Original Article

Can positron emission tomography/computed tomography be predictive of diagnostic success in endobronchial biopsies performed through a fiber-optic bronchoscopy in lung cancer?

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Abstract:

PURPOSE: The purpose of this study is to investigate the effect of homogeneous/heterogeneous (necrotic) involvement and maximum standardized uptake value (SUVmax) value of the lesion on positron emission tomography-computed tomography (PET-CT) of patients who underwent fiberoptic bronchoscopy (FOB) for prediagnosis of lung cancer and biopsy for endobronchial lesion on the diagnostic success of biopsy procedure.

METHODS: Between January 2014 and December 2016, patients with final diagnosis of pulmonary malignancy as determined by FOB biopsy and patients who failed to be diagnosed by FOB biopsy and diagnosed with pulmonary malignancy by a different diagnostic method were examined. These patients were divided into two groups as those with diagnosis by FOB biopsy (Group 1) and those who failed to be diagnosed by this method and diagnosed with pulmonary malignancy by a different diagnostic method (Group 2). The SUVmax values of the two groups were compared with lesion characteristics of homogeneous, heterogeneous involvement/presence of necrotic component as shown by PET-CT. Group data were assessed by Chi-square test and Mann–Whitney U-test. In all tests, $P < 0.05$ was considered significant.

FINDINGS: A total of 193 participants with a mean age of 61 ± 9.4 were included in the study. There were 128 (66.3%) cases in Group 1 and 65 (33.7%) cases in Group 2. The mean SUVmax value was 16.4 in Group 1 and 15.1 in Group 2. There was no statistically significant difference between the two groups ($P = 0.329$). Homogeneous involvement was present in 103 (80.3%) cases in Group 1 versus 42 (64.6%) cases in Group 2. In the presence of homogeneous PET-CT involvement, diagnosis rate by biopsy was significantly higher ($P = 0.016$).

CONCLUSION: We concluded that the high SUVmax value of the mass lesion on PET-CT did not increase the diagnostic value of the biopsy procedure in patients prediagnosed with lung cancer and that the diagnostic success of FOB biopsy was poor in cases where PET-CT showed heterogeneous involvement of the mass lesion.

Keywords:

Fiber-optic bronchoscopy, positron emission tomography, maximum standardized uptake value

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Glucose metabolism has also increased due to rapid cell proliferation in malignant cells. 18-F fluorodeoxyglucose (18F-FDG), a glucose analog used in positron emission tomography (PET) imaging, is quickly taken up by malignant cells but accumulates without being metabolized. Metabolic imaging can be obtained by assessing the cell viability and metabolism of tumors by PET thanks to FDG being retained in the cell due to the high glucose affinity of malignant tumor cells.[1-3] However, the involvement of necrotic areas of tumor cells that have lost their vitality in the tumor appears to be low, which is reflected as heterogeneous involvement in metabolic imaging on PET-computed tomography (PET-CT).[4] The main reason of increased glucose affinity in malignant tumors is the elevated glucose transporter proteins on the membranes of tumor cells.[5] Tumors with high FDG uptake are known to be more metabolically active.[6] FDG uptake is increased with the increasing glucose affinity of the tumor. Tumor aggressiveness, proliferative activation, and cell differentiation also increase in direct proportion with the increase in FDG uptake by the tumor.[2]

Fiber-optic bronchoscopy (FOB) was first performed by Shigeto Ikeda in 1964. It is a diagnostic tool that has been used effectively and safely for a long time in the diagnosis of lung cancer. There are multiple causes that affect the diagnostic success of FOB. Some of the reasons include the type of biopsy method, the number of biopsies, the type of bronchoscopic device used during the procedure (autofluorescent bronchoscope and ultrathin bronchoscope), the sedative drugs used during the procedure, the presence of on-site pathologist in the room, the size of the biopsy, presence or absence of necrosis, and the appearance of the endobronchial lesion (EBL).[7-9]

Numerous studies have reported that high FDG uptake is associated with malignant diagnosis in transbronchial biopsy procedures performed on mediastinal lymph nodes and parenchymal lung lesions.[10,11] On the other hand, there was no study investigating the effect of FDG uptake by the lesion on diagnostic success of biopsies from EBL.

