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Overall survival of patients with non-small cell lung cancer after surgery treatment

Ukupno preživljavanje bolesnika sa nesitnoćelijskim karcinomom pluća nakon hirurškog lečenja

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Abstract

Background/Aim. Lung cancer is one of the most common malignant tumors. About 80% of all lung cancers are non-small cell lung cancer (NSCLC). According to histopathological characteristics, the most common types of NSCLC are squamous cell carcinoma and adenocarcinoma. The aim of this study was to evaluate the overall survival rate in the NSCLC patients initially received surgery according to its histopathological type and T – primary tumor, N –regional lymph nodes, M – distant metastasis (TNM) stages which were treated with surgical treatment, and after that, according to the TNM stage, chemotherapy protocols and/or radiation therapy. **Methods.** This retrospective case series study included all patients with NSCLC admitted to the Military Medical Academy in Belgrade in the period 2010–2015. A total number of selected patients was 85 (27 females and 58 males). **Results.** Out of 41 patients with squamous cell carcinoma, 19.5% deceased. On the other hand, in the group of patients with adenocarcinoma, 43.2% out of 44 patients deceased. The average cumulative survival was statistically significantly lower in the adenocarcinoma patients in comparison to the patients with squamous cell carcinoma (1,605.2 vs.1,304.8 days; $p = 0.005$). On the other hand, the average cumulative survival was statistically significantly lower in our patients in the recurrence group with adenocarcinoma in comparison to the recurrence group with squamous cell carcinoma (1,212.8 vs. 1,835.5 days; $p = 0.032$). **Conclusion.** Adenocarcinoma is more aggressive cancer in comparing to squamous cell carcinoma with lower overall survival in comparing to squamous cell carcinoma. Additional studies are needed to identify risk factors for recurrence after surgery, and to additionally explain role of tumor markers and molecular biological techniques in the progression of this kind of cancer.

Key words:
carcinoma, non-small-cell lung; adenocarcinoma; squamous cell carcinoma; survival; recurrence.

Apstrakt

Uvod/Cilj. Karcinom pluća je jedan od najčešćih malignih tumora. Oko 80% karcinoma pluća jeste nesitnoćelijski karcinom pluća (NSCLC). Na osnovu patohistoloških karakteristika, najčešći tipovi NSCLC su skvamocelularni karcinom i adenokarcinom. Cilj studije bio je da se analizira preživljavanje bolesnika sa NSCLC na osnovu njihovog patohistološkog tipa i T – primarni tumor, N – regionalni limfni nodusi, M – udaljene metastaze (TNM) stadijuma koji su lečeni hiruški, a nakon toga prema TNM stadijumu hemioterapijskim protokolima i/ili radioterapijom. **Metode.** Izvršena je retrospektivna analiza preživljavanja bolesnika sa NSCLC lečenih u Vojnomedicinskoj akademiji u Beogradu u periodu 2010–2015. Ukupan broj bolesnika je bio 85 (27 žena i 58 muškaraca). **Rezultati.** Kod bolesnika sa skvamocelularnim karcinomom stopa smrtnosti bila je 19,5% kod ukupno 41 bolesnika, dok je kod bolesnika sa adenokarci-

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nomom stopa smrtnosti bila 43,2% kod ukupno 44 bolesnika. Prosečno ukupno preživljavanje bilo je statistički značajno kraće kod bolesnika sa adenokarcinomom u poređenju sa onima koji su imali skvamocelularni karcinom (1605,2 vs. 1304,8 dana; $p = 0.005$). S druge strane, prosečno ukupno preživljavanje je bilo statistički značajno kraće kod bolesnika sa adenokarcinomom kod kojih se javio recidiv bolesti u poređenju sa bolesnicima sa skvamocelularnim karcinomom kod kojih se takođe javio recidiv (1212,8 vs. 1835,5 dana; $p = 0.032$). **Zaključak.** Adenokarcinom je mnogo agresivniji karcinom u poređenju sa skvamocelularnim karcinomom sa kraćim ukupnim preživljavanjem. Potrebne su dodatne studije kako bi se identifikovali faktori rizika za pojavu recidiva bolesti nakon hiruškog lečenja i kako bi se dodatno objasnila uloga tumorskih markera i tehnika molekularne biologije u progresiji bolesti.

