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Original Article / Özgün Makale

A comparision of endobronchial ultrasound-guided transbronchial needle aspiration and integrated positron emission tomography-computed tomography in the diagnosis of malignant mediastinal/hilar lymph nodes

Malign mediastinal ve hiler lenf nodlarının tanısında endobronşiyal ultrasonografi rehberliğinde yapılan transbronşiyal iğne aspirasyonunun ve pozitron emisyon tomografisi-bilgisayarlı tomografinin karşılaştırılması

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Background: In this study, we aimed to identify the sensitivity, specificity and diagnostic accuracy of integrated positron emission tomography-computed tomography (PET-CT) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the diagnosis of malignant mediastinal/hilar lymph nodes and to compare with each other.

Methods: Records of 131 patients (96 males, 35 females; mean age 58.3±8.4 years; range 42 to 75 years) with known primary or suspected malignancy who had enlarged and hypermetabolic hilar/mediastinal lymph nodes detected by thoracic CT and at PET-CT and in whom EBUS-TBNA performed for cytologic confirmation of the malignancy between October 2008 and April 2011 were retrospectively analyzed. More invasive procedures including mediastinoscopy/video-assisted thoracoscopic surgery (VATS) were performed in patients who did not receive definite diagnosis using EBUS-TBNA. The maximum standardised uptake value (SUVmax) cut-off level of PET-CT was considered ≥3.0. The sensitivity, specificity, diagnostic accuracy, and negative and positive predictive values of PET-CT and EBUS-TBNA in diagnosis of malignant hilar/mediastinal lymph nodes were calculated. The results were compared with each other.

Results: A total of 191 lymph node stations of 131 patients were aspirated from the LN stations. Of the 142 lymph nodes, 134 were diagnosed with malignancy using EBUS-TBNA, while SUV_{max} value was ≥3.0 in 127 by PET-CT. The sensitivity, spesificity, diagnostic accuracy, and negative and positive predictive values of EBUS-TBNA and PET-CT were 94.3%, 100%, 95.8%, 85.9%, 100% and 89.4%, 18.3%, 71.2%, 37.5%, 76.0%, respectively. With combined use of EBUS-TBNA and PET-CT, the sensitivity increased to 100%.

Conclusion: The sensitivity, specificity, diagnostic accuracy, and negative predictive value and positive predictive value of EBUS-TBNA is higher than PET-CT. Based on conventional data, histological confirmation of PET-CT is necessary in mediastinal staging, due to high level of false positivity of PET-CT. EBUS-TBNA is an effective, reliable and minimally invasive method for histologic confirmation of PET-CT-positive malignant mediastinal/hilar lymph nodes.

Key words: Endobronchial ultrasonography; fine needle aspiration; lung cancer; lymph node; positron emission tomography-computed tomography; staging.

Amaç: Bu çalışmanın amacı, entegre pozitron emisyon tomografisi-bilgisayarlı tomografi (PET-BT) ve endobronşiyal ultrasonografi rehberliğinde yapılan transbronşiyal iğne aspirasyonunun (EBUS-TBİA) malign mediastinal/hiler lenf nodlarının tanısındaki duyarlılığı, özgüllüğü ve tanı değerini saptamak ve birbirleri ile kıyaslamaktır.

Çalışma planı: Ekim 2008 - Nisan 2011 tarihleri arasında bilinen primer malignitesi veya malignite şüphesi olup, bilgisayarlı toraks tomografisinde büyümüş ve PET-BT'de hipermetabolik hiler/mediastinal lenfnodu saptanan ve sitolojik tanı için EBUS-TBİA yapılmış 131 olgunun (96 erkek, 35 kadın; ort. yaş 58.3±8.4 yıl; dağılım 42-75) dosyası retrospektif olarak incelendi. EBUS-TBİA ile kesin tanı konulamayan olgulara mediastinoskopi/video yardımlı torakoskopik cerrahi (VYTC) gibi daha invazif girişimler uygulandı. PET-BT'de malignite için standart maksimum alım (SUDmax) sınır değeri ≥3.0 olarak belirlendi. Malign mediastinal/hiler lenf nodlarının tanısında PET-BT ve EBUS-TBİA'nın duyarlılık, özgüllük, tanı değeri ve negatif ve pozitif öngördürücü değerleri hesaplandı. Sonuçlar birbirleri ile karşılaştırıldı.

