Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1061755
J Health Sci Med 2022; 5(3): 831-838

Mediastinal lymphnode positivity clinical scoring system for lung adenocarsinoma-mediastinal lymph node evaluation and staging

İsmail Ağababaoğlu[1], Özgür Ömer Yıldız[2], Dilek Yapar[3], Hasan Ersöz[4], Seray Hazer[5], Özant Helvacı[6], Selim Şakir Erkmen Gülhan[5], Nurettin Karaoğlanoğlu[2]

[1]Yıldırım Beyazıt University Yenimahalle Research and Training Hospital, Department of Thoracic Surgery, Ankara, Turkey
[2]Yıldırım Beyazıt University, Department of Thoracic Surgery, Ankara, Turkey
[3]Gazi University, Department of Public Health, Ankara, Turkey
[4]Katip Çelebi University, Department of Thoracic Disease, İzmir, Turkey
[5]Atatürk Chest Disease and Thoracic Surgery Research and Training Hospital, Department of Thoracic Surgery, Ankara, Turkey
[6]Yıldırım Beyazıt University Yenimahalle Research and Training Hospital, Department of Nephrology, Ankara, Turkey

Cite this article as: Ağababaoğlu İ, Yıldız ÖÖ, Yapar D, et al. Mediastinal lymphnode positivity clinical scoring system for lung adenocarsinoma-mediastinal lymph node evaluation and staging. J Health Sci Med 2022; 5(3): 831-838.

ABSTRACT

Aim: The study-cohort aims to assess PET-CT's correlation with adenocarcinomas' subtypes and propose a scoring system for mediastinal lymph nodes staging.

Material and Method: The patient cohort is a multicenter, retrospective analysis of 268 patient that underwent surgery for NSCLC adenocarcinoma. Preoperative PET-CT results for mediastinal lymph node staging was pathologically confirmed on tissue specimens obtained at anatomical resection. Statistical evaluation of PET CT, radiological and pathological outcomes were performed on all subgroups.

Results: The low FDG affinity in the lepidic pattern was statistically significant in the study ($p < 0.001$). Among all cases, 65 had an increase in the disease stage to 3B. According to the multivariate logistic regression analysis, Stage 3 disease (OR=2.7), SUV max ≥6.85 (OR=2.1), lepidic type disease (OR=2.6), and tumor size ≥31 mm (OR=2.2) were found to be independently associated with post-op stage 3B disease. Based on their respective odds ratios, points were assigned to each item ranging from 2 to 3. AUC of the scoring system to diagnose post-op stage 3B disease was 0.753 (0.686-0.819), $p<0.001$. The optimal threshold was ≥4 points; this yielded a sensitivity of 80%, a specificity of 64%, a positive likelihood ratio of 2.2, and a diagnostic odds ratio of 7 (95% CI=3.5-13.6).

Conclusion: The lepidic subtype of adenocarcinomas could have a lower FDG affinity. The MLP scoring system based on SUVmax, tumor size, pathological subtype and cancer stage could help the clinicians to evaluate the mediastinal staging in NSCLC Adenocarcinomas accurately.

Keywords: Lung cancer, adenocarcinomas, mediastinal staging, pozitron emission tomography

INTRODUCTION

The most critical step in the surgical treatment of lung cancers is staging. Avoidance of unnecessary surgery depends on it. Furthermore, proper staging leads to improved preoperative planning. In the past, staging necessitated a combination of multiple invasive and non-invasive procedures. Nowadays,the positron emission tomography scan (PET-CT) has become the clinical standard (1). Mediastinal lymph node assessment is probably the most crucial part of the work-up. Computed tomography (CT) has both low sensitivity and specificity in the evaluation of lymph node metastasis (2). For lymph nodes under 1 centimeter, its value is even further reduced for CT (3).

One of the biggest challenges in staging non-small cell lung cancers (NSCLC) with PET-CT is the evaluation of adenocarcinomas and stage 3B cases that have not been detected preoperatively. Lung adenocarcinomas can show heterogeneous assessments in PET-CT Some parenchymal lesions that do not show malignant

Corresponding Author: İsmail Ağababaoğlu , ismailagababaoglu@gmail.com
Received: 22.01.2022 **Accepted:** 19.04.2022

involvement in PET CT may actually be malignant lesions. (4,5). For this reason, invasive staging may be required for patients with preoperatively diagnosed adenocarcinoma.

In 2011, the pathological classification of lung adenocarcinomas was changed (5). Each subtype has the potential to express different metabolic activity at the cellular level, which may lead to varying FDG uptakes. Therefore, in our study, we aimed to evaluate the lung adenocarcinoma subgroups in terms of FDG uptake for diagnosis and mediastinal staging.

