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ORIGINAL ARTICLE / ÖZGÜN MAKALE

The importance of histology in patient selection for platinum-based neoadjuvant treatment in non-small cell lung cancer

Küçük hücreli dışı akciğer kanserinde platin bazlı neoadjuvan tedavi için hasta seçiminde histolojinin önemi

Gökhan Kocaman[1], Yusuf Kahya[1], Elif Berna Köksoy[2], Atilla Halil Elhan[3], Mustafa Bülent Yenigün[1], Murat Özkan[1], Cabir Yüksel[1], Serkan Enön[1], Ayten Kayı Cangır[1], Hakan Kutlay[1], Rıfat Murat Akal[1]

[1]Department of Thoracic Surgery, Ankara University Faculty of Medicine, Ankara, Türkiye
[2]Department of Medical Oncology, Ankara University Faculty of Medicine, Ankara, Türkiye
[3]Department of Biostatistics, Ankara University Faculty of Medicine, Ankara, Türkiye

ABSTRACT

Background: This study aims to evaluate the prognostic factors for overall survival and progression-free survival in non-small cell lung cancer patients receiving platinum-based neoadjuvant therapy.

Methods: Between January 2008 and December 2022, a total of 163 patients with clinical Stages 2B, 3A, and 3B non-small cell lung cancer (148 males, 15 females; mean age: 59.5±7.8 years; range, 33 to 76 years) who underwent operation after neoadjuvant chemotherapy or chemoradiotherapy were retrospectively analyzed. The prognostic factors for overall survival and progression-free survival were evaluated.

Results: Higher major pathological response rate (p=0.021) and lower recurrence rate (p=0.009) were observed in patients with squamous cell carcinoma. The five-year progression-free survival rates were 56.9% and 34.1% for patients with squamous and non-squamous cell cancers (p=0.007) and the five-year overall survival rates were 68.2% and 52.2%, respectively (p=0.046). Squamous cell carcinoma histology was a favorable prognostic factor for both progression-free survival (p=0.008) and overall survival OS (p=0.031).

Conclusion: Tumor histology may serve as a prognostic factor, helping to predict patient outcomes and guide the selection of neoadjuvant therapies before surgery. Currently, platinum-based chemotherapies are still used as a standard. Clinicians should consider tumor histology while deciding on neoadjuvant treatment.

Keywords: Major pathological response, neoadjuvant therapy, non-small cell lung cancer, platinum-based chemotherapy, squamous cell carcinoma.

ÖZ

Amaç: Bu çalışmada platinyum bazlı neoadjuvan tedavi verilen küçük hücreli dışı akciğer kanserli hastalarda genel sağkalım ve progresyonsuz sağkalımın prognostik faktörleri değerlendirildi.

Çalışma planı: Ocak 2008 - Aralık 2022 tarihleri arasında, neoadjuvan kemoterapi veya kemoradyoterapi sonrası ameliyat edilen klinik Evre 2B, 3A ve 3B küçük hücreli dışı akciğer kanserli toplam 163 hasta (148 erkek, 15 kadın; ort. yaş: 59.5±7.8 yıl; dağılım: 33-76 yıl) retrospektif olarak incelendi. Genel sağkalım ve progresyonsuz sağkalımın prognostik faktörleri değerlendirildi.

Bulgular: Skuamöz hücreli karsinomlu hastalarda daha yüksek oranda majör patolojik yanıt (p=0.021) ve daha düşük nüks (p=0.009) gözlendi. Skuamöz hücreli ve skuamöz hücreli olmayan hastalarda beş yıllık progresyonsuz sağkalım oranları sırasıyla %56.9 ve %34.1 (p=0.007) ve beş yıllık genel sağkalım oranları %68.2 ve %52.2 (p=0.046) idi. Skuamöz hücreli karsinom histolojisi hem progresyonsuz sağkalım (p=0.008) hem de genel sağkalım (p=0.031) için olumlu bir prognostik faktör idi.

