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Original Article / Özgün Makale

Prognostic significance of pathological complete response in non-small cell lung cancer following neoadjuvant treatment

Küçük hücreli dışı akciğer kanserinde neoadjuvan tedavi sonrası patolojik tam yanıtın prognostik önemi

Mustafa Akyıl[1], Çağatay Tezel[1], Fatma Tokgöz Akyıl[2], Deniz Gürer[1], Serdar Evman[1], Levent Alpay[1], Volkan Baysungur[1], İrfan Yalçınkaya[1]

[1]Department of Thoracic Surgery, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
[2]Department of Pulmonary Diseases, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Background: This study aims to investigate the factors associated with pathological complete response following neoadjuvant treatment and to examine the prognostic value of pathological complete response in patients with non-small cell lung cancer undergoing surgical resection.

Methods: Between February 2009 and January 2016, a total of 112 patients (96 males, 16 females; mean age 60±8 years; range, 37 to 85 years) with the diagnosis of non-small cell lung cancer who underwent anatomical pulmonary resection after neoadjuvant treatment were retrospectively analyzed. Demographic, clinical, radiological, and pathological characteristics of the patients were recorded. The patients were classified as pathological complete response and non-pathological complete response according to the presence of tumors in the pathology reports. Predictive factors for pathological complete response and its prognostic significance were analyzed.

Results: The mean follow-up was 35±20 (range, 0 to 110) months. Of the patients, 30 (27%) achieved a pathological complete response. Reduction rate in tumor size was significantly higher in the responsive group (32.5±21.6% vs. 19.2±18.8%, respectively) and was a predictor of pathological complete response independent from the T and N factors (p=0.004). Survival of the responsive patients was significantly longer than unresponsive patients (75±9 vs. 30±4 months, respectively; p<0.001). During follow-up, tumor recurrence was seen in 30 patients. Recurrence was observed in only one patient in the responsive group, while 29 patients in the unresponsive group had recurrence or metastasis.

Conclusion: Tumor shrinkage rate after neoadjuvant treatment in non-small cell lung cancer is a predictive factor for pathological complete response. Survival of patients with a pathological complete response is also significantly longer than unresponsive patients.

Keywords: Neoadjuvant treatment, non-small cell lung cancer, pathological complete response.

ÖZ

Amaç: Bu çalışmada cerrahi rezeksiyon yapılan küçük hücreli dışı akciğer kanserli hastalarda neoadjuvan tedavi sonrası patolojik tam yanıt ile ilişkili faktörler araştırıldı ve patolojik tam yanıtın prognostik değeri incelendi.

Çalışma planı: Şubat 2009 - Ocak 2016 tarihleri arasında küçük hücreli dışı akciğer kanseri tanısı konulan ve neoadjuvan tedavi sonrasında anatomik pulmoner rezeksiyon yapılan toplam 112 hasta (96 erkek, 16 kadın; ort. yaş 60±8 yıl; dağılım, 37-85 yıl) retrospektif olarak incelendi. Hastaların demografik, klinik, radyolojik ve patolojik özellikleri kaydedildi. Hastalar patoloji raporunda tümör varlığına göre patolojik tam yanıt ve patolojik tam yanıt olmayanlar olmak üzere sınıflandırıldı. Patolojik tam yanıtın öngördürücü faktörleri ve prognostik önemi incelendi.

Bulgular: Ortalama takip süresi 35±20 (dağılım, 0-110) ay idi. Hastaların 30'unda (%27) patolojik tam yanıt elde edildi. Tümör boyutunda görülen küçülme oranı, yanıt veren grupta anlamlı düzeyde daha yüksek olup (sırasıyla %19.2±18.8'e kıyasla %32.5±21.6), T ve N faktörlerinden bağımsız olarak, patolojik tam yanıtın bir öngördürücü idi (p=0.004). Yanıt veren hastaların sağkalım süresi, yanıt vermeyenlere kıyasla anlamlı düzeyde daha uzundu (sırasıyla, 30±4 aya kıyasla 75±9 ay, p<0.001). Takip süresince 30 hastada tümör nüksü izlendi. Yanıt veren grupta bir hastada nüks gözlenir iken, yanıt vermeyen grupta 29 hastada nüks veya metastaz izlendi.