MATERIAL AND METHOD

The study was approved by the Ethical Committees of the İzmir Katip Çelebi University (Date: 2021, Decision No: 371). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All patients gave written informed consent.

This study is a retrospective analysis of patients that underwent surgery for lung adenocarcinoma. The patients cohort was derived from medical records of Yıldırım Beyazıt University, Ankara Chest Diseases Hospital, and Katip Çelebi University. In our study, in addition to evaluating the FDG affinity of the NSCLC adenocarcimoma subgroups, we aimed to compare the PET-CT mediastinal staging of the subgroups in the new pathological classification with the pathology mediastinal staging that we accept as gold-standard. So, all patients had a preoperative PET-CT and postoperative pathological subtyping results of the adenocarcinoma. The Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma (2011) was used for pathological evaluation (6).

The age and gender of the patients, as well as primary tumor diameter (longest axis that determines the stage), anatomical location of the tumors and the type of surgeries performed were recorded. The stages of the cases were determined with preoperative PET-CT, and standart up-take value (SUV-max) values were added to analysis.The International Cancer Control Association and the American Cancer Committee eighth TNM classification were used for staging (7). Tumoral involvement of the mediastinal lymph nodes and their specific location were derived from pathological records. Lymph node evaluation was done according to Mountain and Dresler's classification (8).

Exclusion criterias were: diabetes or hyperglycemia defined as plasma glucose >140 mg/dL before PET-CT, preoperative chemotherapy and/or radiotherapy, interstitial lung disease, and rheumatological connective tissue disorder. Patients with insufficient data and/or inadequate surgery were excluded. Patients diagnosed with metastatic cancer at sixth-month control were also excluded. (**Figure 1**). Naturally, cases having mediastinal and parenchymal lymph node involvement were not included in this study. In our study, we applied the exclusion criteria to minimize the effect of N1 disease and anatomical location, which we believe that there might be other effective factors to evaluate the distribution of NSCLC adenocarcimoma subgroups in skipped stage 3B cases.

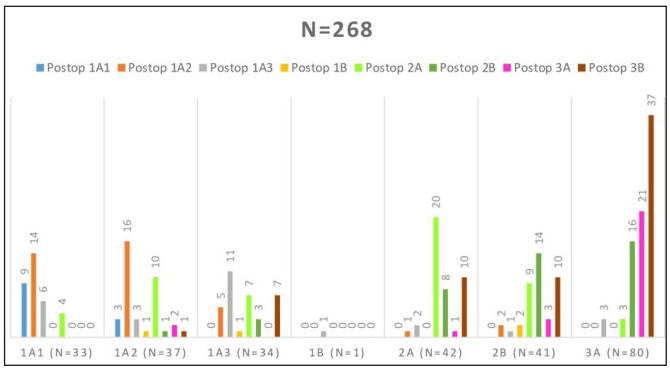

Figure 1. Distribution of PatientsAccordingtoPreoperativestage in thepostoperativeperiod

The surgical approach applied for all patients was anatomical resection and mediastinal lymph node dissection with posterolateral thoracotomy. Since there may not be standardization in mediastinal sampling in anatomical resections performed with thoracotomy and Video-Assisted Thoracoscopy Surgery (VATS), patients who underwent VATS were excluded from the study. Mediastinoscopy, mediastinostomy, and other invasive staging methods cases were not evaluated in this study since mediastinal lymph node stations were not fully exemplified.

All centers used the same device and protocol for PET-CT (ECAT model 951/31, Siemens/ CTI, Knoxville, Tenn.). FDG was synthesized according to the standard method by a high-performance liquid chromatography controlled synthesis modul (9). Patients were instructed to fast for six hours before the imaging and FDG (370 MBq) was administered intravenously. Data were reconstructed into coronal, sagittal, and transverse sections and a three-dimensional rotating projection. SUV-max 2.5 and above for mediastinal lymph nodes were accepted as the cut-off value for malignancy (10).

Statistical analyses were done using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as numbers and percentages for categorical variables and mean±standard deviation, median (IRQ) for continuous variables. Normal distribution for continuous variables

was assessed with visual (histograms and probability graphics) and analytic methods (Kolmogorov-Smirnov and Shapiro-Wilk's test). The data that does not fit the normal distribution, the Mann-Whitney U test was used for comparative analysis between the two independent groups and the independent sample t-test was used for the data that fit the normal distribution. Comparison analyses for categorical variables between separate groups were done by the chi-square test.