Sonuç: Tümör histolojisi, hasta sonuçlarını öngörmeye yardımcı olabilecek ve cerrahi öncesi neoadjuvan tedavilerin seçimini yönlendirebilecek bir prognostik faktör olarak hizmet edebilir. Günümüzde, platin bazlı kemoterapiler hala standart tedavi olarak kullanılmaktadır. Klinisyenler neoadjuvan tedavi kararları verirken tümör histolojisini dikkate almalıdır.

Anahtar sözcükler: Majör patolojik yanıt, neoadjuvan tedavi, küçük hücreli dışı akciğer kanseri, platin bazlı kemoterapi, skuamöz hücreli karsinom.

Corresponding author: Gökhan Kocaman.
E-mail: gkhnkcmn@hotmail.com

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Lung cancer is the second most common cancer type worldwide and the leading cause of cancer-related deaths. Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases.[1] Although surgery is the most effective treatment, only 20% of the patients are direct candidates for surgery. Approximately 30% of patients are diagnosed at a locally advanced stage, and this group requires multimodal treatment strategies.[2]

Although the survival contribution of adjuvant therapy in patients above Stage 1 has been demonstrated, the contribution and role of neoadjuvant therapy still remains controversial.[3] The main goal of neoadjuvant therapy is to reduce tumor size, increase the possibility of surgery, and clear micro-metastatic disease. However, if no response is received, there is a possibility that surgery may be delayed or patient become inoperable.[4] Neoadjuvant or adjuvant platinum-based chemotherapy (ChT) contributes to approximately 5% to five-year overall survival (OS) in resected NSCLC.[4,5] According to the National Comprehensive Cancer Network (NCCN) guidelines, cisplatin+pemetrexed is recommended as a neoadjuvant or adjuvant treatment regimen for non-squamous NSCLC patients who are not candidates for immunotherapy, while cisplatin+gemcitabine/docetaxel regimen is recommended for squamous cell carcinoma (SCC) patients.[1]

In the literature, there are some reports indicating that histology may be a prognostic factor in the treatment of NSCLC and should be considered in treatment selection.[5-13] In two of these studies including platinum-based neoadjuvant ChT, SCC was found to be a positive prognostic factor.[12,13] In the light of these data, we, in the present study, aimed to evaluate the prognostic factors for OS and progression-free survival (PFS) in NSCLC patients receiving platinum-based neoadjuvant therapy.

PATIENTS AND METHODS

This single-center, retrospective was conducted at Ankara University Faculty of Medicine, Department of Thoracic Surgery between January 2008 and December 2022. A total of 163 patients with clinical Stages 2B, 3A, and 3B NSCLC (148 males, 15 females; mean age: 59.5±7.8 years; range, 33 to 76 years) who underwent operation after neoadjuvant ChT or chemoradiotherapy (CRT) were included. Patients who did not undergo curative resection, N3 lymph node metastasis, early stage or metastatic disease, and patients with incomplete follow-up data were excluded from the study. A written informed consent was obtained from each patient. The study protocol was approved by the Ankara University Human Research Ethics Committee (date: 30.09.2024, no: İ08-631-24). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients were staged according to the 8th Edition of the Tumor, Node, Metastasis (TNM) classification. Thoracic computed tomography (CT), cranial CT or magnetic resonance imaging (MRI) and positron emission tomography-CT (PET/CT) were used for staging. For invasive mediastinal staging, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), mediastinoscopy, mediastinotomy or video-assisted thoracoscopic surgery (VATS) were used, when necessary. The patients were evaluated in the Multidisciplinary Thoracic Oncology Council for the treatment plan.