Bulgular: Toplam 131 hastada 191 lenf nodu istasyonundan aspirasyon yapıldı. Yüz kırk iki malign lenf nodundan 134'üne EBUS-TBİA ile malignite tanısı konulurken, 127'sinin PET-BT'de SUD_{max} değerinin ≥3.0 olduğu görüldü. EBUS-TBİA ve PET-BT'nin malign mediastinal ve hiler lenf nodlarının tanısındaki duyarlılık, özgüllük, tanı değeri ve negatif ve pozitif öngördürücü değerleri sırasıyla %94.3, %100, %95.8, %85.9, %100 ve %89.4, %18.3, %71.2, %37.5, %76.0 idi. EBUS-TBİA ve PET-BT'nin birlikte kullanımı ile duyarlılık %100'e ulaştı.

Sonuç: EBUS-TBİA'nın duyarlılık, özgüllük, tanı doğruluğu ve negatif öngördürücü değeri ve pozitif öngördürücü değeri PET-BT'den daha yüksektir. Klasik bilgilere göre PET-BT'nin yanlış pozitiflik oranının yüksek olması nedeni ile mediastinal evrelemede histolojik doğrulamasının yapılması gerekmektedir. EBUS-TBİA, PET-BT pozitif mediastinal/hiler lenf nodlarının histolojik doğrulamasında etkin, güvenilir ve minimal invasiv bir yöntemdir.

Anahtar sözcükler: Endonronşiyal ultrasonografi; ince iğne aspirasyonu; akciğer kanseri; lenf nodu; pozitron emisyon tomografisi-bilgisayarlı tomografi; evreleme.

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Lung cancer is the most common cause of cancer-related death for both men and women in the world,[1] and non-small cell lung cancer (NSCLC) accounts for 75-80% of all lung cancers.[2] In patients suspected of having lung cancer, the presence of mediastinal lymph node (LN) metastasis is a critical determinant for the proper therapy and prognosis. Precise mediastinal nodal staging using image modalities in NSCLC is mandatory for guiding subsequent staging procedures and treatment.

Computed tomography (CT) is the initial method for assessing mediastinal LNs, and those with a short axis exceeding 1 cm are considered abnormal.[3] Positron emission tomography (PET) using fluorine-18 fluorodeoxyglucose (18F-FDG) provides functional information about tumor metabolism and has been used as a non-invasive alternative to contrast-enhanced CT for nodal staging in NSCLC and other non-pulmonary malignancies.[4-7] Current scanning modalities, such as CT and PET, although useful, are not sufficiently sensitive or specific to determine mediastinal nodal involvement.[8] The sensitivity and specificity of CT and PET scanning for predicting malignant involvement of mediastinal lymph nodes were 67-72% and 63-81%, and 46-93% and 86-98%, respectively.[7,9,10]

Diagnosis of malignant mediastinal and hilar LNs is critical for the staging of lung cancer and non-pulmonary malignancies, establishing relapses, and providing the correct treatment strategies. Positron emission tomography, a non-invasive method, has high sensitivity in the determination of malignant intrathoracic LNs. However, due to a high rate of false positivity, especially involving granulomatous and inflammatory diseases, histological verification is often required with more invasive procedures, such as mediastinoscopy/video-assisted thoracoscopic surgery (VATS).[11,12] Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), as a minimally invasive procedure is an alternative to mediastinoscopy.

The American College of Chest Physicians recommends invasive staging with tissue confirmation of suspected metastatic mediastinal LNs.[13] Mediastinoscopies or thoracoscopies have been the diagnostic standard, but less invasive methods have emerged as potential alternatives, such as blind transbronchial needle aspiration (TBNA), EBUS-TBNA, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), and the combination of EBUS-TBNA and EUS-FNA.[14]

We hypothesized that EBUS-TBNA would be more accurate than integrated positron emission tomography-computed tomography (iPET-CT) and that the combination of EBUS-TBNA and iPET-CT would provide complementary staging of the mediastinum in patients suspected of having lung cancer and other non-pulmonary malignancies. The EBUS-TBNA procedure would also decrease the number of mediastinoscopies in NSCLC staging. The aim of this study is to present and compare the sensitivity, specificity, and diagnostic accuracy of iPET-CT and EBUS-TBNA in the diagnosis of malignant mediastinal/hilar LNs.