Sonuç: Küçük hücreli dışı akciğer kanserinde neoadjuvan tedavi sonrası tümör küçülme oranı, patolojik tam yanıtın öngördürücü bir faktörüdür. Ayrıca patolojik tam yanıtlı hastaların sağkalım süresi, yanıt vermeyen hastalara kıyasla anlamlı düzeyde daha uzundur.

Anahtar sözcükler: Neoadjuvan tedavi, küçük hücreli dışı akciğer kanseri, patolojik tam yanıt.

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Correspondence: Mustafa Akyıl, MD. Süreyyapaşa Göğüs Hastalıkları ve Göğüs Cerrrahisi Eğitim ve Araştırma Hastanesi Göğüs Cerrahisi Kliniği, 34844 Maltepe, İstanbul, Türkiye. Tel: +90 216 - 421 42 00 e-mail: makyil@hotmail.com

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Lung cancer is the most common cancer in both genders and is responsible for more than 25% of all cancer-related deaths. Among these cases, the five-year survival rate is below 21%.[1-3] Primary lung cancer mainly consists of small cell lung cancer and non-small cell lung cancer (NSCLC) and the latter represents approximately 85% of the whole.[4] Surgical anatomical resection is the gold-standard treatment option in patients with early stage NSCLC. Only 25% of the lung cancers are eligible for surgery, and the other treatment options of chemotherapy and radiotherapy have been increasingly applied in recent years.[3]

In locally advanced disease, complications of surgical treatment alone have resulted in locoregional failure and distant metastasis and, therefore, neoadjuvant treatment before definitive local treatment has been initiated.[5] In Stage IIIA(N2), progression-free survival is reported to be longer with surgery after chemoradiotherapy with no significant survival advantage.[6] Further studies have proved survival benefit with neoadjuvant chemotherapy.[5] The role of adding neoadjuvant radiotherapy to chemotherapy is not yet clear, since a clear survival benefit compared to sole chemotherapy has not been proven.[7] However, the treatment decision in locally advanced disease is challenging, as it includes a widely heterogeneous patient group and the effective treatment decision should be made by a Medical Council.

Other than Stage III disease, Stage II NSCLC patients may benefit from neoadjuvant treatment.[8] The main advantages of neoadjuvant therapy include diminished tumor volume and improved micrometastasis control, leading to accurate assessment of sensitivity and resistance of the agents and providing better treatment tolerability and earlier cessation of smoking.[9]

Following neoadjuvant treatment, the assessment of pathological response and the prognostic importance of pathological complete response (pCR) in surgical specimens have been questioned recently.[9-11] In cases where the surgical specimens contain no viable tumor cells, naming pCR, the prognosis is reported to be significantly better.[11-13]

The reported pCR rates varies in a wide range. The width of this range mostly depends on the study method, pCR definition, and patient selection criteria. In a series of 127 patients, Coroller et al.[10] reported pCR in 21% and Mouillet et al.[11] in 8%. In local advanced NSCLC, patients with pCR were shown to have a better prognosis than non-pCR patients and were recommended to be restaged in the TNM classification.[14]

These improved survival rates observed in pCR patients have led to the factors associated with complete response to be questioned. Varied results have been published in a limited number of studies investigating this issue and yet, there is no predictor for a better response to neoajuvant treatment. The tumor type is the mostly argued issue that both adenocarcinoma and squamous cell carcinoma are found to be associated with pCR.[11,15,16]

In the present study, we aimed to investigate the factors associated with pCR following neoadjuvant treatment and to examine the prognostic value of pCR in NSCLC patients undergoing surgical resection.

PATIENTS AND METHODS

This single-center, retrospective study was conducted in a tertiary referral center for chest diseases and thoracic surgery between February 2009 and January 2016. A total of 112 patients (96 males, 16 females; mean age 60±8 years; range, 37 to 85 years) with the diagnosis of NSCLC who underwent anatomical pulmonary resection after neoadjuvant treatment were included. Patients who were not followed in our center with missing recurrence or metastasis data were excluded. The study flow chart is shown in Figure 1. A written informed consent was obtained from each patient. The study protocol was approved by the Süreyyapaşa Chest Disease and Thoracic Surgery Training and Research Hospital Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data including demographic, clinical, radiological, and pathological characteristics of the patients, smoking habit, location and size of the tumor, fluorodeoxyglucose (FDG) uptake on positron emission tomography-computed tomography (PET-CT), diagnostic methods,

