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Evaluation of prognostic factors in lung cancers with surgical complete response after induction treatment

İndüksiyon tedavisi sonrasında cerrahi patolojik tam yanıt alınan akciğer kanserlerinde prognostik faktörlerin değerlendirilmesi

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ABSTRACT

Background: This study aims to evaluate long-term results of induction treatment and to investigate prognostic factors affecting survival in non-small cell lung cancer patients with a pathological complete response.

Methods: Between January 2010 and December 2017, a total of 39 patients (38 males, 1 female; mean age: 56.2±8.3 years; range, 38 to 77 years) having locally advanced (IIIA-IIIB) non-small cell lung cancer who were given induction treatment and underwent surgery after induction treatment and had a pathological complete response were retrospectively analyzed. Survival rates of the patients and prognostic factors of survival were analyzed.

Results: Clinical staging before induction treatment revealed Stage IIB, IIIA, and IIIB disease in three (7.7%), 26 (66.7%), and 10 (25.6%) patients, respectively. The five-year overall survival rate was 61.2%, and the disease-free survival rate was 55.1%. In nine (23.1%) patients, local and distant recurrences were detected in the postoperative period.

Conclusion: In patients with locally advanced non-small cell lung cancer undergoing surgery after induction treatment, the rates of pathological complete response are at considerable levels. In these patients, the five-year overall survival is quite satisfactory and the most important prognostic factor affecting overall survival is the presence of single-station N2.

Keywords: Induction treatment, lung cancer, pathological complete response.

ÖZ

Amaç: Bu çalışmada, patolojik tam yanıt veren küçük hücreli dışı akciğer kanserli hastalarda indüksiyon tedavisinin uzun dönem sonuçları değerlendirildi ve sağkalımı etkileyen prognostik faktörler araştırıldı.

Çalışma planı: Ocak 2010 ve Aralık 2017 tarihleri arasında indüksiyon tedavisi verilen ve indüksiyon tedavisinden sonra ameliyat edilen ve patolojik tam yanıt veren ileri evre (IIIA-IIIB) küçük hücreli dışı akciğer kanseri olan toplam 39 hasta (38 erkek, 1 kadın; ort. yaş: 56.2±8.3 yıl; dağılım 38-77 yıl) retrospektif olarak incelendi. Hastaların sağkalım oranları ve sağkalımın prognostik faktörleri değerlendirildi.

Bulgular: İndüksiyon tedavisi öncesi klinik evrelemede üç (%7.7) hastada Evre IIB, 26 (%66.7) hastada Evre IIIA, ve 10 (%25.6) hastada Evre IIIB hastalık izlendi. Beş yıllık sağkalım oranı %61.2 olup, hastalıksız sağkalım oranı %55.1 idi. Dokuz (%23.1) hastada, ameliyat sonrası dönemde lokal nüks veya uzak nüks saptandı.

Sonuç: İndüksiyon tedavisi sonrası ameliyat edilen lokal ileri evre küçük hücreli dışı akciğer kanserli hastalarda, patolojik tam yanıt oranı azımsanamayacak düzeydedir. Bu hastalarda beş yıllık genel sağkalım oldukça memnun edici olup, genel sağkalımı etkileyen en önemli prognostik faktör tek istasyon N2 varlığıdır.

Anahtar sözcükler: İndüksiyon tedavisi, akciğer kanseri, patolojik tam yanıt.

The management of locally advanced (IIIA-IIIB) non-small cell lung cancer (NSCLC) is challenging, and there are different options with proven efficacy in the literature.[1] Currently, the widely adopted clinical approach is multimodal treatment methods; however, the debate regarding the standard treatment protocol is still ongoing. Reasons for obscuring the optimal treatment approach are as follows: (i) the limited number of clinical studies and limited patient populations, (ii) the heterogeneity of disease presentations, and (iii) differences in induction treatment (IT). Despite all of the above, surgery performed after IT (chemotherapy [CHT] and radiotherapy [RT]) has taken its place as a positive prognostic factor among multimodal treatments, as suggested by many centers.[2-9] Following IT, patients with a complete or partial response, downstaged or stable disease, or patients with radiological findings suggesting technically resectable disease are eligible for surgery. Better survival and lower recurrence rates have been shown to be associated with downstaging.[3]