We used receiver operating charecteristic (ROC) analysis to determine cut-off SUV-max and tumor size values to predict Stage 3B disease. The area under the ROC curve (AUC) results were considered excellent for AUC values between 0.9-1, good for AUC values between 0.8-0.9, fair for AUC values between 0.7-0.8, poor for AUC values between 0.6-0.7 and failed for AUC values between 0.5-0.6 (11,12). Yound index was used to decide the cut-off point [the Youden Index is calculated as max (sensitivity + specificity – 1)] (13). Variables that may be independent risk factors for stage 3B in the post-op period were evaluated by multivariate logistic regression analysis. In order to predict the mediastinal involvement of the patients in the preop period (post op stage 3B), a scoring was developed by weighting with the odds ratio (OR) values of independent predictor factors (significant ones in multivariate analysis) (14).

RESULTS

Considering the basal demographic characteristics of the groups; there was no statistical difference between the groups in terms of age distribution (p=0.971), gender (p=0.097), surgical characteristics (p=0.825) and primary tumor size (p=0.493). While there was no significant difference in receiving radiotherapy after the postoperative staging (p=0.683), there was a significant difference was determined in the rate of receiving chemotherapy (p=0.001)(There was no significant difference who delivered radiotherapy after the postoperative staging (p=0.683) whereas there was a significant difference who received chemotherapy (p=0.001) (**Figure 1**)(**Table 1**).

When we examined the pathological subtypes according to SUV-max, the values were; 7.6 (4-12.3) for aciner, 7.8 (5.4-10.4) for micropapillary, 5.1 (2.2-8.1) for lepidic, 7 (3.8-10) for papillary and 9.4 (5.2-13.8) for solid subtypes. The low SUV-max in lepidic pattern was statistically significant (p <0.001).

Postoperative pathological stages were different than pre-operative PET-based staging, as expected. Number of patients that had an upgrade in disease stage to 3B were as follows: nill for 1A1 group, 1(2.7%) for 1A2, 7 (20.6%) for 1A3, nill for 1B, 10 (23.8%) for 2A, 10 (24.4%) for 2B and 37 (56.9%) for3A patients. In total 65 patients were up-staged.

The percentage of patients that was diagnosed postoperatively with stage 3B had no statistically difference according to adenocancer subtype (p=0.198) (**Figure 2**) (**Table 1**).

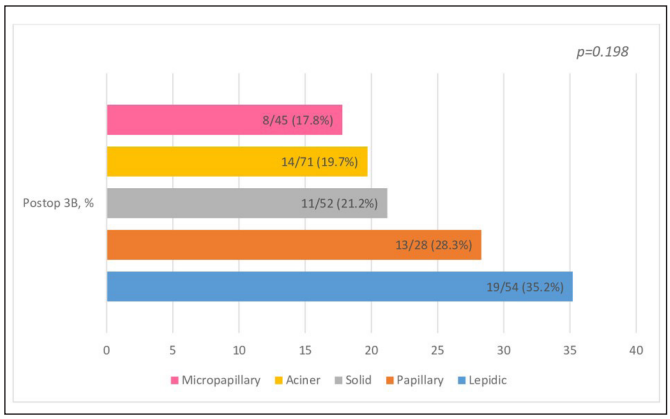

Figure 2. Transition rates to post-operative stage 3B according to histological types

Patients with lepidic subtype cancer tended to have malignant disease within the lesions with SUV-max lesser than 2.5 (p=0.010). The difference was not significant between patients with other subtypes. In addition, Stage 1 disease was marginally associated with lesions with SUV-max less than 2.5 (p=0.049).

The comparison results of the patient groups diagnosed at stage 3B and other stages in the postop period are presented in **Table 2**.The age and gender distributions of both groups were similar. SUV-max and tumor size measurements of the post-op Stage 3B group were significantly higher than the other groups (p <0.001 and p <0.001, respectively). It is noteworthy that 56.9% of pre-operative 3A cases had been diagnosed as 3B disease postoperatively. This is the highest percentage when all cases are considered (p<0.001). The cut-off values that could predict Stage 3B in the postop period for SUV-max and tumor size were examined by ROC analysis (**Table 3**, **Figure-3a**).

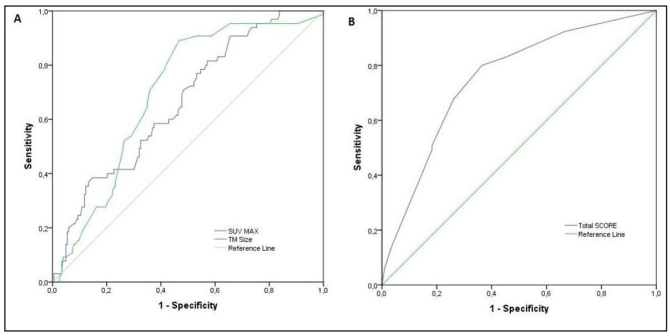

Figure 3.ROC Curves for Postoperative Stage of 3B. The Mediastinal lap Positive Score (MLP-Score) including the Four Markers (Pre-operative Stage, Suv-Max, Histopathology and Radiological Tumor Size) for Predicting the Diagnosis of Postoperative Stage 3B

