

## The factors affecting the distant recurrence in patients with non-small cell lung cancer (NSCLC) and our results

Distant Recurrence in Patients with NSCLC

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### Abstract

**Aim:** The long-term survival in Non-Small Cell Lung Cancer (NSCLC) following tumor-free resection is less than fifty percent. The most important cause affecting the mortality following the resection is the development of recurrence. This study aims to determine the factors affecting the recurrence, to increase the awareness concerning this topic and to enlighten this challenge by virtue of new studies. **Material and Method:** In this study, the data were obtained by studying retrospectively the database of the patients who underwent complete resection due to the NSCLC between January 2008 and December 2012 in our Thoracic Surgery Clinic. The effects of the clinicopathologic variables on the distant recurrence were assessed. **Results:** Fifty male patients (87.7%) and seven female patients (12.3%) with NSCLC were included in the study. Distant recurrence was developed in seven of the patients. During the three-year follow-up, we obtained statistically significant values in comparing the parameters affecting the survival such as differentiation ( $p=0.012$ ), pathological stage ( $p=0.02$ ), development of distant recurrence ( $p=0.014$ ), the location of the distant recurrence ( $p=0.011$ ), the duration spent in the intensive care unit ( $p=0.018$ ), the length of stay ( $p=0.018$ ) and the time for the postoperative distant recurrence (0.048). A statistical significance was detected between the distant recurrence and the hilar lymphadenopathies larger than one centimeter in computerized tomography ( $p=0.049$ ). **Discussion:** We found that the presence of the hilar lymphatic node larger than one centimeter in computerized tomography is the most important parameter in the development of distant recurrence.

### Keywords

Non-Small Cell Lung Cancer; Distant; Recurrence

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## Introduction

While pulmonary carcinoma is the most common in males in terms of incidence and mortality worldwide, it ranks in females in number three in terms of incidence and in number two in terms of mortality following the breast carcinoma. In 2012, it was the cause of 19.4% of the deaths due to cancer with 1.56 million deaths and with 1.82 million new cases. In Non-Small Cell Lung Cancer (NSCLC), the survival following the resection is less than fifty percent (50%) despite the chemotherapy and developed molecular target treatments. Most of the mortality after the resection depends on the development of the recurrence [1]. The aim of this study is to investigate the relationship between the clinicopathological factors and the recurrence in the patients who underwent complete resection.

## Material and Method

Data were created from 50 (fifty) male patients and 7 (seven) female patients who underwent complete resection between January 01, 2008 and December 31, 2012 in our Thoracic Surgery Clinic. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was not obtained from patients due to the retrospective nature of this study. Ethics committee approval was received for this study from the ethics committee of local University (2016/477). All patients were staged with seventh TNM classification which was published in 2009. Follow-up data were completed in January 2016.

The parametric data such as the gender of the patients, their ages, their accompanying diseases, their findings in thoracic computerized tomography (CT) (the presence of the hilar and mediastinal lymphatic nodes larger than one centimeter), mediastinal-hilar lymphadenopathy (LAP) maximum Standard Uptake Value (SUV-max) in the positron emission tomography-computerized tomography (PET-CT), histological type, clinical stage, neoadjuvant chemotherapy (Table 1), pathological findings after the surgery (tumor diameter, differentiation, the presence of N1, the presence of N2, pericapsular invasion in the lymphatic node), pathological stage, the length of stay in the intensive care unit, total length of stay, the development of the distant recurrence, the location of the distant recurrence, the treatment applied after the recurrence, the complications causing mortality, the three-year survival data were studied (Table 2).

In the beginning, the patients were called every two to three weeks and then they were called every three to six months to the control examinations. Three-year follow-up was completed in all patients. There were ten exitus cases (17.5%) at the end of the follow-up. The causes of death included two respiratory failure cases (3.5%), one myocardial infarction case (3.5%), four organ failure cases (7%) and three pneumonia and sepsis (5.3%). Local recurrence was developed in nine patients and distant recurrence was developed in seven of them (12.3%). At the end of this time interval, forty-seven patients (82.5%) were alive.

Descriptive statistics for quantitative data such as mean, maximum, and minimum values were computed. The relationship between the distant metastasis after the surgery and clinicopathologic data were studied through the statistical methods. Statistical analysis was applied by using SPSS for Windows ver-

Table 1. The data of the patients before surgery and the data obtained after pathological investigation.

