Evaluation of the efficacy of pretreatment chest CT markers in predicting response to neoadjuvant chemoradiotherapy in locally advanced non-small cell lung cancer (NSCLC)

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Abstract

Aim: To investigate baseline enhanced chest CT findings that may predict progression or response to neoadjuvant chemoradiotherapy.

Methods: Multiple parameters to be obtained from baseline enhanced chest CT scans of 140 patients with NSCLC who had baseline enhanced chest CT scans before neoadjuvant chemoradiotherapy were noted. In addition to CT features of tumour tissues, age, gender, tumour cell types, lymph node TNM stages, distant metastases on baseline enhanced chest CT, bronchial and vascular invasion were also evaluated. Chest CT findings and changes in tumour tissue at 3 and 6 months during neoadjuvant treatment were noted. Patients were operated after the end of neoadjuvant treatment. It was investigated which parameters could predict response to neoadjuvant treatment and which findings could predict progression.

Results: Progression and mortality rates were found to be low in patients with remission (p<0.001). None of the parameters on baseline chest CT before neoadjuvant treatment predicted response to neoadjuvant treatment. According to the results of the analysis, patients with lymph node station had a 3.69 -fold efect [odds ratio (OR)=3.693, [95% confdence interval (CI)= 1.875–7.274, p=0.041] effect on progression (p<0.001).

Conclusions: It has been observed that any of the parameters that can be obtained from baseline chest CT examination before neoadjuvant treatment are not successful in predicting neoadjuvant treatment response. Lymph node is the only baseline chest CT finding that can predict progression.

Keywords: *Neoadjuvant chemoradiotherapy, non-small cell lung cancer, chest CT, prognosis, pathologic response*

1. Introduction

Lung cancer is the most common cause of cancer-related death worldwide[1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all types of lung cancer, with lung adenocarcinoma and lung squamous cell carcinoma (SCC) accounting for 60% and 15% of histologic subtypes, respectively[1]. With the advent of new developments in neoadjuvant therapy and immunotherapy, the overall survival (OS) of patients with NSCLC has improved significantly. For patients with locally advanced NSCLC, neoadjuvant therapy plays an important role in both staging of lung cancer and providing an opportunity for surgery that effectively improves prognosis[2]. Neoadjuvant chemoradiotherapy (CRT) followed by surgical resection improves survival compared to surgery alone in patients with locally advanced non-small cell lung cancer, especially in patients with a complete pathological response or major pathological response (MPR) (classically defined as a residual tumor burden of <10%)[1]. Neoadjuvant CRT has become a vital strategy to reduce tumor size and facilitate surgical resection[3]. Neoadjuvant CRT also allows interim assessments of response to treatment and prevents the development of micrometastases[4].

Traditional neoadjuvant therapy includes chemotherapy and

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chemoradiation, and revolutionary neoadjuvant therapies for NSCLC are evolving[4]. However, tools and predictive models to estimate the prognosis of patients receiving neoadjuvant therapy followed by lung surgery are still limited[5]. The aim of this study was to evaluate whether chest CT findings can predict neoadjuvant treatment response in patients with locally advanced non-small cell lung cancer.

2. Materials and methods

2.1. Patient Selection and Study Design

This retrospective study was approved by our institutional ethical committee and carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. The requirement for informed consent from the patients was waived due to the retrospective nature of the study.

The American Joint Committee on Cancer (AJCC) TNM staging system is the most commonly used tool to predict recurrence and survival. For the N descriptor, the lymph node (LN) is based on the lymphatic territory involved without any information on the number of dissected LNs (NDLN) and the number of positive LNs (NPLN). Since January 2017, the 8th edition of TNM in Lung Cancer has been used as the standard for non-small cell lung cancer staging. This staging system was used in our study. In this study, all findings that could be obtained from chest enhanced CT examination of patients with locally advanced lung cancer were included in the investigation. For neoadjuvant treatment response, 3rd and 6th month control chest CT scans were performed and changes around the tumor and changes in tumor size were noted. Tumors in remission and operable tumors were operated. Patients who were not operable after neoadjuvant treatment were excluded from the study (Figure 1).

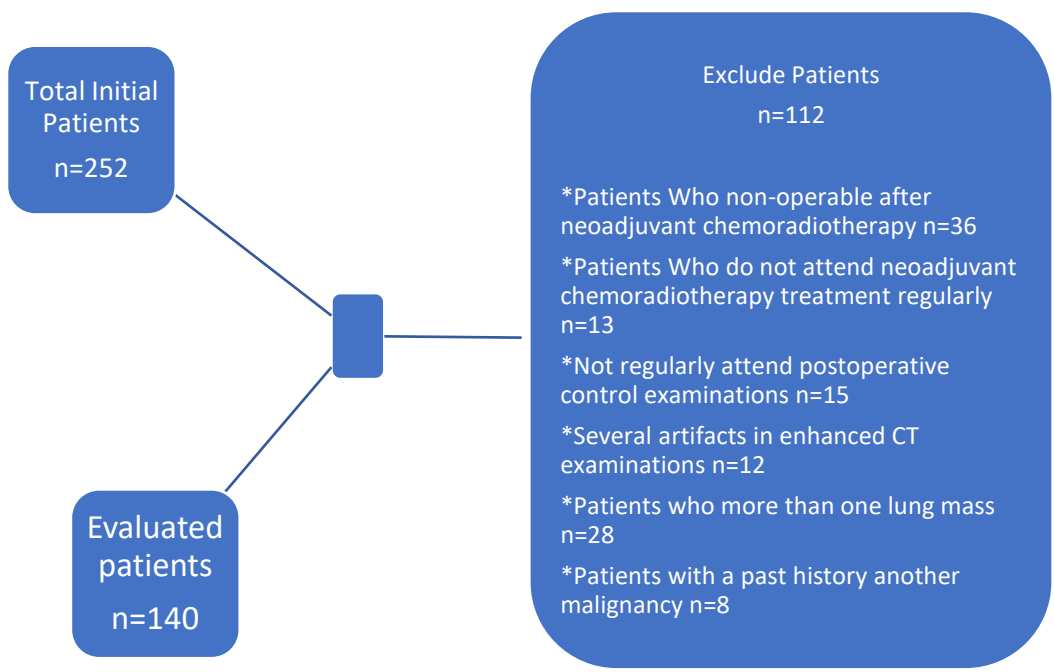
Individuals with diffuse or multiple nodules were excluded. Subsolid, ground glass and cavitary non-solid masses were excluded.