Table 1. Baseline data of patients

Characteristics N=268	Aciner N=71	Micropapillary N=45	Lepidic N=54	Papillary N=46	Solid N=52	p
Age (year) Mean±sd	59.4±8.4	58.4±7.6	59.0±8.8	59.1±6.2	58.9±6.6	0.971*
Sex, n(%)						0.097#
Female	14 (19.7)	10 (22.2)	16 (29.6)	19 (41.3)	12 (23.1)	
Male	57 (80.3)	35 (77.8)	38 (70.4)	27 (58.7)	40 (76.9)	
KT, n(%)						0.001#
No	31 (43.7)	6 (13.3)	22 (40.7)	8 (17.4)	13 (25)	
Yes	40 (56.3)	39 (86.7)	32 (59.3)	38 (82.6)	39 (75)	
RT, n(%)						0.683#
No	57 (80.3)	38 (84.4)	45 (83.3)	34 (73.9)	40 (76.9)	
Yes	14 (19.7)	7 (15.6)	9 (16.7)	12 (26.1)	12 (23.1)	
Surgery Type, n (%)						0.825#
LLL	13 (18.3)	10 (22.2)	13 (24.1)	12 (26.1)	14 (26.9)	
LUL	20 (28.2)	7 (15.6)	12 (22.2)	7 (15.2)	8 (15.4)	
RBI Lobectomy	1 (1.4)	1 (2.2)	2 (3.7)	2 (4.3)	4 (7.7)	
RLL	14 (19.7)	15 (33.3)	13 (24.1)	12 (26.1)	9 (17.3)	
RUL	19 (26.8)	10 (22.2)	13 (24.1)	12 (26.1)	15 (28.8)	
Segmentectomy	4 (5.6)	2 (4.4)	1 (1.9)	1 (2.2)	2 (3.8)	
Primer Tm size Median (IRQ)	25 (15-45)	28 (15.5-43.5)	29.5 (17.8-40)	28 (14.8-48.5)	34 (21-48)	0.493**
Suv max Median (IRQ)	7.6 (4-12.3)	7.8 (5.4-10.4)	5.1 (2.2-8.1)	7 (3.8-10)	9.4 (5.2-13.8)	<0.001**
Suv max, n (%)						0.010#
<2.5	8 (11.3)	4 (8.9)	15 (27.8)	6 (13.0)	3 (5.8)	
≥2.5	63 (88.7)	41 (91.1)	39 (72.2)	40 (87.0)	49 (94.2)	
Postop Stage I						0.049#
Suv max, n (%)	n=22	n=13	n=18	n=12	n=16	
<2.5	8 (36.4)	2 (15.4)	10 (55.6)	5 (41.7)	2 (12.5)	
≥2.5	14 (63.6)	11 (84.6)	8 (44.4)	7 (58.3)	14 (87.5)	
Preop stage, n (%)						0.093#
1A1	5 (7)	7 (15.6)	8 (14.8)	9 (19.6)	4 (7.7)	
1A2	11 (15.5)	6 (13.3)	10 (18.5)	4 (8.7)	6 (11.5)	
1A3	19 (26.8)	3 (6.7)	3 (5.6)	2 (4.3)	7 (13.5)	
1B	0	0	0	0	1 (1.9)	
2A	8 (11.3)	8 (17.8)	8 (14.8)	8 (17.4)	10 (19.2)	
2B	9 (12.7)	10 (22.2)	8 (14.8)	8 (17.4)	6 (11.5)	
3A	19 (26.8)	11 (24.4)	17 (31.5)	15 (32.6)	18 (34.6)	
Postop stage, n (%)						0.258#
1A1	5 (7)	2 (4.4)	2 (3.7)	3 (6.5)	0	
1A2	9(12.7)	7 (15.6)	12 (22.2)	3 (6.5)	7 (13.5)	
1A3	7 (9.9)	2 (4.4)	3 (5.6)	6 (13)	9 (17.3)	
1B	1 (1.4)	2 (4.4)	1 (1.9)	0	0	
2A	14 (19.7)	10 (22.2)	9 (16.7)	10 (21.7)	10 (19.2)	
2B	11 (15.5)	12 (26.7)	4 (7.4)	6 (13)	9 (17.3)	
3A	10 (14.1)	2 (4.4)	4 (7.4)	5 (10.9)	6 (11.5)	
3B	14 (19.7)	8 (17.8)	19 (35.2)	13 (28.3)	11 (21.2)	