PATIENTS AND METHODS

The records of 142 patients with known or suspected organ malignancy who had enlarged and hypermetabolic hilar/mediastinal LNs which had been detected via thoracic CT (LNs with short axis >1 cm) and iPET-CT and for whom EBUS-TBNA had been performed for cytological confirmation of malignancy were examined retrospectively. Out of the 142 patients who met the inclusion criteria, 11 were excluded. Of these 11 cases, eight had benign primary diseases and the other three had inadequate material taken from them by EBUS-TBNA making a diagnosis impossible. The study ultimately included 131 patients (96 males, 35 females; mean age 58.3±8.4 years; range 42 to 75 years) who were diagnosed as malignant between October 2008 and April 2011. All of the patients underwent EBUS-TBNA for staging and/or diagnostic purposes. For staging, LNs with a short axis of >0.5 cm were aspirated during EBUS, even if the maximum standardized uptake value (SUVmax) had been <3.0 on iPET-CT. If EBUS-TBNA was negative for malignancy, more invasive procedures, such as mediastinoscopy/VATS, were performed. The local institutional review board approved the protocol of this study, and the patients gave their informed consent.

Whole body iPET-CT Gemini Dual system (Philips, Cleveland, Ohio, USA) was performed followed by six hours of fasting. The glucose levels of the patients were within normal limits (60-150 mg/dl) prior to examination. Sixty to 90 minutes after intravenous injection of 0.14 mCi/kg of body weight of FDG, whole body acquisition was performed. A spiral CT scan was then conducted and integrated with PET images, and an experienced nuclear medicine physician read the PET images. Standardized uptake values were calculated as the ratio of the regional radioactivity concentration divided by the injected amount of radioactivity normalized to body weight. Integrated PET-CT was considered positive for LNs if the standardized uptake value was ≥3.0. The time interval between the iPET-CT and EBUS-TBNA was a maximum of 15 days. The sensitivity, specificity, diagnostic accuracy, negative predictive value (NPV), and positive predictive value (PPV) of the iPET-CT in the diagnosis of malignant mediastinal/hilar LNs were calculated.

Convex probe EBUS-TBNA from hilar and mediastinal LNs was performed oro- tracheally with the patients in a supine position at the Pulmonary Diseases Department as an outpatient procedure in a dedicated bronchoscopy suite with a 7.5 MHz, BF-UC160F (Olympus Optical CO. Tokyo, Japan) convex probe bronchoscope and a model EU C2000 processor (Olympus Tokyo, Japan). The patients were under local anesthesia (lidocaine) and conscious sedation with intravenous (i.v.) midazolam.

Lymph nodes were identified according to the regional LN classification system developed by Mountain.[15] The LN stations of 2, 4, 7, 10, and 11 were evaluated systematically, and the dimensions of the LN seen on the convex probe were recorded from frozen ultrasound images. An Olympus 22-gauge NA-201SX-4022-C needle was used for the procedure. During the process, for every detected LN, short axis diameter, the station of the LNs and the number of passes per patient and per LN station were recorded. Aspiration from more than one LN at the same lymph node station was not considered, and this was recorded as "lymph node stations". To avoid contamination in lung cancer patients, the N_3 nodes were sampled first, and then the N_2 nodes were punctured.

We could not perform a rapid onsite pathological examination. The materials obtained by the EBUS-TBNA that were placed on the slide were fixed in 95% alcohol and sent to the pathology laboratory. A malignant diagnosis in the cytological examination was considered as the final diagnosis. For the patients whose EBUS-TBNA results were negative for malignancy, more invasive procedures, such as mediastinoscopy/VATS, were conducted to confirm the diagnosis. The patients diagnosed as having lung cancer were staged according to the 1997 tumors, nodes, metastasis (TNM) classification system.

Table 1. The distribution of EBUS-TBNA performed at lymph node stations

Lymph node station	n
2/R	7
4/L	15
3	1
4/R	62
7	58
10/L	3
10/R	6
11/L	20
11/R	19

EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration.

The sensitivity, specificity and accuracy of iPET-CT and EBUS-TBNA used for determining malignant mediastinal/hilar LNs stations were evaluated and compared. Additionally, for the lung cancer cases, the stage of the disease according to the iPET-CT and EBUS-TBNA results were evaluated for every patient and compared. The upstaged and downstaged cases were also evaluated after performing EBUS-TBNA.

