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Correlation between the probability of malignancy and maximum standard uptake values of mediastinal lymph nodes on 18F-FDG positron emission tomography scan sampled by endobronchial ultrasound-guided-transbronchial needle aspiration: A retrospective analysis

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Abstract:

INTRODUCTION: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is frequently used as an important initial investigation for diagnosing and staging for both suspected malignant and benign mediastinal lesions for the last 10 years.

AIM: We aimed to analyze the correlation between probability of malignity by EBUS-TBNA and maximum standard uptake value (SUV_{max}) obtained by 18F-labeled fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET CT).

METHODS: This is a retrospective study using hospitals' database records. Demographic features of the patients, characteristics of the biopsied lymph nodes (LNs), PET-CT results, and SUV_{max} are obtained from hospital database system.

RESULTS: A total of 322 patients underwent EBUS-TBNA for a final diagnosis. The mean age was 59.4 years. The most common final diagnosis was nonsmall cell lung cancer. When we compared the average SUV_{max}, as the SUV_{max} increased, the probability of malignity increased significantly ($P < 0.001$). We studied a Youden index for SUV_{max} and the cutoff point for SUV_{max} was 9 for 54.39% sensitivity and 79.1% specificity.

CONCLUSION: Our study in a real-life setting showed that EBUS-TBNA is effective in diagnosing patients who had mediastinal LNs suspected of malignancy. We also showed that as the SUV_{max} increased, the probability of malignancy increased. We believe that more data are needed from a larger number of patients from different centers.

Keywords:

Endobronchial ultrasound, lung cancer, positron emission tomography-computed tomography, staging

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Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is usually used as an important first choice investigation for diagnosing suspected malignant and benign mediastinal lesions.[1,2] The diagnostic yield of EBUS-TBNA for the detection of malignity for mediastinal enlargements has sensitivity between 88% and 93%.[3] There are some studies examining the relationship between EBUS-TBNA diagnostic utility and computed tomography (CT) staging, positron emission tomography-CT (PET-CT) node maximum standard uptake value (SUV_{max}), and node size calculated by EBUS.[2,4]

Although the size of lymph nodes (LNs) has been shown to be an important predictor of LN metastases, EBUS-TBNA had a sensitivity of 35%, a negative predictive value of 88%, and an accuracy of 88%, in particular small nodes below 10 mm in size.[4,5] Further, as shown in literature, PET scanning for mediastinal staging of lung cancer only has 74% sensitivity and 85% specificity.[6]

Therefore, the aim of our study was to plan a retrospective analysis of EBUS-TBNA in a real-life setting in patients whom were referred with suspected mediastinal lesions to a Chest Diseases Hospital containing an EBUS-TBNA center between December 1, 2012, and January 1, 2016. We aimed to analyze the correlation between probability of malignity by EBUS-TBNA and SUV_{max} obtained by 18F-labeled fluorodeoxyglucose (18F-FDG) PET CT.

Methods

Subject selection

A retrospective analysis of 322 consecutive EBUS-TBNA patients whom were referred to our hospital between December 1, 2012, and January 1, 2016, was performed. Cases were referred for the diagnosis of mediastinal LN enlargements detected on CT scanning. Cases also referred for nodes with an elevated SUV_{max} on PET scanning in which there was a suspicion of malignity based on radiological assessment. All cases of lung cancer, including nonsmall and small cell lung cancer (NSCLC and SCLC) were included. The study was approved by the local institutional review board. The study had been approved by the Ethic Committee of our Hospital's Ethics Committee on November 11, 2017, and the protocol number was 49109414/806.02.02/7826. No written informed consent was taken from patients because of the study's retrospective design. Demographic data, if exists, sites of primary malignancies and tuberculosis (TB) history, CT and PET findings, EBUS findings, stations of aspirated LNs, cytological and histological findings, and final diagnoses were recorded and used from our database.

Radiological evaluation

As this is a real-life study and undergoing EBUS-TBNA was a part of the ongoing standard of care for patients, no specific radiological intervention was made to any patients. Therefore, not all the patients had undergone PET-CT. The indication of EBUS-TBNA in enrolled patients was an LN with a short-axis diameter of >10 mm on the thorax CT. Further, EBUS-TBNA was performed if the LNs had a high FDG uptake on PET-CT scans. PET-CT was performed according to the patients' routine oncological evaluation. The FDG uptake on PET-CT was considered positive if the SUV_{max} was ≥ 2.5.