*Independent Student T-test, #Chi-Square Test, **Mann-Whitney U test

Variables that have independent risk factors for stage 3B in the postoperative period were evaluated by multivariate logistic regression analysis.Variables with p <0.2 as a result of univariate analyzes (**Table 2**) (stage in preop period, suv max, histological type and tm size) were included in the multivariate logistic regression model (**Table 4**).According to the results of the multivariate logistic regression analysis; stage 3 disease (OR=2.7), suv max ≥6.85 (OR=2.1), lepidic type disease (OR=2.6) and tumor size ≥31 mm (OR=2.2) predict postoperative stage 3B disease. According to the scoring system formed by weighting with the OR values from the multivariate logistic regression, the stage 3 disease in the preop period was assigned 3 points, suv max ≥6.85 got 2 points, lepidic type disease 3 points and tumors size ≥31mm as 2 points. The patients can get maximum 10 minimum from 0 points for this scoring. (**Table 4**).

In order to predict mediastinal LAP involvement (The Mediastinal Lymph Adeno-Pathy Positive Score), the optimal cut off obtained by ROC analysis (**Figure-3b**) was found to be 4. For this cut off, diagnostic Odds ratio (DOR), sensitivity and specificity were found 7 (95% CI=3.5-13.6), 80% and 64% respectively (**Table 3**).

Table 2. Evaluation according to the postoperative stage

Characteristics N=268		Stage 3A ve others N=203	Stage 3B N=65	p
Age (year)				0.291*
Mean±sd		58.7±7.4	59.9±8.4	
Sex, n(%)				0.636#
Female		51 (25.1)	20 (30.8)	
Male		152 (74.9)	45 (69.2)	
Histopathology, (%)				0.198#
Aciner		57 (28.1)	14 (21.5)	
Micropapillary		37 (18.2)	8 (12.3)	
Lepidic		35 (17.2)	19 (29.3)	
Papillary		33 (16.3)	13 (20)	
Solid		41 (20.2)	11 (16.9)	
Suv max				
Median (IRQ)		6.8 (3.6-10)	9.2 (6.2-13.2)	<0.001**
Preop stage, (%)				<0.001#
Stage 1		97 (47.8)	8 (12.2)	
Stage 2		63 (31.0)	20 (30.8)	
Stage 3A		43 (21.2)	37 (56.9)	
Suv max, n (%)				0.009#
	<2.5	34 (16.7)	2 (3.1)	
	≥2.5	169 (83.3)	63 (96.9)	
Preop Stage 1A 1B 1C		n=97	n=8	0.264#
	<2.5	34 (35.1)	1 (12.5)	
	≥2.5	63 (64.9)	7 (87.5)	
Preop Stage 2A 2B		n=63	n=20	0.241#
	<2.5	0	1 (5)	
	≥2.5	63 (100)	19 (95)	
Preop Stage 3A		n=43	n=37	NA
	<2.5	0	0	
	≥2.5	43 (100)	37 (100)	
Primer Tm size	Median (IRQ)	25 (15-40)	39 (30-50)	<0.001**
Preop Stage 1A 1B 1		n=97	n=8	0.264#
	<2.5	34 (35.1)	1 (12.5)	
	≥2.5	63 (64.9)	7 (87.5)	
Preop Stage 2A 2B		n=63	n=20	0.241#
	<2.5	0	1 (5)	
	≥2.5	63 (100)	19 (95)	
Preop Stage 3A		n=43	n=37	NA
	<2.5	0	0	
	≥2.5	43 (100)	37 (100)	
Primer Tm size	Median (IRQ)	25 (15-40)	39 (30-50)	<0.001**
Preop Stage 1A 1B	Median (IRQ)	n=97 15 (12-20)	n=8 31 (21.3-38.8)	0.004**
Preop Stage 2A 2B	Median (IRQ)	n=63 30 (25-36)	n=20 31 (28-35)	0.514**
Preop Stage 3A	Median (IRQ)	n=43 59 (47-60)	n=37 46 (35.5-55)	0.122**

*Independent Student T test, #Chi-Square Test, **Mann-Whitney U test, NA: not available

Table 3. Statistical Parameters of Various Diagnostic Approaches for Post-operative 3B Stage

	AUC (95% CI)	P	Cut-off	Sensitivity (%)	Specificity (%)	+LHR	PPV (%)	NPV (%)	Max Youden index
SUV MAX	0.662 (0.590-0.734)	<0.001	≥6.85	70.8	51.7	1.4	31.9	84.7	0.23
TM Size	0.700 (0.632-0.767)	<0.001	≥31	70.8	64.5	1.9	39	87.3	0.35
MLP SCORE (0-10)	0.753 (0.686-0.819)	<0.001	≥4	80	64	2.2	41.3	90.8	0.44

