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Prognostic markers in operated non-small cell lung cancer patients

Salih Cirik[a,*], Hakan Harputluoglu[b]

[a] *Konya City Hospital, Department of Hematology, Konya, Türkiye*
[b] *Inonu University, Faculty of Medicine, Department of Medical Oncology, Malatya, Türkiye*

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Abstract

Aim: The overall survival (OS) of operable lung cancer patients is directly related to clinicopathological features and some laboratory parameters. In this study, we aimed to examine the factors affecting the survival of the operated patients.

Materials and Methods: In our study, we retrospectively analyzed 202 operated-on patients diagnosed with lung carcinoma who were in stages I–IIIA at the time of diagnosis. The clinico-pathological features and some laboratory parameters of the patients included in our study were retrospectively analyzed. The effects of those parameters on the overall survival of the patients and their disease-free survival (DFS) have been investigated.

Results: The age of the patient at the time of diagnosis and the presence of lymphovascular invasion (LVI) were found to be statistically significant in terms of OS ($p<0.05$). Pathological tumor size, LVI, and peri-neural invasion (PNI) parameters were statistically significant for DFS. In addition, neutrophil-lymphocyte ratio (NLR), which is an inflammatory indicator, is an important parameter with statistical significance in terms of both OS and DFS ($p<0.05$).

Conclusion: Our study yielded that LVI and PNI parameters would be beneficial to estimate patients' survival and prognosis. In addition, NLR was observed to have a statistically significant effect on OS and DFS.

Introduction

Globally, lung cancer remains the most common cause of cancer-related deaths, with an estimated 2.1 million new lung cancer diagnoses and 1.8 million deaths in 2018, accounting for approximately one in five deaths and 18.4% of total cancer incidence and cancer-related deaths. Lung cancer was found to be the most frequently diagnosed cancer without sex differentiation (11.6% of total cases). Lung cancer is the most common cancer in men and the most common cause of cancer-related deaths. Breast cancer is the most common cancer diagnosed in women and the most common cause of cancer-related death in women, followed by colorectal cancer and lung cancer in terms of incidence, while lung cancer is the second most common in terms of mortality [1].

Smoking is the best-known etiological factor for lung cancer. The International Cancer Research Center (ICRC) defined at least 50 carcinogens in the smoke fume [2].

Although there is no dominant causative factor that can fully define lung cancer in non-smokers, significant risk factors include environmental exposures such as passive smoking, exposure to radon, air pollution, asbestos or arsenic, as well as a history of lung disease and genetic factors [3].

Lung cancer is generally divided into two main groups, NSCLC (80%) and SCLC (20%). The main types of SCLC include adenocarcinoma (AC), squamous cell carcinoma (SqCC) and large cell carcinoma (LCC) [4,5].

Staging in lung carcinoma

In the staging of lung cancer, the international TNM (primary tumor invasion, local lymph node involvement, intrathoracic or distant metastasis) staging method is employed. The TNM staging method includes prognosis determination, treatment planning, treatment result evaluation, and standard data exchange between different centers. The International Lung Cancer Staging Committee, for this purpose, updated the 6th version of the TNM staging published in 2005 for this purpose in 2009 and published the same in July 2010 as the 7th version [4].

*Corresponding author:
Email address: salihcirik@hotmail.com (Salih Cirik)

Treatment of lung carcinoma

The treatment targets for NSCLC patients depend on the stage of the disease. While for the patients suffering stage 1-3 disease, the purpose is curative treatment, it becomes mitigating symptoms and extending life for the ones suffering stage 4.

Treatment in Stage 1, Stage 2, and Stage 3A

Surgical treatment

Approximately 25% of NSCLC patients receive a stage 1 or 2 diagnosis. The primary curative method is, along with mediastinal lymph node sampling or dissection, surgical resection employing lobectomy or pneumonectomy. In a randomized study, such sublobar resections as wedge resection or segmentectomy had a local recurrence rate higher than lobectomy, while the 5-year survival rate was found to be low [5]. Prospective, non-randomized studies claim that resections limited to patients with small tumors would yield the same results as lobectomy, particularly in older patients and those with limited lung functions [6].

Non-Surgical Treatment

Traditional radiotherapy

Some NSCLC patients in stage 1 or 2 are not candidates for surgical resection, particularly due to impaired lung function. In such cases, the standard of care is radiation therapy (RT) on the primary tumor and related lymph nodes. In a clinical study carried out by randomizing NSCLC patients at various RT doses, the total 60 Gy radiation dose applied in 2 Gy per day fractions for 6 weeks provided the best results in local control and 2-year survival rates [7].