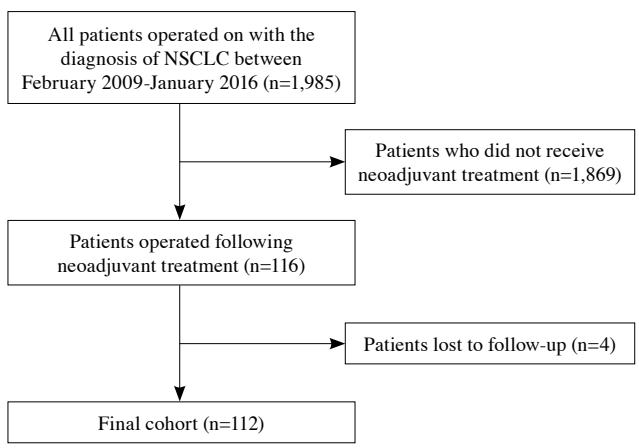

Figure 1. Study flowchart.

and histological types of the tumor were recorded. Clinical staging was supplemented according to the current seventh edition of the Tumor, Node, Metastasis (TNM) Classification of Malignant Tumors.[17] The indications for neoadjuvant treatment and treatment regimen, post-treatment tumor size, and radiological stage were investigated. The surgical resection type was recorded based on the additional invasive procedures to investigate N2 lymph node positivity. The tumor size was determined using pathological evaluation of the resected material. In addition, all patients were evaluated for the development of recurrence or metastasis during follow-up until January 2017. Survival status was also checked using the National Death Reporting System.[18]

Oncological evaluation and surgical method

In our center, a Medical Council including specialists in chest diseases, thoracic surgery, medical oncology, radiology, pathology, and radiation oncology evaluates cases of lung cancer and gives the decision of neoadjuvant treatment. The eligibility of the patient for surgery after the treatment is also evaluated by the Medical Council. After a radiological evaluation, the diagnostic procedures are indicated. These procedures include bronchoscopy, endobronchial ultrasonographic endoscopy (EBUS), transthoracic fine-needle aspiration biopsy (TTFNAB), video-assisted thoracoscopic surgery (VATS), thoracotomy, mediastinoscopy, and mediastinotomy. Detection of a lymph node measuring >2 cm in size on the mediastinal long axis or >1 cm in size on the mediastinal short axis on thoracic CT, or a mediastinal lymph node with a maximum standardized uptake value (SUV_{max}) value of 2.5 on PET-CT is considered metastasis in the radiological staging.[19] A thoracic CT or PET-CT is used for radiological staging after neoadjuvant treatment, and in some cases, staging is performed during a surgical procedure. Re-mediastinoscopy is performed in cases of clinical necessity, since it is advised as a specific and sensitive procedure to avoid unnecessary thoracotomies.[20]

Hematological and biochemical examinations, as well as cardiac and respiratory reserve evaluation are routinely performed before surgery. Anatomical pulmonary resection is performed via thoracotomy or VATS. Either mediastinal lymph node dissection or mediastinal lymph node sampling is performed according to the European Society of Thoracic Surgeons guidelines.[21]

The patients were divided into two groups according to the histopathological examination of the surgical resection material according to the presence of viable tumor cells:

Group 1 (pCR, n=30): Patients without histopathological evidence of tumor cells.

Group 2 (non-pCR, n=82): Patients with histopathological evidence of tumor cells in various sizes.

The clinical and radiological characteristics of all patients were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[22] The sizes of the tumor before and after neoadjuvant treatment were evaluated, and the TNM stage was compared between the groups. In addition, the development of recurrence or metastasis during follow-up and survival rates were compared.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 16.0 software (SPSS Inc., Chicago, IL, USA). The quantitative data were expressed in mean ± standard deviation (SD) or median (min-max), while the qualitative data were expressed in number and frequency. For comparative statistics, a t-test was used for the analysis of quantitative data and a chi-square test was used for the analysis of qualitative data. The diagnostic power of the parameters found to be significant in the diagnosis was evaluated according to the sensitivity, specificity, and cut-off values using the Receiver Operating Characteristic (ROC) curve. Logistic regression analysis was used for independent predictors of pCR. The Kaplan-Meier method was used for survival analysis. A p value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Of all patients, 70 (63%) were diagnosed via fiberoptic bronchoscopy and 31 (27%) via TTFNAB. Other diagnostic methods were mediastinoscopy (n=6), EBUS (n=3), rigid bronchoscopy (n=1), and VATS (n=1). Patient data are shown in Table 1.