+LHR: Positive Likelihood Ratio, PPV: Positive Predictive Value, NPV: Negative Predictive Value, MLP score=The Mediastinal Lap Positive score

Table 4. Multivariate logistic regression analysis on risk factors for positive mediastinal lymphadenopathy and scoring system for the diagnosis of positive mediastinal lymphadenopathy

	Multivariate logistic regression analysis model*		
	Adjusted OR (95% CI)	P	MLP Score (points)
Preop Stage 3A (ref: stage I and II)	2.7 (1.3-5.6)	0.007	3
Histopathology (ref: aciner)			
Micropapillary	0.8 (0.3-2.2)	0.662	3
Lepidic	2.6 (1.1-6.4)	0.037	
Papillary	1.6 (0.6-4.1)	0.331	
Solid	0.8 (0.3-2.1)	0.662	
SUV Max, ≥6.85, (ref: <6.85)	2.1 (1.1-4.2)	0.046	2
TM size, ≥31 (ref: <31)	2.2 (1.1-4.6)	0.049	2

DISCUSSION

Developments in PET-CT technology have reduced diagnostic difficulties in lung cancer. PET-CT aids clinicians in diagnosis, staging and treatment follow-up Hochhegger et al. (1) and Groheux D et al. (15). Nevertheless, lung adenocarcinoma still has potential limitations that is partly because some adenocarcinomas may manifest as subsolid nodule with malignancies commonly have low levels of FDG afinity Erasmus JJ et al. (5). Evaluation of mediastinal lymph nodes and solitary pulmonary nodules is especially challenging Feng M et al. (16). This situation also limits the clinical benefits of PET-CT Song SH et al. (17). The heterogeneous nature of FDG uptake of lung adenocarcinomas requires detailed evaluation. In 2011, the pathological classification of lung adenocarcinomas was changed Erasmus JJ et al. (5). Therefore, evaluating the clinical correlation with PET-CT in newly defined subtypes of lung adenocarcinomas may provide valuable information in daily clinical routine practices.

In the study, SUV-max values were found to be significantly lower in some adenocarcinoma pathological subtypes, especially in lepidic pattern Xiaoliang S et al. (18) and Şanlı B. (19). This represents a different level of glucose metabolism at both the morphological and cellular levels. Early diagnosis and treatment of early stage tumors are crucial for correct intervention. Solitary pulmonary nodules due to adenocarcinomas have a higher potential for being misdiagnosis as benign Erasmus JJ et al. (5), Xiaoliang S et al. (18), Cruickshank A et al. (20). PET-CT is less reliable when the tumor size is less than 8-10 mm, however it yields much better results for tumors larger than 11 mm in size Tang K et al. (21). Also, our results indicate that false negative PET-CT results even for large tumors can be seen lepidic pattern. This finding implies low FDG affinity SPN's might be due to adenorcarcinoma with lepidic pattern. Some certain morphologic findings and anatomical location in chest CT's can be used in such cases. However, this approach is subjective and dependent on the clinician's experience Tang K et al. (21).

The most critical step in determining the correct treatment approach for lung cancers is the correct evaluation of the mediastinal lymph nodes. If N2 disease is not present, curative surgery may be possible Schmidt HM et al. Erasmus JJ et al. (3,5). PET-CT in evaluation of mediastinal lymph nodes have been extensively studided. In a review involving 45 study PET-CT's sensitivity and specificity estimates for the SUVmax ≥2.5 PET-CT positivity criterion were 81.3% (95% CI 70.2 to 88.9) and 79.4% (95% CI 70 to 86.5), respectively. The review has shown that accuracy of PET-CT is insufficient to allow management based on PET-CT alone. In fact, the risk of unforeseen nodal involvement in low-FDG avid tumors has been considered before in the 2014 Revised ESTS guidelines for preoperative mediastinal lymph node staging De-Leyn P et al. (22,23). However, this does not exactly represent the data we want to test or access.

In our study, we tried to reach data that could provide us with new information only in adenocarcinoma subgroups. Therefore, we aimed to minimize the impact of anatomic location and N1 disease in our results. It is a fact that we will have a very high reliability evaluation chance with the programs that can be created with the development of digital algorithms. Thus, it is to be able to see in mediastinal sampling whether the feature of adenocarcinoma subgroups can gain a place in the algorithm. Though this review is limited by heterogenity of the studies. Most of them involve all pathologic subtypes in non-squamous lung cancers Ambrasini et al. (24).