The group of patients undergoing surgery after being deemed resectable in accordance with the clinical restaging, with the outcome of pathological complete response (pCR) is small; however, these patients are the optimal candidates for long-term survival. In the literature, there are few studies including this subgroup, and many important details still remain undefined and the relevant debate continues.[10]

In the present study, we aimed to analyze in detail the clinical and pathological features of patients with pCR who were staged clinically as having locally advanced NSCLC and underwent surgery after being deemed as being resectable following IT and to identify factors affecting survival and recurrence.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Thoracic Surgery between January 2010 and December 2017. A total of 187 patients who were given IT for locally advanced (IIIA-IIIB) NSCLC and underwent surgery after IT were screened. A total of 39 patients (38 males, 1 female; mean age: 56.2±8.3 years; range, 38 to 77 years) with pCR who underwent surgical resection after IT were included in the study. A written informed consent was obtained from each patient. The study protocol was approved by the Istanbul Training and Research Hospital Ethics Committee (date/no: 27.09.2019/2008). The study was

conducted in accordance with the principles of the Declaration of Helsinki.

Clinical stage

All tumors in all patients included were evaluated using preoperative thoracic computed tomography (CT). Positron emission tomography (PET)-CT, cranial magnetic resonance imaging (MRI), and upper abdominal CT were performed in all patients to evaluate distant metastases. In patients suspected of having mediastinal lymph node metastases with radiological imaging methods (CT, PET-CT), procedures such as endobronchial ultrasound (EBUS), mediastinoscopy, and mediastinotomy were performed for disease staging. The 2009 International Association for the Study of Lung Cancer (IASLC) Lymph Node Map was used for the classification of mediastinal lymph nodes.[11] The patients with resectable pN2 disease (single-station or multiple stations) and superior sulcus tumors underwent IT. The T4 tumors were assigned as tumors with a diameter of 7 cm and above in six patients, and tumors invading the carina in one patient. Histopathological evaluations were performed in accordance with the eight edition of the IASLC staging guidelines.[12]

IT and restaging

The IT consisted of double combined treatments with platinum-based CHT agents (platinum/taxane) given every other week for two to six courses. Seven patients were only given induction CHT, and 32 patients were given CHT + RT concurrently. The RT was given at a dose of 45 to 54 Gy before 2014, and full-dose RT consisting of 60 to 66 Gy was given after 2014. Preoperative CHT or CHT+RT was planned based on the common decision of the Oncological Tumor Board. The CHT+RT was given for patients with superior sulcus tumors, and CHT was preferred in the foreground according to the Multidisciplinary Council decision in patients with central tumors. The decision of the oncological tumor board, the response of the patients with a central tumor was evaluated with thoracic CT scan after two cycles of CHT. The operation was planned for patients with tumor regression on thoracic CT after IT. Adjuvant therapy was given to 10 patients to complete the postoperative CHT dose.

The patients were evaluated four to six weeks after IT through radiological methods (CT, PET-CT), and all patients with resectable disease who had downstaging and stable disease underwent EBUS or mediastinoscopy for restaging. The patients who were defined as N2 with EBUS before the treatment underwent restaging

with mediastinoscopy, and those who were defined as N2 with mediastinoscopy before the treatment underwent restaging with EBUS. Following the IT, the patients who were defined as not having pN2 with invasive methods underwent surgery.

Preoperative evaluation and surgical methods

A preoperative routine blood panel, along with pulmonary function tests, electrocardiogram, and blood gases were performed to evaluate pulmonary and cardiac reserves. In patients with low forced expiratory volume in one second (FEV1), diffusion capacity of the lung for carbon monoxide (DLCO) test, and lung perfusion scintigraphy were also performed. Before surgery, fiberoptic bronchoscopy was performed to evaluate the endobronchial lesion and establish a diagnosis. All patients were evaluated by the Multidisciplinary Oncological Tumor Board. The Charlson Comorbidity Index (CCI) was used to assess comorbidities.[13]

In all patients, lobectomy or pneumonectomy, along with open thoracotomy was used as the surgical approach. During surgery, systematic, complete mediastinal lymph node dissection was performed following the planned anatomic resection. In right-sided tumors, sampling was performed at the 2nd, 4th, and 7 to 9th lymph node stations, and in left-sided tumors, the 5 to 9th lymph node stations were sampled. Complete (R0) resection was performed in a tumor freeway at the proximal ends and the mediastinal lymph nodes. In the surgical specimen, no residual tumor tissue and no disease in the dissected mediastinal lymph nodes, both macro- and microscopically, was defined as yP (T0N0M0) pCR.