2.2. Chemoradiotherapy Protocols

Although there was previously no standard treatment management in locally advanced lung cancer, treatment algorithms have recently changed with the integration of immunotherapy into neoadjuvant treatment 6. To the best of our previous knowledge, neoadjuvant therapy may improve resectability by decreasing the T stage and nodal disease stage and increasing local regional control by removing residual tumor and nodal disease 7. Data from phase II trials show that neoadjuvant chemoradiotherapy is well tolerated in active patients with good performance status. In contrast, the survival benefit of neoadjuvant chemoradiation compared with induction chemotherapy has not been clearly established due to inconsistent results of Phase III trials.

Figure 1

The initial overall number of patients, together with the number of patients included in the study, is demonstrated. The number of patients excluded from the study and exclusion criteria of the study are shown.



There are 2 different chemotherapies commonly used with concurrent chemoradiotherapy. The first one is the weekly administration of paclitaxel and carboplatin, while the other is the combination of cisplatin and Etoposide. These two chemotherapy combinations have been compared in a previous clinical trial. Although there was no statistical significance in overall survival, there was a numerical improvement in the cisplatin and Etoposide arm. However, this numerical improvement was associated with an increased toxicity profile 8. All of the patients included in this study were patients who received neoadjuvant chemoradiotherapy and then underwent surgery. The combination of carboplatin and paclitaxel is the chemotherapy protocol used simultaneously with radiotherapy in our center because of its easy tolerability. Therefore, weekly carboplatin and paclitaxel treatment was used in all patients in the study. Radiologic response evaluation was performed 4-6 weeks after completion of chemoradiotherapy and operable patients in remission were operated.

Imaging Technique

Thorax CT scans were performed in a 128-detector scanner (Philips Ingenuity 128; Philips, Eindhoven, The Netherlands). All scans were completed in a single breath-hold in the supine position. The standard scanning area was designated as the space between the apex of the lungs and the costophrenic angles. The CT parameters were designated as follows: 80-120 kVp; 100-200 mAs; gantry rotation time = 0.4 s; pitch = 0.8 or 1; slice thickness = 1 mm; and slice reconstruction = 3 mm; FOV :350 mm. Axial, sagittal, and coronal reformatted images were acquired from the raw slices. The radiation dose received by the patients was calculated as 3-5.5 mSv. The enhanced scan was performed using a high-pressure syringe, injecting non-ionic iodine (iohexol; 350 mg/mL; injection amount, 1.5-2 mL/kg; injection rate, 3 mL/s) intravenously through the elbow. The mediastinum window was set [width, 350 Hounsfield units (HU); level, 40 HU], and the lung window was also set (width, 1,200 HU; level, -600 HU). All raters performed their evaluations using separate individual Intellispace Service Healthcare (IPS) workstations.

CT Evaluation

The pathology results of the tumor tissue, presence or absence of additional comorbidities, smoking history, age and gender were completely concealed from the readers. The readers evaluated the localization of the tumor tissue in two ways: central and peripheral. They noted the segments in which the lesion was located and the longest dimension of the lesions. Readers noted the lesion contours under 4 main headings; 1) round smooth 2) macrolobulated 3) microlobulated 4) spiculated. Readers noted the types of calcification of the lesions under 4 headings; 1) no calcification 2) central calcification 3) eccentric calcification 4) coarse calcification. Necrosis status was categorized under 3 headings; 1) no necrosis 2) <50% necrosis 3) >50% necrosis. The types of atelectasis adjacent to the lesion were noted by the readers under 5 headings. 1) no atelectasis 2) subsegmental 3) segmental 4) lobar 5) total atelectasis.

Figure 2

In the mediastinal window of contrast-enhanced thorax CT examination; Coronal (a) and axial (b) section examination shows a mass lesion in the lower lobe of the left lung. Infracarinal lymph node (solid arrow) , pericardial invasion and accompanying pericardial effusion are seen (hollow arrow) (a, b). After neoadjuvant treatment, it was observed that the mass shrank significantly and pericardial invasion and pericardial effusion decreased (c).

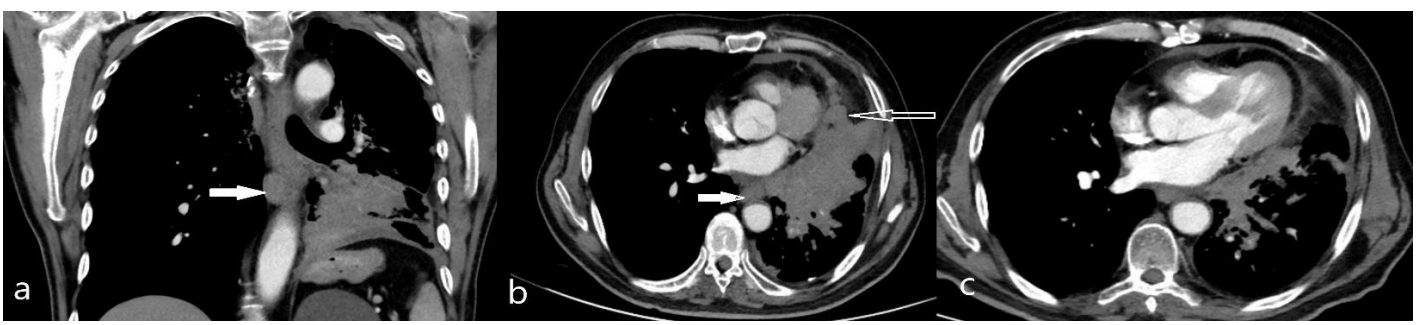
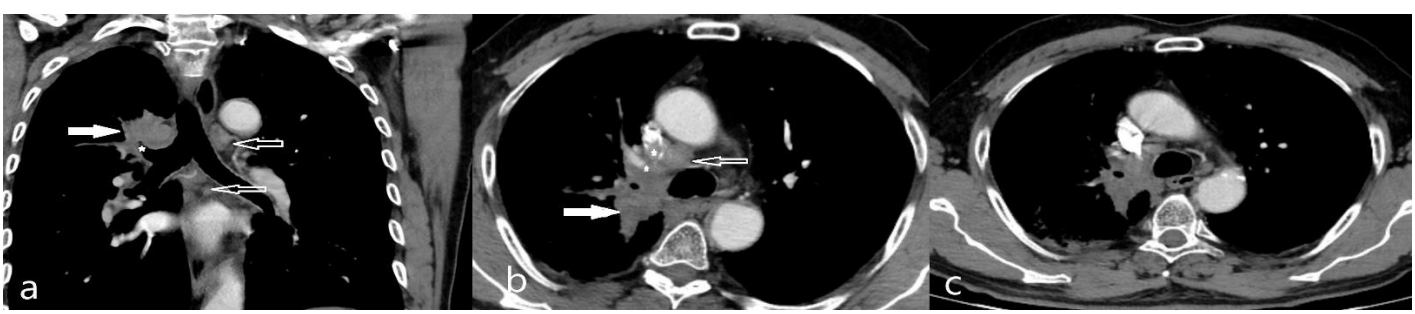