Ključne reči:
pluća, nesitnoćelijski karcinom; adenokarcinom; karcinom skvamoznih ćelija; preživljavanje; recidiv.

Introduction

Today, lung cancer is one of the most common malignant tumor [1–3]. It is a leading cause of cancer-related deaths [1, 3]. About 80% of all lung cancers are non-small cell lung cancer (NSCLC) [4]. In the time of diagnosis more than 65% of patients with NSCLC present with metastatic or locally advanced disease [4, 5]. According to the histopathological characteristics, the most common types of NSCLC are squamous cell carcinoma and adenocarcinoma [6].

Epidemiological data describe high aggressiveness of NSCLC. The overall five-year survival rate for all lung cancer in all stages is 16.8% [7]. This rate varies depending on the stage of lung cancer at the time of the diagnosis: up to 52.2% for localized disease, to 25% for regional metastatic disease, and to 4% for distant metastatic disease.

Non-small cell lung cancer has significant consequences in terms of survival, life quality and decreasing working ability [8]. Once the patient is diagnosed with clinically confirmed NSCLC, a comprehensive therapeutic approach depends on the stage of illness, histology, imaging diagnostics and tumor marker findings. Therapy in patients with NSCLC is a combination of surgical treatment, radiation therapy and/or one of the cytostatic drug treatment protocols [8].

A treatment of choice for patients with NSCLC from I to IIIA stages according to Tumor-Node-Metastasis (TNM) classification is surgery [9]. Patients with resected NSCLC from II to IIIA TNM stages, who have a high risk of relapse, in addition to surgery are treated with adjuvant chemotherapy (cisplatin or carboplatin with gemcitabine, paclitaxel, docetaxel, vinorelbin or pemetrexed) and/or radiation therapy [8, 10]. Patients with stage IIIB and IV NSCLC are usually treated with chemotherapy and radiation therapy. In the treatment of stage I and II NSCLC, radiation therapy alone is considered only when surgical resection is not possible because of limited pulmonary reserve or the presence of comorbidities [11]. Generally, radiation is a reasonable option for lung cancer treatment in patients who are not candidates for surgery [12]. Approximately 80% of patients with NSCLC are considered for chemotherapy at some point during the course of their illness. The current standard of systemic chemotherapy protocols for treatement of patients with NSCLC are platinum-based regimens and second-line chemotherapy [13–17]. Today, in these patients, new molecular-targeted therapies, such as an adjunct to conventional therapy, gefitinib, bevacizumab, erlotinib, pembrolizumab are used [2, 18].

After the treatment of the patients with NSCLC, the expected local and distant recurrence rates following complete resection by surgical stage are 10%, 12% and 15% for local relapse, for I, II and III TNM stages respectively [19]. The expected distant relapses are 15%, 30%, 40% and 60%, for IA, IB, II and III TNM stages, respectively [19].

The aim of this study was to evaluate the overall survival rate in the NSCLC patients according to its pathohistological type and the TNM stages which were treated by surgical treatment and, after that, according to the TNM staging, by chemotherapy protocols and/or radiation therapy.

Methods

This retrospective case series study is designed as a survival analysis according to the histopathological type and TNM stages in the patients with NSCLC. There were 85 selected patients with NSCLC who were treated at the Pulmonology Clinic and the Clinic for Chest Surgery, Military Medical Academy in Belgrade.

The clinical files from all patients with clinically confirmed lung cancer, admitted during 2010–2015 in the Military Medical Academy, were accessed in electronic and hard copies from the hospital registries. The following data were analyzed: demographic characteristics (age, gender), overall survival rate according to the pathohistology type and the TNM stages of NSCLC.

The patients with NSCLC who were treated in our hospital are classified according to the TNM stages [20]. Stage grouping of the TNM subsets was made to provide greater specificity for identifying patients with similar prognosis and options of treatment: T1N0M0 – stage IA; T2N0M0 – stage IB; T1N1M0 – stage IIA; T2N1M0 and T3N0M0 – stage IIB; and T3N1M0, T1N2M0, T2N2M0, T3N2M0 – stage IIIA. Stage IIIB is T4 any N M0 and any T N3M0. Stage IV is any T any N M1.

The patients with I TNM stage were only surgically treated. After surgery, the patients with IIA to IIIA TNM stage were treated with adjuvant chemotherapy which included etoposide and cisplatin (EP/PE protocol), and/or radiation therapy.