Variables	Numbers	%
Gender (Male-Female)	50-7	87.7-12.3
Accompanying Diseases	37	64.9
Hilar LAP larger than one cm in computerized tomography	9	15.8
Mediastinal LAP larger than one cm in computerized tomography	9	15.8
Clinical Stage		
Stage 1	34	59.6
Stage 2	16	28.1
Stage 3	7	12.3
Neoadjuvant Chemotherapy	6	10.5
Histological type		
Squamous-cell	29	50.9
Adenocarcinoma	19	33.3
Large-cell carcinoma	7	12.3
Carcinoid	2	3.3
Differentiation		
Good	16	12.3
Moderate	23	40.4
Poor	18	31.6
Pericapsular invasion	2	3.5
N1 involvement	8	14
N2 involvement	3	5.3
Pathological stage		
Stage 1	29	50.9
Stage 2	25	43.9
Stage 3	3	5.3

LAP: Lymphadenopathies; cm: centimetre; N: Nodal

Table 2. The data obtained before and after surgery is summarized.

Variables	Number	%
Adjuvant treatment	23	40.35
Development of the distant recurrence	7	12.03
Localization of the distant recurrence		
Brain	5	8.7
Bone	1	1.7
Adrenal	1	1.7
Adjuvant treatment after recurrence	13	22.8
Complications	24	42

sion 15.0 (SPSS Inc. Chicago, Illinois, USA). The Kaplan-Meier survival analysis was used for survival and the Cox Regression was used to determine the prognostic factors for the variables with significant differences between the groups. The level of statistical significance was considered as  $p < 0.05$ .

## Results

In the comparison of the distant recurrence with other parameters, the differences between hilar lymphadenopathies larger than one centimeter in computerized tomography were detected as significant ( $p=0.049$ ). In the comparison between the three-year mortality and other parameters, the differences between the tumor diameter in computerized tomography ( $p=0.02$ ), the pathological tumor diameter ( $p=0.003$ ), SUV-max of the tumor in the PET-CT ( $p=0.004$ ) were found as statistically significant (Table 3). In the comparison between the dis-

Table 3. The data containing the numerical values.

Data	minimum value	maximum value	Mean value
Age	40	80	60.2
Tumour diameter in CT (mm)	12	100	41
Pathological tumour diameter (mm)	5	110	39
ASA score	1	4	2.7
SUV-max value of tumour in PET-CT	1.89	47.7	15
Hilar LAP SUV-max value in PET-CT	0	9.58	1.2
Mediastinal LAP SUV-max value in PET-CT	0	6.48	1.01
The length of stay in the intensive care unit (day)	3	34	5.3
Total length of stay (day)	5	38	12
Duration of distant recurrence (month)	3	32	16
Time to mortality (as postoperative months)	0	28	1.8

mm: millimetre; CT: Computerized Tomography; ASA: American Society Anesthesiologists; SUV-max: maximum Standard Uptake Value ; PET-CT: Positron Emission Tomography-Computed Tomography

tant recurrence and other parameters, the differences between the hilar lymphadenopathies larger than one centimeter in computerized tomography were as statistically significant ( $p=0.049$ ). The lonely accompanying disease seen in the patients in whom distant recurrence was developed was Chronic Obstructive Pulmonary Disease (COPD). The most common localization of carcinoma in the patient who developed distant recurrence was the left upper lobe. No primary tumor localization was detected in the left lower lobe and in the right middle lobe. The most commonly seen stage in the patients who developed the distant recurrence was Stage 3. While the most common histological type was adenocarcinoma, no carcinoid tumor was seen. In the patient in which distant recurrence was either developed or not developed, invasion to surrounding tissue, N1, and N2 involvements were seen in a lower ratio.

While the most commonly seen complication was arrhythmia in patients with distant recurrence, no pneumonia, no prolonged air leakage, and no wound site infection were seen. In patients who developed distant recurrence, the organ in which metastasis was most commonly detected was brain. The second most common organs in which metastases were seen were adrenal glands and bone. In the patient who developed distant recurrence, three-year mortality was more observed. When the relationship between the survival and the clinical stage was investigated, the lower survival was in Stage 3, Stage 2, and Stage 1 respectively. Thus, as the stage increases, the risk of an earlier death inpatients increases (Table 4).