Adjuvant therapy

Distant recurrence is the primary cause of death for NSCLC patients who pass away within 5 years after a full surgical resection. Because of this, non-identified micrometastases continue to be a common problem, though cancer seems to be limited to the lungs. Randomized clinical studies provided a final survival rate of 5 to 15% at the 5-year survival rate for stage 2 and stage 3 NSCLC patients who receive adjuvant platinum-based chemotherapy following full surgical resection [8].

Materials and Methods

The files of 202 patients who applied to Inonu University Turgut Ozal Medical Center Medical Oncology Department Clinics and were operated on and diagnosed to have lung carcinoma between January 1, 2009, and January 1, 2018, were evaluated retrospectively in line with the Helsinki Declaration resolutions, patient rights regulations, and ethical rules after receiving Clinical Research Ethical Board approval (Approval No. 2017/23). All eligible patients who fulfill the lung cancer diagnosis with the stage 1, 2, 3A and operated according to their diagnosis criteria was included. Relevant data were collected retrospectively from the hospital's electronic database, hospital automation system, and patient clinic files. A study form was formed in an effort to record patient data. Ages and sexes of the patients, the site of pathological tumor, the number of extracted and positive lymph nodes, the histopathological sub-type and grade of the tumor, the imaging system used to show the lymphovascular invasion (LVI) and perineural invasion (PNI), the period of smoking, the type of operation performed, the tumor's anatomic localization, the total number of leucocytes at the start of treatment (WBC), hemoglobin (HGB), neutrophil (NE), lymphocyte (LY), monocyte (MO), platelets (PLT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, glucose (GLU), creatinine, sodium, potassium, calcium, and C-reactive protein (CRP) levels were evaluated. The influence of those parameters on the OS and DFS of the patients was evaluated. A total of 202 patients, of whom 179 (88.6%) are male and 23 (11.4%) female, with an average age of 61.43 ± 9.26, the youngest being 23 and the oldest being 81, were included in the study. Our study was carried out retrospectively, and no invasive procedure was performed on the patients.

The criteria for inclusion in the study

1. The patients must be older than 18 years old;
2. They must have received a lung histopathological lung cancer diagnosis between January 1, 2009, and January 1, 2018;
3. Their follow-up must have been conducted in our center;
4. Early stage at the time of diagnosis (stage 1A, stage 1B, stage 2A, stage 2B, and stage 3A);
5. The patients must have been operated on for lung cancer treatment.

Exclusion criteria

1. There is a secondary solid organ malignity;
2. Severe coronary failure, which could affect mortality at the time of diagnosis;
3. Pathologically benign lung tumor.

Patient staging was carried out in line with the pathology result of the tissue extracted according to the imaging methods at the time of diagnosis and surgery. The International Association for the Study of Lung Cancer (IASLC) being the valid staging system for lung cancer, the 2009 TNM 7th Version was used, while the staging for the patients of 2017 and later was performed as per JNCC 8. The ages of the patients at the time of diagnosis were recorded. As the date of diagnosis, the date of operation was considered. The tumor size was taken into account according to the maximum diameter of the primary tumor as per the PET-CT or CT result at the time of diagnosis and the pathology report. Tumor location was divided into 5 sub-groups according to the primary tumor's location: upper right lobe, middle right lobe, lower right lobe, upper left lobe, and lower left lobe. Tumor sub-types were analyzed in six groups using the data acquired from hospital automation systems or registered patient files, namely, SqCC, AC, large cell carcinoma, bronchoalveolar carcinoma, small cell carcinoma, and other sub-types. The tumors were graded as well differentiated, medium differentiated, and poorly differentiated. Patients' status as alive or deceased was controlled by the Central Civil Records

System (MERNIS), which scanned their Turkish ID numbers. The smoking period of the patients was calculated in packs per year. DFS was determined by calculating the period of time from diagnosis until recurrence. OS was determined by calculating the period of time in months from the date of diagnosis until the date of the patient's passing away.

Statistical analysis

Data were presented as mean (± standard deviation) and number (percentage). The distribution of the data was tested using appropriate statistical methods. The Kolmogorov-Smirnov test was used to test for normality. Mann-Whitney U test, Pearson chi-square test, Spearmen's correlation coefficient, and within-group correlation coefficient were appropriately used in the statistical analyses. After these analyses, progression-free survival and overall survival were calculated to determine the effect of surgery, surgery type, disease stage, tumour type and other variations on survival time. Kaplan-Meier survival analysis was performed, and p 0.05 was considered statistically significant. IBM SPSS Statistics 22.0 software was used for analyses.