This chemotherapy protocol was applied in the following way: cisplatin 60 mg/m^2 intravenously on day 1 plus etoposide 120 mg/m^2 intravenously on days 1–3 every 21 days for 4 cycles, or cisplatin 80 mg/m^2 intravenously on day 1 plus etoposide 100 mg/m^2 intravenously on days 1–3 every 28 days for 4 cycles.

Radiotherapy was applied in the patients with positive resection surface for malignancy and with N2 TNM stage [8].

Continuous variables were presented as mean ± standard deviation with median values. Categorical variables were reported as frequencies unless otherwise stated. Differences between categorical variables were tested by χ^2-test, while a significance of differences between continuous variables were tested by non-parametric Mann-Whitney *U* test. Overall survival estimates were calculated using the Kaplan-Meier method, and Log-Rank (Mantel-Cox) test to assess differences between two histopathological types of NSCLC (adenocarcinoma vs. squamous cell carcinoma). The patients who stayed alive were censored at the cut-off date, that is, November 2016. A p value < 0.05 was considered statistically significant.

The underlying study was conducted in line with The Declaration of Helsinki and has been approved by the regional Ethics Committee of the Military Medical Academy, decision issued on June 9, 2015.

Results

Demographic patient characteristics are presented in Table 1. The males were significantly predominant in both histopathological groups (80.5% with squamous cell carcinoma, 56.8% with adenocarcinoma). The patients with squamous cell carcinoma were significantly older in comparison to those with adenocarcinoma (median age 63.56 in the group of patients with squamous cell carcinoma; median age 60.03 in the adenocarcinoma group).

In the group of patients with squamous cell carcinoma 19.5% of the patients died or 8 patients out of 41 (Table 2). On the other hand, in the group with adenocarcinoma 43.2% of patient deceased, or 19 patients out of 44. The mortality rate was significantly higher in the group of patients with adenocarcinoma (43.2%) in comparison to 19.5% in the group of patients with squamous cell carcinoma ($p = 0.035$).

Overall survival of the patients according to the histopathological type of NSCLC is presented in Table 2, while the cumulative survival curve (Kaplan-Meier analysis) is given in Figure 1. A statistically significant difference was observed [Log Rank (Mantel-Cox) test; $p = 0.005$] between groups. Cumulative survival was lower in the group with adenocarcinoma in comparison to the group with squamous cell carcinoma (approximately 550 days).

Overall survival of patients with squamous cell carcinoma according to recurrence as well as adenocarcinoma is presented in Table 3. A statistically significant difference between the groups was not observed [Log Rank (Mantel-Cox) test $p = 0.772$; $p = 0.295$, respectively]. On the other hand, the cumulative survival curves of the patients according to the histopathological type of NSCLC in the patients with recurrence (Kaplan-Meier analysis) are given on Figure 2. A statistically significant difference was observed [Log Rank (Mantel-Cox) test $p = 0.032$] between the groups. The cumulative survival was lower in the recurrence group with adenocarcinoma in comparison to the group with squamous cell carcinoma (approximately 620 days). This difference was not shown in the group without recurrence (Figure 3).

Overall survival was estimated and compared among patients according to the initial TNM stage in the patients with squamous cell carcinoma as well as adenocarcinoma. The baseline information is presented in Table 4. No statistical significance was observed among the patients with adenocarcinoma ($p = 0.665$ and the patients with squamous cell carcinoma ($p = 0.576$). No statistically significant survival difference was observed [Log Rank (Mantel-Cox) test] in the patients with adenocarcinoma and those with squamous cell carcinoma.

On the other hand, overall survival among the patients with squamous cell carcinoma and adenocarcinoma patients according to initially TNM stage was estimated. No statistical significance was observed between the patients with adenocarcinoma and squamous cell carcinoma in groups with IIA and IIB stage ($p = 0.278$) in contrasst to patients with IIIA stage ($p = 0.076$) (Figures 4 and 5). However, a statistical significance was observed between patients with adenocarcinoma and squamous cell carcinoma in the groups with IA and IB stage ($p = 0.038$) (Figure 6). Overall survival was lower in the group with adenocarcinoma in comparison to the group with squamous cell carcinoma in the patients with IA and IB stage (approximately 720 days).