Ninety-five patients (85%) had Stage IIIA, 14 patients (12%) had Stage IIB, and three patients (3%) had Stage IIIB disease prior to neoadjuvant therapy (Table 2). In Stage IIB, neoadjuvant treatment was applied for chest wall tumors and pancoast tumors. Neoadjuvant chemotherapy regimens consisted of paclitaxel and carboplatin (n=54, 48%) and cisplatin-docetaxel (n=46, 41%) combinations. The mean radiotherapy dose was 58.5 (range, 45 to 66) Gy.

Table 1. Demographic, clinical, radiological, and pathological characteristics of patients

	All patients			pCR (n=30)			Non-pCR (n=82)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			60±8			60.4±8.2			59.5±8	0.818
Gender										0.862
Female	16	14		4	13		12	15		
Male	96	86		26	87		70	85		
Smoking status										0.163
Ever smoker	10	90		29	97		72	88		
Non-smoker	11	10		1	3		10	12		
Smoking load (pack/years)			30.8±14			34±14			29±1	0.684
Tumor location										0.450
Right upper lobe	65	58		21	70		44	54		
Right lower lobe	10	9		2	7		8	10		
Left upper lobe	29	26		6	20		23	27		
Left lower lobe	5	4		0	0		5	6		
Right middle lobe	3	3		1	3		2	3		
Tumor size at diagnosis (cm)			4.98±1.8			5.2±1.9			4.9±1.9	0.497
Tumor SUV_{max} at diagnosis			15.3±5.7			15.9±6.4			15.1±5.4	0.522
Tumor histology										0.355
Squamous cell carcinoma	66	59		20	67		46	56		
Adenocarcinoma	42	37		10	33		32	39		
Other	4	4		0	0		4	5		
Indication for neoadjuvant treatment										0.450
Clinical N2	75	67		24	80		51	62		
Clinical T4	23	21		4	13		19	23		
Pancoast tumor	14	12		2	7		12	15		
Neoadjuvant chemotherapy regimens										0.361
Paclitaxel-carboplatin	54	48		14	47		40	49		
Cisplatin-docetaxel	46	41		15	50		31	38		
Cisplatin-gemcitabine	7	6		1	3		6	7		
Other	5	5		0	0		5	6		
Type of neoadjuvant treatment										0.345
Chemotherapy	80	71		18	60		62	76		
Radiotherapy	2	27		0	0		2	3		
Chemoradiotherapy	30	2		12	40		18	21		
Radiotherapy dose (Gy)			58.5±8.1			57±7.9			61±6.8	0.342
Radiological tumor size after neoadjuvant therapy (cm)			3.8±1.7			3.4±1.5			3.9±1.8	0.662
Tumor SUV_{max} after neoadjuvant therapy			10.4±4.7			9±5.7			10.8±4.5	0.452
RECIST v1.1* after neoadjuvant therapy*										0.02
Partial response	54	48		21	70		33	40		
Progressive disease	52	47		1	3		5	6		
Stable disease	6	5		8	27		44	54		
Tumor shrinkage rate (%)						33±22			19±19	0.02
Type of surgery										0.057
Lobectomy/bilobectomy	90	80		28	93		62	76		
Pneumonectomy	22	20		2	7		20	24		
Pathological tumor size (cm)			2.6±2.3			3.5±2.0			0.0	<0.001

pCR: Pathological complete response; SD: Standard deviation; SUV_{max}: Standardized uptake value; RECIST: Response Evaluation Criteria in Solid Tumors. * RECIST version 1.1.

Table 2. Clinical and pathological staging before and after neoadjuvant treatment*

	Clinical stage before neoadjuvant treatment	Clinical stage after neoadjuvant treatment	Pathologic
	Number	Number	Number
T0	-	-	30
T1a	4	10	9
T1b	12	22	12
T2a	20	28	14
T2b	20	13	23
T3	33	24	20
T4	23	14	4
N0	26	51	71
N1	10	28	28
N2	76	33	13
IA	-	10	8
IB	-	10	5
IIA	-	23	29
IIB	14	20	17
IIIA	95	49	22
IIIB	3	-	1

* According to the 7th TNM classification of malignant tumors; TNM: Tumor, node, metastasis.

Neoadjuvant treatment was given due to clinically N2 disease in 75 (67%) and clinical T4 disease in 23 patients (21%). The most common cause of a clinical T4 appraisal was mediastinal invasion with other causes being the presence of an additional nodule or major vessel invasion.