The present study is intended to investigate the effect of the maximum standardized uptake (SUVmax) value of the main lesion on PET-CT and the effect of the lesion showing heterogeneous involvement/presence of necrotic component on PET-CT upon the diagnostic success of biopsy procedure in cases of lung cancer with EBL who underwent FOB biopsy.

Methods

Patient population

The patients with centrally located pulmonary lesions who underwent FOB for diagnostic purposes in bronchoscopy unit of the chest disease clinic of our hospital between January 2014 and December 2016 were retrospectively examined in a cross-sectional study. The cases with final diagnosis of primary pulmonary malignancy were distinguished from these cases. These patients were divided into two groups as those who underwent biopsy for EBL detected by FOB and histopathologically diagnosed with primary pulmonary malignancy (Group 1) and those who underwent biopsy for EBL detected by FOB without a resulting diagnosis but diagnosed with primary pulmonary malignancy by a different diagnostic method (Group 2). The first group was named as the group with FOB being used as a diagnostic tool and the second group was named as the group with FOB not being used as a diagnostic tool. The study excluded patients with histopathologic diagnosis of extrapulmonary malignancy, those with endobronchial appearance of extrinsic compression, and whose PET-CT reports were not available [Figure 1]. Approval for the study was obtained from the local ethics committee of our hospital.

Procedures

Fiber-optic bronchoscopy procedure

FOB was performed in patients with centrally located pulmonary tumor on thorax CT or PET-CT. The preprocedural hemogram and coagulometric tests were examined, and no procedure was performed in cases of coagulation disorder (international normalized ratio >1.3) or platelet count <20,000/mm^3 that could interfere with FOB. Written informed consent forms were obtained before any procedure is carried out. In all cases, FOB was performed by oral or nasal route with patients lying in a horizontal position under conscious sedation induced by intravenous midazolam and under local anesthesia using 2% lidocaine (Olympus Co., Tokyo, Japan; Types). During FOB, forceps biopsy and/or brush biopsies were taken from areas within the bronchus that were bronchoscopically evaluated as lumen-protruded tumor or submucosal tumor infiltration (different from normal mucosal appearance, erythematous, vascular

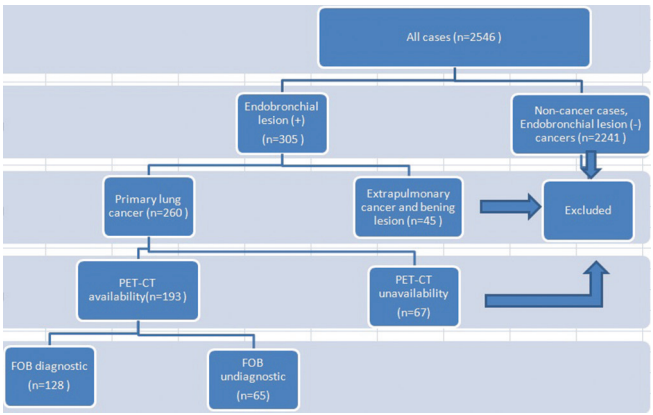

Figure 1: Flowchart

brightness, loss of normal mucous membrane, and areas with narrowed bronchi) in a visible range such as main bronchus, lobe bronchus, and segment or subsegment bronchus. To increase diagnostic success of our FOB procedures, at least five biopsies are performed in EBLs, as recommended in BTS guidelines.[12] Moreover, as a routine practice, the most appropriate location to make a diagnosis is determined based on the reassessment of radiological findings along with bronchoscopic findings; the samples are obtained from the boundaries between pathological tissue and normal tissue, which can reflect the characteristics of tumor tissue better than necrotic areas in lesions, if the lesion is covered by a necrotic layer, while the maximum effort is exerted to obtain tissue samples of adequate size.

Pathological examination

On-site pathologist was not present during the procedure. Before being sent to the pathology laboratory, forceps biopsy specimens were fixed in 95% alcohol, and brush biopsy specimens were spread on the slides with some being fixed in 95% alcohol and some being prepared using the air-drying technique.