Table 1

Demographic characteristics of the patient with non-small cell lung cancer (NSCLC) according to the histopathological type

Patients	Squamous cell carcinoma	Adenocarcinoma	*p* value
Total number, n (%)	41 (48.2)	44 (51.8)	
female	8 (19.5%)	19 (43.2)	0.035*
male	33 (80.5)	25 (56.8)	
Age total (years); mean ± SD (median)	62.07 ± 8.33 (63.56)	58.23 ± 8.34 (60.03)	0.034**
male	61.11 ± 8.31 (61.99)	59.06 ± 8.49 (60.85)	0.375**
female	66.05 ± 7.62 (69.03)	57.14 ± 8.25 (59.01)	0.013**
p value	0.374**	0.112**	

SD – standard deviation; *Pearson χ^2-tests; **Mann-Whitney *U* test.

Table 2

Overall survival of the patients according to a histopathological type of non-small cell lung cancer (NSCLC)

NSCLC	Total number	Deceased n (%)	Censored[1] n (%)	*p**	Survival (days) – estimated mean (95% CI)	*p***
Squamous cell carcinoma	41	8 (19.5)	33 (80.5)	0.035	1,858.3 (1,657.8–2,058.7)	0.005
Adenocarcinoma	44	19 (43.2)	25 (56.8)		1,304.8 (1,044.5–1,565.1)	
Overall	85	27 (31.8)	58 (68.2)		1,605.2 (1,427.2–1,783.2)	

[1]Alive at the end of the follow-up period.
***χ^2-tests; **Log Rank (Mantel-Cox) test; CI – confidence interval.**

Table 3

Distribution of overall survival of the patients with non-small cell lung cancer (NSCLC) according to recurrence

NSCLC	Recurrence	Total number	Deceased n (%)	Censored[1] n (%)	Survival (days) – estimated mean (95%CI)	*p**
Squamous cell carcinoma	Yes	17	4 (23.5)	13 (76.5)	1,835.5 (1,533.8–2,137.3)	0.772
	No	24	4 (16.7)	20 (83.3)	1,857.1 (1,597.6–2,116.5)	
Adenocarcinoma	Yes	30	15 (50)	15 (50)	1,212.8 (903.3–1,522.3)	0.295
	No	14	4 (28.6)	10 (71.4)	1,450.7 (1,032.0–1,869.5)	

[1]Alive at the end of the follow-up period.
***Log Rank (Mantel-Cox) test; CI – confidence interval.**

Table 4

Distribution of overall survival in the patients with non-small cell lung cancer (NSCLC) according to the clinically initial Tumor-Node-Metastasis (TNM) stage

NSCLC	TNM stage	Total number	Deceased n (%)	Censored[1] n (%)	Survival (days) – estimated mean (95%CI)	*p**
Squamous cell carcinoma	IA, IB	10	1 (10)	9 (90)	2008.9 (1750.3–2267.5)	0.576
	IIA, IIB	20	5 (25)	15 (75)	1624.3 (1345.2–1903.4)	
	IIIA	11	2 (18.2)	9 (81.8)	1845.3 (1428.3–2262.3)	
Adenocarcinoma	IA, IB	13	6 (46.1)	7 (53.9)	1290.5 (923.4–1657.6)	0.665
	IIA, IIB	19	7 (36.8)	12 (63.2)	1357.7 (980.7–1734.7)	
	IIIA	12	6 (50)	6 (50)	1116.9 (593.5–1640.3)	

[1]Alive at the end of the follow-up period.
***Log Rank (Mantel-Cox) test; CI – confidence interval.**

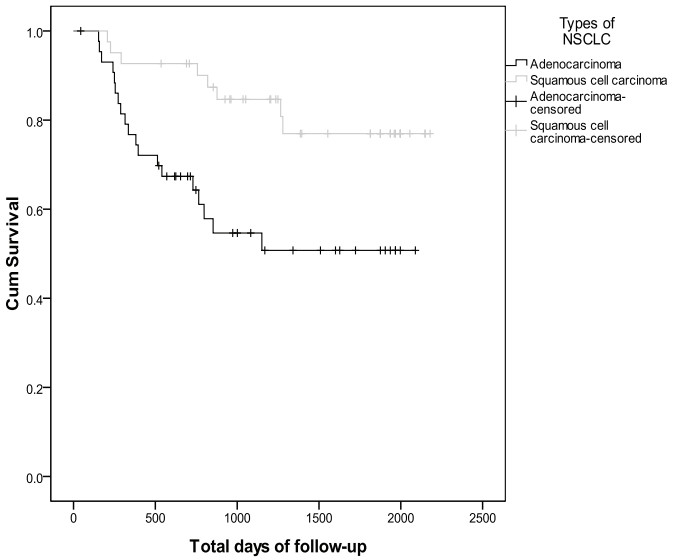

Fig. 1 – Kaplan-Meier analysis – survival curves of the patients according to the histopathology type of non-small cell lung cancer (NSCLC) (censored – alive at the end of the follow-up period).