Patients received at least two cycles of platinum-based doublet ChT. Concurrent 40-55 Gy radiotherapy was administered to patients according to their T status. Within two to four weeks after treatment, the patients were re-evaluated with thoracic CT and PET/CT for treatment response. When necessary, the patients underwent invasive re-staging using EBUS-TBNA. Surgery was performed for patients who did not show significant progression. The decision for adjuvant treatment was based on residual disease status. Major pathological response (MPR) refers to a ≤10% residual tumor in the resected specimen. A pathological complete pathological response (pCR) was defined as the absence of viable tumor cells in the specimen. Mediastinal downstaging (MDS) was defined as clinical N2 and N1 tumors being downstaged to N1 or N0. The patients were followed with thoracic CT every six months for five years, and then annually for lifelong.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 30.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented in mean ± standard deviation (SD), median (interquartile range) (min-max) or number and frequency, where applicable. Differences between two groups for normally distributed continuous variables were evaluated using the Student t-test. The Mann-Whitney U test was used to compare two groups in terms of ordinal or non-normally distributed continuous variables. Overall survival was defined

as the time from the start of treatment until death from any cause or the last follow-up. Progression-free survival was defined as the time from the beginning of treatment until relapse or death occurred, or until the last follow-up period. The survival estimations were performed using the method of Kaplan-Meier

Table 1. Clinicopathological characteristics of patients

	Non-squamous (n=84)			Squamous (n=79)			
Characteristics	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			59±8.1			60±7.4	0.376
Sex							0.076
Male	73	86.9		75	94.9		
Female	11	13.1		4	5.1		
Clinical Stage							0.630
2B	10	11.9		13	16.4		
3A	40	47.6		33	41.8		
3B	34	40.5		33	41.8		
Neoadjuvan therapy							0.357
Chemotherapy	69	82.1		69	87.3		
Chemoradiotherapy	15	17.9		10	12.7		
Resection							0.005
Wedge resection	6	7.1		6	7.6		
Segmentectomy	2	2.4		0	0		
Lobectomy	47	56		24	30.4		
Bilobectomy	2	2.4		5	6.3		
Pneumonectomy	27	32.1		44	55.7		
Chest wall resection							0.904
Present	7	8.3		7	8.9		
Absent	77	91.7		72	91.1		
Surgical margin							0.686
Positive	6	7.1		7	8.9		
Negative	78	92.9		72	91.1		
Pathological N stage							0.002
N0	45	53.6		34	43		
N1	11	13.1		29	36.7		
N2	28	33.3		16	20.3		
Mediastinal downstaging							0.248
Present	36	42.9		41	51.9		
Absent	48	57.1		38	48.1		
Major pathological response							0.021
Present	8	9.5		18	22.8		
Absent	76	90.5		61	77.2		
Pathological complete response							0.056
Present	3	3.6		9	11.4		
Absent	81	96.4		70	88.6		
Adjuvant therapy							0.724
Present	53	66.2		51	68.9		
Absent	27	33.8		23	31.1		
Missing	4	-		5	-		
Recurrence							0.009
Present	47	56		28	35.4		
Absent	37	44		51	64.6		
Status							0.052
Exitus	50	59.5		35	44.3		
Alive	34	40.5		44	55.7		

SD: Standard deviation.

algorithm, and the comparison between groups was evaluated with log-rank test. Multiple Cox proportional hazard model was used to determine independent predictors of an outcome after adjustment for other explanatory variables. Variables were dichotomized for regression analysis and variables with a p-value of less than 0.1 in the univariable Cox proportional hazards regression were selected as candidates for the multivariate model along with all variables of known clinical importance using purposeful selection method. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. A two-tailed *p* value <0.05 was considered statistically significant.