Conducting these studies separately in each pathological subtype such as isolated adenocarcinomas and evaluating the sub-pathological types of adenocarcinoma will provide much more valuable information. Our study is the only study conducted in this respect and our results contain very valuable data. Invasive mediastinal lymph node sampling is recommended for this patient group with insufficient evidence based data which results in unnecessary sampling with EBUS and EUS. Furthermore if sampling is not performed, the rate of unnecessary surgery and more invasive procedures increase Sivriköz CM et al. (25) and Thornblade LW et al. (26). In this dilemma, the desired results are not achieved in this patient group. For such reasons, much more objective quantitative approaches are needed in the evaluation of lung adenocarcinomas.

Patients with lepidic pattern cancers have more mediastinal lymph nodes which are negative preoperatively but postoperatively detected. However, the difference is not statistically significant. Perhaps statistically significant results can be reached in larger series. But the findings led us to steer to a scoring system, which includes tumor size, pre-op stage, SUV-max. That particular system provides better sensitivity and spesificity than PET CT. MLP score has a great negative predictive value when under 4. It is also efficient in predicting post-operative 3B disease risk. We believe MLP score will reduce the rate of unnecessary surgery. Our statistics prove that this scoring system is more valuable than PET CT for each of its components.

The approach defined by the European Society for Medical Oncology in 2013 has had general acceptance in clinical practice Eberhardt WE et al. (27). If the mediastinal lymph node is negative in PET-CT, invasive staging is not recommended. The exceptions to this are; centrally located tumors and N1 lymph node above the long axis of the tumor is >3cm, while Thorax Ct are cases with lymph nodes more than 1 cm in the short axis. Of course, there are also various suggestions from the literature Ambrasini V et al. (24) and Smith DE et al. (28). Tumor localization has an important place in some of the studies. Although it is very logical about lymphatic drainage, classification and evaluation can not be standardized.

Stage 3A is undoubtedly the most troublesome in terms of staging. Tumor size was seen to be significant when over 3 cm and our data is compatible Tang K et al. (21) and Eberhardt et al. (27). For the SUV-max value, higher metabolic levels have better results for positive predictive values Yalçınkaya E et al. (29). This is in line with the hypotheses, which suggest SUV-max cut-off values over 2.5 need to be evaluated for mediastinal lymph nodes Yalçınkaya E et al. (29).

Our scoring system defines a baseline systematic and naturally it has many constraints. Our study includes a retrospective evaluation and was conducted on a limited patient population. For this reason, our results needs testing with prospectively designed multicenter and multinational studies. Tumor volumes instead of the tumor size yield more meaningful results. Mediastinal lymph node localization needs international standardization, after which studies may focus on locations. N1 disease and anatomical location would be appropriate to be included in the evaluation criteria. Of course, standardization of the anatomical location should not depend on subjective criteria.

Finally, our scoring system has a great negative predictive value but an under desired positive predictive value. This may be due to our focus on the goal of reducing the number of cases with unnecessary surgery with correct staging. Despite these limitations, our study is the only study including a large number of patiens, focused on PET-CT with a new pathological classification of lung cancer adenocarcinoma. We believe it will contribute positively to the clinical decision-making process and the future studies in establishing a baseline systematic.

CONCLUSION

Up to date pathological subtypes of lung adenocarcinoma greatly correlate with PET-CT results and clinical features. The lepidic subtype has a lower FDG affinity. Negative PET scan results should be considered in solitary pulmonary nodules especially when lepidic subtype is present, which underlines the importance of surveillance in solitary nodules. Mediastinal staging for lung adenocarcinomas employing clinical scoring with subtype, tumor size, FDG uptake and PET scan stage has a high accuracy. MLP scoring may form the basis for new studies about mediastinal lymph node evaluation and will be able to provide more precise data by adding new criteria.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the İzmir Katip Çelebi University Hospital Ethics Committee (Date: 2021, Decision No: 371).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgement: Our research's data was presented in 19. National Thoracic Surgery Society Congress as 'Oral Presentation' on October 2021.

REFERETNCES

1. Hochhegger B, Alves GR, Irion KL, et al. PET/CT imaging in lung cancer: indications and findings. J Bras Pneumol 2015 May-Jun; 41: 264-74.
2. Zhao L, He ZY, Zhong XN, Cui ML. (18)FDG-PET/CT for detection of mediastinal nodal metastasis in non-small cell lung cancer: a meta-analysis. Surg Oncol 2012; 21: 230-6.