Following neoadjuvant treatment, 55 patients (49%) with a suspected N2 tumor were scheduled for mediastinoscopy, six patients (6%) for re-mediastinoscopy, and three (2%) for extended mediastinoscopy. In addition, resection of aortopulmonary window lymph nodes after VATS was performed in one patient (1%).

After completion of neoadjuvant treatment, the mean resectional surgery duration was 4.2±1 (range, 2 to 7) weeks. Lobectomy was performed in 76 (66%), pneumonectomy in 22 (20%), and bilobectomy in 14 patients (11%). Two patients (2%) underwent a superior sleeve bilobectomy, while two patients (2%) underwent a right upper sleeve lobectomy. The surgical procedure was terminated with an R1 resection in three patients (3%), and an R0 in 109 patient (97%). According to the pathology reports, no tumor cells were found in 30 patients (27%), and they were evaluated as pCR (Table 1).

There was no significant difference in gender (p=0.862), age (p=0.818), smoking habit (p=0.163), tumor characteristics (p=0.355), indications for

Table 3. Comparison of the patients with pT0 and non-pT0 according to clinical staging

	pCR (n=30)	Non-pCR (n=82)	
	Number	Number	*p*
T1a	1	3	0.946
T1b	3	9	
T2a	6	14	
T2b	6	14	
T3	10	24	
T4	4	18	
N0	5	21	0.482
N1	2	8	
N2	23	53	
Stage IIB	2	12	0.278
Stage IIIA	28	67	
Stage IIIB	0	3	

pCR: Pathological complete response.

Table 4. Logistic regression analysis results

	Beta coefficient	Standard error	Wald	Significance	Exponential beta	95% CI
Tumor shrinkage rate	-0.284	0.002	-2.293	0.004	-0.006	-0.010-1.260
T factor	0.037	0.036	0.325	0.746	0.012	-0.059-0.082
N factor	-0.032	0.061	0.274	0.785	-0.017	-0.137-0.104
Constant	0.849	0.207	4.091	<0.0001	0.849	0.437-1.260

Wald: Wald test in the logistic regression; CI: Confidence interval.

neoadjuvant treatment (p=0.45), chemotherapy regimens (p=0.361), and treatment modalities (p=0.345) between the pCR and non-pCR groups. Chemotherapy regimens (p=0.361) and radiotherapy doses (p=0.342) had no effect on pCR. There was no statistically significant difference between the groups in terms of resection type (p=0.057) or the development of bronchopleural fistula during follow-up (p=0.128).

The radiological tumor sizes of pCR and non-pCR groups at the time of diagnosis were 5.2±1.9 vs. 4.9±1.9 cm, respectively (p=0.497). Following neoadjuvant therapy, the mean radiological tumor sizes were similar between the groups (3.4±1.5 cm vs. 3.9±1.8 cm, respectively; p=0.662). In five patients, the mean tumor enlargement ratio was 0.26 (range, 0.1 to 0.5) cm after neoadjuvant treatment. One of those patients was grouped as pT0 (the tumor was 2.0 cm at the time of diagnosis and 2.1 cm before surgery). However, according to the RECIST v1.1 criteria, the partial response rate was higher in the pCR group (p=0.02). The sizes of the tumors decreased to a greater extent in the pCR group (32.5±21.6% vs. 19.2±18.8%, respectively; p=0.002).

There was no statistically significant difference between the groups in terms of the T or N factor of clinical staging (Table 3). Neoadjuvant pre- and post-treatment N factors significantly regressed in both pCR and non-pCR groups (p=0.008 and p<0.001, respectively), indicating a statistically significant difference between the groups (p=0.563).

A logistic regression analysis revealed that radiological tumor size shrinkage independently predicted the pCR apart from T and N factors (Table 4). For a cut-off value of 22.4% of tumor shrinkage after neoadjuvant therapy, the possibility