The endobronchial ultrasound-guided transbronchial needle aspiration procedure

One trained primary operator in the endoscopy unit performed EBUS-TBNA with patients in supine position under conscious sedation (midazolam and fentanyl), through the oral route using a convex Probe Ultrasound Bronchoscope (7.5 MHz, BF-UC160F; Olympus Optical Co., Tokyo, Japan). The new international LN map proposed by the International Association for the Study of Lung Cancer was used to determine the LN stations.[7] If there are multiple suspected LNs, the decision of choosing the LN to puncture depends on the physician's judgment based on findings from the CT or PET-CT scans. Each target nodal station was punctured at least three times with a dedicated 22-gauge needle (NA-201SX-4022, Olympus). The aspirate was then blown onto a glass slide by pushing air using a 20-mL syringe. Aspirated material was also obtained for cell block and *Mycobacterium* and bacterial cultures.

Pathological examination

Some amount of the aspirate was smeared onto glass slides during the procedure; slides were air-dried and fixed immediately with 95% alcohol. They stained with hematoxylin and eosin. The rest of the aspirate was placed into a mixture of formalin and alcohol to obtain a cell block for histological examination.

Mycobacterial cultivation and identification

Fine-needle aspiration biopsy specimens were transported to the microbiology laboratory immediately. The samples were suspended in 1 mL of Middlebrook 7H9 medium and vortexed in the laboratory. The suspensions were then digested and decontaminated by Mycoprosafe (Salubris AS, Istanbul, Turkey) decontamination kit. Mycobacterial cultivation was performed by both MGIT 960 system (BD Biosciences, Sparks, MD, USA) according to the manufacturer's recommendations[8] and Lowenstein–Jensen slants (Salubris AS). An acid-fast smear preparation by Kinyoun staining was also applied to each processed specimen. Differentiation of *Mycobacterium tuberculosis* and nontuberculous mycobacteria was performed by both conventional methods[9] and BD

immunochromatographic tests (BD Biosciences, Sparks, MD, USA). *M. tuberculosis* H37Ra was used as the control strain in all cultivation and identification methods.

Final diagnosis

The final diagnosis was obtained from our database. Patients had a diagnosis of malignity if EBUS-TBNA-aspirated materials contained malignant cells. Diagnosis of TB was made according to the following criteria: granulomatous inflammation and the presence of acid-fast bacilli on microscopy or a positive culture for *M. tuberculosis*. Diagnosis of sarcoidosis was considered according to these three criteria: compatible clinical and radiographic manifestations, exclusion of other diseases that may present similarly, histopathologic detection of noncaseating granulomas.

Statistical analysis

Data were analyzed with MedCalc software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013). The mean, standard deviation, median, minimum value, and maximum values of the continuous variables were given. Since continuous variables were not the normally distributed, it was performed by nonparametric tests. Mann–Whitney U-test was used in independent groups. Nominal variables were presented with their frequencies and percentages. Receiver operating characteristic (ROC) curve was used for the determination of cutoff value for obtaining the best sensitivity and specificity of SUVmax between benign and malign lesions. The level of statistical significance was determined as $P < 0.05$.

Results

In our study, 322 patients underwent EBUS-TBNA for a final diagnosis. There was a male preponderance (230, 71.4%), with an average age of 59 years (range 16–86). Of the 322 patients referred, 182 were subsequently diagnosed with lung cancer (56.4%): 33 (10.2%) SCLC and 149 (46.2%) NSCLC, and 18 (5.5%) extra thoracic cancer [Table 1]. 59 (18.3%) patients were diagnosed with sarcoidosis and 9 (2.7%) with TB. Fifty-one patients either had a diagnosis of reactive LN or anthrocosic LNs. Three patients could not have a diagnosis with EBUS-TBNA alone but needed mediastinoscopy.