Figure 3

In the mediastinal window of contrast-enhanced thorax CT examination; (a) It is seen that the mass located in the upper lobe (solid arrow) of the right lung infiltrated the posterior bronchus of the right upper lobe (marked with asterisks) and caused thrombus in the superior vena cava and bronchial artery(marked with asterisks), (b). Lymph nodes located at stations 7 and 4L are also seen(hollow arrow). In the thorax CT examination obtained after neoadjuvant treatment; It shows that the thrombus in the superior vena cava has regressed, but there is no change in the size of the mass (c).



parenchymal changes around the tumor tissue were noted by the readers under 7 headings; 1) normal parenchyma 2) ground glass 3) reticular changes (lymphatic) 4) ground glass + reticular changes 5) mosaic attenuation 6) consolidation 7) bronchiectasis. The stage of vascular infiltration of the masses was noted by the readers under 6 headings. 1) absent 2) pulmonary trunk 3) main 4) lobar 5) segmental 6) VCS (Figure 2,3).

The stage at which the masses had respiratory tract infiltration was noted by the readers under 5 headings. 1) no airway infiltration 2) trachea 3) main bronchi 4) intermediate bronchus 5) lobar bronchus (Figure 2,3). The presence or absence of cardiac infiltration of tumor tissue was noted under 4 headings; 1) absent 2) pericardial infiltration 3) infiltration up to myocardium 4) presence of intrachamber thrombus(Figure 2).

Readers noted which lymph node stations had pathologic lymph nodes (lymph nodes with a short axis >10 mm). The presence of distant metastasis on CT scan before neoadjuvant treatment was noted. The presence or absence of pleural effusion in the hemithorax of the lesion was noted (Figure 2,3).

Lung tumours were contoured by three expert readers on the Workstation (Intelli SpacePhilips [IPS], The Netherlands) using a freehand tool to manually segment the lesion. The readers were blinded to the actual histopathologic diagnosis of all cases.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 25.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as number and percentage, and continuous measurements were summarized as mean and standard deviation (median (median) and minimum-maximum where necessary). The Kolmogorov-Smirnov test was used to determine whether the parameters in the study were normally distributed. Mann Whitney U test was used for parameters that did not show normal distribution. Chi-square test was used to compare categorical expressions. Cox Regression test was used to analyze the factors affecting remission and progression. Kaplan Meier test was used in survival analysis. Statistical significance level was taken as 0.05 in all tests.

3. Results

The enhanced chest CT scans, demographic data and number of comorbidities evaluated in the patient groups included in the study are given in Table 1.

Progression and mortality rates were found to be low in patients with remission ($p<0.001$). No significant difference was found between the other parameters in Table 2 ($p>0.05$).

The rate of progression was higher in cases with n2 and n3 in TNM staging ($p<0.001$). The rate of calcification was higher in patients with progression ($p=0.005$) and the rate of pericardial invasion was higher ($p=0.008$). In addition, vascular invasion rate was high in patients who developed progression ($p=0.003$). The mean age of patients with progression was low ($p=0.038$). No significant difference was found between the other parameters in Table 3 ($p>0.05$).

The factors affecting progression were analyzed with Cox regression model in Table 4. Univariate analysis revealed a statistically significant difference between lymph node station, calcification, presence of pericardial invasion, presence of vascular invasion and age variables. In the multivariate cox regression analysis, parameters that were found to be significant in the univariate analysis results were included. According to the results of the analysis, patients with lymph node station 3 had a 3.69 -fold efect [odds ratio (OR)=3.693, [95% confdence interval (CI)= 1.875–7.274, $p=0.041$] effect on progression ($p<0.001$), (Table 4).

Overall survival was 40.1 (months) and progression free survival was 14.8 (months) (Figure 4).

4. Discussion

The aim of this study was to investigate which of the findings on pretreatment chest enhanced CT scan is more successful in predicting histologic response to neoadjuvant therapy in patients with locally advanced NSCLC. Neoadjuvant therapy followed by surgery has recently been applied as a multimodal treatment for locally advanced NSCLC[6]. Accurate patient stratification is becoming increasingly important. Pathological tumor-lymph node-metastasis (pTNM) classification is the most important and routinely applied prognosis prediction tool for malignant disease. MPR or complete pathologic response has been associated with long-term overall survival (OS) in NSCLC patients undergoing neoadjuvant therapy[7,8]. Prognostic information to predict response to treatment in the setting of neoadjuvant therapy can help establish criteria for selecting appropriate surgical candidates [9].

In the study, lymph node stage grouping was performed in patients with lung tumors. It was observed that lymph node stage was not significant in terms of response to neoadjuvant treatment. However, lymph node stage was shown to be effective in progression. Especially in the multivariant analysis, N0 and/or N3 stage group was found to be effective on the progression time. In lung cancer TNM staging 8th edition, N stage varies according to the localisation of lymph nodes. In this study, T stage in TNM staging and lymph node stage and metastasis were investigated separately in terms of both progression and response to treatment. The study showed that N stage was more effective in progression than both T and M stage. In other words, advanced N stage is a poor prognosis in terms of progression independent of TNM staging.

There are many previous studies on whether the contours of lung tumors affect the response to radiotherapy[10]. However, there is no consensus on this issue[8-12]. In our study, tumor contours were not associated with response to neoadjuvant treatment. Similarly, tumor contours were not associated with the time of progression.

