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Original Article

Which factors significantly reduce long-term survival after pulmonary metastasectomy?

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ABSTRACT

Background: In this study, a survival analysis was performed of patients who underwent pulmonary metastasectomy over the past 10 years in our clinic. We aimed to elucidate the factors that significantly affected overall survival and identify subgroups of patients who may not benefit from pulmonary metastasectomy.

Materials and Methods: We retrospectively reviewed 68 patients with a history of extra-thoracic malignancy who underwent pulmonary metastasectomy between January 2009 and December 2018. The overall survival rate was analyzed according to age, sex, histological type of the primary tumor, metastatic side, surgical approach type, pulmonary resection type, number of nodules resected, disease-free interval, and nodal status.

Results: The actuarial survival rate after pulmonary metastasectomy was 78% (95% confidence interval [CI]: 71-84) at 2 years and 48% (95% CI: 41-52) at 5 years. Patients with disease free interval < 12 months had a far worse survival rate ($p = 0.001$). Patients with sarcoma had a significantly worse prognosis than those with epithelial tumors or melanoma ($p = 0.001$). Patients with negative nodal status had a significantly better prognosis ($p = 0.001$), while patients with metastatic hilar lymph nodes also had significantly better survival compared to patients with metastatic mediastinal lymph nodes (N2) ($p = 0.001$).

Conclusions: Tumor histology is the main determinant of overall survival and prognosis after pulmonary metastasectomy. The presence of multiple metastases in different unilateral lobes and N2 disease appeared to be the worst prognostic factors. Patients with either of these two significant negative prognostic factors should be evaluated carefully via a multidisciplinary approach and pulmonary metastasectomy should be performed only in selected patients.

Keywords: metastasectomy, pulmonary, negative prognostic factors, long term survival

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Introduction

Debate regarding the efficacy of pulmonary metastasectomy (PM) began 35 years ago. A complete PM improves the survival of patients with controlled primary tumor sites. Removing as little healthy lung tissue as possible while obtaining clear margins is the main goal of PM. Although the impact of lymph node dissection on survival remains unclear, it is recommended to ensure correct staging for further oncological treatment. Histological confirmation of metastasis is necessary to increase the cure rate [1]. Lung metastases are rarely symptomatic, where metastases that do cause symptoms generally fall outside the criteria for PM, which are typically based on the opinion of a multidisciplinary team.

In this study, a survival analysis was performed of patients who underwent PM over the past 10 years in our clinic. We aimed to elucidate the factors that significantly affected overall survival and identify subgroups of patients who may not benefit from PM.

Material and Methods

We retrospectively reviewed 117 patients with a history of extra-thoracic malignancy who underwent complete curative resection of pulmonary nodules between January 2009 and December 2018. Of these patients, 58% presented with pulmonary metastases (n = 68), 28% were newly diagnosed with non-small-cell lung cancer (secondary primary/metachronous lung cancer; n = 32), and 14% had benign lesions (n = 17). The study was approved by the institutional review board (No: 20-35 / 9.5.2020) and conducted in accordance with the principles of the Declaration of Helsinki.

All patients were evaluated by a multidisciplinary team, including a surgeon, oncologist, and radio-oncologist, and received chemotherapy before PM. Thin-slice computed tomography (CT) scans were performed no later than 30 days after surgery and 18F-Fluorodeoxyglucose positron emission tomography/CT was used to rule out extrathoracic metastases and assess the degree of lymph node involvement [2].

All of the patients included in this study had their primary tumors controlled, no extrapulmonary metastases, and a limited number of pulmonary lesions that could all be removed; moreover, it was confirmed that the patients could tolerate resection of all lesions. Pa-

tients with primary lung carcinoma, an unresectable primary tumor, possible extrathoracic metastasis, preoperatively detected pleural carcinomatosis, predicted incomplete metastasectomy, or benign lesions were excluded from the study. Moreover, putative clinical prognostic factors, such as the number of metastases, lymph node involvement, and the disease-free interval (DFI) were evaluated before surgery, although we did not exclude patients with a short DFI, suspected mediastinal lymph node metastasis, or high number of metastases (where these factors were presumed to be relative contraindications in some previous studies) [3,4].