Postoperative follow-up

Mortality was defined as death events during the hospitalization period and within 90 days of hospital discharge. Follow-ups were performed with physical examination and thoracic CT once every three months for the first two years, every six months at two to five years, and once a year thereafter. Ten patients were given adjuvant CHT. In patients with recurrence, the patterns of recurrence were evaluated using methods such as PET-CT, bronchoscopy, EBUS, fine needle aspiration biopsy, and scalene lymph node biopsy.

Local recurrence at follow-up was defined as recurrence of ipsilateral lung lesions, mediastinal involvement, and recurrence in the bronchial stump. Distant recurrences were defined as the development of tumors in the brain, liver, bone, contralateral lung, and adrenal glands.

Table 1. Demographic and histopathological features of patients

Variables	n	%	Mean±SD
Age (year)			56.2±8.4
<65	35	89.7	
≥65	4	10.3	
Sex			
Male	38	97.4	
Female	1	2.6	
Charlson Comorbidity Index			
2	21	53.8	
3	13	33.3	
4	2	5.1	
5	3	7.7	
cT Stage			
T1	2	5.1	
T2	8	20.5	
T3	22	56.4	
T4	7	17.9	
cN Stage			
N0	4	10.3	
N1	14	35.9	
N2	21	53.8	
cTNM			
IIB	3	7.7	
IIIA	26	66.7	
IIIB	10	25.6	
Lymph node involvement			
Single station	16	41	
Multiple stations	5	12.8	
Days from IT to surgery			40.6±6.5
yTNM			
IA2	8	20.5	
IA3	2	5.1	
IB	6	15.4	
IIA	4	10.3	
IIB	18	46.2	
IIIA	1	2.5	
Resection type			
Lobectomy	26	66.7	
Pneumonectomy	13	33.3	
Histology			
Adenocarcinoma	12	30.8	
Squamous cell carcinoma	27	69.2	
Chemotherapeutic agents			
Docetaxel + cisplatin	5	12.8	
Paclitaxel + cisplatin	13	33.3	
Paclitaxel + carboplatin	15	38.5	
Etoposide + cisplatin	6	15.4	
IT chemotherapy cycles			
2	10	25.6	
4-6	29	74.4	
IT Radiotherapy dose			
≤60 Gray	19	59.4	
>60 Gray	13	40.6	
Lymph node removed			14.8±8.4
Number of removed lymph nodes			
<10	10	25.6	
>10	29	74.4	
Adjuvant therapy			
None	29	74.4	
Chemotherapy alone	10	25.6	

SD: Standard deviation; CCI; Charlson Comorbidity Index, IT; Induction treatment.

Demographic data, length of hospital stay, mortality, histopathological characteristics, recurrence rates, and overall survival (OS) and disease-free survival (DFS) rates at five years were analyzed.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented in mean ± standard deviation (SD) or median (min-max), while categorical variables were presented in number and frequency. Demographic and clinical characteristics such as age and length of hospitalization were tested for normal distribution using the Kolmogorov-Smirnov test. The independent t-test was used to compare the group means for these variables, and the chi-square test was used to compare morbidity between two groups. Risk analysis affecting mortality was evaluated by

Table 2. Risk factors affecting mortality in the first 90 days

	Mortality negative		Mortality positive		
	n	%	n	%	p
Age (year)					0.475
<65	31	88.6	4	100	
≥65	4	11.4	0	0	
Sex					0.732
Male	34	97.1	4	100	
Female	1	2.9	0	0	
Side					0.609
Left	12	34.3	2	50	
Right	23	65.7	2	50	
Charlson Comorbidity Index					0.318
2	20	57.1	1	25	
>2	15	42.9	3	75	
Induction treatment					0.323
CHT	7	20	0	0	
CHT-RT	28	80	4	100	
Induction treatment chemotherapy cycles					0.556
2	10	28.6	0	0	
4-6	25	71.4	4	100	
Radiotherapy dose					0.279
≤60 Gy	18	64.3	1	25	
>60 Gy	10	35.7	3	75	
yTNM					0.179
I	16	45.7	0	0	
II	18	51.4	4	100	
III	1	2.9	0	0	
Resection					0.099
Lobectomy	25	71.4	1	25	
Pneumonectomy	10	28.6	3	75	
Histopathology					0.792
Adenocarcinoma	11	31.4	1	25	
SqCC	24	68.6	3	75	
Adjuvant					0.556
Negative	25	71.4	4	100	
Positive	10	28.6	0	0	