Results

A total of 202 patients, of whom 179 (88.6%) were male and 23 (11.4%) females, were included in the study. The ages of the patients attending the study were between 23 and 81, while the average age of the entire group was 61.43±9.26 years. While the age average of the male patients was 61.75±9.08 that of the female patients was 58.87±10.43. The patients were grouped into 2 groups: 60 years or younger (1st group) and 61 years or older (2nd group). In the survival analysis thereafter, the OS in the 1st group was 69.54±5.41 months, and the figure in the 2nd group was found to be 56.88±4.57 months. When they were divided into two groups and analyzed, age was statistically significant for the OS ($p<0.05$). The greater the age at the time of diagnosis, the lesser the OS ($p = 0.037$). The age, however, was found not to have a statistically significant effect on the DFS in the survival analysis ($p>0.05$).

In our study, 122 (66.3%) out of the 202 patients were alive, and 80 (39.7%) had passed away. The OS parameter was calculated considering the number of deceased patients. As per the survival analysis, the OS was found to be 63.30±5.51 months. With regard to sex, while the OS in male patients was 58.52±3.29 months, the same in females was found to be 77.58±10.49 months. While the OS in the recurrence patients was 38.32±4.21 months, it was 76.54±4.39 months among the non-recurrence patients. As a recurrence was observed in the follow-up of 55 (27.2%) patients, the DFS parameter was obtained from them. Accordingly, the DFS of the patients taking part in the study was found to be 33.80±2.25 months.

The patients were analyzed in five different groups: right lung upper, right lung middle, right lung lower, left lung upper, and left lung lower lobe. 58 patients (28.7%) were in the left lung upper lobe, 46 (22.8%) in the right lung upper lobe, 44 (21.8%) in the right lung lower lobe, 40 (19.8%) in the left lung lower lobe, and 14 (6.9%) in the right lung middle lobe group. In the survival analysis, it was observed that tumor localization did not have a statistically significant effect on survival ($p > 0.05$).

Table 1. Patient demographics and clinical characteristics.

	Number of Patients (n: 202)	(%)
Sex		
Male	179	88.6
Female	23	11.4
Age, Years		
Median	61	
Range	23-81	
ECOG		
0	71	35.2
1	91	45
2	42	20.8
Status		
Death	80	39.7
Alive	122	60.3
Tumor Location		
Right Upper	46	22.7
Right Middle	14	6.9
Right Lower	44	21.8
Left Upper	58	28.8
Left Lower	40	19.8
Type of Operations		
Lobectomy	125	61.9
Pneumonectomy	37	18.3
Wedge resection	20	9.9
Other	20	9.9
Tumor Dimensions(mm)		
Man	46.27±27.58	
Women	32.30±18.69	
Total	44.68±27.05	
Pathological Subtype		
Adenocarcinoma	90	40.55
Squamous cell carcinoma	81	40.11
Not other specified	31	15.34

With regard to the types of operations administered to the patients, 125 (61.9%) had lobectomy, 37 (18.3%) had pneumonectomy, 20 (9.9%) had wedge resection, and 20 (9.9%) had other operations. It was observed that the type of operation did not have a significant effect on OS and DFS in the survival analysis ($p > 0.05$).

The average pathological tumor size of the patients included in the study was 44.68±27.05 mm, with a median value of 40 (2-170) mm. The average pathological tumor size in the male patients was 46.27±27.58 mm, with a median value of 45 (2-170) mm. In female patients, the average pathological tumor size was 32.30±18.69 mm, with

Table 2. Relationship of OS and PFS with NLR, LVI and PNI.

	Number of patients (n = 202)	PFS months (Range)	p value	OS months (Range)	p value
NLR					
<4	149	34.23±2.24	**p<0.05**	68.30±8.43	**p<0.05**
≥4	53	14.45±3.34		29.60±13.22	
LVI					
Positive	100	24.16±5.36	**p<0.05**	51.72±4.53	**p<0.05**
Negative	102	36.57±4.42		70.71±4.76	
PNI					
Positive	56	23.10±5.37	**p<0.05**	49.42±5.31	p>0.05
Negative	146	33.97±4.02		66.18±4.16	

a median value of 27 (4–80) mm. In the survival analysis carried out as the patients were grouped with regard to pathological tumor size from 0 to 40 mm (1st group) and 41 mm and over (2nd group), there is a statistically significant relation between pathological tumor size and DFS, while the DFS period decreased as the size of the pathological tumor increased ($p = 0.034$). The pathological tumor size, however, did not have a statistically significant impact on the OS ($p>0.05$).

