

## Analysis of factors affecting long-term survival in surgically-treated second primary lung cancer patients with previous malignancy

Malignite tanılı opere edilmiş ikinci primer akciğer kanserli hastaların uzun dönem sağkalımını etkileyen faktörlerin analizi

Ayşe Gül Ergönül<sup>1</sup> Ali Özdiş<sup>1</sup> Tevfik İlker Akçam<sup>2</sup> Kutsal Turhan<sup>1</sup> Alpaslan Çakan<sup>1</sup> Ufuk Çağırıcı<sup>1</sup>

<sup>1</sup>Ege University Faculty of Medicine, Department of Thoracic Surgery, İzmir, Turkey

<sup>2</sup>Dr.Suat Seren Chest Diseases and Surgery Training and Research Hospital, İzmir, Turkey

### Abstract

**Aim:** Multiple cancer rates increase with an average increased lifespan. Therefore, many malignant patients are at high risk for a second primary malignancy. This study aims to evaluate lung cancer patients with a previous malignancy.

**Materials and Methods:** Forty-five patients who underwent resection for a second primary lung cancer in our department between January 2007 and June 2013 were reviewed retrospectively.

**Results:** The patients included 37 (82.2%) males and eight (17.8%) females. When the patients were evaluated for the first primary malignancy, the distribution of the malignancies according to the systems was 14 (31.1%) urogenital malignancies, ten (22.2%) respiratory, six (13.3%) hematological, six (13.3%) endocrine, five (11.1%) malignancies, and four (8.9%) integumentary malignancies. The comparison of the site of primary malignancy and survival data showed that the rates of long-term survival were shorter in patients with gastrointestinal system malignancies and the difference was statistically significant ( $p=0.028$ ). The long-term survival of patients who received chemotherapy after the resection of the first primary lung cancer was significantly shorter ( $p=0.016$ ).

**Conclusion:** The follow-up of patients should be done more carefully by the consideration of the positive effects of early diagnosis on cancer prognosis and keeping in mind the risk of primary lung cancer development in a patient with other system malignancy. We especially recommend caution in administering chemotherapy to patients with double primary tumors after a lung cancer operation.

**Keywords:** Lung cancer, second primary neoplasm, operation.

### Öz

**Amaç:** Yaşam süresi uzadıkça multipl kanser görülme sıklığı giderek artmaktadır. Bundan dolayı birçok maligniteli hastada ikinci bir primer kanser ortaya çıkma ihtimali bulunmaktadır. Bu çalışmada, öncesinde başka bir malignite tanısı bulunan primer akciğer kanserli hastalar değerlendirildi.

**Gereç ve Yöntem:** Kliniğimizde Ocak 2007 ile Haziran 2013 arasında öncesinde başka bir malignite tanısı bulunan ve buna ilave olarak primer akciğer kanseri nedeniyle opere edilen 45 hasta retrospektif olarak değerlendirildi.

**Bulgular:** Hastalar 37 (%82.2) erkek, 8 (%17.8) kadından oluşmaktaydı. İlk primer tanı grupları değerlendirildiğinde, 14 (%31.1) hastada ürogenital sistem malignitesi, 10 (%22.2) hastada respiratuar sistem, 6 (%13.3) hastada hematolojik malignite, 6 hastada (%13.3) endokrin organ malignitesi, 5 (%11.2)'inde gastrointestinal sistem ve 4 (%8.9) hastada deriye ait malignite varlığı mevcuttu. İlk primer tanı grupları ile uzun dönem sağkalım analizi yapıldığında, gastrointestinal sistem malignitesi bulunan hastalarda sağkalımın istatistiksel olarak daha düşük olduğu görüldü ( $p=0.028$ ). Yine akciğer operasyonu sonrasında kemoterapi alan hasta grubunda uzun dönem sağkalım daha kısaydı ( $p=0.016$ ).