There was no significant difference between the subgroups of non-small cell lung tumors in terms of response to neoadjuvant treatment or progression times. These results obtained in our study were consistent with the literature [12,13]. As a matter of fact, lung tumors are divided into two groups as small cell and non-small cell in terms of treatment protocol [8,13].

Localization and infiltrating localization of lung tumors are very important in terms of surgery [14,15]. In the literature, the relationship between postoperative response and localization has been examined [16-18]. In our study, regardless of the areas infiltrated by tumor tissue, the lobe in which the tumor tissue was located, whether it was in a single lobe or extended to more than one lobe, and whether the lesion was centrally or peripherally localized were noted separately. It was observed that the localization of tumor tissue in the lung parenchyma had no effect on neoadjuvant treatment response or progression time.

Recently, the number of studies investigating the relationship between tumor contours in the lung and other localizations and tumor subtypes and grades has increased[19-22]. Tumor contour is one of the most frequently used parameters in tumor analysis, especially in studies performed with artificial intelligence[19,23,24]. It is an accepted fact that spiculated and microlobule lesions suggest malignant tumors [24,25]. In this study, tumor contours were divided into 4 groups by the readers and the relationship between tumor contour and response to neoadjuvant treatment and progression times were examined, but no significant relationship was found.

Table 1

Number of parameters analyzed in the patients included in the study

	Number (n)	Percentage (%)
Gender		
Woman	29	20.7
Male	111	79.3
Cigarette	71	50.7
Emphysema	86	61.4
Comorbidity	120	85.7
DM	9	7.5
HT	6	5.0
History of non-acc malignancy	16	13.3
Previous history of lung disease	31	25.8
Atherosclerotic coronary heart disease	34	28.3
DM and HT	24	20.0
Tissue cell type		
Adenocarcinoma	42	30.0
Squamous HC carcinoma	55	39.3
Neuroendocrine carcinoma	33	23.6
Mucinous adenocarcinoma	10	7.1
Lymph node stage		
0	33	23.6
N1	25	17.9
N2	51	36.4
N3	31	22.1
Baseline CT metastasis	57	40.7
Lung	15	26.3
Brain	9	15.8
Neighbor bone	13	22.8
Distant bone	4	7.0
Surrenal	3	5.3
Lung + brain	3	5.3
Brain + surrenal	3	5.3
Abdomen	5	8.8
Abdomen + surrenal	2	3.5
Lesion localization		
Central	82	58.6
Peripheral	58	41.4
Lobe		
Right upper	50	35.7
Right low	21	15.0
Right middle	7	5.0
Lef upper	51	36.4
Left low	11	7.8
Single lobe		
Single	111	79.3
More than one	29	20.7
Lesion contour		
Round smooth	19	13.6
Lobule	32	22.9
Microlobule	17	12.1
Spiculated	72	51.4
Calcification	66	47.1
Central	15	22.7
Eccentric	26	39.4
Rough	25	37.9
Necrosis		
No necrosis	73	52.1
<%50	39	27.9
>%50	28	20.0
Necrosis 3rd month		
No necrosis	89	63.6
<%50	33	23.6
>%50	18	12.9
Necrosis 6 months		
No necrosis	84	60.0
<%50	32	22.9
>%50	24	17.1
Atelectasis adjacent to the mass	93	66.4
Subsegmental	55	59.1
Segmental	30	32.3
Lobar	6	6.5
Total	2	2.2
Presence of atelectasis on 3rd month Chest CT	99	70.7
Subsegmental	64	64.6
Segmental	23	23.2
Lobar	7	7.1
Total	5	5
Presence of atelectasis on 6th month Chest CT	105	75.0
Subsegmental	51	48.6
Segmental	41	39.0
Lobar	11	10.5
Total	2	1.9
Pleural effusion	37	26.4
Pleural effusion (3rd month Chest CT)	55	39.3
Pleural effusion (6th month Chest CT)	62	44.3
Lung parenchyma adjacent to the lesion		
Normal	11	7.9
Ground glass	8	5.7
Reticular changes (lymphatic)	71	50.7
Ground glass + reticular	25	17.9
Mosaic perfusion	13	9.3
Consolidation	12	8.6
ACC parenchyma adjacent to the lesion (3rd month Chest CT)		
Normal	10	7.1
Ground glass	7	5.0
Reticular changes (lymphatic)	58	41.4
Ground glass + reticular	43	30.7
Mosaic perfusion	6	4.3
Consolidation	16	11.4
ACC parenchyma adjacent to the lesion (6th month Chest CT)		
Normal	15	10.7
Ground glass	7	5.0
Reticular changes (lymphatic)	49	35.0
Ground glass + reticular	47	33.6
Consolidation	8	5.7
Bronchilectasis	14	10.0
Bronchial invasion	89	63.6
Trachea	1	1.1
Main	20	22.5
Intermediate Bronchus	48	43.9
Lobar bronchus	20	22.5
Vascular invasion	84	60.0
Pulmonary trunk	1	1.2
Main	25	29.8
Lobar	28	33.3
Segmental	22	26.2
VCS	8	9.5
Pericardial invasion	57	40.7
Pericardium	48	84.2
Myocardium	6	10.5
Intra-chamber thrombus	3	5.3
Relapse	83	59.3
Progression	72	51.4
Remission		
Yes	99	70.7
Progression without remission	41	29.3
Mortality	59	42.1
	Mean±Ss	**Med (Min-Max)**
Age	63.6±10.1	64 (14-82)
Lesion long size	54.6±23.3	52.5 (14-143)
Average follow-up time	30.7±15.8	28.1 (4.4-68.8)
Progression time	14.8±10.7	12.4 (2.56-50.1)
Mean follow-up time - progression time	15.5±14.3	8.4 (3.9-48.8)

Table 2

Distribution of the analyzed parameters of the patients with and without remission