Integrated positron emission tomography/computed tomography

Patients with at least 8 h of fasting and normal blood glucose levels were included in the procedure. The PET/CT image was obtained using the Philips Gemini TF ultra-speed integrated PET-CT imaging system. PET images were taken from vertex to the upper thigh with orally enhanced CT slices acquired with sectional thickness of 5 mm. Images were obtained 60 min after the injection of 370–550 MBq (5–15 mCi) F-18 FDG. Oral contrast agent was given at the time of FDG injection.

The demographic findings, smoking history, and thoracic CT findings of the patients were recorded. The appearance of bronchoscopically detected EBLs was recorded separately as lumen-protruded lesion and submucosal infiltration. The diagnoses made by FOB, final diagnoses of the patients with failed diagnosis, final diagnostic methods, histopathological types, and stages of malignancies were recorded.

PET-CT findings of the patients were examined. The SUVmax value of the main mass lesion biopsied on PET-CT and its homogeneous or heterogeneous involvement characteristics (the presence of necrotic component) in metabolic imaging were recorded. The clinical, radiological features, SUVmax values, and main lesion characteristics of homogeneous, heterogeneous involvement/presence of necrotic component based on PET-CT were compared between diagnostic FOB group and nondiagnostic FOB group.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (IBM Inc. Released 2008. SPSS Statistic for Windows Chicago, USA) program. In descriptive statistics, continuous variables were expressed as mean ± standard deviation and categorical variables as percentage. Group data were assessed by Chi-square test and Mann–Whitney U-test. To determine independent predictors of biopsy positivity, all relevant variables were considered in multivariate logistic regression analysis. Logistic regression analysis was performed using forward likelihood ratio method, and $P < 0.05$ was considered as significant.

Results

During the study period, 2546 patients underwent FOB for various reasons. EBL was detected in 305 of these cases. Out of these cases, 67 were excluded due to unavailability of PET-CT reports, 25 were excluded due to having benign lesions, and 20 were excluded due to being diagnosed with extrapulmonary cancer [Figure 1]. A total of 193 patients with a mean age of 61 ± 9.4 (min 34–max 85) who were reported to have primary pulmonary malignancy were included in the

Table 1: Demographic and radiological characteristics of patients

Cases	Group 1 (*n*=128)	Group 2 (*n*=65)	*P*
Age (years)	60.6±9.3	61.8±9.7	0.432
Sex (f/m)	31 (24.2%)/97 (75.8%)	10 (15.4%)/55 (84.6%)	0.156
Smoking history (yes/no) *n*, (%)	118 (92.2%)/10 (7.8%)	60 (92.3%)/5 (7.7%)	0.976
Smoking (pack-years)	44.9±19.2	38.9±13	0.082
Dimensions of the mass on chest CT	49±21.3	50.8±22.3	0.585
Location of the mass on chest CT			
Right upper lobe *n*, (%)	46/(35.9%)	16/(24.6%)	0.111
Right middle lobe *n*, (%)	16/(12.5%)	6/(9.2%)	0.499
Right lower lobe *n*, (%)	18/(14.1%)	11/(16.9%)	0.599
Left upper lobe *n*, (%)	38/(29.7%)	23/(35.4%)	0.421
Left lower lobe *n*, (%)	10/(7.8%)	9/(13.8%)	0.184

CT=Computed tomography, F=Female, M=Male

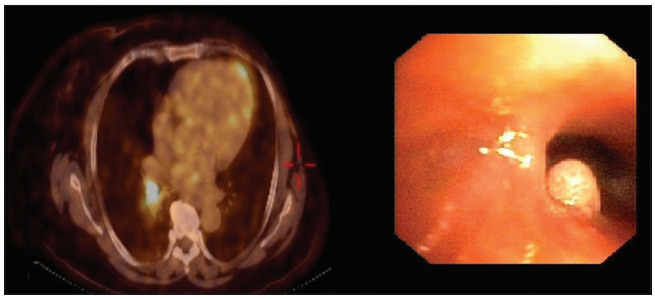

Figure 2: Appearance of endobronchial lesion at the entrance of the right lower lobe on positron emission tomography-computed tomography