Corresponding Author: Tevfik İlker AKÇAM

Dr.Suat Seren Chest Diseases and Surgery Training and Research Hospital, İzmir, Turkey

Received: 19.01.2015

Accepted: 04.02.2015

**Sonuç:** *Kanserde erken tanının prognoza olumlu etkisi düşünüldüğünde maligniteli olgularda primer bir akciğer kanseri gelişme riski her zaman akıldan tutularak, bu olguların takibinde daha dikkatli olunmalıdır. Özellikle akciğer kanseri operasyonu sonrası çift primerli bu hastalara kemoterapi uygulanması konusunda çok dikkatli olunmasını öneriyoruz.*

**Anahtar Sözcükler:** *Akciğer kanseri, ikinci primer malignite, operasyon.*

## Introduction

The second primary malignancy incidence in cancer patients is 1.7-3.9% (1). The occurrence of two primary malignancies in the same person is influenced by several factors. Multiple primary cancers may result from the treatment of the first tumor or the association of risk factors, among patient-specific factors (genetic predisposition, immunodeficiency, smoking, diet, age, occupational exposure, etc.) (1-5). It is known that the lungs are the most common location of metastasis for malignant tumors (6). Therefore, when a second lesion is detected in the lungs of a patient who has been previously diagnosed with any organ or tissue malignancy, the question of whether it is a second primary or a metastasis comes to mind. The detection and management of this condition has great importance for patient prognosis. The present study investigated 45 patients who previously had malignancy in other organs and who were also surgically treated in our clinic due to primary lung cancer. In a general context, the objective was to demonstrate the malignancies associated with lung cancer. As a secondary aim, the major factors affecting survival were investigated.

## Materials and Methods

Forty-five patients who underwent resection for secondary primary lung cancer in our department between January 2007 and June 2013 were reviewed retrospectively. The patients were evaluated in terms of age, gender, comorbid disease, smoking history, lung cancer stage and histopathology, adjuvant therapy, disease free survival, and long-term survival. For the purpose of acquiring a general approach, the first malignancies of the patients were classified into organ systems. Additional treatments received by the patients after the lung operation were recorded. The possible effects of these variables were analyzed.

Long term survival and disease free survival were analyzed with the Kaplan-Meier method. The log-rank test was used to evaluate statistical significance of the potential factors affecting long term survival and disease free survival. *P* values less than 0.05 were considered statistically significant.

## Results

The patients included 37 (82.2%) males and eight (17.8%) females, and their mean age was  $63.7 \pm 8.9$

years (range: 36-76 years; median: 66.0 years). 12 (26.7%) patients had no smoking history, 25 (55.6%) patients had a history of 1-40 pack years, and eight (17.8%) patients had a history of more than 40 pack years. Twenty-eight (62.2%) patients had comorbid diseases, such as diabetes mellitus, chronic obstructive lung disease, and hypertension. Thirty-four (75.6%) patients were classified as early stage (stage I) and 11 (24.4%) were classified as advanced stage (stage II-III and IV) non-small cell lung cancer.

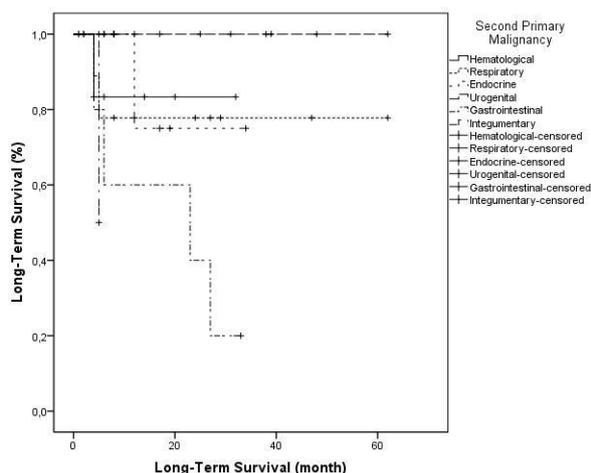
According to histopathological diagnosis, 20 (44.4%) patients had adenocarcinoma, 15 (33.3%) had squamous cell carcinoma, four (8.9%) had large cell carcinoma, three (6.7%) had carcinoid tumor, two (4.4%) had mucoepidermoid carcinoma, and one (2.2%) had adenoid cystic carcinoma. The type of resection was anatomic in 23 (51.1%) patients and non-anatomic in 22 (48.9%) patients. Sixteen (35.6%) patients had adjuvant therapy postoperatively and 10 (22.2%) of these patients had chemotherapy only. When the patients were evaluated for the first primary malignancy, the distribution of the malignancies according to the systems was 14 (31.1%) urogenital malignancies, ten (22.2%) respiratory malignancies, six (13.3%) hematological malignancies, six (13.3%) endocrine malignancies, five (11.2%) gastrointestinal malignancies, and four (8.9%) integumentary malignancies. The mean of duration between two primary malignancies was  $41.18 \pm 54.26$  months (range: 0-204 months). In the follow-up, recurrence was seen in five (11.1%) patients, and nine (20.0%) of the patients died. The mean long-term survival was  $18.00 \pm 16.13$  months (range: 1-62 months), respectively.