RESULTS

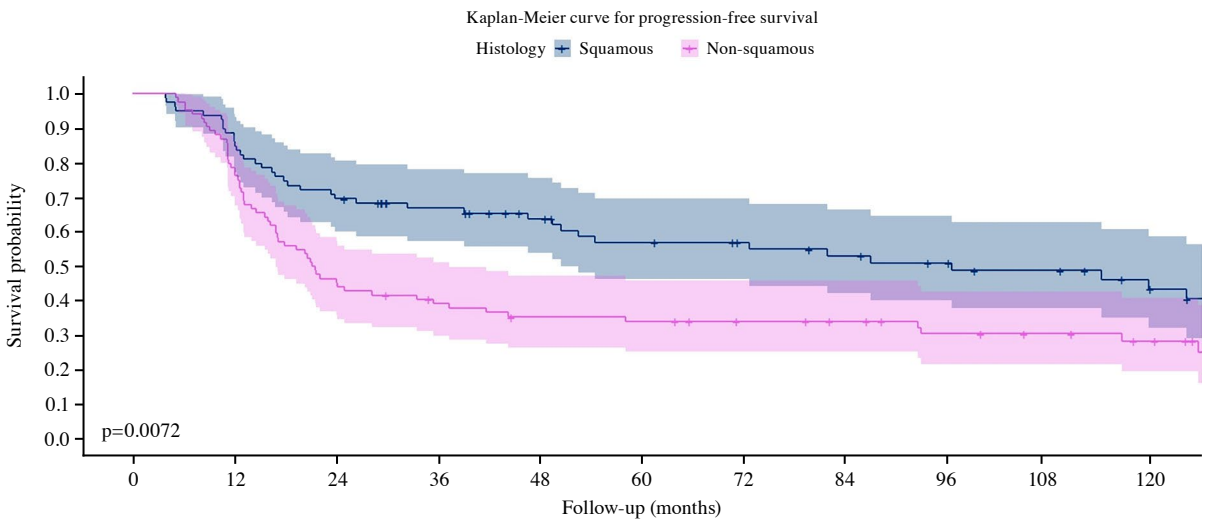
The histopathological distribution of NSCLC was as follows: 66 (40.5%) adenocarcinoma (AC), 79 (48.5%) SCC, and 18 (11%) other histopathological types of tumors (adenosquamous cell, large cell, and pleomorphic carcinoma). Mediastinal downstaging was observed in 77 (47.2%) patients, MPR was observed in 26 (16%), and pCR was observed in 12 (7.4%) patients. Both MPR (40%/11.6%, p=0.001, respectively) and pCR (24%/4.3%, p=0.004, respectively) were higher in patients receiving neoadjuvant CRT than in patients receiving neoadjuvant ChT.

The patients were divided into two groups: SCC and non-SCC. Higher MPRs (p=0.021) and a lower recurrence rate (p=0.009) were observed in patients with SCC. Additionally, there was a significant difference between the two groups in resection type distribution (p=0.005) and pathological N status (p=0.002) (Table 1).

The median follow-up period was 49.4 (range, 4 to 192) months, the five-year PFS rate was 45.2±4% (3rd year: 52.6%, median 44.3 months, 95% CI: 11.2-77.3), and the five-year OS rate was 59.7±4% (3rd year: 70.6%, median 114.2 months, 95% CI: 83.5-144.8).

There were no significant differences in PFS between males and females (p=0.685), clinical stage (p=0.177), neoadjuvant treatment type (p=0.556), resection type (p=0.903), pathological N status (p=0.2), MDS (p=0.390), MPR rate (p=0.271), and adjuvant treatment status (p=0.406). However, significant differences were observed in terms of histology (5-year PFS rate: SCC/non-SCC: 56.9±5.9%/34.1±5.2%, p=0.0072, respectively) (Figure 1) and surgical margin (p=0.012) for PFS.

There were no significant differences in OS between males and females (p=0.947), neoadjuvant



Histology	Number at risk										
	Squamous	79	70	55	46	39	33	30	27	24	21	16
	Non-squamous	84	66	39	31	27	26	23	21	17	15	12
		0	12	24	36	48	60	72	84	96	108	120

Follow-up (months)

Figure 1. Progression-free survival analysis according to histology.