The DFI was defined as the time between the treatment of the primary tumor and diagnosis of metastases. An age analysis was performed by dividing the patients into three groups: young adults (<35 years), adults (35-55 years), and seniors (>55 years). The DFI was classified as <12 months, 12–36 months, or >36 months.

Non-anatomic wedge resection with safe margins was performed if metastases were located in the lung periphery; anatomic pulmonary resection were performed if the metastasis was centrally located, there were multiple lesions in the same segment or lobe, and a wedge resection was not anatomically feasible to remove all metastases. In addition, if a preoperative histological analysis suggested possible primary lung cancer, the patient underwent pulmonary anatomic resection and lymphadenectomy.

The mediastinal lymph nodes were sampled or dissected in all PM patients. The lymph nodes were sampled mostly during the earlier part of our study, and were dissected during PMs for the last 5 years. The regional lymph node classification of Mountain and Dresler was used [5]. Mediastinal lymph node metastases were referred to as N2 disease, hilar lymph node metastases as N1 disease, and the absence of lymph node metastasis as N0 disease.

No patient had a germ cell tumor, and primary tumors were classified as one of three histological types: epithelial tumor, sarcoma, or melanoma. Epithelial tumors included colorectal carcinoma, head and neck carcinoma, breast carcinoma, renal cell carcinoma, hepatocellular carcinoma, prostate carcinoma, and uterine carcinoma. Sarcomas included soft tissue sarcoma, osteosarcoma, synovial sarcoma, and uterine leiomyosarcoma.

All patients were reviewed retrospectively. The overall survival rate was analyzed according to age, sex, histological type of the primary tumor, metastatic side (right vs. left), surgical approach type (video-assisted thoracic surgery [VATS] vs. open thoracotomy), pulmonary resection type (wedge vs. anatomical resection), number of nodules resected (solitary vs. multiple), DFI, and nodal status (N0–N2).

Statistical Analysis

Survival estimates were calculated with the Kaplan–Meier method and compared with the log-rank test. Overall survival was defined as the time between the first metastasectomy and last follow-up or death. Data are presented as a mean \pm standard error of the mean. IBM SPSS Statistics for Windows software (version 22.0; IBM Corp., Armonk, NY, USA) was used for the statistical analyses. A *p*-value < 0.05 was considered significant.

Results

Sixty-eight patients who underwent complete PM were included in the study. There were 37 males (54.4%) and 31 females (45.6%). The mean age was 51 years (range: 16–76 years). Young adults comprised 13% of the cohort (*n* = 9), while adults comprised 47% (*n* = 32) and seniors 40% (*n* = 27). Twenty-three patients (34%) had a DFI of 0–12 months, 38 (56%) had a DFI of 12–36 months, and 7 (10%) had a DFI of ≥ 36 months. Eleven patients had preoperative symptoms (16%); one had hemoptysis, four had shortness of breath, three had chest pain, and three had persistent cough. Postoperative complications were reported in 10 patients (15%); atrial fibrillation, *n* = 5; prolonged air leak, *n* = 3 [all sarcoma patients], pneumonia, *n* = 1; and chylothorax, *n* = 1). No postoperative deaths were recorded. The mean hospital stay after surgery was 5.2 days (range: 2–28 days).

