Smyrna Tıp Dergisi ***Araştırma Makalesi***

Factors Affecting the Recurrence of Secondary Pulmonary Malignancies Following Complete Pulmonary Metastasectomy
Tam Pulmoner Metastazektomiyi Takiben Sekonder Pulmoner Malignite Ortaya Çıkmasını Etkileyen Faktörler

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Summary
Objective: Although a long-term survival can be achieved in selected group patients who have complete pulmonary metastasectomy; some patients from this group turn up with recurrence. Aim of the study was to determine the factors affecting the recurrence following complete resections for pulmonary metastases.
Material and Methods: A total of 160 patients who had pulmonary metastasectomy owing to the diagnosis of pulmonary metastatic disease between June 2001 and June 2009 were accepted to the study. Patients were divided into two groups: Group A (n:23, developing recurrence) and Group B (n:137, not developing recurrence). Both of the groups were studied and compared with each other in terms of age, gender, primary tumor histology, number of per-operative metastatic lesions during the first pulmonary metastasectomy, type of surgical technique applied, the interval between the diagnosis of the primary malignancy and the initial pulmonary metastasis. Statistical comparisons were carried out with chi-square and Mann Whitney U tests. Correlations were calculated using Spearman's correlation test. P value <0.05 was accepted as statistically significant.
Results: An increasing rate of recurrence was calculated in patients who had developed their first pulmonary metastases at an early age or those who had a shorter metastasis-free interval and had a non-epithelial type of primary malignancy. Furthermore, the existence of recurrence was associated with a shorter life time expectancy. However, the number of per-operative metastatic lessions or the type of surgical technique applied in the first pulmonary metastasectomy did not have an influence on the recurrence of the pulmonary metastases.
Conclusion: Considering the potential mortality and morbidity of surgery, surgical treatment may be avoided in group of patients with a high risk of developing early recurrence and this group of patients may be accepted for oncological treatment.
Key words: Pulmonary metastases, pulmonary metastasectomy, recurrence

Özet
Amaç: Akciğer metastazektomisi uygulanan seçilmiş hasta grubunda uzun dönem sağkalım sağlanabilse de bu gruptaki bazı hastalarda nüks gelişmektedir. Çalışmanın amacı akciğer metastazları için yapılan komplet rezeksiyonları takiben nüks gelişmesini etkileyen faktörleri belirlemektir.
Gereç ve Yöntem: Haziran 2001 ve Haziran 2009 tarihleri arasında akciğer metastazı nedeniyle ameliyat edilen 160 hasta çalışmaya kabul edildi. Hastalar nüks gelişen (Grup A, n:23) ve nüks gelişmeyen (Grup B:137) olmak üzere iki gruba ayrıldı. Her iki grup yaş, cinsiyet, primer tümör histolojik tipi, ilk metastaz ameliyatı sırasında saptanan metastatik odak sayısı, uygulanan cerrahi tipi ve primer malignite tanısı ile ilk akciğer metastazı alınması arasında geçen süre açısından karşılaştırıldı. İstatistiksel karşılaştırılma ki-kare ve Mann Whitney U testleri ile yapıldı. Korelasyonlar Spearman'ın korelasyon testi ile hesaplandı. <0.05 olarak hesaplanan p değerleri istatistiksel olarak anlamlı kabul edildi.
Bulgular: İlk akciğer metastazı erken yaşta gelişen, metastazsız geçen sürenin kısa olduğu ve nonepitelyal tipte primer malignitesi olan hastalarda nüks gelişme oranının arttığı saptandı. Ayrıca nüks varlığının daha kısa yaşam süresine sebep olduğu bulundu. Ancak ameliyat sırasında saptanan metastatik lezyon sayısı ile ilk akciğer metastazektomisi sırasında uygulanan cerrahi tekniğin akciğer metastazlarında nüks gelişmesinde etkili olmadığı görüldü.

Sonuç: Cerrahinin mortalite ve morbiditesi göz önüne alındığında, erken dönem nüks gelişme riski yüksek olan hasta grubunda cerrahi tedaviden kaçınılmalı ve bu hasta grubu onkolojik tedaviye yönlendirilmelidir.
Anahtar kelimeler: Akciğer metastazları, akciğer metastazektomisi, nüks

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Introduction

The lungs are one of the most common sites for malignant tumors to produce metastases via the blood (1). Although the local treatment of primary malignant tumors involves surgery or radiotherapy, the existence of metastatic disease requires systemic treatment such as chemotherapy. It is known that surgery, combined with systemic treatment, supplements the expected life time of patients with lung-limited metastatic disease (1). For this reason, by the end of twentieth century, resections performed for pulmonary metastases in selected groups of patients had become the leading cause of treatment modality.