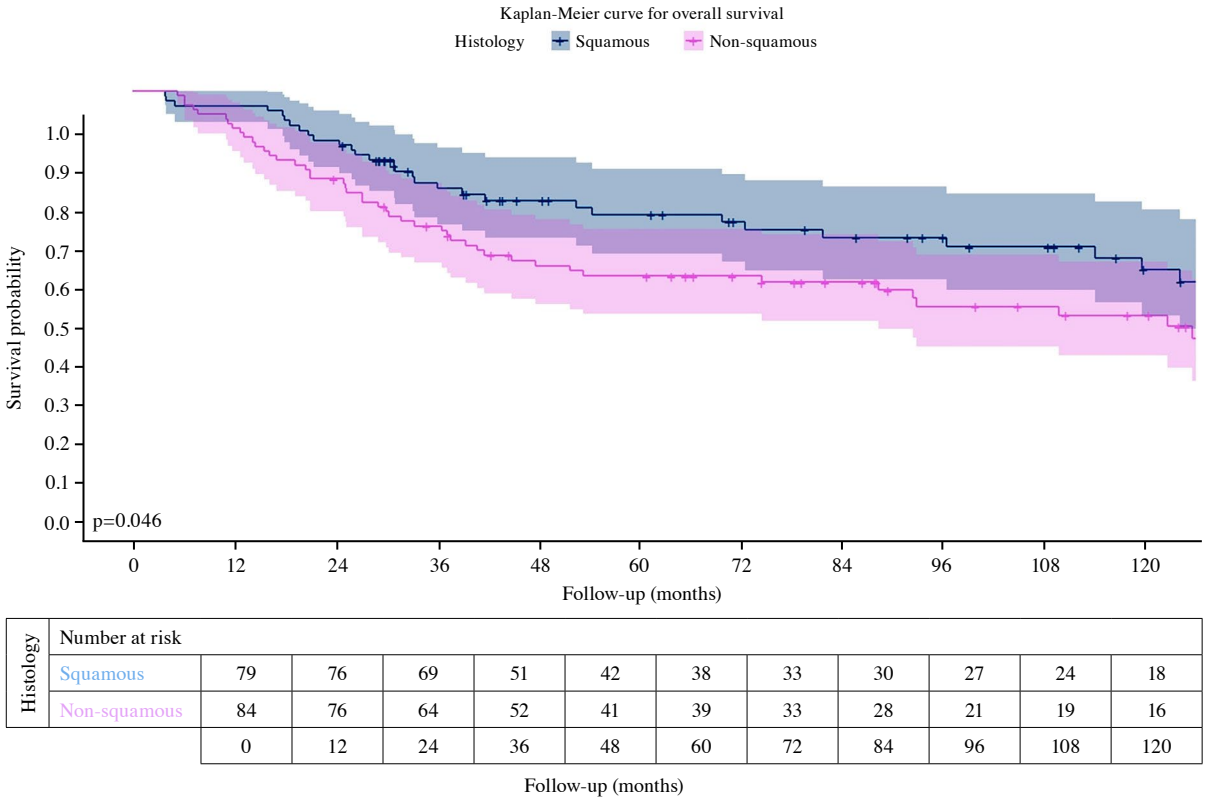


Figure 2. Overall survival analysis according to histology.

treatment type (p=0.956), resection types (p=0.824), pathological N status (p=0.250), MDS (p=0.873), MPR (p=0.276), and adjuvant treatment status (p=0.411). However, significant differences were observed in terms of histology (five-year OS rate: SCC/non-SCC: 68.2±5.6%/52.2±5.6%, p=0.046, respectively) (Figure 2), clinical stage (p=0.029), and surgical margin status (p=0.022) for OS.