	No Remission (n=41)	Remission Available (n=99)	p†
	n(%)	n(%)	
Gender			
Woman	11 (26.8)	18 (18.2)	0.251
Male	30 (73.2)	81 (81.8)	
Cigarette	21 (51.2)	50 (50.5)	0.939
Emphysema	26 (63.4)	60 (60.6)	0.756
Comorbidity	34 (82.9)	86 (86.9)	0.544
Tissue cell type			
Adenocarcinoma	13 (31.7)	29 (29.3)	0.636
Squamous HC carcinoma	13 (31.7)	42 (42.4)	
Neuroendocrine carcinoma	12 (29.3)	21 (21.2)	
Mucinous adenocarcinoma	3 (7.3)	7 (7.1)	
Lymph node stage	35 (85.4)	74 (74.7)	0.169
0	6 (14.6)	27 (27.3)	0.405
N1	9 (22)	16 (16.2)	
N2	17 (41.5)	34 (34.3)	
N3	9 (22)	22 (22.2)	
Baseline CT metastasis	17 (41.5)	40 (40.4)	0.908
Lesion localization			
Central	21 (51.2)	61 (61.6)	0.256
Peripheral	20 (48.8)	38 (38.4)	
Lob			
Right upper	17 (41.5)	33 (33.3)	0.701
Right low	4 (9.8)	14 (17.2)	
Right middle	3 (7.3)	4 (4)	
Lef upper	14 (34.2)	37 (37.3)	
Left low	3 (7.3)	8 (8.1)	
Single lobe			
Single	34 (82.9)	77 (77.8)	0.494
More than one	7 (17.1)	22 (22.2)	
Lesion contour			
Round smooth	3 (7.3)	16 (16.2)	0.088
Lobule	6 (14.6)	26 (26.3)	
Microlobule	8 (19.5)	9 (9.1)	
Spiculated	24 (58.5)	48 (48.5)	
Calcification			
Central	8(38)	11(24.4)	0.534
Eccentric	4(19)	16(35.5)	
Rough	9(42.8)	18(40)	
Necrosis			
No	20 (48.8)	53 (53.5)	0.802
<%50	13 (31.7)	26 (26.3)	
>%50	8 (19.5)	20 (20.2)	
Necrosis 3rd month			
No	24 (58.5)	65 (65.7)	0.592
<%50	10 (24.4)	23 (23.2)	
>%50	7 (17.1)	11 (11.1)	
Necrosis 6 months			
No	21 (51.2)	63 (63.6)	0.382
<%50	11 (26.8)	21 (21.2)	
>%50	9 (22)	15 (15.2)	
Atelectasis	31 (75.6)	62 (62.6)	0.139
Atelactasis 3rd month	32 (78)	67 (67.7)	0.220
Atelactasis Month 6	34 (82.9)	71 (71.7)	0.163
Pleural effusion	12 (29.3)	25 (25.3)	0.624
Pleural effusion (3rd month)	19 (46.3)	36 (36.4)	0.271
Pleural effusion (6th month)	21 (51.2)	41 (41.4)	0.288
Lung parenchyma adjacent to the lesion			.
Normal	1 (2.4)	10 (10.1)	0.245
Ground glass	1 (2.4)	7 (7.1)	
Reticular changes (lymphatic)	19 (46.3)	52 (52.5)	
Ground glass + reticular	9 (22)	16 (16.2)	
Mosaic perfusion	6 (14.6)	7 (7.1)	
Consolidation	5 (12.2)	7 (7.1)	
Lung parenchyma adjacent to the lesion 3 months			
Normal	2 (4.9)	8 (8.1)	0.404
Ground glass	-	7 (7.1)	
Reticular changes (lymphatic)	17 (41.5)	41 (41.4)	
Ground glass + reticular	13 (31.7)	30 (30.3)	
Mosaic perfusion	3 (7.3)	3 (3)	
Consolidation	6 (14.6)	10 (10.1)	
Lung parenchyma adjacent to the lesion 6 months			
Normal	5 (12.2)	10 (10.1)	0.095
Ground glass	1 (2.4)	6 (6.1)	
Reticular changes (lymphatic)	9 (22)	40 (40.4)	
Ground glass + reticular	15 (36.6)	32 (32.3)	
Consolidation	3 (7.3)	5 (5.1)	
Bronchiectasis	8 (19.5)	6 (6.1)	
Bronchial invasion	27 (65.9)	62 (62.6)	0.718
Vascular invasion	25 (61)	59 (59.6)	0.879
Pericardial invasion	16 (39)	41 (41.4)	0.793
Progression	36 (87.8)	51 (51.5)	**<0.001****
Mortality	28 (68.3)	31 (31.3)	**<0.001****
	Mean±Ss	**Mean±Ss**	**p‡**
Age	63.7±9.3	63.6±10.5	0.865
Size of the lesion long axis	57.5±25.3	53.5±22.5	0.558

DM: diabetes mellitus, HT: hypertension, VCS: vena cava superior

Table 3

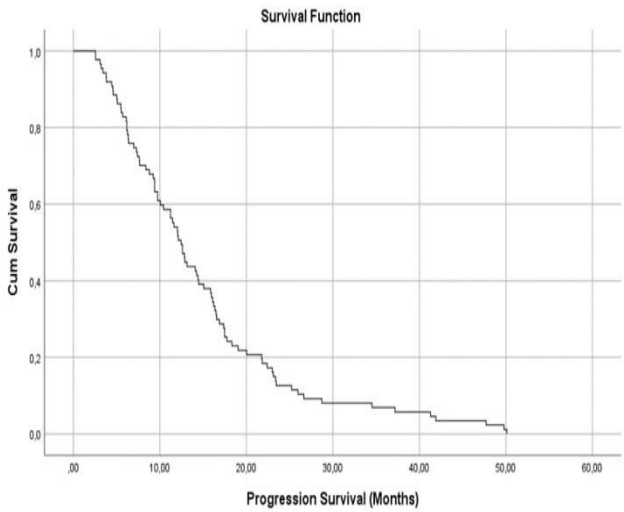
Distribution of analyzed parameters of progressing and non-progressing patients