RESULTS

The EBUS-TBNA procedure was performed on 191 LN stations in 131 cases with 361 passes (Table 1). The mean passes per LN station and per patient were 1.89 and 2.74, respectively. When all of the patients were taken into consideration, the mean number of sampled lymph node stations per patient was 1.45. One hundred and fifty-one LN stations were sampled in 93 of the lung cancer patients for staging, and in these patients, the mean number of lymph node stations per patient was 1.62. The average LN short axis was calculated as 1.8±1.2 (range, 0.5-4.0) cm.

The SUVmax for all aspirated LN stations was recorded, and the mean SUVmax was 8.9±5.7 (range, 0-24.6). There were 49 hilar LN stations (N1 or N3) and 142 mediastinal LN stations (N_2 or N_3) according to the results of EBUS-TBNA, and no complications were seen.

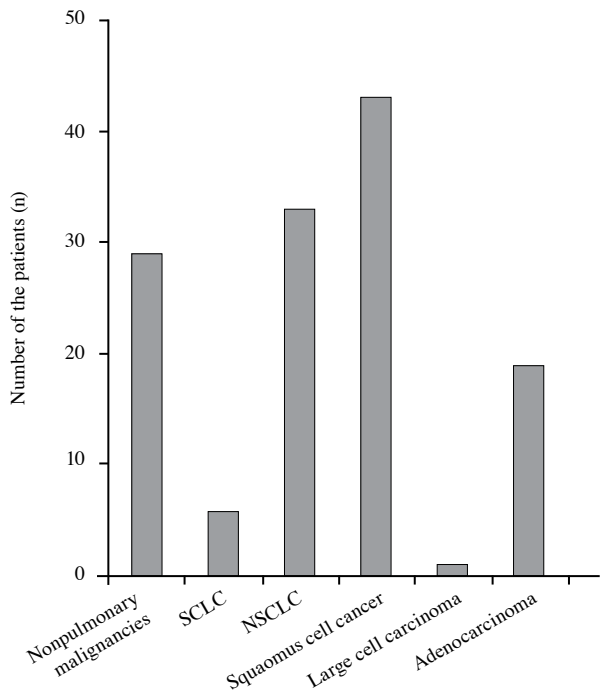

Figure 1. The distribution of primary malignancies. SCLC: Small cell lung cancer; NSCLC: Non-small cell lung cancer.

Table 2. The false positive, true positive, false negative and true negative values of iPET-CT and EBUS-TBNA

	True positive	False positive	True negative	False negative
	n	n	n	n
iPET-CT	127	40	9	15
EBUS-TBNA	134	0	49	8

iPET-CT: Integrated positron emission tomography-computed tomography; EBUS-TBNA: Endobronchial ultrasound guided transbronchial needle aspiration.

Of the 131 cases included in the study, 102 were diagnosed as primary lung cancer, and 29 had non-pulmonary malignancies (Figure 1). The EBUS-TBNA procedure was performed for diagnostic (stage 4 disease) and/or staging purposes for 9, 41, and 52 lung cancer patients, respectively.

Integrated PET-CT showed 40 false positive, 127 true positive, 15 false negative, and nine true negative LN stations (Table 2). Among the false positive stations with iPET-CT, 40 (100%) had been diagnosed as nonmalignant with EBUS-TBNA, and these diagnoses were confirmed by more invasive procedures.

Accepting the SUVmax level of ≥3.0 as being positive for malignancy, 167 of 191 LN stations were found to be positive, and 24 were negative. Of these 24 stations, 15 were diagnosed as malignant at the final diagnosis, with 14 of these having been diagnosed by EBUS-TBNA. Furthermore, malignant cells were determined at 134 of 191 LN stations by performing EBUS-TBNA, and non-malignant material was obtained at 57 LN stations using the same procedure. In these 57 stations, more invasive procedures were performed for a definitive diagnosis. In the end, 49 of these EBUS-TBNA negative stations were diagnosed as non-malignant, whereas eight stations were malignant. Using the iPET-CT, the SUVmax values of 40 (81.6%) of these 49 stations were ≥3.0. Twenty (50%) of the 40 iPET-CT positive stations were diagnosed with epithelioid granuloma (16 tuberculosis, 4 sarcoidosis) by EBUS-TBNA, which was later confirmed by more invasive procedures.