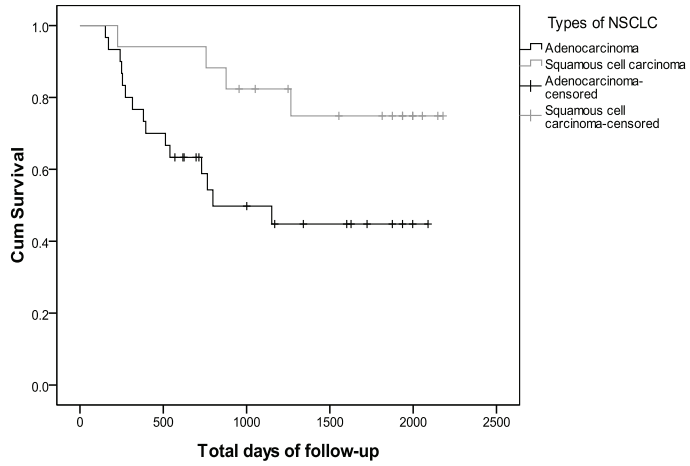

Fig. 2 – Kaplan-Meier analysis – survival curves in the patients with recurrence according to histopathology type of non-small cell lung cancer (NSCLC) (censored – alive at the end of the follow-up period). Log Rank (Mantel-Cox) test (p = 0.032).

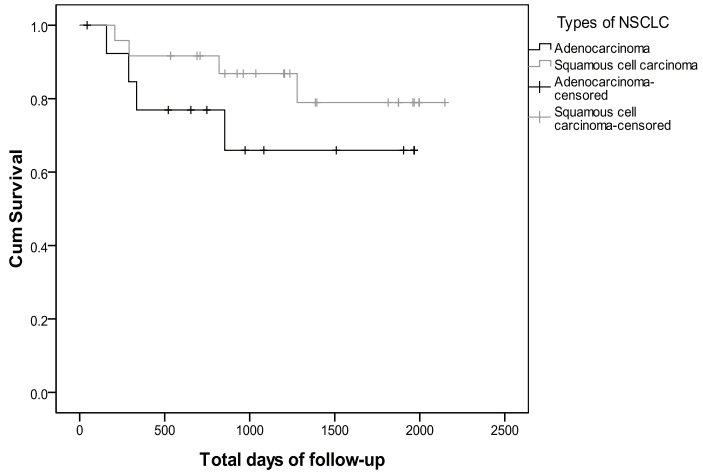

Fig. 3 – Kaplan-Meier analysis – survival curves in the patients without recurrence according to histopathology type of non-small cell lung cancer (NSCLC) (censored – alive at the end of the follow-up period). Log Rank (Mantel-Cox) test (p = 0.252).

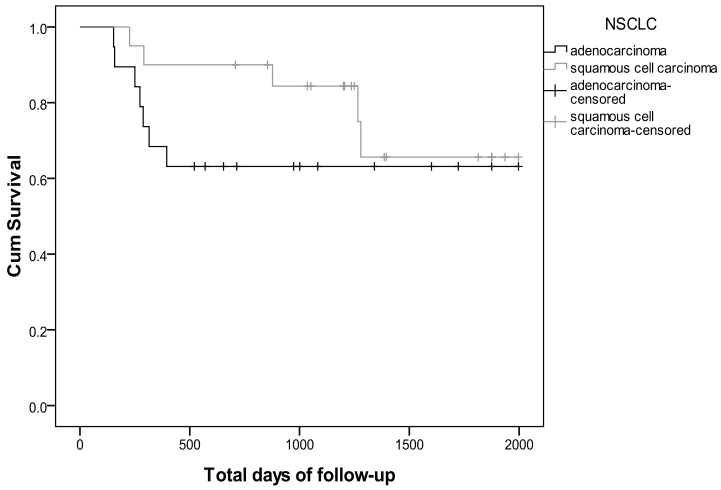

Fig. 4 – Kaplan-Meier analysis – survival curves in the patients with non-small cell lung cancer (NSCLC) in IIA and IIB Tumor-Node-Metastasis (TNM) stage according to histopathology type (censored – alive at the end of the follow-up period). Log Rank (Mantel-Cox) test (p = 0.278).