	No Progression (n=53)	Progression Available (n=87)	p†
	n(%)	n(%)	
Gender			
Woman	10 (18.9)	19 (21.8)	0.674
Male	43 (81.1)	68 (78.2)	
Cigarette	26 (49.1)	45 (51.7)	0.759
Emphysema	30 (56.6)	56 (64.4)	0.360
Comorbidity	48 (90.6)	72 (82.8)	0.200
Tissue cell type			
Adenocarcinoma	17 (32.1)	25 (28.7)	0.670
Squamous HC carcinoma	23 (43.4)	32 (36.8)	
Neuroendocrine carcinoma	10 (18.9)	23 (26.4)	
Mucinous adenocarcinoma 3	3 (5.7)	7 (8)	
Lymph node stage	37 (69.8)	72 (82.8)	0.074
0	17 (32.1)	16 (18.4)	**<0.001****
N1	13 (24.5)	12 (13.8)	
N2	21 (39.6)	30 (34.5)	
N3	2 (3.8)	29 (33.3)	
Baseline CT metastasis	17 (32.1)	40 (46.0)	0.104
Lesion localization			
Central	33 (62.3)	49 (56.3)	0.489
Peripheral	20 (37.7)	38 (43.7)	
Lob			
Right upper	13 (24.5)	37 (42.5)	0.357
Right low	11 (20.8)	10 (12.5)	
Right middle	3 (5.7)	4 (4.6)	
Lef upper	24 (45.3)	27 (30.9)	
Left low	2 (3.8)	9 (10.3)	
Single lobe			
Single	40 (75.5)	71 (81.6)	0.385
More than one	13 (24.5)	16 (18.4)	
Lesion contour			
Round smooth	9 (17)	10 (11.5)	0.757
Lobule	13 (24.5)	19 (21.8)	
Microlobule	6 (11.3)	11 (12.6)	
Spiculated	25 (47.2)	47 (54)	
Calcification			
Central	10(18.8)	9(10.3)	**0.005****
Eccentric	2(3.7)	32(36.7)	
Rough	5(9.4)	8(9.1)	
Necrosis			
No	29 (54.7)	44 (50.6)	0.778
<%50	15 (28.3)	24 (27.6)	
>%50	9 (17)	19 (21.8)	
Necrosis 3rd month			
No	30 (56.6)	59 (67.8)	0.355
<%50	14 (26.4)	19 (21.8)	
>%50	9 (17)	9 (10.2)	
Necrosis 6 months			
No	29 (54.7)	55 (63.2)	0.072
<%50	10 (18.9)	22 (25.3)	
>%50	14 (26.4)	10 (11.5)	
Atelectasis	33 (62.3)	60 (69)	0.415
Atelectasis 3rd month	36 (67.9)	63 (72.4)	0.571
Atelectasis Month 6	39 (73.6)	66 (75.9)	0.763
Thickening of pleural effusion	18 (34)	19 (21.8)	0.115
Pleural effusion (3rd month)	22 (41.5)	33 (37.9)	0.674
Pleural effusion (6th month)	23 (43.4)	39 (44.8)	0.869
Lung parenchyma adjacent to the lesion			
Normal	6 (11.3)	5 (5.7)	0.381
Ground glass	2 (3.8)	6 (6.9)	
Reticular changes (lymphatic)	26 (49.1)	45 (51.7)	
Ground glass + reticular	12 (22.6)	13 (14.9)	
Mosaic perfusion	5 (9.4)	8 (9.2)	
Consolidation	2 (3.8)	10 (11.5)	
Lung parenchyma adjacent to the lesion 3 months			
Normal	3 (5.7)	7 (8)	0.728
Ground glass	2 (3.8)	5 (5.7)	
Reticular changes (lymphatic)	19 (35.8)	39 (44.8)	
Ground glass + reticular	20 (37.7)	23 (26.4)	
Mosaic perfusion	2 (3.8)	4 (4.6)	
Consolidation	7 (13.2)	9 (10.3)	
Lung parenchyma adjacent to the lesion 6 months			
Normal	6 (11.3)	9 (10.3)	0.387
Ground glass	2 (3.8)	5 (5.7)	
Reticular changes (lymphatic)	22 (41.5)	27 (31)	
Ground glass + reticular	19 (35.8)	28 (32.2)	
Consolidation	1 (1.9)	7 (8)	
Bronchilectasis	3 (5.7)	11 (12.6)	
Bronchial invasion	33 (62.3)	56 (64.4)	0.802
Vascular invasion	29 (54.7)	55 (63.2)	**0.003****
Pericardial invasion	29 (54.7)	28 (32.2)	**0.008***
Mortality	17 (32.0)	42 (48.2)	**<0.001****
	Mean±Ss	**Mean±Ss**	**p‡**
Age	64.9±12.1	62.8±8.7	**0.038***
Lesion long axis dimension	54.6±24.4	54.6±22.8	0.899

*DM: diabetes mellitus, HT: hypertension, VCS: vena cava superior, *p<0.05, **p<0.01, †: Chi-square, ‡: Mann Whitney U*

Figure 4

Graph of progression free survival and overall survival times of patients.



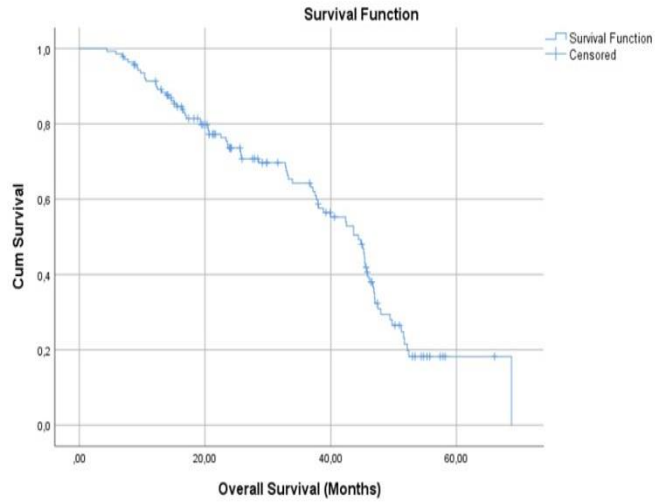


Table 4

Cox regression model of factors affecting progression

	p	Exp(B)	95% CI	
			Lower	Upper
Lymph node station				
0	**0.001****			
N1	0.406	1.388	0.640	3.009
N2	0.058	1.862	0.978	3.542
N3	**<0.001****	3.693	1.875	7.274
Presence of calcification	0.207	1.333	0.853	2.083
Vascular invasion	**0.003****	1.473	1.125	3.652
Presence of pericardial invasion	0.324	0.783	0.482	1.272
Age	0.079	1.024	0.997	1.052

***p<0.01, Cox regression*

Necrosis and cavity are not uncommon findings in lung tumors [9,26]. Lesions with cavities were not included in the study. The presence of necrosis (0, <50%, >50%) on the baseline enhanced CT scan before neoadjuvant treatment was analyzed by the readers. In addition, necrosis rates at the 3rd and 6th month of the treatment follow-up were noted. The presence or absence of necrosis before treatment or necrosis developing during treatment was not associated with neoadjuvant treatment response or time to progression.