CHT: Chemotherapy; RT: Radiotherapy; Gy: Gray; SqCC: Squamous Cell Carcinoma; yTNM: Tumor, nodes, and metastases after induction therapy.

chi-square test. Survival probabilities were estimated using the Kaplan-Meier method. A *p* value of <0.05 was considered statistically significant.

RESULTS

Of the patients, four (10.3%) were aged ≥65 years, and the remaining 35 (89.7%) were aged <65 years. The tumor was left-sided in 14 (35.9%) patients and right-sided in the remaining 25 (64.1%) patients. The IT was given to 21 (53.8%) patients for N2 disease and to 18 (46.2%) patients for tumor invasion. In 21 patients with N2 disease, the diagnosis was made through EBUS, anterior mediastinotomy, mediastinoscopy, and PET-CT in six, one, nine, and five patients, respectively. Histopathological examinations revealed

that 16 (41%) patients were single-station N2 positive, while the remaining five (12.8%) were multiple-station N2. In three patients, clinical downstaging could not be determined following IT. In patients with pN0 disease, EBUS and mediastinoscopy after IT were performed in nine and 30 patients, respectively for restaging. The median number of CHT cycles was four (range, 2 to 6). Demographic and histopathological features of the patients are given in Table 1.

The IT included CHT + RT in 32 (82.1%) patients, and CHT only was given in the remaining seven (17.9%) patients. Pneumonectomy was performed in 13 (33.3%) patients, and lobectomy was preferred in the remaining 26 (66.7%) patients. Carinal sleeve pneumonectomy and chest wall resection was

Table 3. Evaluation of prognostic factors affecting survival

	5-year OS (%)	Mean survival (months)	95% CI	*p*
Age (year)				0.337
<65	62.7	75	61-90	
≥65	50	53	11-94	
Resection type				0.113
Lobectomy	67.6	81	65-96	
Pneumonectomy	51.3	53	30-76	
Side				0.307
Left	55.1	58	37-79	
Right	65.1	79	61-95	
Charlson Comorbidity Index				0.377
2	66.4	80	62-97	
>2	55	58	39-76	
Induction treatment				0.597
CHT	68.6	74	51-98	
CHT-RT	59.7	72	55-88	
Histopathology				0.700
Adenocarcinoma	56.3	52	35-73	
Squamous cell carcinoma	63	75	58-91	
Adjuvant				0.497
Negative	58.2	70	52-87	
Positive	68.6	74	53-94	
cN2				0.005
Single cN2	76.7	91	76-106	
Multiple cN2	40	28	15-41	
Induction treatment chemotherapy cycles				0.519
2	68.6	74	53-94	
4-6	58.7	70	53-88	
IT Radiotherapy dose				0.847
≤60 Gy	60.5	73	54-92	
>60 Gy	64.1	34	23-45	

OS: Overall survival; CI: Confidence interval; CHT: Chemotherapy; RT: Radiotherapy; IT: Induction treatment; Gy: Gray.

performed in one (7.6%) patient each. Chest wall resection was performed in 11 (42%) of 26 patients who underwent lobectomy.

Histopathology revealed an adenocarcinoma in 12 (30.8%) patients and squamous cell carcinoma (SqCC) in 27 (69.2%) patients. Mortality was encountered in the first 90 days in four (10.3%) patients. Risk factors affecting mortality in the first 90 days are given in Table 2.

Lymph nodes at an average of six stations were sampled intraoperatively. The mean number of removed lymph nodes was 14.8±8.4. The mean follow-up was 45.0±30 (range, 0 to 106) months. The mean OS was 73.8±7.2 (95% CI: 59,6-88.0) months, and the mean five-year OS was 73.8±7.2 months. When IT was analyzed, neither CHT nor CHT+RT showed any significant effect on OS (p=0.597). Factors affecting OS are given in Table 3. The OS of patients with single-station pN2 was better than in patients with multiple-station pN2 (p=0.005) (Figure 1).

