170 (60.5)	49.6	1.20 (0.85–1.71)	0.31
	Anatomical	111 (39.5)	43.1		
Completeness of resection	R0	274 (97.5)	48.1	2.41 (0.98–5.89)	0.05
	R1	7 (2.5)	17.2		

Abbreviations: CI, confidence interval; GU, genitourinary; HNC, head and neck cancer; HR, hazard ratio; OS, overall survival; PM, pulmonary metastasectomy; TTLM, time to lung metastasis; VATS, video-assisted thoracic surgery.
Note: Statistically significant *p*-values in bold.

Table 3 Multivariable analysis of factors influencing patient survival after pulmonary metastasectomy

Factor	Factor levels	Multivariable HR (95% CI)	*p*-Value
Age	≥ 66 vs. < 66 y	1.97 (1.36–2.85)	**0.0003**
Primary site	GU vs. non-GU	0.30 (0.15–0.60)	**0.0008**
Completeness of resection	Incomplete versus complete	3.53 (1.40–8.91)	**0.007**

Abbreviations: CI, confidence interval; CRC, colorectal cancer; GU, genitourinary; HR, hazard ratio.

selected cardiorespiratory fit patients with controlled metastatic disease. For nonsurgical candidates, radiotherapy and ablation therapy have been proposed.[8] Recent guidelines of the National Institute for Health and Care Excellence and the National Comprehensive Cancer Network recommend to consider PM within the multidisciplinary management of metastatic colorectal[9] and head and neck cancer.[10]

In 1997, Pastorino et al published the outcomes of 5,206 PMs from 18 major thoracic surgical departments from Europe, the United States, and Canada, participating in the International Registry of Lung Metastases established in 1990. This largest to date, multicenter retrospective study including patients with lung metastases of various primary origin identified complete (R0) resection, number of metastases, and long disease-free interval (DFI) as major prognostic factors after PM. Reporting survival rates after complete PM of 36% at 5 years, 26% at 10 years, and 22% at 15 years versus 13% at 5 years and 7% at 10 and 15 years after incomplete resection, the authors strongly supported the concept of a curative-intent PM.[11]

Completeness of resection, germ cell histology, and DFI ≥36 months were independent positive prognostic factors in another retrospective large cohort study by Casiraghi et al on a group of 575 patients with mixed origin lung metastases

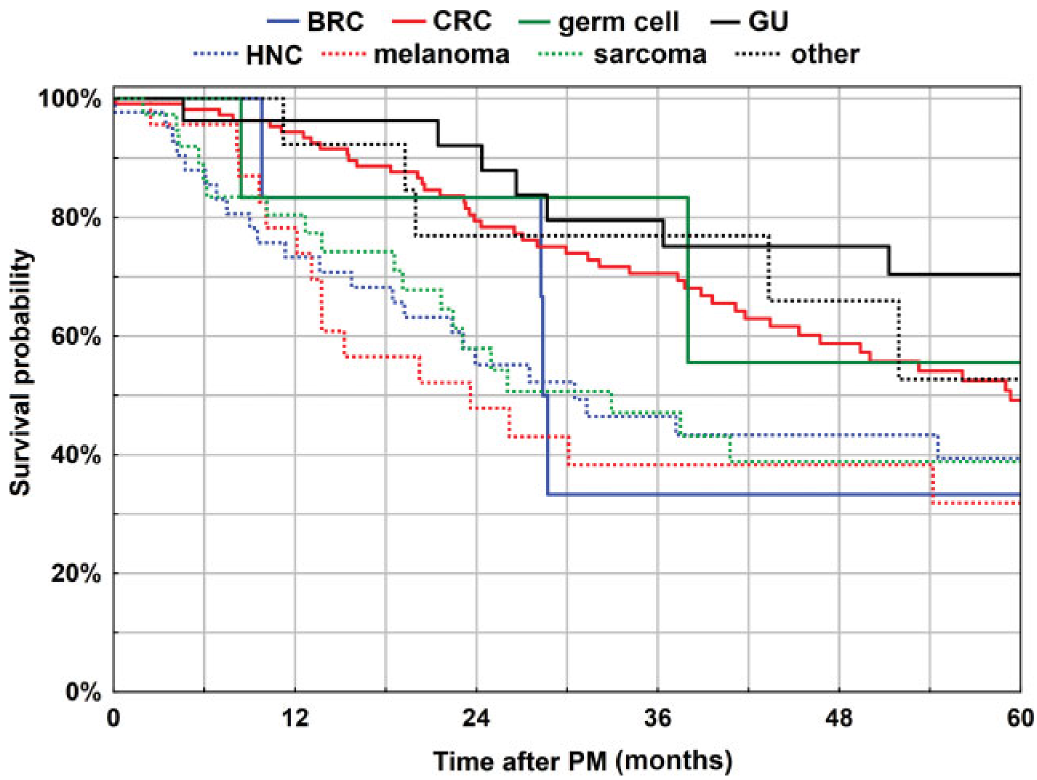

Fig. 2 Overall survival after first PM according to primary site. BRC, breast cancer; CRC, colorectal cancer; GU, genitourinary cancer; HNC, head and neck cancer; PM, pulmonary metastasectomy.