Calcification is not uncommon in both benign and malignant lung tumors [27,28]. While eccentric calcification is more common in malignant lesions, coarse and central calcification is more common in benign lesions[29-31]. Our aim in this study was to evaluate whether calcification can predict response to treatment or progression. In the study, there was no significant difference in response to neoadjuvant treatment in cases with and without calcification , but progression was more common in cases with calcification (especially eccentric calcification).

We examined whether the presence of atelectasis in the neighborhood of the mass was associated with response to neoadjuvant treatment. Atelectasis was classified as 4 types by the readers. Both the baseline enhanced CT scan at the time of diagnosis and the presence of atelectasis at 3 and 6 months during treatment follow-up were noted. However, atelectasis both at baseline enhanced CT scan and during treatment was not associated with neoadjuvant treatment response or time to progression.

The presence of pleural effusion in the hemithorax with tumor tissue was examined both at baseline enhanced chest CT examination and at 3 and 6 months during the treatment period. However, pleural effusion at any period was not associated with neoadjuvant treatment response or time to progression.

Density changes other than atelectasis around the tumor tissue were examined both at baseline enhanced chest CT examination and at 3 and 6 months during the treatment period. However, peritumoral density changes in any period were not correlated with neoadjuvant treatment response or time to progression.

There was no significant difference in response to neoadjuvant treatment in patients with bronchial invasion, vascular invasion and pericardial invasion compared to patients without these invasions. However, progression was observed earlier in patients with bronchial, vascular and pericardial invasion compared to those without. Especially vascular invasion had a greater effect on progression compared to the others. It is not surprising that progression is seen earlier in cases with vascular invasion. The ease of spread of micrometastases and/or tumour cells via haematogenous route especially in cases with vascular invasion is already known in other tumours[1,8,13]. We think that the fact that the lymph node stage is another effective factor in the progression of lung tumours supports this idea.

Previous studies have shown that neoadjuvant treatment has a positive effect on both progression free survival and overall survival[2,8,27]. In this study, both progression times were longer and mortality was lower in patients in remission.

Limitations

Our study has some limitations. The main ones are; 1) Using artificial intelligence and obtaining quantitative data, especially in the evaluation of tumor heterogeneity and tumor contours, would have made our study much more valuable. 2) The fact that metabolic tumor volume (MTV) was not evaluated from PET CT examinations before neoadjuvant treatment can be considered one of the limitations of our study. However, due to the retrospective nature of the study, most of the patients did not have a PET CT scan after neoadjuvant treatment. 3) Since the study was not interobserver, the concordance of the chest CT findings between the readers and their usability in routine clinical practice could not be examined.

5. Conclusion

None of the findings on chest CT examination before neoadjuvant therapy have been shown to be successful in predicting response to neoadjuvant therapy. The findings that can predict progression on a baseline chest CT scan are vascular invasion, lymph node staging and pericardial invasion. Vascular invasion, lymph node stage advanced cases, pericardial invasion and calcification during baseline chest CT scan are findings that can predict progression. Lymph node is the most valuable of these in predicting progression.

Statement of ethics

The ethical approval was provided by the Clinical Research Ethics Committee of the Adana City Training and Research Hospital on 2023, with decision number 2767.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7-33.
https://doi.org/10.3322/caac.21654
2. Wang Q, Wang S, Sun Z, Cao M, Zhao X. Evaluation of log odds of positive lymph nodes in predicting the survival of patients with non-small cell lung cancer treated with neoadjuvant therapy and surgery: a SEER cohort-based study. BMC Cancer. 2022;22:801.
https://doi.org/10.1186/s12885-022-09908-3
3. Shen J, Sun N, Zens P et al. Spatial metabolomics for evaluating response to neoadjuvant therapy in non-small cell lung cancer patients. Cancer Commun (Lond). 2022;42:517-535.
https://doi.org/10.1002/cac2.12310
4. Saw SPL, Ong BH, Chua KLM et al. Revisiting neoadjuvant therapy in non-small-cell lung cancer. Lancet Oncol. 2021;22:e501-e516.
https://doi.org/10.1016/S1470-2045(21)00383-1
5. Rosner S, Liu C, Forde PM et al. Association of Pathologic Complete Response and Long-Term Survival Outcomes Among Patients Treated with Neoadjuvant Chemotherapy or Chemoradiotherapy for NSCLC: A Meta-Analysis. JTO Clin Res Rep. 2022 Jul 31;3(9):100384.
https://doi.org/10.1016/j.jtocrr.2022.100384
6. Godoy LA, Chen J, Ma W P et al. Emerging precision neoadjuvant systemic therapy for patients with resectable non-small cell lung cancer: current status and perspectives. Biomark Res 2023;11:7.
https://doi.org/10.1186/s40364-022-00444-7
7. Blumenthal GM, Bunn PA Jr, Chaft JE et al. Current Status and Future Perspectives on Neoadjuvant Therapy in Lung Cancer. J Thorac Oncol 2018;13:1818-31.
https://doi.org/10.1016/j.jtho.2018.09.017
8. Liang J, Bi N, Wu S et al. Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. Ann Oncol. 2017;28):777-783.
https://doi.org/10.1093/annonc/mdx009
9. Cheng Y, Chen ZY, Huang JJ et al. Efficacy evaluation of neoadjuvant immunotherapy plus chemotherapy for non-small-cell lung cancer: comparison of PET/CT with postoperative pathology. Eur Radiol. 2023;33:6625-6635.
https://doi.org/10.1007/s00330-023-09922-4
10. Khorrami M, Jain P, Bera K et al. Predicting pathologic response to neoadjuvant chemoradiation in resectable stage III non-small cell lung cancer patients using computed tomography radiomic features. Lung Cancer. 2019;135:1-9.
https://doi.org/10.1016/j.lungcan.2019.06.020
11. Yue D, Liu W, Chen C et al. Circulating tumor DNA predicts neoadjuvant immunotherapy efficacy and recurrence-free survival in surgical non-small cell lung cancer patients. Transl Lung Cancer Res. 2022;11:263-276.
https://doi.org/10.21037/tlcr-22-106
12. Bao Y, Gu C, Xie H et al. Comprehensive study of neoadjuvant targeted therapy for resectable non-small cell lung cancer. Ann Transl Med. 2021;9:493.
https://doi.org/10.21037/atm-21-1134
13. Tanahashi M, Suzuki E, Yoshii N et al. Role of fluorodeoxyglucose-positron emission tomography in predicting the pathological response and prognosis after neoadjuvant chemoradiotherapy for locally advanced non-small-cell lung cancer. Interact Cardiovasc Thorac Surg. 2022;35:113.
https://doi.org/10.1093/icvts/ivac113
14. Zhang J, Zhao X, Zhao Y et al. Value of pre-therapy 18F-FDG PET/CT radiomics in predicting EGFR mutation status in patients with non-small cell lung cancer. Eur J Nucl Med Mol Imaging. 2020;47:1137-1146.
https://doi.org/10.1007/s00259-019-04592-1
15. Chetan MR, Gleeson FV. Radiomics in predicting treatment response in non-small-cell lung cancer: current status, challenges and future perspectives. Eur Radiol. 2021;31:1049-1058.
https://doi.org/10.1007/s00330-020-07141-9
16. Dissaux G, Visvikis D, Da-Ano R et al. Pretreatment 18F-FDG PET/CT Radiomics Predict Local Recurrence in Patients Treated with Stereotactic Body Radiotherapy for Early-Stage Non-Small Cell Lung Cancer: A Multicentric Study. J Nucl Med. 2020;61:814-820.
https://doi.org/10.2967/jnumed.119.228106
17. Nestle U, Schimek-Jasch T, Kremp S et al. Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomized, controlled trial. Lancet Oncol. 2020;21:581-592.
https://doi.org/10.1016/S1470-2045(20)30013-9
18. Khorrami M, Prasanna P, Gupta A, Patil P et al. Changes in CT Radiomic Features Associated with Lymphocyte Distribution Predict Overall Survival and Response to Immunotherapy in Non-Small Cell Lung Cancer. Cancer Immunol Res. 2020;8:108-119.
https://doi.org/10.1158/2326-6066.CIR-19-0476
19. Bortolotto C, Lancia A, Stelitano C et al. Radiomics features as predictive and prognostic biomarkers in NSCLC. Expert Rev Anticancer Ther. 2021;21:257-266.
https://doi.org/10.1080/14737140.2021.1852935
20. Liberini V, Mariniello A, Righi L et al. NSCLC Biomarkers to Predict Response to Immunotherapy with Checkpoint Inhibitors (ICI): From the Cells to In Vivo Images. Cancers (Basel). 2021;13:4543.