Metastasectomy was performed by videothoracoscopy in 29 cases (43%), and by open thoracotomy in 39 cases (57%). In total, 45 (66%) wedge resections and 23 (34%) anatomical pulmonary resections, including 16 (23.5%) lobectomies, 6 (9%) segmentectomies, and 1 (1.5%) pneumonectomy, were performed. In addition to pulmonary resection, one patient needed a chest wall resection, and diaphragmatic resection was performed in another case. Unilateral recurrent PM was performed in three patients and bilateral consecutive PM was performed in two others. Thirty-three patients (48%) had a

solitary metastasis, and thirty-five (52%) had multiple metastases. A solitary metastasis was detected in 48% of epithelial tumors (*n* = 25), 46% of sarcomas (*n* = 6), and 66% of melanomas (*n* = 2). The histopathology report revealed 52 epithelial tumor metastases (76%), 13 sarcoma metastases (19%), and 3 melanoma (5%) metastases. Epithelial tumor metastases (*n* = 52) included 2 uterine carcinomas (1 endometrium carcinoma and 1 cervix carcinoma), 2 hepatocellular carcinomas, 30 colorectal carcinomas (23 colon carcinomas and 7 rectal carcinomas), six breast carcinoma, 6 head and neck carcinomas (3 laryngeal carcinomas, 2 nasopharyngeal carcinomas, and 1 parotid gland tumor), 4 renal cell carcinomas, and 2 prostate carcinomas. Sarcoma metastases (*n* = 13) included five osteosarcomas, one soft tissue sarcoma, three synovial sarcomas, and four uterine leiomyosarcomas (Table 1). Mediastinal lymph node metastases (N2) were detected in 9 cases (13%); (21%) hilar lymph nodes (N1) were positive in 14 cases, and 45 patients (66%) had N0 disease. Three patients with sarcoma, 3 patients with colorectal carcinoma, 2 patients with head and neck and 1 patient with uterine carcinoma metastases had N2 disease.

Table 1. Patient characteristics.

Variables	Number of patients (<i>n</i> =68)	Percent (%)
Male	37	54.4%
Female	31	45.6%
Young adults	9	13%
Adults	32	47%
Seniors	27	40%
DFI <12 months	23	34%
DFI 12–36 months	38	56%
DFI >36 moths	7	10%
VATS	29	43%
Thoracotomy	39	57%
Wedge reseccion	45	66%
Anatomical resection	23	34%
N2 disease	9	13%
N1 disease	14	21%
N0	45	66%
Solitary metastasis	33	48%
Multiple metastases	35	52%
Epithelial tumors	52	76%
Sarcoma	13	19%
Melanoma	3	5%

Abbrev.: DFI; disease-free interval

Table 2. Patients survival rates according to analyzed variables.

Variable	2-year survival rate (%)	5-year survival rate (%)	p
Male	75±4%	32±2%	0.001
Female	92±3%	68±3%	
Young adults	100%	65±3%	0.349
Adults	80±3%	52±2%	
Seniors	56±2%	38±2%	
DFI <12 months	42±2%	10±2%	0.001
DFI 12-36 months	92±2%	64±2%	
DFI >36 months	100%	86±2%	
VATS	75±5%	38±2%	0.653
Thoracotomy	75±3%	58±2%	
Wedge resection	82±3%	70±2%	0.007
Anatomical resection	82±2%	38±2%	
N2 disease	0%	0%	0.001
N1 disease	38±2%	0%	
N0	100%	72±5%	
Solitary metastasis	68±2%	50±5%	0.826
Multiple metastases	84±2%	50±3%	
Multiple metastases within same lobe	80±5%	63±2%	0.027
Multiple metastases in different unilateral lobes	88±2%	0%	
Epithelial Tumors	82±5%	52±3%	0.001
Sarcoma	82±3%	38±2%	
Melanoma	65±5%	60±2%	