A total of 511 nodal stations were sampled in benign lesions. The nodal stations sampled were 2R, 2 L, 4R, 4 L, 7, 10, and 11. A total of 191 nodal stations were sampled in malignant lesions. The nodal stations sampled were 4R, 4 L, 7, 10 and 11. In both benign and malignant groups, the most frequent biopsied station was 7. The distribution of LN stations according to malignity is summarized in Table 2. Of the 182 NSCLC patients, 65 patients diagnosed as lung adenocarcinomas, 67 squamous cell carcinoma, and 17 without differentiation. Majority of the cancer patients were stage 4 [Table 1]. A total of 124 LNs which are punctured by EBUS-TBNA have a SUVmax. Fifty-seven of the malignant lesions and 67 of the benign lesions which are proven by EBUS-TBNA cytology have a SUVmax.

Table 1: The distribution of final diagnosis obtained by endobronchial ultrasound-guided transbronchial needle aspiration

Subgroups	*n* (%)
Diagnosis	
SCLC	33 (10.2)
NSCLC	149 (46.2)
Sarcoidosis	59 (18.3)
TB	9 (2.7)
Extrathoracic malignity	18 (5.5)
Other	54 (16.7)
Stage	
1A	10 (3.1)
1B	9 (2.7)
2A	16 (4.9)
2B	27 (8.3)
3A	19 (5.9)
3B	38 (11.8)
4	63 (19.5)

Other: Reactive LN, anthracotic LN, nondiagnostic in 3 patients. NSCLC: Nonsmall cell lung cancer, SCLC: Small cell lung cancer, TB: Tuberculosis, LN: Lymph node

Table 2: The distribution of the malignant and benign lymph nodes according to the lymph node map stations

Final diagnosis	2R	2L	4R	4L	7	10	11
Benign LN	1	1	147	81	203	45	33
Malignant LN	0	0	55	29	81	12	14
Total number of LN biopsied	1	1	202	110	284	57	47

LN: Lymph node

According to the PET-CT SUVmax, the highest SUV_{max} was in the station 10 [Table 3]. The average median SUV_{max} for benign lesions was 5.6 (2.4–23.4), and the average median SUV_{max} for malignant lesions was 9.5 (3–38.2) [Table 4]. When we compared the average SUVmax, as the SUV_{max} increased, the probability of malignity increased significantly ($P < 0.001$). When we made an ROC curve, the predictive value was 68% for EBUS-TBNA ($P < 0.05$) [Figure 1]. This value is the power of determining the malignity in the whole LNs which are punctured and also have SUV_{max} in study population. We studied a Youden index for SUV_{max} and this index determined the SUV_{max} as 9 for 54.39% sensitivity and 79.1% specificity. The SUV_{max} is correlated with the diagnosis.

Discussion

Our study showed that EBUS-TBNA is frequently used to confirm the diagnosis in patients which have suspected

Table 3: The average maximum standard uptake values according to the lymph nodes biopsied by endobronchial ultrasound-guided transbronchial needle aspiration

LN stations	SUV_{max}	
	Mean±SD	Median (minımum-maximum)
2R	6±3.3	4.8 (2.4-12.7)
2L	7.4±2	7.4 (6-8.9)
4R	8.2±6.5	5.7 (2.5-38.2)
4L	7.8±5.7	6.6 (2.3-25.4)
7	8.2±5.3	6.1 (2.5-25.5)
10	9.1±7.2	6.2 (2.3-36.8)
11	7.6±5.8	5 (3.2-17.8)

SUV_{max}: Maximum standard uptake value, SD: Standard deviation, LN: Lymph node

Table 4: The average maximum standard uptake values of the benign and malignant lymph nodes punctured by endobronchial ultrasound guided transbronchial needle aspiration

	n	Mean±SD	Median (minimum-maximum)
EBUS-TBNA			
SUV_{max}			
Benign	67	6.79±4.43	5.60 (2.40-23.40)
Malignant	57	10.62±7.15	9.50 (3.00-38.20)

SUV_{max}: Maximum standard uptake value, SD: Standard deviation, EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration

mediastinal LN enlargements, avoiding unnecessary invasive techniques in the majority of the cases. None of our patients required overnight admission. This finding supports the study demonstrating that EBUS-TBNA is well tolerated under conscious sedation in outpatient clinics.[10] Further, we showed that as the SUV_{max} increased, the probability of malignity increased significantly.