Weinlechner performed the first pulmonary metastasectomy in 1882 by resecting lung metastasis that he coincidentally identified during the resection of a chest wall tumor (2). However, pulmonary metastasectomy, as a planned surgical procedure, was first described by Torek in 1930 (3). In 1939, Barney and Churchill announced the first long-term survival results of patients after pulmonary metastasectomy for lung metastasis of hypernephroma (4).

Malignant tumors spread by hematogenous, lymphatic, aerogenous or direct invasion pathways. The biology of the underlying primary malignancy, the resistance of the host and the mechanism of spreading modify the localization pattern and grades of growth for metastases. Generally, malignant cells of tumors join the efferent circulation and are sequestered by capillary beds upon their first meeting. The fact that the first capillary beds of all organs except those that drain into the portal system are in lungs, supports the idea that the pulmonary metastases can be multiple, bilateral or peripheral in nature. Tumor cells reaching the lungs adhere to the capillary endothelium and grow by invading the parenchyma. Some tumor cells joining the pulmonary circulation may head to the systemic circulation by anatomic shunts, thus by passing capillary beds. The malignant cells penetrating the lungs by lymphatic pathways can show different localization characteristics or may invade the lungs diffusely, as in lymphangitic spread in breast cancer. As the metastases grow, they may directly invade nearby structures.

Pulmonary metastases are rarely associated with symptoms. Previous studies report the incidence of symptoms to lie in the range 13%-28% (5). Furthermore, less than 5% of patients complain about dyspnea, chest pain, cough and hemoptysis (6).

Pulmary metastases are sometimes recognized as definitely bordered opacities as they rarely appear in miliary formations. A routine chest X-ray can be used to follow-up the potential parenchymal changes in the lungs following the resection of the primary tumor. Furthermore, some studies have suggested that chest X-ray is succesful in identifying current pulmonary metastases in only half of cases (7). Computed tomography (CT) is able to identify pulmonary nodules ranging from 1 to 10 mm. Margaritora et al. reported that CT has 48% sensitivity in identifying pulmonary nodules with a diameter less than 6 mm (8). Positron emission tomography (PET) is also helpful, particularly in assessing pulmonary metastases after the treatment of primary soft tissue malignancies. On the contrary, the use of PET to identify extra-pulmonary metastases avoids the need for pointless surgical interventions. Lucas et al reported that PET showed 86.7% sensitivity and 100% specificity in identifying pulmonary metastases originating from soft tissue malignancies (9).

At present, systemic treatment combined with surgical resection, remains the most efficient treatment method for metastatic lung tumors. Satisfying long-term survival can be achieved in selected groups of patients following pulmonary metastasectomy, although some patients from this group turn up with ipsilateral/contralateral recurrence at an early stage. It is a known fact that

early recurrence is a bad prognostic factor. Hence, identifying patients with a higher risk of recurrence is important for selecting suitable cases for pulmonary metastasectomy.

The aim of the study was to examine patients who underwent pulmonary metastasectomy and to determine the factors affecting the recurrence of the lung metastases.

Material and Methods

This study was carried out in 2017 by retrospectively examining 169 patients who were identified as having surgery owing to the diagnosis of pulmonary metastatic disease between June 2001 and June 2009 in Istanbul University, Department of Thoracic Surgery. Of those, 9 cases whose post-operative pathological examination was reported as incomplete resection were excluded. The remaining 160 patients were divided into two groups: Group A (n:23, developing recurrence) and Group B (n:137, not developing recurrence).

All the patients were physiologically evaluated by respiratory function testing and by testing the diffusing capacity of the lung for carbon monoxide. Patients with chronic diseases were assessed for convenience before surgery by consultations from related medical departments. CT scans were carried out one week, at most, before surgery and represented the last radiological examination. To ensure that the primary cancer was under control prior to pulmonary metastasectomy, X-ray scans, ultrasonography, CT scans, magnetic resonance imaging (MRI) and a variety of tumor-specific markers, were used, depending on the localization of the primary tumor.