Abbrev.: DFI; disease-free interval

After a mean follow-up of 39.65 ± 12.3 months, 33 patients (48.5%) had died. The mean survival time after PM was 61 ± 5.5 months. The actuarial survival rate after PM was 78% at 2 years and 48% at 5 years. The 2- and 5-year actuarial survival rates according to age, sex, DFI, nodal status, histology, number of metastases, surgery type, surgical approach, and metastasis side are shown in Table 2. Overall, patients with sarcoma had a significantly worse prognosis than those with epithelial tumors or melanoma ($p = 0.001$). Patients with breast carcinoma in the epithelial tumor group had a better prognosis ($p = 0.001$). Patients with DFI < 12 months had a far worse survival rate ($p = 0.001$). Female patients had significantly better overall survival compared to male patients ($p = 0.038$). N0 patients had a significantly better prognosis compared to N1 and N2 patients ($p = 0.001$), while N1 patients had

significantly better survival compared to N2 patients ($p = 0.001$). Lastly, we performed a subgroup analysis, dividing the patients with multiple metastases into “multiple metastases within the same lobe” and “multiple metastases in different lobes” groups: the former group had a significantly better 5-year overall survival compared to the latter group (67.7 ± 7.6 vs. 37 ± 3.3 months; 63% vs. 0%, $p = 0.027$). Age, number of metastases, surgery type, metastasis side, and surgical approach did not affect long-term survival.

Discussion

The lung is the one of the most common sites of metastases, and PM is widely considered an effective treatment for patients with oligometastases, which is characterized by limited systemic tumor metastasis [6]. The main objectives of PM are to confirm the metastatic nature of the disease and increase survival. In addition, a personalized approach to treatment has redefined the role of PM, as a method for obtaining metastatic samples to identify changes in biomarkers or resistance patterns, so that oncological treatment can improve patient outcomes [7].

Complete PM refers to the removal of all detectable metastases with a negative margin, although the evolution of millimetric lung metastases left behind is also interesting [8]. Pulmonary metastases occur when primary cancer cells detach after local growth, migrate through the systemic circulation, and lodge in the lungs. They receive their blood supply from the pulmonary arteries (84%) or bronchial arteries (16%) [9]. Thin-slice multi-detector row CT scanning, which we routinely perform before PM, can be used to evaluate the lungs in 1-mm sections within 5 seconds, for a detection sensitivity comparable to intraoperative bimanual palpation during thoracotomy [10]; however, its sensitivity for proven pulmonary metastases is only approximately 80% [11]. Even though impalpable or undetected metastases cannot be removed, that does not mean that they do not exist. Even if we assume that the patient has undergone a complete PM, there may be still some viable millimetric metastases. Moreover, circulating tumor cells, which are presumed to be dormant before implantation and become active after implantation, have been detected by reverse transcription-polymerase chain reaction and immunocytochemical methods [12,13]. Thus, “complete” might only be a relative term for metastasectomy procedures. Many retrospective studies have reported that PM increased survival [14,15]. In our study, we aimed

to identify factors that significantly influence the overall survival of patients after PM based on our 10-year clinical experience.

The overall 5-year survival rate after PM ranges from 30% to 40% [16,17]. However, the 5-year survival rate was higher, at 48%, in our study. Several negative prognostic factors are known to be responsible for the large difference in survival rate among populations of patients undergoing PM. Prognostic factors for poor survival include a short DFI, multiple lung metastases, and thoracic mediastinal/hilar lymph node involvement [18].

A shorter DFI is associated with a poorer prognosis in patients with a history of malignancy [18]. In our study, patients with a short DFI (<12 months) had a significantly lower 5-year overall survival rate (9%, 23.6 ± 3.8 months) compared to the other patients, as expected ($p = 0.001$).

Although there seems to be a consensus that a solitary pulmonary metastasis is a better prognostic factor for 5-year overall survival than multiple metastases; we did not detect any difference between the solitary and multiple metastasis groups in our study [19,20]. Thus, the presence of “multiple metastases” did not appear to be an important variable, whereas the presence of “metastases in different lobes” was a significant negative prognostic factor. However, we did not spot any related similar results on this matter in literature; but we know that different lung segments have their own unique lymphatic drainage pathways to the mediastinal nodes so we can speculate that separate metastases in different lobes may induce greater lymph node metastasis which eventually reduces survival [2,21].

