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Retrospective analysis of false positive ratio of our patients with lung cancer at positron emission tomography-CT screen

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Abstract:

BACKGROUND: In lung cancer, staging is necessary to give the best treatment to the patient and to estimate the best prognosis. The aim of this study was to compare the pathology results of the lung masses and mediastinal lymph nodes and to evaluate the sensitivity and specificity values of positron emission tomography–computerized tomography (PET-CT) and to determine the maximal threshold of maximum standardized uptake volume (SUV_{max}).

MATERIALS AND METHODS: We retrospectively evaluated the PET-CT SUV_{max} values and pathology results of the patients who had a mass, mediastinal lymph node, or scalene lymph node in our patients between 2016 and 2018.

RESULTS: Fifty-one people and 75 pathology materials were included in our study. We used the receiver operating characteristic curve analysis to determine the cutoff value for SUV_{max} value and calculated the cutoff value as 6.65. In our study, the sensitivity and specificity were calculated as 63% and 71%, respectively. We calculated the positive predictive value as 73.5% and the negative predictive value as 61%.

CONCLUSION: As a result, considering the common inflammatory and granulomatous diseases seen in our country, we concluded that benign diseases should be considered before malignancy in SUV_{max} value below 6.6. We continue to add new patients and new data to our study to find the most appropriate threshold of SUV_{max} value for the health values of our country.

Keywords:

Diagnosis, false positive, lung cancer, positron emission tomography–computerized tomography, tuberculosis

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Introduction

Lung cancer is the most common type of cancer in the world for many years. In 2012, it is estimated that there are 1.8 million new cases worldwide. The disease is the most common type of cancer in men worldwide (1.2 million, 16.7% of the total). Its incidence in Central and Eastern Europe is 53.5/100,000. Although the rates are slightly lower in women, it is mostly seen

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in North America (%0,0033.8) and in northern European countries(%0,0023.7).

As well as its frequency, lung cancer increases its severity with its mortality. Lung cancer is the most common cause of death of cancer worldwide and is estimated to be responsible for one in five (1.59 million deaths, 19.4% of the total).[1]

Because of respiratory tract cancer in Turkey it is 75,993 patients have been lost their lives in 2014. This constitutes 31.1% of all cancer-related deaths.[2]

Even though the continuous development of lung cancer treatment, unfortunately, its prognosis is still very poor.

According to the studies, prognosis is associated with the stage of clinical diagnosis; the 5-year survival rate is 38%–67% in Stage 1, but only 1% in Stage 4.[3] If patients with lung cancer accept surgery at an early stage, the 10-year survival rate can be 88%.[4] For this reason, early diagnosis and timely treatment is very important in patients with lung cancer.

Diagnosis of the disease is often based on pathological examination with appropriate method (bronchoscopic biopsy/transthoracic fine-needle aspiration biopsy/surgery) after the detection of mass by computed tomography.

For patients, correct staging is essential to obtain the most effective treatment and to estimate the best prognosis. Using floro-2-deoxy-glucose (FDG), both computed tomography (CT) and positron emission tomography (PET) play an important role in the diagnosis and staging of lung cancer. In addition to mediastinal lymph node metastases, FDG-PET is highly sensitive in detecting extrathoracic metastases.[5]

PET, based on the fact that malignant cells have a higher rate of glycolysis than most of the surrounding normal cells. Glucose is also rapidly metabolized by tissues involved in granulomatous or inflammatory processes, and therefore, there will be some false positive results.[6] One of the reasons for false positivity is tuberculosis (TB), which is a common disease in the world and in our country.

Frequency of TB was reported as 17.3/100,000 in Turkey.[7]

Therefore, it is too much important for patient and health management to be careful, in terms of false positives that may increase during PET-CT use in staging lung cancer. In our study, we aimed to evaluate the sensitivity and specificity of PET-CT and to calculate the best threshold of SUV_{max} by comparing the pathology results of the mediastinal lymph nodes.

Materials and Methods

Working group

We retrospectively evaluated the PET-CT FDG results of the patients who had a mass in the lung, mediastinal lymph node, or scalene lymph node between 2016 and 2018. We compared the pathological manifestations with the samples that were available for tissue diagnosis (mediastinoscopy/lobectomy/segmentectomy/pneumonectomy/scalar lymph node biopsy).

Our study complies with the Declaration of Helsinki.