A significant relationship was found between pathologic tumor size and total extracted lymph nodes ($p<0.05$), the correlation value was $R = 0.269$ at a low association. Again, a significant relation was found between the pathological tumor size and the existence of a positive lymph node ($p<0.05$), with the correlation value being $R = 0.398$, revealing a low-level relation. While a statistically significant relation was found between the pathological tumor size and LVI ($p<0.05$), no statistically significant relation was observed between PNI ($p > 0.05$). It was observed that the DFS period dropped with statistical significance in the presence of a positive lymph node ($p<0.05$). It was, however, found that the existence of a positive lymph node did not have a significant effect on OS ($p > 0.05$).

Out of the patients included in the study, 125 (61.9%) were diagnosed by BT, and 77 (38.1%) were diagnosed using PET-CT. In the patients who are diagnosed by using CT, a significant ($p<0.05$) and very strong relationship was found between the imaging size and pathological tumor size, with a correlation value of $R = 0.915$. In the patients diagnosed by using PET-CT, a significant ($p<0.05$) and very strong relationship was observed between imaging size and pathological tumor size, with a correlation value of $R = 0.892$. A very strong relationship for the in-grade correlation between CT and PET-CT in determining the imaging size, with a correlation value of $R = 0.958$. Both methods were observed to have equal sensitivity in determining the lesion size.

Of the patients, 107 (53%) received chemotherapy, while 95 (47%) received no chemotherapy. 35 patients (17.3%) received 1st-stage chemotherapy, 17 (8.4%) received 2nd-stage chemotherapy, and 6 (3%) received 3rd-stage chemotherapy. Of the patients who were administered adjuvant chemotherapy, 67 (33.2%) received Vinorelbine plus Cisplatin, 15 (7.4%) Gemcitabine plus Cisplatin, 12 (5.9%) Paclitaxel plus Carboplatin, 3 (1.5%) Docetaxel plus Cisplatin, 3 (1.5%) Vinorelbine plus Carboplatin, 2 (1%) Etoposide plus Cisplatin, 2 (1%) Cisplatin, 2 (1%) Gemcitabine, and 1 (0.5%) Gemcitabine plus Carboplatin treatment. It was observed that the type of adjuvant chemotherapy did not have a statistically significant effect on OS and DFS ($p > 0.05$). Since there is insufficient data for the 1st, 2nd, and 3rd-stage chemotherapy patients, no survival analysis was carried out for them.

Out of the patients attending the study 90 (44.5%) had SqCC, 81 had AC, and 31 (15.34%) had other histopathologic subtypes. The patients were divided into 3 groups: 1st group SqCC carcinoma, 2nd group AC, and 3rd group all other subtypes. In the DFS analysis, it was found that in the AC group, the DFS period increased significantly in comparison to other groups (p 0.05). It was, however, observed that the histopathological subtype had no statistically significant effect on the OS ($p > 0.05$). While the most common tumor subtype in males is SqCC with 88 patients (49.2%), the most common tumor subtype in females is AC with 18 patients (78.3%). The Pearson chi-square test revealed that sex was significant in determining tumor subtype ($p<0.05$). While a relationship between the tumor subtype and LVI was observed ($p<0.05$), no relationship was found between it and PNI ($p > 0.05$). Also, no association was observed between tumor subtype and smoking ($p<0.05$)

From the patients attending the study, the smokers or former smokers consumed 38.75±31.03 packs per year, with a median value of 36 (0–200) packs per year. Male patients consumed 40.82±31.85 packs/year at a median value of 40 (0–200), and females consumed 22.61±16.75 packs/year at a median of 30 (0–45). The analysis showed that the smoking period did not have a statistically significant effect on OS and DFS ($p>0.05$). In a very small part of the biopsy results of the patients included in the study (21/202), the grade parameter was analyzed. Since there is insufficient data, that parameter was not included in the statistical study in the survival analysis.

Demographic data and clinical characteristics of the patients are shown in Table 1. With the existence of LVI, both OS and DFS periods decreased with statistical significance ($p<0.05$). When LVI was positive, the OS period was 51.72±4.53 months, while it was 70.71±4.76 when it

was negative. In the absence of PNI, the DFS period was found to drop with statistical significance ($p<0.05$). But PNI's existence did not have a statistically significant effect on the OS ($p > 0.05$).