Malignant hilar and/or mediastinal LNs were determined with EBUS-TBNA in 89 cases and with more invasive procedures in eight. In 85 of these 89 cases, there results were positive with iPET-CT. If EBUS-TBNA had not been performed, a mediastinoscopy would have been unavoidable in order to confirm the iPET-CT findings.

According to the final diagnosis of EBUS-TBNA or other invasive procedures used to ascertain the malignant mediastinal or hilar LN stations, the sensitivity, specificity, diagnostic accuracy, PPV, and NPV of iPET-CT were 89.4%, 18.3%, 71.2%, 76.0%, and 37.5%, respectively. The same values for EBUS-TBNA were calculated as 94.3%, 100%, 95.8%, 100%, and 85.9%, respectively (Table 3).

Ninety-six of the 102 lung cancer patients had NSCLC. The frequency of mediastinal LN metastasis (N_2 and N_3) was detected as 79% in both adenocarcinoma and squamous cell cancer and at a rate of 69.6% in NSCLC, for which subtypes cannot be determined. When the iPET-CT and EBUS-TBNA findings of the 96 cases who were diagnosed as NSCLC were examined, 73 (76.0%) of the patients who were identified as having N stage according to iPET-CT had no change after the EBUS-TBNA findings, and 23 (24.0%) patients with nodal status were downstaged after EBUS-TBNA. This downstage was then confirmed by invasive procedures. It was determined that 11 of the 23 nodal status cases had changed from N_2 to N_0, five cases had moved from N_3 to N_2, three cases had gone from N_3 to N_0, three cases had changed from N_1 to N_0, and one case had been downstaged from N_2 to N_1. In our series, 15 (15.6%) cases would not have been presented with the surgical

Table 3. The sensitivity, specificity, diagnostic accuracy, positive predictive value and negative predictive value of iPET-CT and EBUS-TBNA

	Sensitivity	Specificity	Negative predictive value	Positive predictive value	Diagnostic accuracy
	%	%	%	%	%
iPET-CT	89.4	18.3	37.5	76.0	71.2
EBUS-TBNA	94.3	100	85.9	100	95.8

iPET-CT: Integrated positron emission tomography-computed tomography; EBUS-TBNA: Endobronchial ultrasound guided transbronchial needle aspiration.

option if the decision had been based solely on the iPET-CT findings. However, all of these cases were correctly staged by EBUS-TBNA.

DISCUSSION

In cases in which cancer has been confirmed or when cancer is suspected, the cytological and histological diagnosis of the suspicious mediastinal or hilar LNs plays a strategic role in evaluating the disease, deciding on the proper treatment, and determining the prognosis. In NSCLC cases, the mediastinal LN is the region in which metastasis is most often seen.[16]

Integrated PET-CT is more accurate than CT for mediastinal staging. However, due to the limited diagnostic specificity for identifying mediastinal metastases, tissue proof of iPET-CT positive lesions is recommended to prove that they are truly malignant before denying surgical resection.[17-19] The SUVmax value above the 2.5 cutoff is generally accepted as malignant in iPET-CT, but Seijo et al.[20] reported that TBNA of LNs with a SUVmax of less than 3.0 is rarely diagnostic, and an SUVmax of 3.0 may be a more appropriate cutoff.

Darling et al.[21] determined the accuracy of PET-CT in mediastinal staging compared with invasive mediastinal staging either by mediastinoscopy alone or by a mediastinoscopy combined with a thoracotomy. They reported the sensitivity of PET-CT as 70% [95% confidence interval (CI), 48-85%] and the specificity as 94% (95% CI, 88-97%). The PPV and NPV were 64% (95% CI, 43-80%) and 95% (95% CI, 90-98%), respectively. In this study, based on PET-CT alone, eight patients would have been denied potentially curative surgery if the mediastinal abnormalities detected by PET-CT had not been evaluated with an invasive mediastinal procedure. In our series, 23 cases (24.0%) with nodal status were downstaged by performing EBUS-TBNA, and this was confirmed by more invasive procedures, such as mediastinoscopy/VATS. Fifteen (15.6%) of the patients would have lost the opportunity for surgery intervention if they had been staged based only on the iPET-CT findings. All of these cases were correctly staged by EBUS-TBNA.