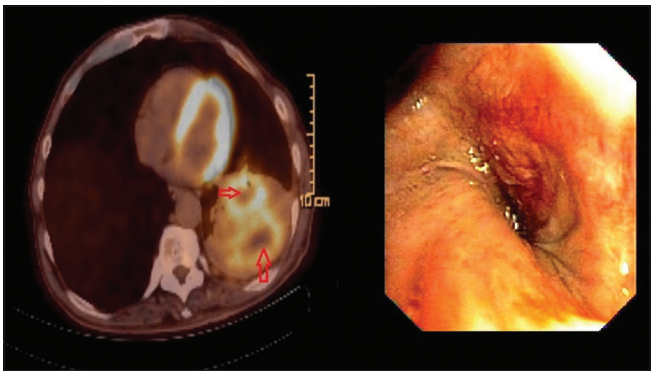

Figure 3: Appearance of submucosal infiltration at the entrance of the left lower lobe on positron emission tomography-computed tomography

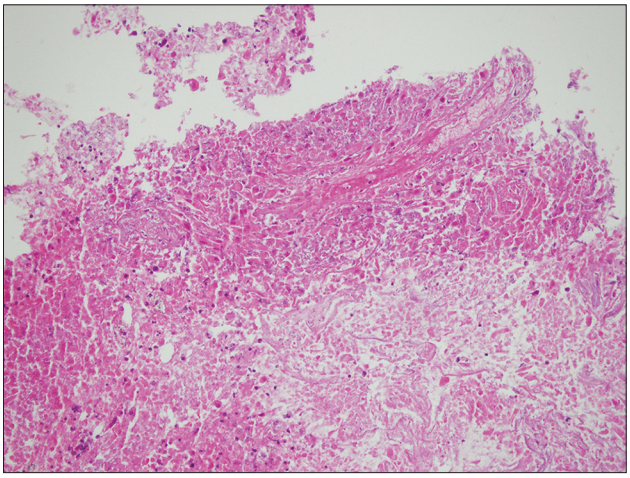

Figure 4: Necrotic tissue. No architectural and cellular details are visible (H and E, ×200)

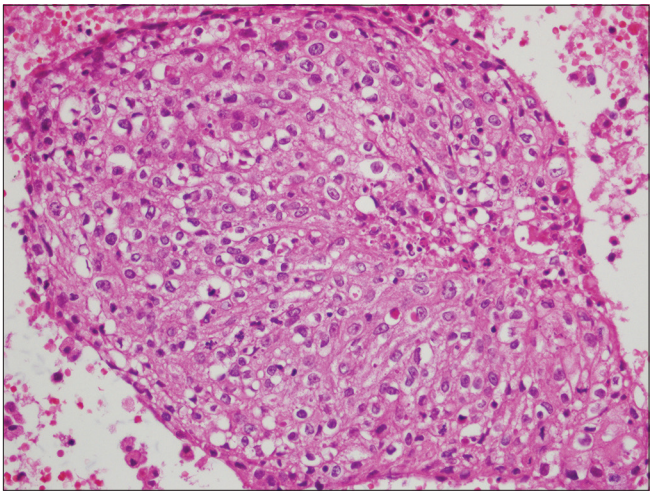

Figure 5: Squamous cell carcinoma. Architectural and cellular details are visible (H and E, ×400)

study. Out of the cases, 41 (21.2%) were female and 152 (78.8%) were male. The mean age was 57.5 ± 11.3 for female patients and 62 ± 8.6 for male patients. Out of the cases, 178 (92.2%) were smokers and 15 (7.8%) were nonsmokers. The mean smoking history was 42.5 ± 17.4 pack-years. The most common thoracic CT finding was central mass with 193 (100%) cases. The mean long-axis diameter of the masses on thoracic CT was 49.6 ± 21.6 mm. The anatomical localizations of the masses were right upper lobe in 62 (32.1%) cases, left upper lobe in 61 (31.6%) cases, and left lower lobe in 19 (9.8%) cases [Table 1].

In the study, there were 128 (66.3%) cases in diagnostic FOB group (Group 1) versus 65 (33.7%) cases in nondiagnostic FOB group (Group 2) [Figures 2 and 3].