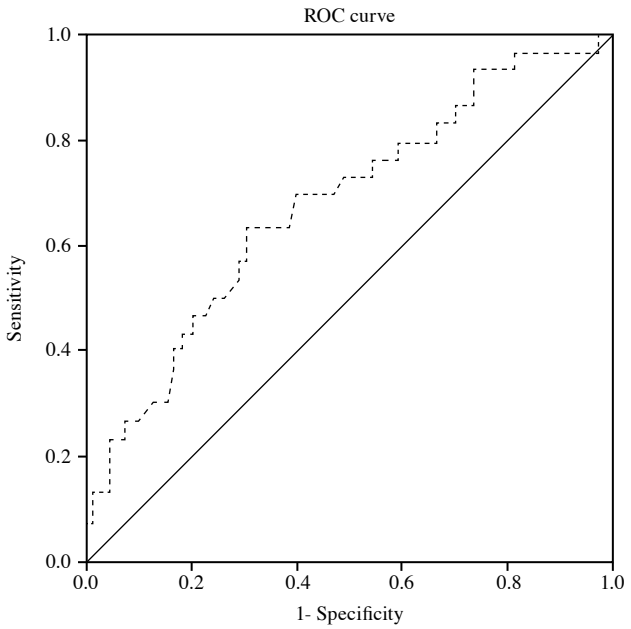

Figure 2. ROC curve for tumor shrinkage.
ROC: Receiver operating characteristic.

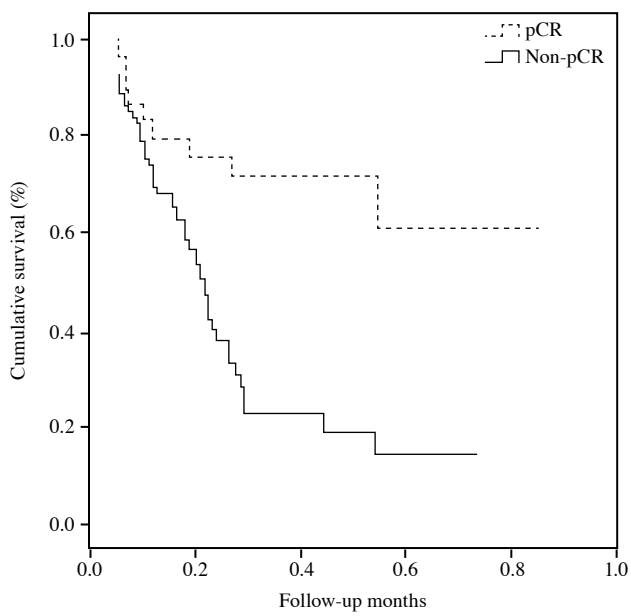

Figure 3. Survival curve for pCR and non-pCR patients.
pCR: Pathological complete response.

of pCR increased with 75% sensitivity and 63% specificity (the area under the curve value for tumor size was 0.676; p=0.004) (Figure 2).

The mean follow-up was 38±3 (range, 1 to 132) months. During follow-up, 15 patients (13%) had a recurrence and 15 patients (13%) had a distant organ metastasis. Six patients (5%) patients died within the first postoperative 30 days in the non-pCR group, while no mortality was observed within the initial postoperative 30 days in the pCR group. During follow-up, 62 patients (55%) died. The median survival was longer in the pCR group (75±9 vs. 30±4 months, respectively; p<0.001) (Figure 3). Recurrence was observed in only one patient (3%) in the pCR group, while 29 patients (35%) had recurrence or metastasis in the non-pCR group.

DISCUSSION

In the present study, more than one-fourth of the NSCLC patients who received preoperative cancer treatment were found to have pCR. In the pCR group, after neoadjuvant treatment, a marked decrease in the tumor size was observed radiologically, and this appears to be the first reported demonstration of this relationship. In addition, the disease-free survival of these patients was better and the length of time until recurrence was longer.

It has been reported that pCR patients who receive preoperative treatment have a longer survival time, compared to patients with early-stage NSCLC.[11,12] Katakami et al.[13] reported a five-year survival rate of 79% for NSCLC patients who had a complete response after neoadjuvant treatment. Similarly, Mouillet et al.[11] found a statistically significant higher five-year survival rate (80%) and Melek et al.[14] reported this figure as 72%. In a study conducted by Betticher et al.,[12] the rate of distant metastasis and recurrence was lower in pCR patients who underwent surgery after three cycles of neoadjuvant chemotherapy. Other studies also demonstrated that the rate of recurrence or metastasis was lower in patients with established pCR.[23,24] In line with the literature, the present study found that survival time was significantly longer in the pCR group and that the rate of recurrence or metastasis was lower than that of the non-pCR group. Thus, identifying these patients beforehand is of great importance for clinicians, as the achievement of pCR strongly predicts a favorable prognosis.