In the literature for PET, the median sensitivity and specificity were 85% (interquartile range, 67-91%) and 90% (interquartile range, 82-96%), respectively.[7,17,22,23] In our series, the sensitivity, specificity, diagnostic accuracy, PPV, and NPV of PET-CT for the malignant mediastinal or hilar LN stations were 89.4%, 18.3%, 71.2%, 76.0%, and 37.5%, respectively. Yasufuku et al.[17] discovered that the sensitivity, specificity, accuracy, PPV and NPV of PET in the prediction of mediastinal LN staging were 80%, 70.1%, 46.5%, 91.5%, and 72.5%, respectively. These results were consistent with ours, except for the specificity of iPET-CT, which was lower in our series since most of the cases included were iPET-CT-positive for mediastinal and/or hilar LNs. Herth et al.[3] detected maligancy by EBUS-TBNA in 9.3% of cases with LNs which had been discovered in radiological exams and PET. In our study, 14 (58.3%) of 24 LN stations with an SUVmax of <3.0 in PET-CT were diagnosed as malignant by EBUS-TBNA. However, the majority (eight LN stations) of these LNs were >1 cm at EBUS, which differs from the Herth study. In that study,[3] the malignancy level was accepted as >2.5 in PET-CT. These two studies may explain the high rate of malignancy in PET-negative LN stations in our study. Furthermore, 16 of 40 LNs which were iPET-CT-positive, but non-malignant with EBUS-TBNA were diagnosed as tuberculous adenitis. This is thought to be another factor that decreased the specificity of iPET-CT in our series. Similarly, Kuo et al.[4] compared the accuracy of nodal diagnosis by using EBUS-TBNA and PET in a country where tuberculosis is endemic, and PET had a low specificity (18.9%) and a low PPV (44.4%).

Bellek at al.[24] evaluated the role of PET-CT in mediastinal lymph node staging in NSCLC and reported the sensitivity, specificity, diagnostic accuracy, PPV, and NPV of PET-CT as 86.7%, 65.5%, 72.7%, 56.5%, and 90.5%, respectively.

In our series, the sensitivity, specificity, diagnostic accuracy, PPV, and NPV of EBUS-TBNA to ascertain the malignant mediastinal or hilar lymph node stations were calculated as 94.3%, 100%, 95.8%, 100%, and 85.9%, respectively. In the study by Yusufuku et al.,[17] these rates were 92.3%, 100%, 98.0%, 100%, and 97.4%, respectively while Çetinkaya et al.[25] reported the sensitivity, specificity, PPV, NPV, and accuracy of EBUS-TBNA in the detection of mediastinal metastasis as 95%, 100%, 100%, 83%, and 96%, respectively.

Inflamatory reactions of LNs may lead to accumulation of FDG, resulting in false positive results at PET-CT.[17] Our study revealed 40 false positive stations by iPET-CT, whereas all of these cases were diagnosed correctly using EBUS-TBNA. Sixteen of these (40%) were diagnosed as tuberculosis. Since the incidence of tuberculosis is high in Turkey, the false positive results of iPET-CT for malignancy are higher.

Kennedy et al.[26] reviewed 153 patients undergoing EBUS-TBNA for suspected malignant LNs in the mediastinum by CT imaging. In 17 of the 153 patients, (11%) non-caseating granulomas were identified by EBUS-TBNA while eight (5.2%) had sarcoid-like

lymphadenopathy mimicking cancer recurrence. Another eight (5.2%) who had been diagnosed with new mediastinal lymphadenopathy with no prior history of cancer had a clinical syndrome consistent with sarcoidosis. One other patient with a history of breast cancer was diagnosed with a non-tuberculous mycobacteria infection. No patient required mediastinoscopy in the Kennedy review.

We concluded that the sensitivity, specificity, NPV, PPV, and diagnostic accuracy of EBUS-TBNA is higher than iPET-CT. Although iPET-CT has been used successfully in mediastinal staging, histological confirmation is necessary for PET-positive cases since false positivity of iPET-CT is high. The EBUS-TBNA procedure offers an effective, accurate, minimally invasive strategy for histological confirmation of iPET-CT-positive hilar and mediastinal LNs.

Declaration of conflicting interests

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