Bronchoscopic appearances were classified as lumen-protruded EBL in 68 (53.1%) cases and submucosal infiltration in 60 (46.9%) cases in Group 1 whereas lumen-protruded EBL in 30 (46.1%) cases and submucosal infiltration in 35 (53.9%) cases in Group 2. Out of cases in Group 1, 110 (85.9%) cases underwent forceps biopsy and 23 (18%) cases underwent forceps biopsy plus brush biopsy, whereas in Group 2, these rates were 63 (96.9%) and 3 (4.6%), respectively [Table 2].

PET-CT showed mean SUVmax values of 16.0 in all cases. The mean SUVmax value was 16.4 ± 9.7 in Group 1 and 15.1 ± 6.9 in Group 2. There was no statistically significant difference between the two groups (P = 0.329). On the other hand, homogeneous involvement was reported in 103 (80.3%) cases in Group 1 versus 42 (64.6%) in Group 2, and heterogeneous/necrotic involvement was reported in 25 (19.5%) cases in Group 1 versus 23 (35.4%) in Group 2. Pathologic diagnosis was made by EB biopsy in 103 (71%) of 145 cases who were reported to have homogeneous involvement, whereas only 25 cases (52%) of necrotic/heterogeneous involvement were able to be diagnosed [Figures 4 and 5]. In the presence of homogeneous PET-CT involvement, diagnosis rate by biopsy was significantly higher (P = 0.016) [Table 3]. In this study, cutoff levels of sensitivity, specificity, positive predictive value, and negative predictive value for a homogenous uptake on PET-CT were found to be 80.4%, 35.3%, 71%, and 47.9%, respectively.

Table 2: Case distribution by endobronchial lesions and biopsy methods

Cases	Group 1 (*n*=128)	Group 2 (*n*=65)
Endobronchial lesion *n*, (%)	68 (53.1%)	30 (46.1%)
Submucosal infiltration *n*, (%)	60 (46.8%)	35 (53.8%)
Forceps biopsy (*n*/%)	110 (85.9%)	63 (96.9%)
Forceps biopsy and brush biopsy *n*, (%)	23 (17.9%)	3 (4.6%)

Table 3: The relationship of SUV_{max} value/ homogeneous involvement

	Group 1 (*n*=128)	Group 2 (*n*=65)	*P*
SUV_{max} value (mean)	16.4±9.7	15.1±6.9	0.329
Homogeneous involvement on PET/CT *n*, (%)	103 (80.4%)	42 (64.6%)	0.016

Table 4: Final histopathological diagnosis distribution by cases

Cases	Group 1 (*n*=128)	Group 2 (*n*=65)
Squamous cell carcinoma *n*, (%)	62 (48.4%)	15 (23.1%)
Small cell carcinoma *n*, (%)	33 (25.8%)	12 (18.5%)
Non-small cell carcinoma *n*, (%)	16 (12.5%)	22 (33.8%)
Adenocarcinoma *n*, (%)	12 (9.4%)	14 (21.5%)
Carcinoid tumor *n*, (%)	4 (3.2%)	1 (1.5%)
LCNEC *n*, (%)	-	1 (1.5%)

LCNEC: Large-cell neuro-endocrine carcinoma

The percentage of submucosal infiltration was found to be 46.8% in Group 1 and 53.8% of patients in Group 2. No difference was found between the two groups regarding the presence of submucosal infiltration ($P = 0.308$). Furthermore, the probability of a homogeneous/necrotic-heterogeneous uptake on PET-CT was found to be independent from the presence of a submucosal lesion ($P = 0.869$).

In a multivariate logistic regression analysis including tumor morphology, biopsy methods, and PET-CT findings, brush biopsy and homogenous/necrotic uptake on PET-CT were found to be independent predictors of a positive biopsy (for brush biopsy, $P = 0.016$, odds ratio (OR): 4.69, 95% CI: 1.34–16.45 and homogeneous uptake on PET-CT, $P = 0.021$, OR: 2.24, 95% CI: 1.13–4.46).

As per histopathological diagnosis, the distribution of squamous cell carcinoma was 62 cases (48.4%) in Group 1, while nonsmall cell carcinoma was found in 22 cases (33.8%) in Group 2 [Table 4]. Diagnosis was established by CT-guided transthoracic biopsy in 33 (50.7%) of the cases, by endobronchial ultrasound (EBUS) in 2 (3.1%) cases, and by surgical biopsy in 30 (46.2%) cases in Group 2.