The reported rate of nodal involvement ranges from 12% to 32%; the 5-year survival of PM patients is highest when there is no lymph node invasion, and poorest when there is lymph node invasion [22,23]. Ercan et al. [22] reported a rate of lymph node involvement of 28.6% in metastatic lung carcinoma, with poor survival observed in patients with lymph node metastases. Pfannschmidt et al. [23] detected lymph node metastases in 29% of patients; the 3-year survival rate for patients with negative lymph node status was 69%, compared to 38% in the presence of lymph node metastasis. In our study, the rate of nodal involvement was 34%, and the 5-year survival rate of the N0 patients (69%) was significantly better than that of the N1 (9%) and N2 (0%) patients ($p = 0.001$). All of our patients with

N2 disease ($n = 9$) died within 1 year after PM. Furthermore, the N1 patients had a significantly better survival rate than the N2 patients ($p = 0.001$). A more obvious difference was seen between the 2-year survival rates of the N1 and N2 subgroups (37% vs. 0%). Thus, N1 and N2 should not be considered together in terms of prognosis, although we found no study that emphasized the prognostic superiority of N1 over N2.

The histology and genotype of the primary tumor are among the most important factors in prognosis and survival after PM. The mechanism of metastasis varies depending on the histological type of the tumor: colorectal metastases have a high rate of pleural invasion, and of interstitial and aerogenous spread of floating cancer cells, which are in turn associated with a high rate of local recurrence [24]. Melanoma does not show pleural invasion, but is associated with a higher probability of perivascular growth and an increased incidence of lymphangitic spread [25]. Compared to other tumors, our patients with pulmonary metastatic sarcoma (38%) had the lowest overall survival following PM ($p = 0.001$), as expected because sarcomas are fast-growing tumors with relatively short doubling-times). Most studies have reported that patients with sarcoma have a worse prognosis compared to those with other malignancies, with 5-year survival rates after PM reported at 25–40% [26,27]. Regarding our patients with epithelial tumors, the breast cancer patients had a significantly higher overall survival (90%) than all other epithelial tumor subgroups. This also explained why females had a significantly better survival rate than males. However, this finding was not consistent with the literature; Staren et al. reported a 5-year survival rate of 36%, while Tanaka et al. reported a rate of 30% for breast cancer patients after PM [28,29]. Unexpectedly, patients with head and neck carcinoma had the second highest survival rate (67%) among the epithelial tumor subgroups; previous studies reported 5-year survival rates of up to 40% [30]. Surprisingly, we observed high overall survival in patients with melanoma ($n = 3$, 67.3 ± 34 months; 64%) compared to the previously reported rate (27%) [31]. However, the limited number of cases with melanoma prevented us from establishing any firm hypothesis.

If a tumor is aggressive and has a short doubling time, tumor debris may transition to full-grown metastasis, thus leading to a poor prognosis (as typically observed in patients with sarcoma). Aggressive tumors

are likely to be associated with multiple metastases, short DFI, or nodal metastases and, consequently, poor survival. The prognosis is favorable for less aggressive tumors with a moderate doubling time.

The main limitations of this study are the small patient group and its single-center retrospective design. Moreover, the carcinoembryonic antigen level, which is a putative negative prognostic factor, was not analyzed, and genotype analysis was not performed. Moreover, no patient had a germ cell tumor, and only a small number of patients had melanoma; thus, the patient group showed a relative lack of diversity.

In conclusion, tumor histology is the main determinant of overall survival and prognosis after PM. In our study, significant negative prognostic factors included multiple metastases in different unilateral lobes, a short DFI (< 12 months), both mediastinal and hilar lymph node involvement, and sarcoma metastasis. The presence of multiple metastases in different unilateral lobes and N2 disease appeared to be the worst prognostic factors. Thus, preoperatively, patients with either of these two significant negative prognostic factors should be evaluated carefully via a multidisciplinary approach, and PM should be performed only in selected patients.

Declaration of conflicting interests

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Ethics Approval

The study was approved by the institutional review board (No: 20-35/9.5.2020) and conducted in accordance with the principles of the Declaration of Helsinki.

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