There was no significant difference in terms of survival between the categories of age, gender, smoking history, presence of comorbid disease, stage and histopathology of lung cancer and type of resection (Table-1). The comparison of the site of primary malignancy and survival data showed that the rates of long-term survival were shorter ( $18.60 \pm 12.93$  months; range 4-33 months) in patients with gastrointestinal system malignancy and the difference was statistically significant ( $p=0.028$ ) (Figure-1). The long-term survival of patients who received chemotherapy after the resection of first primary lung cancer was significantly shorter ( $9.40 \pm 7.24$  months) than who had not received chemotherapy ( $20.46 \pm 17.17$  months) ( $p=0.016$ ) (Figure-2).

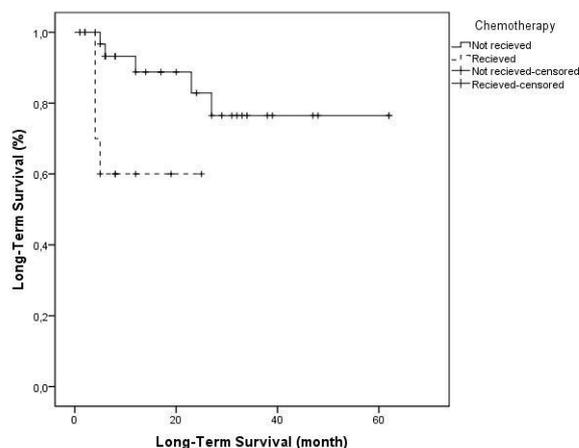
**Table-1.** Long-term Survival According to Clinical and Histopathological Parameters.

	Long-Term Survival		p
	Alive	Exitus	
<b>Sex</b>			
Male	30	7	0.890
Female	6	2	
<b>Age (Years)</b>			
0-59	11	1	0.292
≥ 60	25	8	
<b>Smoking History (pack years)</b>			
0	10	2	0.735
1-40	19	6	
>40	7	1	
<b>Co-morbid Disease</b>			
Present	23	5	0.954
Absent	13	4	
<b>Stage</b>			
Early	28	6	0.632
Advanced	8	3	
<b>Type of Resection</b>			
Anatomic	20	3	0.290
Non-Anatomic	16	6	

The first and second primary malignancies were compared in terms of stage and histopathological type. There was no difference according to histopathological type, but it was determined that respiratory system malignancies frequently developed as a second primary malignancy in patients with advanced stage lung cancer and the difference was statistically significant ( $p=0.039$ ).



**Figure-1.** Long-term survival analysis according to the system of second primary malignancy.



**Figure-2.** Long-term survival analysis of patients who received only chemotherapy as adjuvant therapy.

## Discussion

In addition to increased life span and the current increase in the number of options for diagnosis and treatment, the incidence of a second primary malignancy in a different organ or in the same organ in the same patient is increased. The incidence of second primary malignancy depends on the affected organ, and the occurrence of a second tumor in the same organ has been identified mostly in the colon, breasts, and ovaries (1,2,4,7). The incidence of a second primary lung malignancy in a patient with a malignancy in an organ other than the lungs is 1.6-3% (8).