Both of the patient groups were studied and compared with each other in terms of age, gender, histological type of the primary tumor, metastasis-free interval, the number of per-operative metastatic lesions, the type of surgical technique applied. Age was recorded for two groups as an arithmetic mean (in years). The histological type of the primary tumor (TPT) was divided into two main types: epithelial and non-epithelial. Epithelial types of tumor included breast, thyroid, renal cell, colorectal, liver, bladder, uterus, vulva, testicular carcinomas and malignant melanoma. Non-epithelial tumors included osteosarcoma, chondrosarcoma, Ewing sarcoma and synovial sarcoma. The metastasis-free interval (MFI) was defined as the time between the diagnosis of the primary tumor and the diagnosis of pulmonary metastasis by the first metastasectomy, and was calculated as the arithmetic mean in months. The number of metastatic lesions (NML) was defined as the number of lesions counted peri-operatively during the first pulmonary metastasectomy. Type of resections (TOR) were separated into two groups; anatomic resections including segmentectomy, lobectomy and pneumonectomy; and non-anatomic resections including wedge resection, pulmonary nodule resection and combination of these techniques. Survival time (ST) was the period between the first pulmonary metastasectomy and the death of deceased patients or the last follow-up date of living cases. ST was reported as the arithmetic mean in months for both groups.

As the distribution of data rising from the two study groups was not homogeneous, non-parametric tests were used for statistical evaluation. Comparisons were carried out with chi-quared and Mann Whitney U tests. Correlations were calculated using Spearman's correlation test. P value <0.05 was accepted as statastically significant.

Results

The final analysis for this study involved 160 patients who had pulmonary metastasectomy carried out between June 2001 and June 2009. Table 1 shows the general patient data. Mean patient age was 39.5 years (range: 11-79 years). The median age was 27 in Group A and 43 years in Group B (p=0.02).

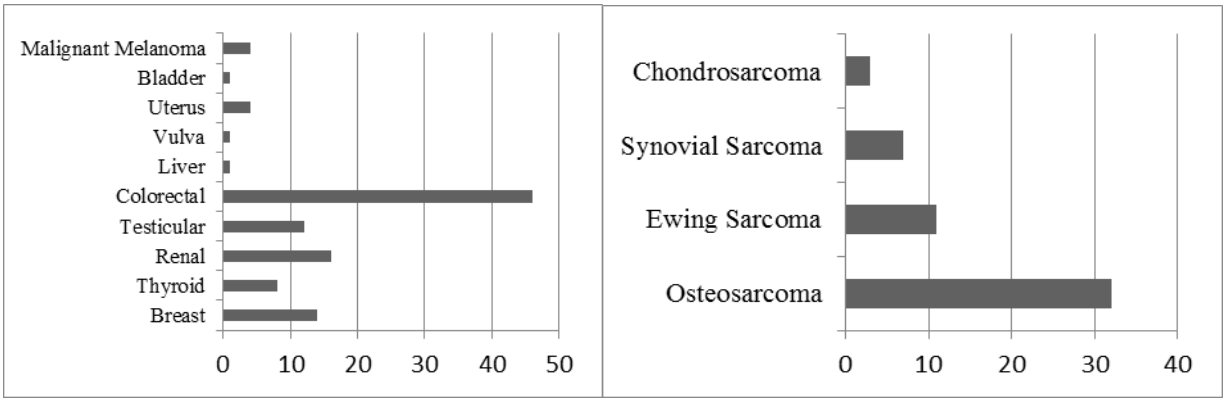
In total, 85 patients (53%) were male and 75 patients (47%) were female. Although 11 males and 12 female patients developed recurrence, the male/female ratio in Group B was 74/63 (p=0.58). According to the ethiology of the primary tumor, 107 patients (66%) had epithelial malignancies while 53 patients (34%) had non-epithelial types of malignancies. Epithealial types of tumor included breast carcinoma (in 14 patients), thyroid carcinoma (8), renal cell carcinoma (16),

testicular carcinoma (12), colorectal carcinoma (46), liver carcinoma (1), vulva carcinoma (1), uterus carcinoma (4), malignant melanoma (4) and bladder carcinoma (1). Non-epithelial types of primary tumor included 32 osteosarcomas, 11 Ewing sarcomas, 7 synovial sarcomas and 3 chondrosarcomas. Looking more closely at the type of the primary tumor, of the 23 malignancies that developed recurrence, 19 involved non-epithelial tumors. Moreover, of the 137 malignancies that did not develop recurrence, 103 exhibited an epithelial histological type (p=0.001). Data relating the histological type of the primary malignancies is given in graph 1.