Fluorodeoxyglucose positron emission tomography-CT examination

All body scannings were performed by Siemens Biograph DUO PET/BT (USA). Blood glucose levels were adjusted to 150 mg/dl 6 h before screening. The scannings were performed using intravenous contrast medium for covering the vertex and upper thigh level while the patient was in supine position. The Farmasotik dose was taken to be 7–8 mCi position number 8 position duration 3 min. For attenuation correction and anatomic accuracy, a low-dose cross-section thickness of 3 mm CT was evaluated together.

Image examination and analysis

Image analysis was performed by a nuclear medicine specialist. The standardized uptake values (SUVs) were obtained by the calculation of the amount of FDG by body weight and by the corrected calculation of regional attenuation in the target tissue. Mediastinal lymph nodes were considered positive when the involvement was higher than intravenous involvement and was named according to lymph nodes Mountain and Dresler lymph node map.

Histopathological lymph node sample and analysis

Sampling was performed by the same surgeon who had knowledge about PET-CT results through lobectomy, segmentectomy, pneumonectomy, mediastinoscopy, or lymph node dissection. Mediastinal lymph nodes were performed according to the Mountain and Dresler lymph node map according to the naming of PET-CT. The chronic inflammatory process is called granulomatous changes and anthracosis benign pathology; adenocarcinoma, squamous cell carcinoma, bronchoalveolar cancer, small-cell lung cancer, and metastases of extrapulmonary malignancies were collected in the malignant group.

Data analysis

The results were obtained by comparing the results of PET-CT and histopathological examination. According

to the results of PET-CT, FDG involvement was detected as false positive in the absence of malignancy in histopathological examination; lesions with FDG involvement and histopathologically diagnosed as malignant were positive; false negative results with no FDG involvement but with histopathological features; histopathologically, nonmalignant and noninvolvement PET-CT studies have been evaluated as true negative.

Statistical analysis

Data were analyzed with SPSS Package Program version 19.0 (IBM Co., Somers, NY, USA). In the presentation of descriptive data, number, percentage, mean, standard deviation, median, minimum, and maximum were used. Receiver operating characteristic (ROC) curve analysis was used to determine the threshold value of SUV_{max} for use in the differentiation of benign malignant. According to the result of analysis of benign malignancy, SUV_{max} cutoff value was accepted as 6650. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated according to this value. $P < 0.05$ was accepted for statistical significance.

Results

Nine (17.6%) female and 42 (82.4%) male patients were included in the study. The researches included were 75 pathological materials, of which 32.0% (n = 24) were mass and 68.0% (n = 51) were lymph nodes. 15.7% (n = 8) of the lymph nodes, right upper paratracheal (2R), 35.3% (n = 18) right lower paratracheal (4R), 23.5% (n = 12) subcarinal,[7] 5.9% (n = 3) left upper paratracheal (2 L), 9.8% (n = 5)

Table 1: Lymph nodes location and pathology results (right upper paratracheal [2R], right lower paratracheal [4R], subcarinal [7], left upper paratracheal [2L], left lower paratracheal [4L])

	n (%)
Lymph node placement	
2R	8 (15.7)
4R	18 (35.3)
7	12 (23.5)
2L	3 (5.9)
4L	5 (9.8)
Supraclavicular	5 (9.8)
PET involvement	
Available	73 (97.3)
Not available	2 (2.7)
Pathology	
Benign	34 (45.3)
Malign	41 (54.7)
Diagnosis	
Benign cytology	29 (38.7)
Adenocarcinoma	12 (16.0)
Squamous cell carcinoma	18 (24.0)
Bronchoalveolar cancer	2 (2.6)
Small-cell lung cancer	6 (8.0)
Nonlung cancer	8 (10.7)

PET: Positron emission tomography

Table 2: Coordinates of the curve

Test result variable(s): SUV_{max}		
Positive if greater than or equal to[a]	Sensitivity	1 - Specificity
−1.0000	1.000	1.000
1.0350	0.951	1.000
2.3350	0.927	1.000
2.7000	0.902	1.000
3.0000	0.854	1.000
3.2500	0.829	1.000
3.3500	0.829	0.971
3.5000	0.829	0.941
3.7500	0.805	0.912
3.9500	0.756	0.882
4.0500	0.732	0.853
4.1500	0.732	0.765
4.2500	0.707	0.765
4.4000	0.707	0.706
4.6000	0.683	0.618
4.8500	0.683	0.588
5.1350	0.683	0.441
5.4350	0.683	0.353
5.6150	0.634	0.324
5.7650	0.610	0.324
6.1500	0.610	0.294
6.6500	0.610	0.265
6.9300	0.585	0.147
7.1800	0.585	0.118
7.4500	0.561	0.118
7.5500	0.537	0.118
7.6500	0.488	0.118
8.2950	0.463	0.118
8.8950	0.439	0.088
9.0350	0.415	0.088
9.2850	0.390	0.088
9.5500	0.317	0.088
9.8500	0.293	0.088
10.8000	0.268	0.088
11.7000	0.244	0.088
11.9000	0.244	0.029
12.4000	0.220	0.029
14.0500	0.195	0.029
15.5000	0.171	0.029
15.8000	0.098	0.029
16.5000	0.073	0.029
17.8650	0.049	0.029
22.0650	0.024	0.000
26.5000	0.000	0.000