EBUS-TBNA for diagnosis of malignity in the mediastinal nodes is a very effective, and this technique has low (about 1%) rate of complications.[11-15] In diagnosing and staging of NSCLC, reports from different centers show considerable variation of EBUS-TBNA diagnostic utility (71%–99%),[15-19] with sensitivity (46%–97%) and negative predictive value (60%–99%).[20] Further, in patients previously treated with neoadjuvant therapy, EBUS-TBNA has a high diagnostic accuracy rate.[21] In our study, only three patients needed mediastinoscopy for diagnosis. 56.4% of the cases diagnosed and staged by EBUS-TBNA not requiring invasive techniques. Majority of our cases were NSCLC as expected. Further, in 18 cases, metastasis from extrathoracic malignity to mediastinal LNs was obtained by EBUS-TBNA without difficulty.

Patients with a diagnosis of granulomatous inflammation by pathology were often being prescribed diagnostic anti-TB therapy due to the prevalence of TB.[22,23]

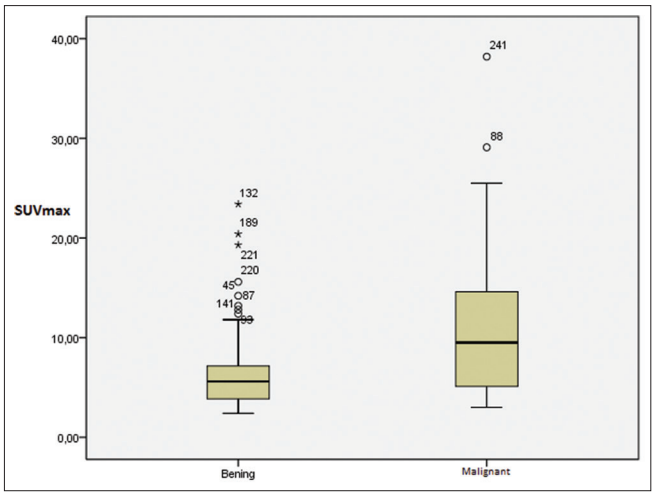

Figure 1: The median maximum standard uptake values of the benign and malignant lymph nodes

However, after anti-TB treatment, such patients should clinically improve. It should also be kept in mind that there is different final diagnosis with granulomatous inflammation obtained by EBUS-TBNA. TB is most common cause of infectious granulomas, but it is not the only reason. In our study, nine patients had a diagnosis of TB according to the following criteria: granulomatous inflammation and the presence of acid-fast bacilli on microscopy, or a positive culture for *M. tuberculosis*.

In our study, the average median SUV_{max} for benign lesions was 5.6, and the average median SUV_{max} for malignant lesions was 9.5. These findings show that benign lesions could also have high SUV_{max} as expected. However, when we compared the average SUVmax, as the SUV_{max} increased, the probability of malignity increased significantly. In addition, when we made an ROC curve comparing the probability of malignity and SUVmax, the predictive value was 68%. A value of 9 for SUV_{max} was determined for 54.39% sensitivity and 79.1% specificity.

There were studies showing that EBUS-TBNA may be helpful in determining lymphoma with a sensitivity range from 76% to 90.9%; however, new studies showed that reactive LN diagnosed by EBUS-TBNA may have a final diagnosis as lymphoma by thoracotomy.[24-26] More biopsy specimens, using flow cytometry and immunohistology, may help increase the diagnostic utility of EBUS-TBNA for lymphoma. In our study, although we use cell blocks during the EBUS-TBNA which can increase the diagnostic utility of the procedure, none of the patients diagnosed as lymphoma by EBUS-TBNA.[27]

The limitations of our study are its observational, single–center, and retrospective study design. Cases which diagnosed malignant with EBUS-TBNA were not confirmed by invasive surgical sampling. However, as

this is a real-life study, in the literature, false-positive malignity results have rarely been observed following TBNA and EBUS-TBNA.[28-30] Not all the patients had PET-CT results and the number of PET-CT nodal SUV_{max} data was limited by incomplete reporting and lack of availability of all PET scans which were performed in different centers.

Conclusion

Our study in a real-life setting showed that EBUS-TBNA is safe and effective in diagnosing patients who had mediastinal LNs suspected of malignity. We also showed that as the SUV_{max} increased, the probability of malignity increased. We believe that more data are needed from a larger number of patients from different centers.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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