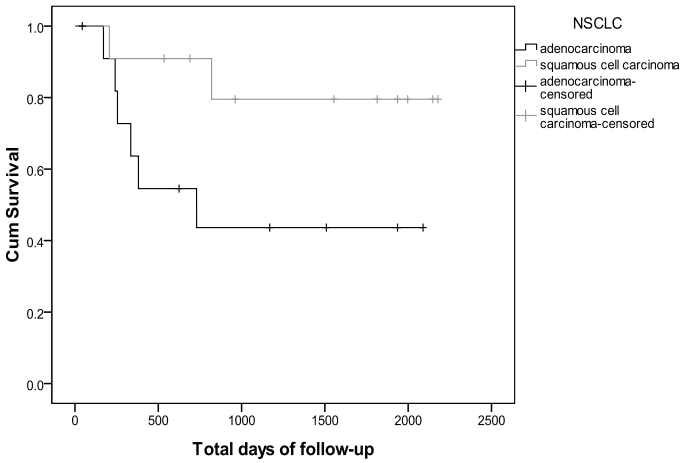

Fig. 5 – Kaplan-Meier analysis – survival curves in the patients with non-small cell lung cancer (NSCLC) in IIIA Tumor-Node-Metastasis (TNM) stage according to histopathology type (censored – alive at the end of the follow-up period). Log Rank (Mantel-Cox) test (p = 0.076).

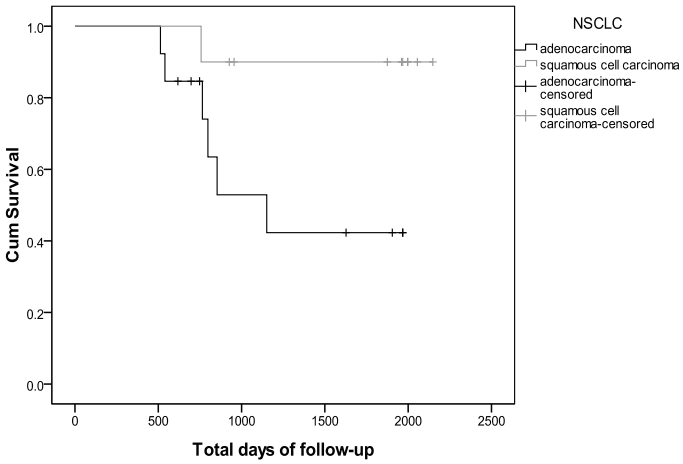

Fig. 6 – Kaplan-Meier analysis – survival curves in the patients with non-small cell lung cancer (NSCLC) in IA and IB Tumor-Node-Metastasis (TNM) stage according to pathohistology type (censored – alive at the end of the follow-up period). Log Rank (Mantel-Cox) test (p = 0.038).

Discussion

On the base of the Global Burden of Disease methodology, investigators estimated that there were 17,481 million cancer cases and 8,713 million deaths in 2015. Between 2005 and 2015, incident cancer cases increased by 33% [3]. Incidence of tracheal, bronchus and lung cancer was estimated to be 2,019 milion cases, and it is located on the second place after breast cancer (2.422 million cases). Non-small cell lung cancer continues to be one of the major causes of cancer-related deaths [2]. Therefore, our study was aimed to assess overall survival in the patients with NSCLC according to the TNM stages and pathohistological type of NSCLC.

After surgical resection of the tumor, adjuvant chemotherapy was considered a standard modality of treatment for NSCLC in the last 15 years [14–18, 21]. On the other hand, the molecularly targeted therapy significantly improved the outcomes of the treated patients with metastatic form NSCLC [2, 18]. However, for the majority of the patients, platinum-based chemotherapy remains the gold standard treatment and has to significantly improve median survival outcomes to about 10–11 months survival [22].