[a]The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values. The test result variable (s): SUV_{max} has at least one tie between the positive actual state group and the negative actual state group. SUV_{max}: Maximum standard uptake value

left lower paratracheal (4 L) and 9.8% (n = 5) was located in the supraclavicular region [Table 1].

The average of SUV_{max} was 7.4 ± 4.7, and the median was 5.6 (min: 0.0 and max: 25.5).

ROC curve analysis was used to determine the threshold value of SUV_{max} in the distinction of benign–malignant pathology. The analyses included were 41 malignant[1] and 34 benign[2] pathology [Tables 2-4]. The area under the curve in the ROC curve analysis was 0.637 (95% confidence interval [CI]: 0.504–0.771) (P = 0.042). According to the result of the analysis of benign and malignant, SUV_{max} estimation value was accepted as 6650 [Figure 1].

Discussion

Lung cancer is the most common cancer in men in Turkey and its incidence rate is 52.5/100,000. This rate is 8.7/100,000 in women. In lung cancer, more than half of the patients are diagnosed at advanced stage.[8]

Early diagnosis is vital in lung cancer. Although CT provides three-dimensional imaging of the lungs, it does not provide information about physiological/metabolic features. PET goes beyond anatomical imaging to enable the characterization and measurement of biological processes at the cellular level. Combined PET-CT technology provides the clinician with clear information about where healthy lung tissue terminates and where tumor tissue begins.[9]

PET-CT is mainly based on the fact that malignant cells will consume more glucose than normal tissue. The most commonly used radiopharmaceutical agent is the glucose analog used to monitor glucose transport and metabolism 2-(fluorine-18 [18F])-floro-2-deoksi-d-glucose (FDG), where 18F is a positron spreader that creates the high-energy photons. The rate of cellular glycolysis is reflected by the degree of FDG involvement and can be determined from the correction data by imaging data, so that the photons are not attenuated by body tissues.[10]

PET-CT is also of great benefit for staging, especially in nonsmall-cell lung cancer (NSCLC). The sensitivity and specificity of the CT evaluation performed to identify lymph node metastasis in a rectopposed study by Silvestri *et al*.[11] were 51% (95% CI: 47%–54%) and 85% (95% CI: 84%–88%), respectively. The same values for PET-CT were 74% (95% CI: 69%–79%) and 85% (95% CI: 82%–88%), respectively. Again in the same study, false positive rate was 15%–20% and false negative rate was 10%–15%. Most of the false positives are inflammatory diseases. Because of the inactive TB lymph nodes that are not bred by live TB, it is difficult

Table 3: Distribution of pathological materials according to 6.650 maximum standard uptake values (sensitivity: 61%, specificity: 73.5%, positive predictive value: 73.5%, negative predictive value: 61%, accuracy rate: 66.7%)

	SUV_{max} <6.650, *n* (%)	SUV_{max} ≥6.650, *n* (%)	Total, *n* (%)
Benign (%)	25 (61.0) (73.5)	9 (26.5) (26.5)	34 (45.3) (100.0)
Malign (%)	16 (39.0) (39.0)	25 (73.5) (61.0)	41 (54.7) (100.0)
Total	41 (100.0) (54.7)	34 (100.0) (45.3)	75 (100.0) (100.0)

SUV_{max}: Maximum standard uptake value

Table 4: Sensitivity, Specificity, positive predictive value, negative predictive value, and accuracy ratio of maximum standard uptake values according to receiver operating characteristic curve analysis

SUV_{max}	Sensitivity	1 - Specificity	PPV	NPV	Accuracy ratio
−1.0000	1.0000	1.0000	0.547	-	0.547
3.5000	0.829	0.941	0.515	0.222	0.480
4.4000	0.707	0.706	0.547	0.455	0.520
5.6150	0.634	0.324	0.703	0.605	0.653
5.7650	0.610	0.324	0.694	0.590	0.640
6.1500	0.610	0.294	0.714	0.600	0.653
6.6500	0.610	0.265	0.735	0.610	0.667
6.9300	0.585	0.147	0.828	0.630	0.707
10.8000	0.268	0.088	0.786	0.508	0.560
15.5000	0.171	0.029	0.875	0.493	0.533