Table 2. Cox regression analysis for progression-free survival

	Univariable			Multivariable		
Variables	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.018	0.993-1.045	0.162			
Male *vs*. female	0.874	0.455-1.680	0.686			
Non-squamous *vs* squamous	1.700	1.149-2.516	**0.008**	1.724	1.153-2.580	**0.008**
Clinical Stage 3 *vs*. 2	1.834	0.955-3.522	0.068	1.670	0.856-3.258	0.133
Neoadjuvant CRT *vs*. ChT	1.174	0.688-2.002	0.557			
Pneumonectomy *vs*. other resections	1.078	0.731-1.590	0.704			
Surgical margin positive *vs*. negative	2.269	1.172-4.393	**0.015**	2.584	1.322-5.051	**0.006**
Pathological N2 *vs*. N0-1	1.441	0.948-2.189	0.087	1.195	0.774-1.843	0.422
MDS present *vs*. absent	0.844	0.573-1.244	0.392			
MPR present *vs*. absent	0.722	0.404-1.293	0.274			
Adjuvant therapy present *vs*. absent	1.204	0.776-1.870	0.407			

HR: Hazard ratio; CI: Confidence interval; CRT: Chemoradiotherapy; ChT: Chemotherapy; MDS: Mediastinal downstaging; MPR: Major pathological response.

Table 3. Cox regression analysis for overall survival

	Univariable			Multivariable		
Variables	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.025	0.996-1.054	0.090	1.034	1.004-1.063	**0.023**
Male *vs*. female	1.025	0.493-2.131	0.947			
Non-squamous *vs*. squamous	1.555	1.005-2.406	**0.048**	1.623	1.046-2.518	**0.031**
Clinical Stage 3 *vs*. 2	3.087	1.249-7.628	**0.015**	3.612	1.444-9.032	**0.006**
Neoadjuvant CRT *vs*. ChT	1.017	0.562-1.838	0.956			
Pneumonectomy *vs*. other resections	1.260	0.817-1.941	0.296			
Surgical margin positive *vs*. negative	2.328	1.106-4.898	**0.026**	2.344	1.103-4.979	**0.027**
Pathological N2 *vs*. N0-1	1.314	0.822-2.100	0.253			
MDS present *vs*. absent	0.965	0.628-1.483	0.873			
MPR present *vs*. absent	0.693	0.357-1.345	0.279			
Adjuvant therapy present *vs*. absent	0.820	0.511-1.317	0.412			

HR: Hazard ratio; CI: Confidence interval; CRT: Chemoradiotherapy; ChT: Chemotherapy; MDS: Mediastinal downstaging; MPR: Major pathological response.

Multivariate regression analysis identified histology (p=0.008) and resection margin (p=0.006) as independent prognostic factors for PFS (Table 2) and age (p=0.023), histology (p=0.031), clinical stage (p=0.006) and resection margin (p=0.027) for OS (Table 3).

DISCUSSION

Locally advanced (Stage 3) NSCLC includes a mixed group of patients with Stage 3A: T1a-T2b/N2, T3/N1, T4/N0-1; Stage 3B: T1a-T2b/N3, T3-4/N2 and Stage 3C: T3-4/N3. While neoadjuvant therapy can be considered in Stage 3A and well-selected 3B patients, it is not recommended in Stage 3C patients.[14] Some reports have shown that Stage 2B (T1a-T2b/N1, T3N0) patients may also benefit from neoadjuvant treatment.[15,16] The NCCN guidelines also state that Stage 2 patients who may require adjuvant treatment can be directed to neoadjuvant treatment.[1] Therefore, we included patients with non-N3, Stage 2B-3A-3B NSCLC in our study.

In the current study, the median follow-up was 49.4 months, five-year PFS rate was 45.2%, and five-year OS rate was 59.7%. Mediastinal downstaging was observed in 77 (47.2%) patients, MPR in 26 (16%), and pCR in 12 (7.4%). These results are consistent with those of various neoadjuvant therapy studies.[9-18]

In a study by Paul et al.,[15] 136 clinical Stage 3A (clinical N2) patients receiving neoadjuvant treatment (12.5% CRT, 87.5% ChT) were examined. A total of 52% MDS and two (1.4%) pCRs were observed. The median follow-up was 42 months. The five-year OS rate was 33%. Although this study included a similar proportion of patients receiving neoadjuvant CRT as in our study (12.5% and 15.3%, respectively), the pCR rate was found to be lower (1.4% and 7.4%, respectively), and the five-year OS rate was also found to be lower than that in our study (33% and 59.7%, respectively). This may be due to the fact that all patients in the study were clinical N2.