Local (n=3, 7.7%) or distant (n=6, 15.4%) recurrences were detected in a total of nine (23.1%) patients. Local recurrences were in the form of mediastinal recurrence in two patients and ipsilateral
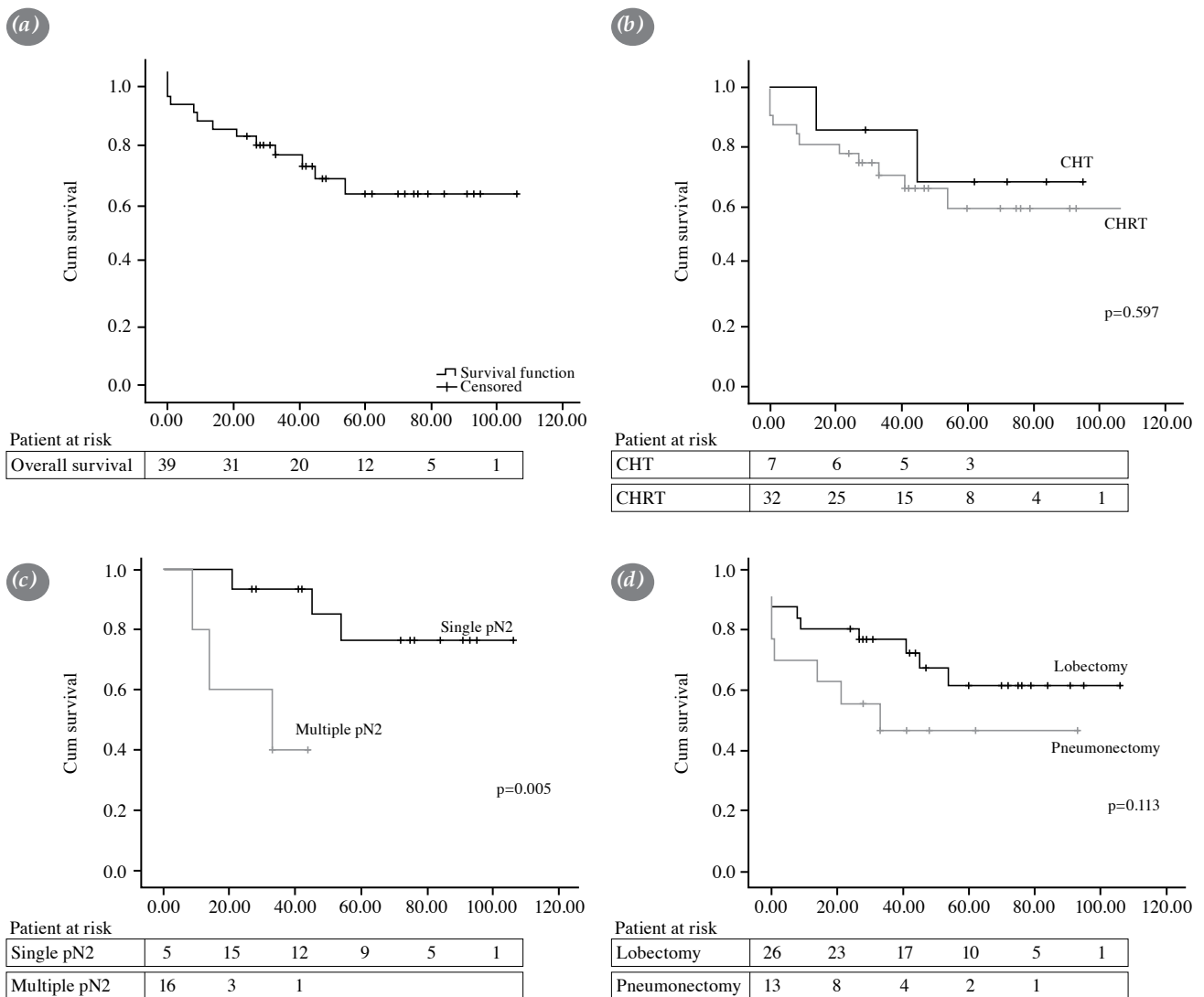
Figure 1. Kaplan-Meier curves of factors affecting survival. **(a)** General survival curve of complete response after IT. **(b)** Survival curve of complete response after chemotherapy or chemoradiotherapy (p=0.597). **(c)** Survival curve of pN status before the IT (p=0.005). **(d)** Survival curve of resection types of the complete response after IT (p=0.113).