3. Schmidt-Hansen M, Baldwin DR, Hasler E, Zamora J, Abraira V, Roqué I Figuls M. PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer. Cochrane Database Syst Rev 2014; 2014(11): CD009519.
4. Sara V, Jason MA, Angela T, Adam P, Giuseppe A, Aman SC. The role of positron emission tomography in the diagnosis, staging and response assessment of non-small cell lung cancer. Ann Transl Med 2018; 6: 95.
5. Erasmus JJ, Macapinlac HA. Low-sensitivity FDG-PET studies: less common lung neoplasms. Semin Nucl Med 2012; 42: 255-60.
6. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011; 6: 244-85.
7. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016; 11: 39-51.
8. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997; 111: 1718-23.
9. Hamacher K, Coenen HH, Stöcklin G. Efficient stereospecific synthesisof no-carrier-added 2-(18F)-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. J Nucl Med 1986; 27: 235-8.
10. Öztaş S, Öztürk AV,Acartürk E, et al. The role of tumor SUVmax/lymph node SUVmax ratio viewed on PET-CT in the detection of mediastinal metastasis in patients with lung cancer. Turk Gogus Kalp Dama 2012; 20: 544-51.
11. Obuchowski NA. Receiver operating characteristic curves and their use in radiology. Radiology 2003; 229: 3–8.
12. Metz CE. Basic principles of ROC analysis. Semin Nucl Med. 1978; 8: 283–98.
13. Böhning D, Holling H, Patilea V. A limitation of the diagnostic-odds ratio in determining an optimal cut-off value for a continuous diagnostic test. Stat Methods Med Res 2011; 20: 541-50.
14. Zogheib E, Cosse C, Sabbagh C, et al. Biological scoring system for early prediction of acute bowel ischemia after cardiac surgery: the PALM score. Ann Intensive Care 2018; 8: 46.
15. Groheux D, Quere G, Blanc E, et al. FDG PET-CT for solitary pulmonary nodule and lung cancer: A literature review. Diagn Interv Imaging 2016; 97: 1003-17.
16. Feng M, Yang X, Ma Q, He Y. Retrospective analysis for the false-positive diagnosis of PET-CT scan in lung cancer patients. Medicine (Baltimore) 2017; 96: e7415.
17. Song SH, Ahn JH, Lee HY, et al. Prognostic impact of a nomogram based on whole tumor size, tumour disappearance ratio on CT and SUVmax on PET in lung adenocarcinoma. Eur Radiol 2016; 26: 1538–46.
18. Xiaoliang S, Rong N, Zhenxing J, Xiaonan S, Yuetao W. Role of PET/CT in management of early lung adenocarcinoma. American J Roentgenol 2020; 214: 437-45.
19. Şanlı BA, Ulugün Fİ, Karaçam V, et al. Positron emission tomography/computed tomography findings of lung invasive adenocarcinoma subgroups and comparison of their short-term survivals. Turk J Thoracic Cardiovasc Surg 2021; 29: 370-6.
20. Cruickshank A, Stieler G, Ameer F. Evaluation of the solitary pulmonary nodule. Intern Med J 2019; 49: 306-15.
21. Tang K, Wang L, Lin J, Zheng X, Wu Y. The value of 18F-FDG PET/CT in the diagnosis of different size of solitary pulmonary nodules. Medicine (Baltimore).2019; 98: e14813.
22. De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg. May 2014; 45: 787-98.
23. De Leyn P, Lardinois D, Van Schil PE, et al. ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. Eur J Cardiothorac Surg. Jul 2007; 32: 1-8.
24. Ambrosini V, Nicolini S, Caroli P, et al. PET/CT imaging in different types of lung cancer: an overview. Eur J Radiol 2012; 81: 988-1001.
25. Sivrikoz CM, Ak I, Simsek FS, Döner E, Dündar E. Is mediastinoscopy still the gold standard to evaluate mediastinal lymph nodes in patients with non-small cell lung carcinoma?. Thorac Cardiovasc Surg 2012; 60: 116-21.
26. Thornblade LW, Wood DE, Mulligan MS, et al. Variability in invasive mediastinal staging for lung cancer: a multicenter regional study. J Thorac Cardiovasc Surg 2018; 155: 2658-71.
27. Eberhardt WE, De Ruysscher D, Weder W, et al. Panel Members. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol 2015; 26: 1573-88.
28. Smith DE, Fernandez AJ, Da Lozzo A, Montagne JA, Beveraggi E, Dietrich A. Accuracy of positron emission tomography and computed tomography (PET/CT) in detecting nodal metastasis according to histology of non-small cell lung cancer. Updates Surg 2019; 71: 741-6.
29. Yalcınkaya E, Anar C, Yavuz YM, et al. Prognostic importance of SUVmax value in PET/CT and correlation SUVmax Value between lymph node, distant metastasis in non-small cell lung cancer. Izmir Gogus Hastanesi Derg 2015; 24: 127-37.