treated by PM over a 10-year period in a single institution. The study confirmed even higher post-PM survival rates reaching 46% at 5 years and 29% at 10 years after complete (R0) resection versus 20% at 5 and 10 years after incomplete (R1) resection.[12] Cheung et al also identified germ cell histology and DFI $\geq$36 months as positive survival prognosticators after PM in a group of 243 patients with the lung metastases of mixed origin. Synchronous metastases, multiple metastases, and incomplete resection were independently associated with a worse OS.[13] In our study group, the 5-year OS after complete (R0) resection was 48.1%, which was higher compared with the 5-year OS rate of 17.2% in a small subgroup of patients (2.5%, $n = 7$) in whom the lung lesions were not completely resected. Incomplete resection was identified as an independent negative post-PM survival prognosticator in our study population ($p = 0.007$).

There was no association between germ cell histology and better post-PM OS in our study cohort. Eight (2.8%) patients with germ cell lung metastases had indeed better 5-year OS rate compared with the rest of the group (62.7 vs. 46.9%, respectively), however, without statistical significance ($p = 0.49$). This may have resulted from the small number of patients with the germ cell histology. It is noteworthy that 30 (10.7%) of our patients with GU lung metastases had significantly better survival than 251 (89.3%) patients with non-GU origin (5-year OS rate 69.7 vs. 44.4%, respectively; $p = 0.02$) (►**Fig. 2**). Based on multivariable analysis, the GU origin of pulmonary metastases was an independent positive survival prognosticator in our cohort. Among 30 patients with GU metastases, there were 23 (76.6%) with metastatic renal cell carcinoma, 3 with bladder cancer, 2 with prostate cancer, and 2 with genital cancer. Similar high post-PM survival rates (5-year OS of 75%) in metastatic renal cell carcinoma have been reported by Meacci et al.[14] We hypothesize that outstanding GU histology-associated OS rates observed in our cohort may be a sequel of a careful patient selection.

Interestingly, our univariable Cox proportional hazard model analysis demonstrated that patients in the age of 66 years and older had significantly worse survival compared with the younger patients (5-year OS rate 33.6 vs. 54.8%, respectively; $p = 0.0007$). Patient age at PM was identified as independent prognostic factor in our multivariable analysis. However, taking into consideration acceptable survival rate, we would recommend a curative-intent PM in cardiorespiratory fit elderly patients in whom complete resection of metastatic lesion is possible. Similar conclusion was made by Barone et al who reported even less favorable 5-year OS rate of 21.2% in elderly patient group after complete (R0) metastasectomy for CRC.[15]

Unlike many authors, we found no significant relationship between the onset of pulmonary metastases (synchronous vs. metachronous) or TTLM ($\geq$12 vs. $<$12 months) and prognosis in our study group.[11–13,16] We preferred using the term "TTLM" instead of "DFI" as we do not believe that patients developing metastatic disease were "disease free." Number, size, and distribution of the lung lesions were of no prognostic significance in our cohort.

Our study has several limitations: (1) the single-center retrospective design; (2) postoperative outcomes and survival rates were evaluated in patients highly selected for a curative intent surgery; (3) heterogeneous primary tumor histology might have influenced OS in the whole group; (4) due to lacking standard, the prognostic impact of mediastinal/hilar lymphadenectomy could not be assessed; and (5) there was no control group which would include patients managed nonoperatively to compare the outcomes with. Considering the patient recruitment difficulties ($n = 93$) encountered by the authors of the multicenter randomized Pulmonary Metastasectomy in Colorectal Cancer trial, assessing whether PM really provides survival benefits compared with nonsurgical treatment for metastatic CRC, which led to early study termination, we presume that a well-designed large multicenter cohort study including a control group and a longer follow-up period could also efficiently be the value of the PM for particular types of metastatic cancer.[17]

Conclusion

Our 10-year single-center experience demonstrates that PM is associated with long-term survival benefits. Patient age, primary tumor histology, and feasibility of complete resection should be taken into consideration during multidisciplinary patient selection for pulmonary metastasectomy.

Conflict of Interest
None declared.

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