PPV: Positive predictive value, NPV: Negative predictive value, SUV_{max}: Maximum standard uptake value

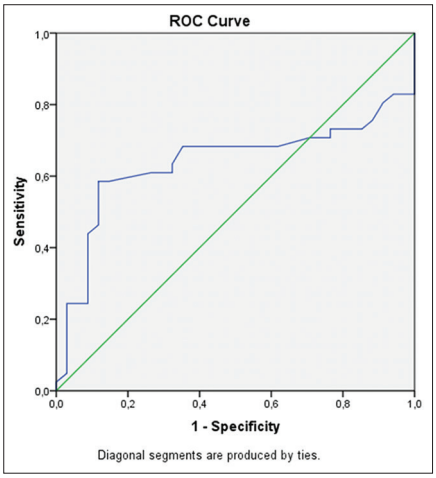

Figure 1: Receiver operating characteristic curve analysis

to distinguish between noncalcified lymph node TB and metastatic lymph nodes.[12] Kang *et al*.[13] suggested that 18F-FDG showed low diagnostic sensitivity in the differentiation of NSCLC and lung TB. However, Shaw *et al*.[14] have argued that PET-CT is a valuable method to exclude mediastinal lymph node involvement in NSCLC, even in a high TB-endemic region, and that the PET-CT

positive results should not necessarily exclude potential TB stated that they should. In addition, granulomatous diseases such as sarcoidosis may mimic malignant diseases with mediastinal lymph node involvement in PET-CT.[15] Anthrax in the lymph nodes may be associated with malignancy and TB, or it may cause high FDG PET involvement alone.[16]

The overlap between the standardized uptake value (SUV) in malignant and benign lesions has led to the investigation of several dichotomization methods, such as the use of SUV cutoff thresholds, dual tracer imaging, dual time point imaging, or delayed imaging. There is, however, no consensus about the use of ^{18}F-FDG PET to differentiate TB from malignancy or other granulomatous or other inflammatory lesions.[17]

In another study with 87 histologically confirmed patients with lung malignancy and 46 patients with histologically confirmed TB lesions, 1st h SUV and 2nd h SUV values of malignant lung lesions were significantly higher than TB lesions.[18]

In countries such as India, Indonesia, and China, where TB is endemic, improving control of TB can help improve the diagnostic accuracy of PET-CT in lung cancer. Despite the decrease in frequency in recent years in Turkey, in terms of TB continues to take place in the list of priority countries of the World Health Organization. 13,378 TB cases of TB in Turkey entered the record in 2014. The rate of the cases was 19.8 in 100,000 in men and 14.6 in 100,000 in women.[19]

In Western countries, the prevalence of SUV_{max} of 2.5 is considered to be a cutoff value for benign and malignant lesions.[20] However, using the same value in countries where TB is endemic reduces the diagnostic value of PET-CT in lung cancer.

According to a study conducted by Goo *et al*.[21,22] in South Korea, increased SUV_{max} values in the focal pulmonary lesions were observed above the 2.5% of the TB-max values and in the study performed by Kumar *et al*. The sensitivity and specificity values of PET-CT were 87% and 70%, respectively. Shaw *et al*.[14] reported that an SUV_{max} cutoff of 4.5 could increase diagnostic accuracy from 64.0% to 84.7% compared to a cutoff of 2.5. In a retrospective study of 75 pathological specimens, we found that the mean SUV_{max} values of PET-CT were 7.4 ± 4. We used the ROC curve analysis to determine the cutoff value for SUV_{max} value in benign–malignant, and we calculated the cutoff value as 6.65. In our study, the sensitivity and specificity were 63% and 71%, respectively. We calculated the positive predictive value as 73.5% and the negative predictive value as 61%.

In countries with widespread TB, progressing to TB control and improving the threshold value of PET-CT may be promising to reduce the false positive PET-CT ratio in lung cancer.

The limitations of our study were retrospective file scanning and the lack of sample number.

Conclusion

Although our study was performed on the basis of the retrospective data of 51 patients and 75 pathological materials, we concluded that benign diseases should be considered before malignancy in the SUV_{max} value below 6.6 when considering the common inflammatory and granulomatous diseases commonly seen in our country. We continue to add new patients and new data to our study to find the most appropriate threshold value for our country's health values.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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