In the comparison between the parameters affecting three-year survival such as differentiation ( $p = 0.012$ ), postoperative stage ( $p = 0.027$ ), the development of distant recurrence ( $p = 0.014$ ), the localization of the distant recurrence ( $p = 0.011$ ), the length of stay in the intensive care unit ( $p=0.018$ ), hospitalization time ( $p = 0.018$ ) and postoperative duration of distant recurrence (0.048), we found statistically significant values. Table 5 shows the results of the Kaplan-Meier survival analysis by determining the main factor of differentiation groups. Survival graphs related to differentiation, postoperative stage, and localization of the distant recurrent are shown in Figure 1, 2, and 3, respectively. Values closer to the statistically significant value were found between the pathological tumor diameter and tumor SUV-max in PET-CT.

Table 4. Parameters affecting three-year survival and p-values.

Parameter	p-value	HR	95% CI
Differentiation (Severe)	0.012	2,05	(1,17-3,11)
Postoperative stage (Stage 2)	0.027	1,94	(1,19-2,27)
Development of distant recurrence (month)	0.014	1,37	(1,08-1,87)
Localization of the distant recurrence	0.011	1,17	(1,03-1,32)
Complications	0.090	--	
Treatment applied after the recurrence	0.895	--	
Tumour diameter in CT (mm)	0.194	--	
Pathological tumour diameter (mm)	0.069	--	
The length of stay in the intensive care unit (day)	0.018	1,87	(1,12-2,24)
The length of stay (day)	0.018	1,21	(1,04-1,42)
PET-BT tumour SUV-max value	0.013	1,68	(1,11-2,13)

mm: millimetre; CT: Computerized Tomography; SUV-max: maximum Standard Uptake Value; PET-CT: Positron Emission Tomography-Computed Tomography

Table 5.

Differentiation	Mean	Standard Error	Median
Good	0,0	0,0	0,0
Medium	1,21	0,55	0,4
Severe	9,33	3,11	5,1
Amount	4,91	1,41	1,8

## Discussion

Following the surgery of pulmonary cancer, recurrence is the most important cause of the failure in treatment. The recurrence percentage of patients with cancer is between 30% and 70% [2]. The recurrence ratio within two years following the surgery is more than 80% (early recurrence) and the ratio of repeating five years later (late recurrence) was 9% [3,4].

In NSCLC cases, various prognostic factors have been defined. Age, gender, pulmonary functions, accompanying diseases, the performance status of the patient, tumor stage, tumor type, molecular biological factors are primary factors affecting the prognosis [5]. Tumor stage is the most important among these factors. In a study conducted by Stanley et al. [6], seventy-seven factors having the potential to affect the pulmonary cancer were investigated and it was seen that fifty of them affect the prognosis. The three most important among these fifty prognostic factors were identified as the physical performance status of the patient, the extensity of the patient and the loss of weight for the last six months. We obtained statistically significant values consistent with the literature in comparison between the parameters affecting three-year survival such as differentiation, postoperative stage, development of the distant recurrence, the localization of the distant recurrence, the length of stay in the intensive care unit, the total length of stay in the intensive care unit and the duration of the distant recurrence.

It is obvious that surgical resection is a treatment method being more effective compared to other treatment forms. The patients of Stage III constitute the most critical patient group for the resection decision. The treatment should be planned by assessing the situation of the primary lymphatic nodes and it should be selective in the decision of resection in this patient group. There are many surgical series reporting results being much different from each other in the treatment of the N2 stage IIIa patients [7]. For fifty-seven patients with NSCLC diagnosis that we have studied, the mean survival duration was found as 29.6 months and the three-year survival ratio was

found as 82.5%. When we compared our mean survival values, we revealed that these values were higher. We suggest that this is due to the inclusion of the patients who underwent complete resection.

Pulmonary carcinoma is seen particularly in the fifth and sixth decades of the life and the number of cases seen under thirty-five years old is quite small [8]. In our study, the mean age of fifty-seven patients was 59.7 years. No statistically significant difference was found between age and recurrence.

The male/female ratio of our patients was 7.1/1. In other studies, performed in our country, this ratio was found as 3.5 to 9.5/1 [9]. The reason why the number of our female patients is lower can be explained by the fact that smoking is not common in our country.

In the literature, there are many studies showing that the prognosis is better in males compared to females. In a meta-analysis of 2531 patients performed by Albain et al. [10], they have reported that the survival in males was shorter. In our study also, three-year mortality was found as negative in all of the female patients that is consistent with the literature and no recurrence was seen in six of the seven female patients (85.7%). In our results, there was no statistically significant difference between recurrence and gender.