CHT: Chemotherapy; CHRT: Chemoradiotherapy; IT: Induction treatment.

Table 4. Factors affecting DFS

	5-year OS (%)	Mean survival (months)	95% CI	p
Side				0.144
Right	60.3	71	54-89	
Left	45.9	46	28-63	
cN2				0.014
Single cN2	70.8	80	63-96	
Multiple cN2	40	27	13-41	
IT				0.274
CHT	68.6	74	51-98	
CHT-RT	52.1	60	45-76	
IT Chemotherapy cycles				0.658
2	60	64	43-85	
4-6	53.7	61	43-79	
IT Radiotherapy dose				0.655
≤60 Gy	55	63	44-82	
>60 Gy	49.5	32	25-43	
Resection type				0.002
Lobectomy	67.6	78	62-93	
Pneumonectomy	27.4	32	16-48	
Adjuvant				0.658
Negative	53.7	61	43-79	
Positive	60	64	43-85	

DFS: disease-free survival; OS: Overall survival; CI: Confidence interval; IT: Induction treatment; CHT: Chemotherapy; RT: Radiotherapy; Gy: Gray.

Table 5. Survival in patients with pCR following IT

Author	Year	n	pCR (n)	pCR (%)	IT protocol	5-year overall survival (%)
DeCamp et al.[29]	2003	105	12	11.4	CHT+RT (total dose: 60 Gy)	N/A
Machtay et al.[8]	2003	53	7	13.2	CHT+RT (total dose: 45-54 Gy)	48 (pCR+pPR)
Cerfolio et al.[21]	2009	216	71	32.8	CHT+RT (total dose: 60 Gy)	N/A
Steger et al.[30]	2009	107	19	17.7	CHT+RT (total dose: 45 Gy)	56
Friedel et al.[28]	2010	120	15	12.5	CHT+RT (total dose: 45 Gy)	67
Weder et al.[26]	2010	176	36	20.4	CHT alone (20%). CHT+RT (80%) (total dose: 45 Gy)	56
Kim et al.[31]	2011	233	52	22.3	CHT+RT (total dose: 43 Gy)	58
Lococo et al.[10]	2012	137	37	27	CHT+RT (total dose: 50 Gy)	64
Mouillet et al.[19]	2012	492	41	8.3	CHT alone	80
Pless et al.[17]	2015	232	27	11.6	CHT alone (51%). CHT+RT (49%) (total dose: 44 Gy)	N/A
Counago et al.[18]	2018	247	32	13	CHT alone (52.5%) + CHT+RT (47.4%) (total dose 44-66 Gy)	N/A
Melek et al.[22]	2019	416	72	17.3	CHT alone (69%). CHT+RT (31%) (45-66 Gy)	72
Current study	2020	187	39	20.8	CHT alone (18%). CHT+RT (82%) (45-66 Gy)	61.2

pCR: Pathologic complete response; IT: Induction treatment; CHT: Chemotherapy; RT: Radiotherapy; Gy: Gray; N/A: Not available; pPR: Pathologic partial response.

lung recurrence in one patient. Evaluation of distant recurrences revealed that four patients had lung metastases in the contralateral lung, one had a recurrence in the contralateral lung, liver, and the adrenal gland, and the remaining one had brain metastasis. Median DFS was 76 (95% CI: 42-109) months. The five-year DFS rate was 55.1%. The type of resection and multiple pN2 was the prognostic factor affecting DFS. Factors affecting DFS are given in Table 4.