In a randomized Phase 3 study by Scagliotti et al.,[16] 270 patients with Stage 1B-3A NSCLC were included. A total of 129 patients were randomized to surgery after neoadjuvant ChT (cisplatin+gemcitabine) and 141 patients were randomized to surgery alone. The pCR rate was similar to our study (4% and 4.3%, respectively). Of note, neoadjuvant ChT seemed to be more advantageous for both PFS (p=0.003) and OS (p=0.02). While there was no significant difference in terms of PFS (p=0.83) and OS (p=0.94) for Stage 1B-2A patients, in Stage 2B-3A patients both PFS (three-year PFS 36.1%/55.4%, p=0.002, respectively) and OS (p<0.001) were significantly different in favor of neoadjuvant ChT. The authors concluded that neoadjuvant therapy was effective in patients with Stage ≥2B NSCLC as in our study.

In a meta-analysis including 2,385 Stage 1B-3A patients, a 13% decrease in the risk of mortality was observed in patients receiving neoadjuvant

ChT compared to patients who did not receive ChT. An increase in the five-year OS rate from 40 to 45% and an increase in the five-year relapse-free survival rate from 30 to 36% were observed with neoadjuvant ChT.[4] Although this large-scale study demonstrated the benefit of neoadjuvant therapy, its survival results were still below those of our study (five-year OS: 45% and 59.7%, respectively).

In a recent study in Netherlands, Joosten et al.[17] examined 9,591 patients with clinical Stage 3A NSCLC. Surgery was performed after neoadjuvant treatment in 4.5% of the patients. A pCR was observed in 33% and 11% of the patients after CRT and ChT, respectively. The five-year OS rate after neoadjuvant treatment was 54%. Although the pCR rates in this study were slightly higher than those in our study (33%/24% for CRT and 11%/4.3% for ChT, respectively) the OS rate was lower than that in our study (54%/59.7%, respectively).

In a study by Kumar et al.[18] including 44 Stage 2A-3B patients, the pCR rate was 22.7% and the MPR rate was 29.5%. While the median follow-up was 35.9 months, the three-year disease-free survival (DFS) and OS were 49.3% and 60.2%, respectively. Although neoadjuvant CRT was not used in this study, a pCR rate of 22.7% was observed. This may be due to the small number of patients, as well as the fact that carboplatin-pemetrexed regimen was administered to patients with AC. Due to local regulations in our country, access to pemetrexed in neoadjuvant setting is limited. However, the three-year PFS and OS rates in our study are higher than the aforementioned study (52.6%/49.3% for PFS, 70.6%/60.2% for OS, respectively).

In Stokes et al.'s[19] study, 6,544 Stage 2B patients who underwent surgery were examined. Adjuvant ChT was administered to 37.8% of the patients, adjuvant CRT to 13.1%, neoadjuvant treatment to 18.3% and surgery alone to 30.9%. The five-year OS for adjuvant ChT, neoadjuvant treatment and surgery alone was 59.5%, 58.4% and 52.9%, respectively. There was no significant difference in the risk of death between patients who received neoadjuvant or adjuvant therapy before and after propensity score matching. In a meta-analysis conducted by Lim et al.,[20] no significant difference was observed in OS (p=0.91) and DFS (p=0.70) rates between patients who received neoadjuvant or adjuvant ChT. Based on these studies, the choice of neoadjuvant or adjuvant treatment should be made on a patient-by-patient basis.

Classical prognostic factors in patients receiving neoadjuvant therapy include complete resection, tumor stage regression, and pCR.[2] The MPR (viable tumor cells <10%) has been frequently used as a prognostic factor in recent studies.[21] We also used the MPR in the survival analyses in our study; however, we were unable to obtain significant results. This may be related to the small number of patients with MPR (n=26, 16%) in our study.