When the patients were staged according to IASLC 2009 TNM 7th Edition, stage 1A contained 53 patients (26.2%), stage 1B contained 36 (17.8%), stage 2A contained 70 (34.7%), stage 2B contained 34 (16.8%), and stage 3A contained 9 (4.5%). In the survival analysis performed according to the stages, the median value of the OS was 31.66 (0.03-93.37) months, stage 1B 23.69 (0.17-108.40) months, stage 2A 27.29 (0.43-96.47) months, stage 2B 29.53 (0.37-89.73) months, and stage 3A 19.30 (2.40-57.87) months. In the study, it was observed that the stage did not have a statistically significant effect on OS or DFS ($p > 0.05$).

We grouped our cases with regard to NLR and investigated its effect on survival. Considering the cut-off value as 4.0, we grouped the ones up to 4 (1st group) and the ones equal to or over 4 (2nd group). 1st group: Of the patients, 107 (53%) received chemotherapy, while 95 (47%) received no chemotherapy. 35 patients (17.3%) received 1st-stage chemotherapy, 17 (8.4%) received 2nd-stage chemotherapy, and 6 (3%) received 3rd-stage chemotherapy. Of the patients who were administered adjuvant chemotherapy, 67 (33.2%) received vinorelbine plus cisplatin; 15 (7.4%) received gemcitabine plus cisplatin; 12 (5.9%) received paclitaxel plus carboplatin; 3 (1.5%) received docetaxel plus cisplatin; and 3 (1.5%) received docetaxel plus cisplatin. Vinorelbine plus carboplatin, 2 (1%) etoposide plus cisplatin, 2 (1%) cisplatin, 2 (1%) gemcitabine, and 1 (0.5%) gemcitabine plus carboplatin treatment. It was observed that the type of adjuvant chemotherapy did not have a statistically significant effect on OS and DFS ($p > 0.05$). Since there is insufficient data for the 1st, 2nd, and 3rd-stage chemotherapy patients, no survival analysis was carried out for them.

Out of the patients attending the study 90 (44.5%) had SqCC, 81 had AC, and 31 (15.34%) had other histopathologic subtypes. The patients were divided into 3 groups: 1st group SqCC carcinoma, 2nd group AC, and 3rd group all other subtypes. In the DFS analysis, it was found that in the AC group, the DFS period increased significantly in comparison to other groups ($p<0.05$). It was, however, observed that the histopathological subtype had no statistically significant effect on the OS ($p > 0.05$). While the most common tumor subtype in males is SqCC with 88 patients (49.2%), the most common tumor subtype in females is AC with 18 patients (78.3%). The Pearson chi-square test revealed that sex was significant in determining tumor subtype ($p<0.05$). While a relationship between the tumor subtype and LVI was observed ($p<0.05$), no relationship was found between it and PNI ($p > 0.05$). Also, no association was observed between tumor subtype and smoking (p 0.05); the first group contained 149 (73.8%), and the second group contained 53 (26.2%) patients. OS in the 1st group was 68.30± 8.43 months, while in the 2nd group it was 29.60±13.22 months. In the study, it was observed that NLR had a statistically significant effect on OS or DFS ($p<0.05$). The higher the NLR at the time of diagnosis, the lower were both OS and DFS significantly ($p<0.05$). The relationship of OS and PFS with NLR, LVI, and PNI is shown in Table 2. WBC, HGB, NE, LY, MO, PLT, AST, ALT, total protein, albumin, GLU, creatinin, sodium, potassium, calcium, and CRP parameters of the patients at the beginning of the treatment were not found to have a statistically significant effect on OS or DFS ($p>0.05$).

Discussion

Lung carcinomas are caused by respiratory tract epithelia and pulmonary parenchyma. They are divided into two groups, namely NSCLC and SCLC. At the time of diagnosis, only 15% of the patients are detected at an early stage of the disease. In spite of improvements in surgery and new chemotherapeutic agents, not much development has been realized in prognosis and survival in the last 20 years [1]. In our study involving early-stage 202 patients who were operated on and received lung cancer diagnosis, we investigated the relation between age, sex stage, pathological subtype, tumor's grade class, imaging system used for diagnosis, recurrence, type of operation, tumor's anatomic localization, chemotherapy employed in the treatment, smoking history, and OS or DFS.