The rates of pCR differ among the conducted studies in the literature, ranging from 0 to 34% (Table 5).[14,25,26] Betticher et al.[12] reported pCR in 14 (19%) of 75 patients; however, they included tumors containing necrosis and fibrosis at a rate of ≥95%. Cerfolio et al.[25] also reported pCR in 19 (34%) of 56 patients, but defined pCR as the presence of viable tumor cells in ≤1% of the entire field of pathological examination. In the present study, the absence of any viable tumor cells in the pathological examination was defined as pCR, and a similar pCR rate was found.

To the best of our knowledge, there is no study examining the link between lymph node involvement or pancoast tumors and pCR. Albain et al.[6] found pCR in 14% of the patients who received neoadjuvant treatment only due to their N2 status. In another study including 574 N2 patients, pCR was detected in 13% of the cases.[27] In previous studies where pancoast tumors are considered an indication for neoadjuvant therapy, Rusch et al.[28] and Kunitoh et al.[29] detected pCR in 26% and 21% of their cases, respectively. In another study involving only cases with a pancoast tumor, the pCR rate was found to be 32%.[30] In our study, we found no statistically significant correlation between N2 and neoadjuvant treatment, although the ratio of patients who received neoadjuvant treatment for an N2 tumor was relatively higher. The pCR rate in cases with pancoast tumors was found to be closer to the rate reported in the literature.[30]

According to the histological type of tumors, variable results have been reported in the literature. Pisters et al.[15] found a statistically significantly higher rate of pCR in patients with adenocarcinoma. Mouillet et al.[11] reported squamous cell carcinoma as the sole predictor of pCR. Similarly, some other authors found higher rates of pCR in patients with squamous

Table 5. Rate of patients with pCR in the literature

	All patients	pCR	pCR
	Number	Number	%
Coroller et al.[10]	127	27	21.3
Depierre et al.[23]	173	19	11
Pisters et al.[15]	73	9	12
Mouillet et al.[11]	492	41	8
Cerfolio et al.[25]	56	19*	33.9
Betticher et al.[12]	75	14**	19
Roth et al.[26]	28	0	0
Melek et al.[14]	416	72	17
Present study	112	30	26.7

pCR: Pathological complete response; * Pathological complete response rate was defined as the presence of viable tumor cells ≤1% in histopathological examination; **These authors defined pathological complete response rate as the presence of tumors containing ≥95% necrotic and fibrotic tissue.

cell carcinoma.[10,31] A recent study concluded that squamous cell carcinoma responded better to neoadjuvant chemotherapy and that major pathological response criteria for adenocarcinoma and squamous cell carcinoma should be different.[16] In the present study, the pCR rate was higher in the patients with squamous cell carcinoma, but without a statistical significance. This may be due to the effect of genetic factors or molecular markers, rather than due to the tumor histology. Further researches would improve our understanding of this issue.

The results of the previous studies are in favor of an increased respectability of platinum-based regimens.[5] In the present study, chemotherapy regimen showed no significant effect on PCR rates. Cisplatin-docetaxel combination regimen had a slightly higher PCR rates, although the difference was not significant. Future studies may shed light into the therapeutic effect of immunotherapy and be helpful to identify the most effective chemotherapy combination. The addition of radiotherapy to neoadjuvant chemotherapy was also reported to increase the rate of pCR; however, the pathological response did not increase overall survival.[32,33] In our study, the patients with neoadjuvant chemoradiotherapy had a higher rate of pCR, while no statistically significant correlation was observed. Although the form of treatment is often not statistically significant, it may be helpful to better identify the molecular markers and determine the most appropriate individualized treatment modality.

The present study indicated a greater shrinkage in tumor size in the pCR group. To the best of our knowledge, there are two studies investigating this relationship before. Pisters et al.[15] in a series of 21 patients, and Cerfolio et al.[25] in a series of 36 patients found no significant relationship between change in the tumor size and pCR. Of note, in both studies, the sample size was lower than in our study. The rate of reduction in tumor size may be an indicator of response to neoadjuvant treatment. However, further studies are needed in this area.

The main limitations of the present study are its single-center and retrospective design. The main strengths of the study include close follow-up of the patients in the tertiary referral setting and the availability of complete, detailed documentation of the patients.

In conclusion, pathological complete response can be achieved in a significant number of non-small cell lung cancer patients undergoing surgical resection after neoadjuvant treatment. Patients with a pathological complete response have significantly better survival. The rate of shrinkage in tumor size following neoadjuvant treatment may be helpful in predicting pathological complete responses.

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