DISCUSSION

Researchers have suggested that, in patients with locally advanced NSCLC, surgical treatment alone or only oncological treatment have a lower success rate than combined treatment (IT + surgery) in disease control, local or distant recurrence rates, and long-term survival, and despite the related ongoing debate, combined treatments have found their place in clinical practice.[2,5,6,9,14-18] In the multi-center, randomized study of European Organisation for Research and Treatment of Cancer-08012 (EORTC-08012), combined treatment facilitated, simplified, and reduced surgical treatment by regressing primary cancer and mediastinal involvement, allowed metastases that were undefined at the beginning of treatment to be approachable and dealt with, led to better use of medications before surgery through the vascular integrity of the tumor, and the surgery prevented the possibility of any residual tumor tissue in locally advanced disease.[6] Many studies have shown that, along with IT, better survival rates are obtained with downstaging or pCR.[2,4,8,10,15,19-22] The pCR rates in these studies are reported ranging from 4 to 34%. In the present study, the pCR rate was 20.8%. The discrepancy in the pCR rates can be explained as follows: (i) the differences in the definition of pCR, (ii) treatment protocols of CHT or CHT+RT given as IT, and (iii) histological types. As an example of the differences in the clinical definition of pCR, Cerfolio et al.[23] defined pCR as a 1% or less of viable tumor cells detected on pathological examination of the entire resected specimens. In the present study, pCR was defined as no residual tumor tissue and mediastinal lymph node metastases left behind.

Studies have shown that the addition of an RT protocol to IT increases the chances of obtaining pCR, compared to patients receiving CHT only. In particular, in the European Society for Medical Oncology Clinical Practice Guidelines, it is stated that the rate of pCR is higher in patients undergoing CHT compared to those receiving CHT only.[16] The reason for this finding is

stated as more efficient locoregional control with the addition of RT and lower rates of local recurrence. In the study of Cerfolio et al.,[9] only 30% of patients could be performed surgical treatment following IT, and the reason was suggested to be insufficient treatment response. In this regard and in the light of recent guidelines, the main factor in overall survival, local control of disease, and conversion to surgical treatment is performing effective IT. In the 8805 study of the Southwest Oncology Group (SWOG),[24] IT consisted of the full treatment dose of RT combined with platinum-based CHT, and compared to other studies, about 85% of patients were referred for surgery after IT. In the present study, 286 patients with locally advanced NSCLC were evaluated after IT, 187 (65%) of whom were given the chance of surgical exploration, and a pCR was achieved in 39 (20.8%) of these patients. In IT, combining RT and CHT increases the pCR, and relevant studies have shown that CHT has no negative impact on mortality and morbidity.[25-27] In the study of Galetta and Spaggiari,[25] induction CHT led to a significant increase in the morbidity rates. However, the mortality rates were acceptable, given that the patients had advanced tumors. Similarly, Weder et al.[26] reported mortality as 3% in their series consisting of patients who underwent surgical resection after IT. In the present study, IT, the dose of RT, and tumor diameter had no influence on mortality in patients with pCR. Accordingly, we believe that CHT increases the rate of pCR, despite challenging surgical technique. We consider that the most important reason for the high mortality rates in patients undergoing pneumonectomy is due to the low number of patients and the higher postoperative complications in patients receiving RT.

In the present study, the five-year survival rate in the pCR group was 61.2%. The resection type, tumor size, adjuvant treatment, and the IT protocol had no influence on survival. In the literature, five-year survival rates vary between 48 and 80% in studies with pCR groups (Table 5). Friedel et al.[28] performed a Phase II study and reported a five-year survival rate as 66.7% in the pCR group and, compared to patients without pCR, the difference was statistically significant. Lococo et al.[10] also showed that the type of resection and adjuvant treatment were significant factors for survival of patients with pCR. In the present study, adjuvant treatment and resection type had no influence on survival, contrary to the findings in the literature.

In the literature, patients with pCR are predominantly ≤65 years old.[3] Lococo et al.[10] reported that the pCR response was similar in

patients aged ≥65 years, although the DFS time was found to be longer in those aged ≤65 years than those ≥65 years. In our study, the rate of patients aged ≥65 years with pCR was found to be 10.3%. However, the effect of geriatric age group on disease survival and DFS was not detected. We believe that the most important reason for pCR being detected more than ≥65 years is the better performance of the patients and the fact that they are more adapted to CHT and RT.