In a single-centered study carried out by Kefeli et al. [9] in 2015, 1031 patients participated. The patients were divided into 2 groups: 60 years old or younger (1st group) and over 60 years old (2nd group). The OS among the patients over 60 years old was lower in a statistically significant manner (p 0.05). As per the survival analysis in our study, the patients were grouped into 2 groups: 60 years or younger (1st group) and over 60 years (2nd group). The OS in the 1st group was 69.54±5.41 months; it was 56.88±4.57 months in the 2nd group. The age was found to be statistically significant for OS ($p<0.05$). In accordance with the literature, the higher the age at the time of diagnosis in our study, the lower the OS dropped in a statistically significant manner ($p = 0.037$). However, in our study, it was observed that age did not have a statistically significant effect on DFS ($p>0.05$).

In a study carried out by Kacan et al., the relationship between the patients' Hgb and LDH levels and survival was investigated. While Hgb level did not have any relation with survival, considering the cut-off as per the LDH 246 U/L, in the group with a higher LDH ($n = 21$), total survival in comparison to the lower LDH group ($n = 37$) was found to be shorter, which was statistically significant ($p<0.05$) [12]. In our study, however, it was shown that the patients' Hgb and LDH levels were not statistically related to both OS and DFS ($p>0.05$). We think that this is caused by an insufficient number of patients or patient distribution. Determination of thrombocytosis as a bad prognostic factor implies the release of tumor-related interleukin and other cytokines. Furthermore, in the presence of thrombocytosis, the mediators directly secreted from the thrombocytes could cause metastasis or tumor invasion. 510 patients who received an NSCLC diagnosis between 2006 and 2009 without prior treatment were evaluated in a prospective study performed by Yu et al. The PLT cut-off value was taken as 300 x 10^3/µL while the median DFS period was 34 months for the patients with PLT < 300 x 10^3/µL, it was 27.4 months in the group with PLT > 300 x 10^3/µL, which was found to

be statistically significant. However, no correlation was found between the patients' PLT value, age, sex, smoking history, tumor histopathology, or grade [13]. In our study, a 400 x 10^3/µL cut-off value was taken for PLT. When the group with PLT < 400 x 10^3/µL is compared to the PLT ≥ 400 x 10^3/µL group, it was shown to have no statistical relation with total survival or DFS parameters (p>0.05). The reason for this, we believe, is an insufficient number of patients or patient distribution. New and more detailed studies are necessary in this matter.

AC is the most frequent lung cancer, responsible for 40% of lung cancers, 60% of NSCLC, and 70% of surgically resected cases [5, 14]. In developing countries, including Turkey, SqCC is the most common histopathological type of primary lung cancer. In Turkey, however, the number of SqCC diagnoses decreases every day while the number of AC diagnoses increases. In our study, 90 patients (44.55%) had SqCC, 81 (40.5%) had AC, and 31 (15.34%) had other histopathological sub-types. It is known from previous studies that there is no statistically significant difference between the OS and DFS of patients evaluated according to histopathological subtypes [15, 16]. In our study, as per the DFS analysis where the patients were divided according to histopathological subtype as 1st group SqCC, 2nd group AC, and 3rd group other sub-types, the DFS period dropped significantly in the AC group in comparison to others (p<0.05). However, between the tumor subtype and OS, no statistically significant relationship was found (p>0.05).

In our study, when the patients were staged according to IASLC 2009 TNM 7th Edition, stage 1A contained 53 patients (26.2%), stage 1B contained 36 (17.8%), stage 2A contained 70 (34.7%), stage 2B contained 34 (16.8%), and stage 3A contained 9 (4.5%) patients. In the survival analysis carried out according to stages, the median value of the OS was 31.66 (0.03-93.37) months, stage 1B patients 23.69 (0.17-108.40) months, stage 2A patients 27.29 (0.43-96.47) months, stage 2B patients 29.53 (0.37-89.73) months, and stage 3A patients 19.30 (2.40-57.87) months. In the study, it was observed that stage did not have a statistically significant effect on OS and DFS (p>0.05).

In our study, the patients were evaluated in 5 groups: right lung upper, right lung central, right lung lower, left lung upper, and left lung lower lobes. Likewise, in our study, 58 patients (28.7%) were in the left lung upper lobe, 46 (22.8%) were in the right lung upper lobe, 44 (21.8%) in the right lung lower lobe, 40 (19.8%) in the left lung lower lobe, and 14 (6.9%) in the right lung central lobe. It was observed that the tumor localization did not have a statistically significant effect on the OS or DFS (p>0.05). In our study, the average smoking quantity of the smokers or former smokers was 38.75±31.03 packs, and their median value was 36 (0–100) packs/year. The smoking period of the male patients was 40.82±31.85 packs per year, with a median value of 40 (0–200) packs per year; that of the female patients was 22.61±16.75 packs per year, with a median value of 30 (0–45). In the analysis carried out, the smoking period was found not to have a statistically significant effect on OS or DFS (p>0.05).