https://doi.org/10.3390/cancers13184543
21. Seban RD, Mezquita L, Berenbaum A et al. Baseline metabolic tumor burden on FDG PET/CT scans predicts outcome in advanced NSCLC patients treated with immune checkpoint inhibitors. Eur J Nucl Med Mol Imaging. 2020;47:1147-1157.
https://doi.org/10.1007/s00259-019-04615-x
22. Rosner S, Liu C, Forde PM et al. Association of Pathologic Complete Response and Long-Term Survival Outcomes Among Patients Treated With Neoadjuvant Chemotherapy or Chemoradiotherapy for NSCLC: A Meta-Analysis. JTO Clin Res Rep. 2022;3:100384.
https://doi.org/10.1016/j.jtocrr.2022.100384
23. Zarogoulidis P, Matthaios D, Kosmidis C et al. Effective early diagnosis for NSCLC: an algorithm. Expert Rev Respir Med. 2021;15:1437-1445.
https://doi.org/10.1080/17476348.2021.1969916
24. Han Y, Ma Y, Wu Z et al. Histologic subtype classification of non-small cell lung cancer using PET/CT images. Eur J Nucl Med Mol Imaging. 2021;48:350-360.
https://doi.org/10.1007/s00259-020-04771-5
25. Koyasu S, Nishio M, Isoda H et al. Usefulness of gradient tree boosting for predicting histological subtype and EGFR mutation status of non-small cell lung cancer on 18F FDG-PET/CT. Ann Nucl Med. 2020;34:49-57.
https://doi.org/10.1007/s12149-019-01414-0
26. Dissaux G, Visvikis D, Da-Ano R et al. Pretreatment 18F-FDG PET/CT Radiomics Predict Local Recurrence in Patients Treated with Stereotactic Body Radiotherapy for Early-Stage Non-Small Cell Lung Cancer: A Multicentric Study. J Nucl Med. 2020;61:814-820.
https://doi.org/10.2967/jnumed.119.228106
27. Leader AM, Grout JA, Maier BB et al. Single-cell analysis of human non-small cell lung cancer lesions refines tumor classification and patient stratification. Cancer Cell. 2021;39:1594-1609.
https://doi.org/10.1016/j.ccell.2021.10.009
28. Kan CFK, Unis GD, Li LZ et al. Circulating Biomarkers for Early Stage Non-Small Cell Lung Carcinoma Detection: Supplementation to Low-Dose Computed Tomography. Front Oncol. 2021;11:555331.
https://doi.org/10.3389/fonc.2021.555331
29. Hattori A, Suzuki K, Takamochi K et al. Japan Clinical Oncology Group Lung Cancer Surgical Study Group. Prognostic impact of a ground-glass opacity component in clinical stage IA non-small cell lung cancer. J Thorac Cardiovasc Surg. 2021;161:1469-1480.
https://doi.org/10.1016/j.jtcvs.2020.01.107
30. Akinci D'Antonoli T, Farchione A, Lenkowicz J et al. CT Radiomics Signature of Tumor and Peritumoral Lung Parenchyma to Predict Nonsmall Cell Lung Cancer Postsurgical Recurrence Risk. Acad Radiol. 2020;27:497-507.
https://doi.org/10.1016/j.acra.2019.05.019
31. Nakanishi Y, Masuda T, Yamaguchi K et al. Pre-existing interstitial lung abnormalities are risk factors for immune checkpoint inhibitor-induced interstitial lung disease in non-small cell lung cancer. Respir Investig. 2019;57:451-459.
https://doi.org/10.1016/j.resinv.2019.05.002