Discussion

A total of 193 cases were examined in our study in which we examined the relationship between FOB biopsy and PET-CT findings in patients with centrally located EBL and a final diagnosis of primary lung cancer. No correlation was detected between the higher SUVmax value on PET-CT and the diagnostic success of the procedure. There was no statistically significant difference between SUVmax values between diagnostic FOB group and nondiagnostic FOB group ($P = 0.329$). However, the diagnostic success rate of FOB biopsy was significantly low ($P = 0.016$) in patients with PET-CT findings of metabolic heterogeneous involvement in the main lesion and the presence of necrotic components.

FOB is the main diagnostic method in the histopathological diagnosis of lung cancer, especially in endoscopically visible lesions located inside the bronchus. Biopsy by FOB is a procedure with high diagnostic success in lung cancer.[13,14] In our reports, the diagnostic success rate of the procedure was calculated as 66.3%. In visible EBLs, although diagnostic success rates of bronchoscopy differ between different series, the overall diagnostic success rate is higher than 85%.[12] In our study, we believe that lower rates of diagnostic success may be related to the subject selection (those who had a PET-CT scan) originating from the design of the study and exclusion of patients who had a visible EBL (112 patients) from the study, due to the study design. Greses *et al*.[15] reported a diagnostic sensitivity of 69.6% for endobronchial biopsy in their report of 151 cases and showed that one of the most important variables affecting diagnosis rate is the presence of necrosis in biopsy material. The diagnostic success increased by 2.6-fold in the absence of necrosis in the biopsy material. Again, the diagnostic accuracy was 5.2 times higher in the absence of necrosis in the biopsy specimen in the study by Cataluña *et al*.[16] regarding the factors that were effective in the diagnostic accuracy of bronchial biopsies.

Tumors have two forms of heterogeneity: intertumoral heterogeneity and intratumoral heterogeneity. Intertumoral heterogeneity caused by different biological characteristics and subtypes of similar malignancies is better known and described than intratumoral heterogeneity caused by neoplastic and nonneoplastic cells, ischemic and necrotic areas in the tumor.[17] There are studies indicating that intratumoral heterogeneity is a poor prognostic indicator.[18] Shin *et al*.[19] reported that necrosis is associated with hypoxia, has a poor prognosis, and is treatment resistant in patients with primary pulmonary lymphoma presenting as a necrosis. In this case, tumor with central necrosis was defined as a photopenic defect on PET. Nuclear medicine methods such as PET-CT, (68Ga) DOTA-octreotate PET, and single photon emission CT, which are an imaging method for evaluating cell viability and metabolism, are very useful in showing intratumoral heterogeneity.[4]

Buchpiguel *et al*.[20] reported, in a case report of necrosis due to radiation therapy in brain tumors, that PET-CT may be superior to magnetic resonance and CT in posttreatment necrotic areas of brain tumors and that necrotic areas are characterized by hypometabolic areas due to reduced glucose consumption and decreased FDG uptake. Animal studies[21] have shown that different areas such as necrotic areas, granulation tissues, and viable tumor tissues within a malignant tumor lesion can be easily distinguished by FDG uptake at different rates. Clinical studies have also shown that malignant tumor lesions with high FDG accumulation have higher metabolic activity and that PET-CT can better assess proliferative activity in tumor tissue, which is useful in distinguishing between fibrotic tissue and viable tumor tissue.[22-24] Necrotic areas within the tumor show less FDG uptake, and tumor necrosis is considered as false-negative areas in PET-CT imaging.[25,26] In our study, diagnostic success by biopsies taken from the endobronchial component of the masses with heterogeneous involvement on PET-CT was significantly lower than those with homogeneous involvement. We think that the possible cause is that the tumors with heterogeneous involvement contain less viable and more dead/necrotic tumor cells compared to those with homogenous involvement and that this heterogeneity is reflected in the endobronchial component of the masses. The new data obtained in this study may be clinically relevant as defined below: additional methods that may increase the diagnostic success of the procedure should be used in patients with lung cancer who will undergo a FOB procedure, considering that the presence of heterogeneous uptake on PET-CT may suggest that the likelihood of diagnostic success of the procedure is low if an heterogeneous uptake is present. In previous studies, a brush biopsy or needle aspiration biopsy added to a forceps biopsy was proven to increase diagnostic success in EBLs, and the size and the number of biopsy fragments were found to correlate with diagnostic success.[12,27,28] In the presence of heterogeneous uptake on PET-CT, the number and the size of biopsy fragments to be taken by forceps biopsy may be increased or brush biopsy or needle aspiration biopsy may be performed in addition to a forceps biopsy in such cases. Several studies reported that a rapid on-site evaluation accompanied with biopsy procedures might increase the diagnostic performance of biopsy procedures.[29] Furthermore, we believe that working with an on-site pathologist specialized in cases of heterogeneous uptake on PET-CT may also increase diagnostic success.