Table 1. *Demographic and clinical analysis of patients*

Parameters	**Group A (Developing Recurrence)**	**Group B (Not Developing Recurrence)**	**Total**	**P Value**
Age (mean, years)	27	43	39.5	0.02
Male/Female (n)	11/12	74/63	85/75	0.58
TPT(Epithelial/Non-epithelial) (n)	4/19	103/34	107/53	0.001
NML (n)	2	2	2	0.18
TOR(Anatomic/Nonanatomic) (n)	3/20	41/96	44/116	0.84
MFI (mean, months)	19.6	27.2	26.1	--
ST (mean, months)	11	20	16.5	0.01

Graph 1. *Epithelial and non-epithelial primary tumors developing pulmonary metastases*

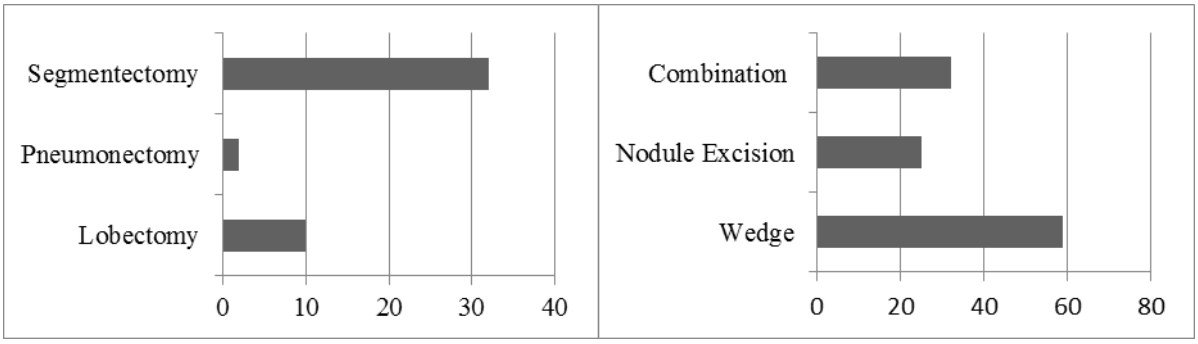


The mean number of metastatic lesions discovered in the first pulmonary metastasectomy for both Group A and Group B patients was identical (mean=2, range: 1-14, p=0.18). This value lays between 1 and 8 in Group A (developing recurrence) and between 1 and 14 in Group B (not developing recurrence).

The operations were completed with anatomic resections in 44 (27%) and non-anatomic resections in 116 (73%) cases. Surgeries that included both types of resections were recorded as anatomic resections. In the anatomic resections group, there were 10 lobectomies, 2 pneumonectomies and 32 segmentectomies. There were 59 wedge resections, 25 nodule excisions and 32 cases involving both of these two methods. Anatomic resections were performed in 3 of the 23 patients developing recurrence and in 41 of the 136 patients not developing recurrence (p=0.84). The distribution of the surgical type applied is given in graph 2.

MFI was calculated as the time between the diagnosis of the primary tumor and the diagnosis of the pulmonary metastasis by the first metastasectomy; median MFI was calculated as 26.1 months over the entire cohort of patients. MFI was 19.6 months in Group A (developing recurrence) and 27.2 months in Group B (not developing recurrence). This information supports the idea that cases developing recurrence had a shorter MFI.

Graph 2. *Type of resections applied for pulmonary metastasectomy*



Mean ST of the patients with secondary pulmonary malignancies accepted for the study was 16.5 months (Range: 2-180 months). Mean ST was 11 months (Range: 2-180 months) for Group A (developing recurrence) and 20 months (Range: 3-150 months) Group B (not developing recurrence), respectively (p=0.01).

A negative correlation was identified between the patient age and the recurrence of malignancy (p=0.02). Also, a positive correlation between recurrence and the non-epithelial type of the primary tumor was discovered (p=0.0001). There was also a negative correlation between recurrence of the metastasis and ST (p=0.01). Also, a negative correlation between the non-epithelial type of primary malignancy and ST was identified (p=0.005).