In our study, the males were more often in both the squamous cell carcinoma and adenocarcinoma groups. The men were more likely to develop tracheal, bronchus and lung cancer comparing to women, with 1 in 18 men and 1 in 45 women developing this cancer group between the birth and the age 79 years [3]. Similarly, in the United States, lung cancer ranks on the second place in both genders, with the estimated 115,060 new cases in men and 106,070 in women [23]. The estimated numbers of lung cancer cases worldwide has increased by 51% since 1985 (a 44% increase in men and a 76% increase in women). The higher increasing rates in women has been attributed to the fact that cigarette smoking in female gender peaked two decades later than in male [23].

Our patients with squamous cell carcinoma were significantly older in comparison to the adenocarcinoma patients. This ratio is explained by the fact that squamous cell carcinoma is connected with many risk factors, smoking, diet and food supplements, alcohol, air pollution, etc [9], while adeno-

carcinoma, although most cases are seen in smokers, develops more frequently than squamous cell carcinoma in individuals who have never smoked [6]. Due to this, adenocarcinoma earlier is diagnosed in comparison to squamous cell carcinoma.

The patients with adenocarcinoma were known to result in poorer prognosis comparing to squamous cell carcinoma patients [24]. Similarly, in our study, the mortality rate was significantly higher in the group with adenocarcinoma (43.2%) in comparison to 19.5% in the group with squamous cell carcinoma. In relevant literature, generally, it is reported that and the five-year survival rate of the patients with stage IA, IB, IIA and IIB NSCLC is about 49%, 45%, 30 and 31%, respectively [25]. For stage IIIA and IIIB NSCLC, this rate is about 14%, and 5%, respectively.

Overall survival of the patients according to recurrence is very important. Recurrence rates reported following surgical cancer resection range from 30% to 75% [26]. The majority of recurrent tumors are distant and more than 80% of recurrences occur within the first 2 years after resection. Cumulative survival was lower in the recurrence group of patients with adenocarcinoma in comparison to the group with squamous cell carcinoma, that is, about 620 days. This information support the fact that adenocarcinoma is more aggressive cancer in comparing to squamous cell carcinoma.

The complete resection of early stage NSCLC is the best treatment option. However, the post-resection recurrence rates remain high [27]. Right from the start of the therapy, in the patients with NSCLC, complete removal needs to be ensured both macroscopically and microscopically, because there are often occult micro-metastatic cancer cells undetected by standard staging methods, already present systemically at the time of the surgery, suggesting that there is an underestimation of the true tumor stage. Second, dissemination of cancer cells might occur during the handling of the tumor in the course of the surgery [27].

Statistically significant difference in overall survival according to the TNM stages was not observed between the patients with adenocarcinoma and those with squamous cell carcinoma. However, statistically significant was observed between our patients with adenocarcinoma and squamous cell carcinoma in the groups with IA and IB TNM stage, but this difference was not shown between the other groups (IIA, IIB and IIIA). Overall survival rate was lower for about 720 days in the group with adenocarcinoma of IA and IB stage in comparison to the group with squamous cell carcinoma of the same stage. This also supports the fact that adenocarcinoma is more aggressive cancer in comparing to squamous cell carcinoma.

After curative resection, the patients with lung cancer at the same TNM stage show wide variations in their incidence of recurrence [27]. The current TNM staging system, which is based on clinical and pathological findingshas the limit of its usefulness. Predicting the cases exactly in which the disease is likely to relapse can help guide the administration of adjuvant therapies. There are two methods for identifying factors related to recurrence following surgery: tumor markers and molecular biological techniques. Excellent prognostic markers for predicting the postoperative recurrence of cancer are KRAS, Ki-67, p16, epidermal growth factor receptor (EGFR), etc. An extensive pathological investigation is also important, because the histological differentiation, vessel invasion, lymphatic permeation and pleural invasion reported poor prognostic factors for the disease-free survival [28, 29].

Conclusion

Adenocarcinoma is more aggressive cancer in comparing to squamous cell carcinoma with lower overall survival. Cumulative survival was lower about 550 days in adenocarcinoma patients in comparison to patients with squamous cell carcinoma. On the other hand, cumulative survival was lower in the recurrence group of patient with adenocarcinoma in comparison to the recurrence group with squamous cell carcinoma, about 620 days.

Additional studies are needed to identify risk factors for recurrence after surgery as well as those which could additionally explain role of tumor markers and the molecular biological techniques in the progression of this kind of a cancer.

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