There is also a correlation between FDG uptake by the tumor and tumor growth and invasion.[30-32] FDG uptake is higher with more aggressive the tumors and greater cell differentiation and proliferative activation.[2] There are numerous studies reporting that high FDG uptake is closely associated with malignancy in differentiation between malignant and benign tumors and in biopsy procedures.[10,33,34] Umeda *et al*.[35] performed biopsy on 201 peripheral lung lesions using a virtual bronchoscopic navigation and showed that high FDG uptake for these procedures was predictive of diagnostic success (SUVmax ≥2.8; OR, 3.57). In another study, Börekçi *et al*.[11] found that SUVmax involvement of mediastinal lymph nodes in mediastinal staging of lung cancers on PET-CT affects the diagnostic success of transbronchial needle aspiration (TBNA) biopsy procedure ($P = 0.046$). The present study demonstrated that PET SUVmax ≥5 resulted in an 11-fold increase in TBNA positivity ($P < 0.01$). Our study showed mean SUVmax values of 16 in all cases. Mean SUVmax value was 16.4 in diagnostic FOB group versus 15.1 in nondiagnostic FOB group. Our study showed no statistically significant difference between the diagnostic success of the biopsy procedure and the SUVmax value of the tumor, which is not consistent with the literature. The possible reason for the inconsistency with the literature is that all of the cases consist of those with malign diseases. The results cannot be generalized because of the single-center nature of the study. Other limitations of our study are loss of data due to the retrospective nature of the study and lower sample size in some cancer subgroups (adenocarcinoma-carcinoid tumors). The role of PET-CT in cancers with low FDG uptake on the diagnostic value of FOB biopsy can be investigated by conducting controlled studies with adequate sample size on this subject, especially in cancers with relatively low FDG uptake such as well-differentiated adenocarcinomas.

In our study, a diagnosis could be made using different methods in 65 patients who could not be diagnosed by FOB biopsies. Thirty-three out of 65 patients underwent a CT-guided biopsy (CT-guided tru-cut biopsy in 28 patients and CT-guided transthoracic fine-needle biopsy in 5 patients), 30 patients were diagnosed by EBUS, and 2 patients were diagnosed by surgical biopsies. We believe that these procedures were diagnostic in Group 2 since larger tissue fragments could be obtained, and necrotic areas could be avoided in CT-guided fine-needle biopsies. The majority of patients diagnosed by EBUS (26 patients [86.6%]) underwent a lymph node fine-needle aspiration biopsy. We believe that a diagnosis could be made since the characteristics of primary lesions on PET-CT may differ from those of lymph nodes. Furthermore, necrotic areas could be avoided in patients who underwent a biopsy from the primary lesion (4 patients) as the EBUS fine-needle aspiration biopsy procedures were real-time procedures.

Conclusion

We aimed to contribute to the literature by drawing attention to a different aspect of PET-CT, which is mostly

used for mediastinal staging of lung cancers and for screening distant metastases. In our study, we found that, in cases with prediagnosis of lung cancer, the high SUVmax value of the mass lesion on PET-CT did not increase the diagnostic value of the biopsy procedure, and the chances of establishing a diagnosis might still be high even when SUVmax value is low. We also concluded that the diagnostic success rate of FOB biopsy is low when PET-CT shows heterogeneous involvement of the mass lesion, and different methods can be used for definite diagnosis in these cases.

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Conflicts of interest
There are no conflicts of interest.

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