Associating the high WBC with the bad prognosis could either be infection or bone marrow retention in addition to the leukocytosis related to cytokines secreted by tumoral cells. Furthermore, it implies that the mediators released by leucocytes could increase, which would make tumor progression or metastasis easier. Hao et al. retrospectively evaluated the data of 208 patients who were operated on between 2010 and 2016 due to NSCLC and researched the effect of WBC number on OS and DFS. If the number of WBC determined after adjuvant chemotherapy is higher than 7x10^3/µL it was determined to be a bad predictive factor for DFS and OS (respectively, p = 0.05 and p <0.05) [14]. In a study performed by Tomita et al. [15] between 2000 and 2005, containing 289 NSCLC patients with surgical resection, the frequency of pre-surgery leukocytosis, anemia, and thrombocytosis was respectively 4.15% (12/289), 35.64% (103/289), and 9.34% (27/289). For leukocytosis, the cut-off value of 10 x 10^3/µL was taken, while the 5-year survival of the patients with and without leukocytosis was respectively determined as 25.0% and 69.17% (p<0.05). Similarly, the patients with anemia (13 g/dl in males and 12 g/dl in females) were shown to have a significantly worse prognosis than the patients without anemia. Their 5-year survival was determined to be respectively 50.10% and 76.84% (p<0.05). In the same study, with the existence of thrombocytosis (the ones larger than 320x10^3/µL), when the 5-year survival of the patients was compared with those without thrombocytosis, it was found to be 42.55% and 69.56%, respectively. Thrombocytosis is likewise observed to be a bad prognostic factor (p<0.05). In our study, WBC values were analyzed as lower than 11x10^3/µL (1st group) and above 11x10^3/µL (2nd group). When those groups were compared, no statistically significant difference was found between OS and DFS (p>0.05). We believe that this is caused by an insufficiency in the number of patients or patient distribution. Increasing cytological and biochemical studies on those issues will shed light on the issue.

As confirmed by the literature, the treatment methods preferred in the adjuvant treatment do not differ with statistical significance, nor are they superior to each other with regard to both OS and DFS. Their only difference is the side effect profile. In our study, no statistically significant difference was found between the effects of adjuvant chemotherapy methods in compliance with the literature (p>0.05).

The population demographics of lung cancer patients are evolving, while the number of older patients with many comorbidities attending surgical treatment is increasing. Furthermore, the diagnosis studies, surgical techniques, and management of those patients are improving gradually, which has caused an increase in survival in the last decade. Because of this, the OS data related to the patients who have undergone surgical intervention recently must be revised. The purpose of the study carried out by Moon et al. [16] is to perform an OS analysis between the two methods in NSCLC patients who were administered lobectomy or segmentectomy with a mass size of ≤ 2 cm. The patients were selected from the SEER program supported by the National Cancer Institute, which contains the epidemiological, pathological, and survival data of the entire cancer cases in 18 different regions throughout the USA since 1972. The Seer population is quite represented

with regard to geography, socio-economic status, race, ethnic origins, and age. 14549 patients out of the 15358 were subjected to lobectomy and 8092 to segmentectomy. After the analysis was carried out, the 5-year OS was 76% for the lobectomy group and 74.4% for the segmentectomy group. As proven statistically, there was no significant difference in general survival in the patients subjected to lobectomy versus segmentectomy. In our study, when the patients were classified according to the type of operation they underwent, 125 (61.9%) underwent lobectomy, 37 (18.3%) underwent pneumonectomy, 20 (9.9%) underwent wedge resection, and 20 (9.9%) were in the other operations group. We observed that the type of operation did not have a statistically significant effect on general and DFS in the survival analysis, consistent with the literature ($p > 0.05$).

Almost all cancers develop in the context of infections, chronic irritations, and inflammations. The most recent studies have proven that the systemic inflammatory response is a very important factor in the formation and spread of cancer. The cytokines whose release is stimulated due to inflammation impair DNA and increase angiogenesis and tumor invasion. Tumor cells secrete various chemokines that attract neutrophils, monocytes, and lymphocytes. In the first phases of tumor development, those cells provide an effect that stimulates growth and angiogenesis. Although the inflammatory response has an antitumor effect, that response has changed in people who develop cancer [17]. The studies showed in a statistically significant manner that when NLR has been impaired in favor of neutrophils, this would be a bad diagnostic factor with regard to survival. Leucocytes and mediators, as well as lymphocytes and cytokines, are released, which are considered to be key factors for the concepts of tumor growth, invasion, and metastasis, are known, and make us think about the treatment protocol formats in the future, not to mention that it confirms the NLR value's being an important parameter for survival.