In patients with locally advanced NSCLC, better survival results have been reported in patients with single N2 before IT than in those with multiple N2.[10,22,23] Lococo et al.[10] considered multiple pN2 as a poor prognostic factor in terms of survival. In our study, the five-year survival rate in single-station N2 diseases was 76.7% in patients with pCR, and the five-year survival rate in multiple N2 diseases was 40% (p=0.005). On the other hand, resection type had no influence on survival in the present study; however, rates of DFS were better and significant in patients who underwent lobectomy. The reasons for the high survival rates in the present study can be explained as follows: *(i)* IT was given in accordance with recent guidelines and a Surgical Council (including a surgeon, clinician, oncologist, and physiotherapist) was formed with the aim of surgical patient selection after IT; thus the whole procedure was meticulous and deliberate, *(ii)* the patient population of the present study was heterogeneous and patients with locally advanced disease with superior sulcus tumors were included together with patients with pN2 disease, and *(iii)* postoperative follow-ups and rehabilitation were performed systematically.

In locally advanced disease, patients with an SqCC had higher rates of pCR.[19,22] In the study of Melek et al.,[22] pCR was observed in 39 (16.4%) of 238 patients who had an SqCC and underwent surgery after IT, and pCR was observed in nine (8.1%) patients in 111 patients with an adenocarcinoma (p=0.024). Additionally, in the same study, only 28% of patients with an SqCC and 38.7% of patients with an adenocarcinoma were given CHT (p=0.018). In the present study, 69.2% of patients with pCR had an SqCC, and histopathology type had no influence on survival (p=0.700).

The influence of IT on survival was evaluated in the pCR group, and the comparison of patients given CHT and those given CHT only revealed no significant difference. The five-year survival rates were calculated as 59.7% and 68.6% (p=0.59). Similarly, Higgins et al.[5] performed IT as CHT in 31 patients and CHT+R in 71 patients. Rates of pCR and survival were not statistically significantly different between the groups (CHT 41%, CHT+RT 39%) (p=0.65). In the study of Melek et al.,[22] the rate of pCR was higher in patients given CHT+RT, although comparisons with CHT revealed no statistically significant difference in terms of survival. However, Toyooka et al.[32] performed a study in 50 patients, and their patients who were given induction CHT+RT (n=35) had better survival rates, compared to patients given CHT only (n=15) (p=0.002). The pCR was obtained in 20.6% of patients given CHT+RT, and in 6.7% of patients given CHT only.

Studies in the literature have reported low rates of recurrence in patient groups with pCR.[15,19,22] Mouillet et al.[19] reported recurrence as 4.8% and DFS as 80.1% in their pCR group, and the difference in DFS was statistically significant in their patients with SqCC and pCR. In the study of Melek et al.,[22] these same rates were reported as 23.6% and 72%, respectively. However, the study of Lococo et al.[10] was different from the aforementioned studies, since recurrence was observed in 17 (46%) patients. Their five-year DFS rate was 61%, and DFS was statistically significantly different in patients given adjuvant treatment. In the present study, DFS was seen in 55.1% of patients, and recurrence was encountered in nine (23.1%) patients. Analyses of these recurrences revealed that 66.6% were observed in distant organs. The most important factor influencing DFS was resection type and multiple pN2.

The retrospective nature of the study, the limited number of patients, and the fact that more than one surgeon was involved may have led to bias. In addition, N2 disease being a heterogeneous group is another bias. Multivariate analysis could not be performed due to the small number of patients. Due to the missing of the PET-CT data of patients, pCR rates were not specified in the study. Lack of information about the performance status of patients receiving IT and comparison of patient selection criteria in IT are other limitations. Furthermore, survival results could not be compared with the other non-small cell cancers, which can be deemed as another limitation.

In conclusion, multimodality treatment has a very important place in locally advanced disease; however, there is still no consensus in the literature. The results of the present study showed that, in patients with pathological complete response, resection type and induction chemotherapy and chemotherapy + radiotherapy did not affect survival. Although the surgical approach following induction chemotherapy + radiotherapy is

challenging, the chances of pathological complete response and downstaging are increased. Additionally, chemotherapy + radiotherapy and chemotherapy have no effect on mortality. The most important prognostic factor in survival is the single-station N2. Therefore, we recommend that adjuvant therapy should be given to patients with multiple clinical N2 due to poor survival results, even if they have a pathological complete response. Nevertheless, further, prospective, randomized studies are needed to confirm these findings.

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