The incidence of a second primary tumor increasing to 10-20% in early stage lung cancer patients who live more than three years indicates the importance of follow-up of lung cancer patients (1). If the second primary tumor is operable in these cases, the five-year survival is >30% and the 10-year survival is >20% (3). Therefore, early detection of the second primary cancer will increase the chance of treatment and extend the life span. In the present study, the long-term survival was  $18.00 \pm 16.13$  months (range: 1-62 months).

In a study similar to the present study, organ tumors that developed prior to lung cancer were investigated and the most common groups of tumors associated with lung cancer were breast and prostate tumors (8). In the present study, this was evaluated based on groups and the urogenital system tumors were placed on top. However, there was no significant difference in long-term survival in the patient groups with different tumors in the other study, whereas the long-term survival was lower in the group with gastrointestinal system tumors compared to the other groups in the present study. Furthermore, another study that investigated second primary tumors associated with gastric cancer emphasized that the associated tumor groups had no effect on survival (9).

In some studies, the most common histological type was epidermoid carcinoma in patients who developed a second primary tumor, which was followed by epidermoid/small-cell and epidermoid/adenocarcinoma combinations (3,4). In the series of the present study, the most common histological type was adenocarcinoma (44.4%), followed by squamous cell carcinoma (33.3%), and large-cell carcinoma (8.9%).

The incidence of lung cancer is approximately 10%, after head and neck malignancies. The incidence of a synchronous lung tumor in these cases is 1%, whereas the incidence of a metachronous tumor increases to 10% in patients who have survived  $\geq 3$  years (7,10). When the location of primary malignancies was analyzed in the present study, the second most frequent group was respiratory system malignancies with ten cases (22.2%); laryngeal cancer and lung cancer were included in this group. Similar etiological reasons are indicated for this association, and the effect of smoking is ranked first. Smoking is known to be a very important etiological agent for head, neck, lung, uterus, and breast cancers (1,3,5). Therefore, periodic chest radiography and bronchoscopic examinations are recommended for patients in the high-risk group. Smoking cessation following the detection of the first malignancy extends the time of developing a second primary malignancy. In the present study, 33 (73.3%) patients were smokers; however, although smoking had an effect on survival for disease-free survival and long-term survival, there was no statistical significance. Additionally, among etiological factors, genetic studies in recent years have begun to demonstrate that some mutations cause a predisposition to cancer. While p53 gene mutation is important in the lungs, it has been reported that the BRCA1 mutation in breast cancer might be associated with multiple malignancies (11,12).

The occurrence of a second malignancy in a patient with an existing malignancy can be a coincidence or a multifactorial process. Many factors are questioned regarding the occurrence of secondary cancers. This

was particularly clear after radiotherapy (RT), chemotherapy (CT) or combined treatments. While evaluating treatment-related carcinogenic effects, it is difficult to differentiate due to the combined administration of therapeutic agents. However, all secondary cancers are not due to treatment. Cases have been reported in which colon cancer developed due to pelvic radiotherapy for the treatment of the previous malignancy and acute leukemia due to the effect of previous chemotherapy on bone marrow (1,13,14). Malignancies secondary to chemotherapy and radiotherapy generally affect the bone marrow; however, these malignancies have also been reported to cause solid cancers (15). Furthermore, some studies have demonstrated that post-breast cancer RT causes lung malignancy (16).

In general, studies indicate that second primary tumors should be treated independently of the first disease. However, when the additional treatment received by the patients in the present series and the survival data were analyzed, the long-term survival was statistically lower in the patients who received post-resection chemotherapy due to primary lung cancer. This was considered to be a result of the side effects of the chemotherapy or the patients being at a more advanced stage of cancer.

### Conclusion

In conclusion, when considering the positive effect of early diagnosis on the prognosis, more care should be taken in the follow-up of the patients with non-pulmonary cancer by keeping in mind the risk of developing a primary lung cancer. When a second primary cancer is detected, it is recommended to treat it independently of the first cancer. Since the long-term survival was shorter in the patients with gastrointestinal system malignancy, particularly in the present study, as distinct from other studies, more frequent pulmonary scanning is required in the follow-up of such patients. We recommend caution in the administration of chemotherapy to such patients with double primary tumors, after a lung cancer operation.

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