Discussion

Distant metastasis is a sign of systemic spread and one of the most important negative prognostic factor. The lungs are the second most common organs after the liver that meet up with metastases. Pulmonary metastases occur in 20% to 54% of all malignancy cases (10,11).

The results of surgical resections for pulmonary metastases show a large scale of variation. Long- term survival is achieved in some cases while other patients gain no benefit from surgery. Some previous studies have suggested that patients can have a long survival time without any surgery for metastases (12) while other studies report a survival rate of under 5% for 10 months and 5 years without any surgery and also that this rate can be raised up to 43% when appropriate surgery is applied (13).

Pulmonary metastases develop recurrence in 50% to 67% of patients in spite of complete surgical resection (14,15). There is insufficient information in the existing literature with regards to the factors affecting the recurrence of secondary pulmonary malignancies. The present study retrospectively investigated the cases which received pulmonary metastasectomy over an approximate 8 year period for recurrence and the factors affecting this condition.

The mean age was 27 years in the group of patients developing recurrence (Group A) compared to 43 years in the group of patients who did not develop recurrence (Group B). It was discovered that the rate of recurrence was

significantly higher in cases who faced their first pulmonary metastases at an early age (p=0.02). While 23 of the cases developing recurrence involved 11 males (48%) and 12 females (52%), there were 74 males (54%) and 63 females (46%) cases in the group that did not develop recurrence (p=0.58). The gender of the patients did not show any significant relationship with the recurrence of secondary pulmonary malignancies.

Some previous studies (15,16,17) have reported MFI as an important prognostic factor for recurrence after pulmonary metastectomies, while others (18,19) declared that MFI had no influence upon recurrence. Ishiara et al. reported that patients with an MFI longer than 10 years had a good prognosis when treated effectively with pulmonary metastasectomy (20). The overall group of patients accepted for this study had a median MFI of 26.1 months (Range: 2-124 months); mean MFI for group A (developing recurrence) and group B (not developing recurrence) was 19.6 months and 27.2 months, respectively. Therefore, it was clear that the patients who were developing recurrence had a shorter MFI.

Watanebe et al. suggested that the patients with solitary pulmonary metastatic lesions had a longer survival time and a lower risk of recurrence (21), while Kandioler et al. found no significant relationship between the number of metastatic lesions and the development of recurrence (22). Girard et al. reviewed resectable lung metastases and discovered that the number of metastatic lesions did not relate to the incidence of recurrence (23). Vogt-Moykops et al. further reported a lower potential of recurrence in cases with 5 or less metastatic lesions (24). Both of our current patient groups had the same median value of 2 for the number of metastatic lesions (p=0.18). This data revealed that the development of recurrence did not have any significant relationship with the number of metastatic lesions discovered during the first pulmonary metastasectomy.

Despite of advanced CT and PET scanning techniques, undiagnosed pulmonary nodules may exist in 37% of patients, and 20% of those nodules are considered to be malignant. For this reason, video assisted thoracoscopic surgery (VATS), which does not allow manual palpation during pulmonary metastasectomy still seems risky for some authors (25). Saito et al., however, reported that the type of surgery applied to 165 pulmonary metastasectomy operations showed no statistical difference in terms of recurrence and survival (26). Similarly, this study did not show any significant differences for the type of surgical technique in relation to the recurrence of metastatic disease (p=0.84).

The recurrence rate of pulmonary metastatic lesions primarily originating from epithelial tumors was reported as 30.6% by Rena et al. (27), and 8% by Casali et al (28). Chen et al. announced a recurrence rate of 71% after performing pulmonary metastasectomy for lung lesions originating from primary non-epithelial tumors (29). Current study included 23 primary tumors developing lung metastases, the primary tumor was epithelial in 4 (17%) of these cases, and non-epithelial type in 19 (83%) cases (p=0.001). Significant difference was found between the epithelial and non-epithelial types of primary malignancies related to pulmonary metastases developing recurrence.

Although pulmonary metastasectomy has become a standard method of treatment for various metastatic malignancies of the lung, the factors affecting disease recurrence after surgery are still debated. As a result, the rate of recurrence increases in patients who developed their first pulmonary metastases at an early age,or those who have a shorter metastasis-free interval and have a non-eptihelial type of primary malignancy. Furthermore, the existence of recurrence is associated with a shorter life time expectancy. Considering the potential mortality and morbidity of surgery, surgical treatment may be avoided in group of patients developing recurrence and this group of patients may be accepted for oncological treatment.

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