In many studies, it is reported that there is no significant difference between the histologic type and the survival [11]. Tanaka et al. [12] report that cell type is not influential on survival in T1-2N1M0 cases with NSCLC in which resection was performed. Fang et al. [13] have reported in their study, that neither resection type nor histologic type has any significant effect on survival. While the most common histologic type was adenocarcinoma in patients who developed distant recurrence, no carcinoma tumor was seen. In our study, when all stages were studied, the effect of the cell type on survival could not be shown.

The presence of tumors with a diameter larger than three centimeters is interpreted as the poor prognosis. In the literature, in a study conducted by Vansteenkisre JF et al. [14], with one hundred twenty-five cases it was shown that the survival is longer in a patient with NSCLC in which tumor diameter was less than three centimeters. In our study, tumor diameter was studied in both computerized tomography and pathologically and no statistically significant difference was detected between both parameters and the recurrence. Despite this, the differences between both parameters and gender, clinical stage and mortality (for three years) were statistically significant.

There is a relationship between the distant recurrence and advanced T and N stage. The incidence of distant metastasis increases in those with N2 disease [15]. N1 positiveness was detected in eight of our thirty-seven cases and N2 positiveness was detected in three of them. Both N1 and N2 involvements were lower in our patients in which distant recurrence was detected. However, the difference between N1 and N2 involvement and the recurrence was not significant.

In our study, in patients who did not developed local recurrence and in those who developed distant recurrence, while the least commonly seen stage was Stage III, the most commonly seen stage was Stage I. In the patients who developed distant recurrence, while the least commonly seen stage was Stage II, the most commonly seen stage was found as Stage III, but no statistically significant difference was detected. When we investigated the relationship between the mortality time (post-operative months) and the clinical stage, it was seen that the risk of losing a patient in an earlier period increases as the

stage rises. This demonstrates us that the tumor stage is an important factor in terms of mortality time. Again in our study, the differences between the tumor diameter in CT, pathological tumor diameter, mediastinal LAP SUV-max in PET-CT, hilar LAP SUV-max in PET-CT, the presence of hilar LAP larger than one centimeter in computerized tomography were detected as statistically significant in the comparison of the clinical stage with other parameters. In the comparison of other parameters, no statistically significant difference was detected.

When the diagnosis is established for the patients with NSCLC, distant organ metastasis is detected in forty percent (40%) of them. The most common extra-thoracic metastatic regions were found as follows: brain (43%), adrenal glands (40%), liver (40%), bone (33%), kidneys (23%) and abdominal lymphatic nodes (30%) [16]. In our study also, the organ in which metastasis was detected most commonly was brain that is consistent with the literature. However, we could not detect a statistically significant difference between the distant recurrence and the organ where the metastases took place.

Complications concerning the cardiovascular system are the main complications that can be encountered after the surgery of pulmonary carcinoma. Arrhythmia, myocardial infarction (MI) and cardiac failure are the most commonly observed complications. Arrhythmia is developed depending on the width of the resection, on the patient age, and particularly on the intrapericardial pneumonectomy procedures [17]. While the most commonly seen complication was arrhythmia in patients who developed distant recurrence, neither prolonged air leakage nor wound site infection was seen. In our study, we could not detect any relationship between the recurrence and the complications. Like in any work, there are some limitations in our study such as a small number of patients, gender inequality, because of the retrospective nature of the research. This might have led to selection bias.

### Conclusion

In our study, we detected that the most important prognostic factors affecting the three-year survival were differentiation, post-operative pathological stage, the development of distant recurrence, the localization of distant recurrence, time of post-operative distant recurrence, the length of stay in the intensive care unit, the total length of stay. These prognostic factors that we have detected should be evaluated in all patients after the surgery.

We found that the presence of the hilar lymphatic node larger than one centimeter in CT is the most important parameter in the development of distant recurrence. As a result, our study in which many parameters were assessed reveals the importance of the detection of the parameters leading to distant recurrence and their prevention besides the treatment regimens of pulmonary carcinoma. The assessment of mediastinal and hilar lymphatic nodes in detail by means of radiological examinations before the surgery and absolutely histopathologically in case of suspicion plays a vital role. Furthermore, we suggest that the additional systemic dissection of the mediastinal lymphatic node is obligatory in the prevention of the distant recurrence.

### Scientific Responsibility Statement

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of*

*the preparation and scientific review of the contents and approval of the final version of the article.*

#### **Animal and human rights statement**

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

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#### **Conflict of interest**

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