In the study carried out by Scilla et al. between 2000 and 2010, on 276 patients who received NSCLC diagnoses, the cut-off value for NLR was taken as 5. Accordingly, while the general survival was 26 months in the NLR<5 group, it was found to be 11 months in the NLR≥ 5 group ($p<0.05$). In this study, it was verified that the NLR value measured at the time of diagnosis and the general survival were reversely related [18]. In the analysis carried out between 2011 and 2015 by Merrigi et al., covering 5 centers and 63 patients with NSCLC whose mutation in EGFR was positive, the relation between NLR and survival was studied. The NLR value was obtained by dividing the proportion of the absolute neutrophil and absolute lymphocyte numbers in the blood panel. The average NLR value was found to be 3.5, and the cut-off value accordingly was 3.5. The patients with a NLR<3.5 were taken as the 1st group, where there were 40 patients, while the ones with a NLR≥3.5 were considered the 2nd group, where 23 patients were covered. In the 1st group, the general survival average was 21 months, compared to 8.3 months in the 2nd group, which was found to be statistically significant ($p=0.013$). With regard to DFS, the average time in the first group was 12 months, which was 6.5 months in the second group and was statistically significant ($p = 0.025$) [19].

In the study carried out by Zhang et al. between 2013 and 2015, where the clinical data on the NSCLC patients were retrospectively analyzed, covering 127 patients with positive EGFR mutations, the effects of NLR and lymphocyte/monocyte ratio on the general and DFS of the patients who were treated using epithelial growth factor-tyrosine kinase inhibitor (EGFR-TKI) were evaluated. A statistically significant relationship was found between DFS, OS, and NLR (p 0.05). The NLR cut-off value was taken as 2.9. In patients with NLR≤2.9, general survival was determined to be 32.6 months; the same was 20.9 months for patients with NLR>2.9. In the patients with an NLR smaller than 2.9, the DFS was 17.7 months, compared to 10.6 months for those with an NLR > 2.9. No significant relationship was found between the lymphocyte/monocyte ratio and either DFS or OS [20].

In our study conducted in the center, the cut-off value for the NLR rate has been determined as 4. Current neutrophil and lymphocyte numbers were obtained from hemogram test results and rated. We grouped our cases with regard to NLR and researched their effect on survival. Considering the cut-off value as 4.0 and assessing the ones up to 4 (1st group) and the ones equal to or higher than 4 (2nd group), the 1st group included 149 (73.8%) and the 2nd group included 53 (26.2%) patients. While the general survival in the 1st group was 68.30±8.43, months, it was 29.60±13.22 months in the 2nd group. In the study carried out, NLR was observed to have a statistically significant effect on general survival and DFS ($p<0.05$). As the NLR at the time of diagnosis increased, general survival was found to reduce significantly ($p<0.05$).

Conclusion

Lung cancer is a very serious global public health problem, as it is the most frequent cause of death throughout the world. As seen in our study, smoking history is the most important and avoidable etiological reason.

In our study, it was observed that the parameters NLR and LVI had a statistically significant effect on general survival. NLR, LVI, PNI, pathological tumor size, histopathological subtype, and existence of positive lymph node parameters were found to be statistically significant for a DFS. These parameters were considered beneficial in estimating survival and prognosis if their stated cut-off values were employed.

Today, much more up-to-date markers, such as NLR, are required in estimating prognosis and survival. Routinely performed laboratory analyses could, in fact, be predictive for the evaluation of treatment response due to their showing anti-tumor immunity and systemic inflammatory response. We believe that in the coming years, routine utilization of this or similar parameters through guides could come onto our agenda.

Ethical approval

This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the local Institutional Review Board (Inonu University Clinical Research Ethics Committee, Approval No: 2017/23).

Disclosure

This paper is based on the internal medicine specialty thesis of SC.

Conflict of interest

None declared.

Authorship contributions

Concept –S.C, H.H.; Design – S.C, H.H; Supervision – S.C, H.H.; Materials – S.C.; Data collection &/or processing S.C.; Analysis and/or interpretation – S.C.; Literature search – S.C.; Writing – S.C.; Critical review – S.C, H.H.

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