To date, few studies have examined the relationship between the histological types and ChT response.[6-13] In the study of Georgoulias et al.,[6] 441 Stage 3B-4 patients were randomized into docetaxel-cisplatin or gemcitabine-docetaxel treatment groups. While patients with non-AC histology had a better response in the cisplatin arm, patients with AC had a better response in the gemcitabine arm. In a randomized Phase 3 study by Scagliotti et al.,[7] 1,725 Stage 3B-4 patients were randomized to cisplatin+gemcitabine *vs*. cisplatin+pemetrexed arms. Improved OS results were obtained with cisplatin+pemetrexed for non-SCC patients and cisplatin+gemcitabine for SCC patients. Hirsch et al.[8] reported in their review that histology might be a prognostic factor for advanced NSCLC.

In a Phase 2 study by Betticher et al.[9] including 90 pathological N2 patients who were administered neoadjuvant cisplatin-docetaxel, a higher response (p=0.007) and MDS (p=0.049) were observed in patients with SCC. In a study by Melek et al.[10] including 416 locally advanced NSCLC patients receiving neoadjuvant treatment, the five-year OS rate was 52.8% and the pCR rate was 16.4% in SCC *vs*. 8.1% in ACs (p=0.024). In a study by Yağcı et al.[11] which included 154 patients with locally advanced NSCLC who received neoadjuvant treatment, the pCR rate was 12.3%. The five-year DFS rate was 28.1% for AC and 45% for SCC patients (p=0.04). In our study, similar to the aforementioned studies, higher MPRs were obtained (p=0.021) with lower recurrence rates (p=0.009) in SCC patients. More importantly, SCC patients were found to be more advantageous in terms of both PFS (p=0.007) and OS (p=0.046).

In their study, Mouillet et al.[12] combined two French Phase 3 platinum-based neoadjuvant ChT studies and examined the results in 492 Stage 1B-2 patients. In both the univariate and multivariate analysis, SCC was found to be a positive risk factor for both OS and DFS. In a study by Liao et al.,[13] 62 Stage 3 (N2) NSCLC patients who were administered neoadjuvant cisplatin-docetaxel were evaluated. Better

response rates were observed in patients with SCC (68% *vs*. 33%, p=0.006) and SCC histology was identified as an independent positive prognostic factor (p=0.001). Similar to these studies, SCC histology was found to be an independent positive prognostic factor for both PFS (p=0.008) and OS (p=0.031) in our study.

The main strength of this study is that it is a single-center study including a focused population with a relatively long follow-up period. However, since it covered a 15-year period, the main limitation is the heterogeneity that occurs due to changes in diagnosis, staging and treatment methods over time. Additionally, due to its retrospective nature, unavoidable selection biases may have developed among the patient groups. Further multi-center, large-scale, prospective studies are needed to establish more definite conclusions on this subject.

In conclusion, tumor histology may serve as a prognostic factor, helping to predict patient outcomes and guide the selection of neoadjuvant therapies before surgery. Currently, platinum-based chemotherapies are still used as a standard. Clinicians should consider tumor histology while deciding on neoadjuvant treatment. The inclusion of tumor histology in decision-making emphasizes the need for personalized treatment plans to maximize the efficacy of neoadjuvant therapies. Further research is needed to explore histology-specific responses to platinum-based chemotherapy, as this may lead to the development of more targeted neoadjuvant regimens.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea, design, data processing, analysis, literature review, writing article: G.K.; Design, writing the article: Y.K.; Data collection, processing, writing the manuscript: E.B.K.; Statistical analysis: AH.E.; Concept, control: M.B.Y.; Design and control: M.Ö.; Supervision, literature review, writing the article: C.Y.; Analysis and interpretation: S.E.; Control, references: A.K.C, H.K.; Design, supervision, writing the article, critical review: M.A.

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