Combined transbronchial needle aspiration and positron emission tomography for mediastinal staging of NSCLC

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ABSTRACT: There are no data available combining transbronchial needle aspiration (TBNA) of mediastinal lymph nodes and positron emission tomography (PET) in the staging of nonsmall cell lung cancer (NSCLC).

The aim of the current study was to determine if these two methods can enhance the negative predictive value of the individual modality alone, for a specific lymph node station, and if this integrated approach can reduce the number of mediastinoscopies.

A total of 113 patients with enlarged mediastinal lymph nodes ($\geqslant 1$ cm), who underwent both TBNA and PET scanning, were included. In 51 patients, histopathology, confirmed by surgical lymph node dissection, was compared with PET results and TBNA.

Sensitivity, specificity, positive predictive value, negative predictive value and accuracy to detect malignant lymphadenopathy was 68 (13/19), 89 (119/134), 46 (13/28), 95 (119/125) and 86% (132/152) for PET, respectively; 54% (6/11), 100 (53/53), 100 (6/6), 91 (53/58) and 92% (59/64), respectively for TBNA; and 100 (11/11), 94 (50/53), 79 (11/14), 100 (50/50) and 95 (61/64) for combined TBNA and PET, respectively.

Combination of transbronchial needle aspiration and positron emission tomography has the potential to allow adequate mediastinal staging of nonsmall cell lung cancer with enlarged lymph nodes in most patients without the need for mediastinoscopy.

KEYWORDS: Bronchoscopy, lung cancer, mediastinoscopy, transbronchial needle aspiration

The mediastinal lymph node staging is important because in patients with potentially resectable lung cancer it allows differentiation between inoperable ($\geqslant$ Stage IIIB-malignant contralateral lymph nodes; N3 in tumour node metastases (TNM) classification) and operable stages ($\leqslant$ Stage IIIA-malignant ipsilateral lymph nodes; N2 in TNM classification) [1]. Moreover, the benefits of neoadjuvant chemotherapy prior to surgical resection of Stage IIIA having an ipsilateral lymph node involvement (N2 station) have been demonstrated [2, 3]. Patients without malignant lymph node involvement can be treated with surgery.

A computed tomography (CT) scan is useful in the evaluation of the primary tumour (T status) and also identifies significant lymph node enlargement [4]. The pooled sensitivity of CT and position emission tomography (PET) scanning in the staging of lung cancer is 0.57 and 0.84, respectively, and specificity of 0.82 and 0.89, respectively [5]. Therefore, tissue confirmation is

required. In a recent meta-analysis the sensitivity of transbronchial needle aspiration (TBNA) for mediastinal lymph nodes was 0.76 and specificity was 0.96 [6]. The reported sensitivity and specificity of cervical mediastinoscopy is 80–85% and specificity 100% [7]. Mediastinoscopy is performed in the operating room with general anaesthetic and has a morbidity and mortality of 2 and 0.08% respectively [7]. Flexible bronchoscopy is most often the first diagnostic procedure performed to obtain a pathological diagnosis in patients with suspected lung cancer, and TBNA of mediastinal lymph nodes as a staging procedure, and can be routinely performed during the same session, guided by enlarged lymph nodes, on CT scanning. A positive TBNA may preclude the need for additional surgical staging of the mediastinum [4]. The average negative predictive value of TBNA for lymph nodes has been reported as 71% [6].

However, to the best of the current authors' knowledge, there are no data concerning an

integrated approach of TBNA of mediastinal lymph nodes and PET scanning for correctly identifying a malignant or nonmalignant lymph node. Therefore, the aims of present study were to determine if combining TBNA of enlarged mediastinal lymph nodes and PET scanning can enhance the negative predictive value of TBNA or PET alone, for a specific lymph node station and if this integrated approach has the potential to reduce the number of mediastinoscopies.

METHODS
The current authors retrospectively reviewed patients with nonsmall cell lung cancer (NSCLC), who had undergone both TBNA of mediastinal lymph nodes and PET scanning as staging procedures, over a period of 3 yrs. A total of 446 patients who underwent TBNA during the study period were screened, of whom 202 patients had also undergone a PET scan. Amongst these 202 patients, 113 patients, who were diagnosed to have NSCLC, were included. The remaining 89 patients had other malignancies, other than NSCLC or benign disease. Surgical histology confirmation of TBNA cytology was available in 51 patients.

A total of 113 patients were included in the current study. Their mean ± SD age was 65 ± 9 yrs; 75 were males and 38 were females. Ethics approval was obtained from the Ethics Committee at the University Hospital Basel (Basel, Switzerland).

Bronchoscopy
Bronchoscopy and TBNA were performed under local anaesthetic and a combination of midazolam and hydrocodone was used for the sedation [8]. TBNA was performed when a significant enlarged mediastinal lymph node ($\geqslant 1$ cm in diameter) was detected on a CT scan of the chest. When coupled with a diagnostic bronchoscopy, TBNA of the mediastinal lymph nodes was initially performed, in order to avoid needle contamination [9]. TBNA sampling was always undertaken on the contralateral side of the tumour. TBNA was performed using a 22-gauge cytological needle (Bard, Billerica, MA, USA). TBNA aspirates were flushed with normal saline in a test tube and fixed with alcohol. Rapid onsite cytology

was not used. Cytological specimens were reported as either positive for malignancy, negative for malignancy or an inadequate specimen when lymphocytes were not found in the specimen. TBNA was performed by the consultant or the trainee supervised by the consultant.

Positron emission tomography
PET scanning was performed with a dedicated PET scanner, 60 min after an *i.v.* injection of 5 MBq·kg^{-1} body weight of ^{18}F-fluoro-2-deoxyglucose (FDG) on an ECAT EXACT PET scanner (Siemens Medical Solutions, Knoxville, TN, USA). Patients had to fast for a minimum of 12 h prior to the administration of FDG, in order to minimise insulin activity. The scanning encompassed an emission scan (1 min) using ^{68}Ge line sources and interactive image reconstruction. Images were read by two experienced nuclear medicine physicians (blinded to the pathology results) and their consensus was classified as either: negative, no typical uptake for malignancy (standard uptake value <2.5); or positive, typical uptake for malignancy (standard uptake value $\geqslant 2.5$). A PET scan was performed within 2 weeks of the bronchoscopy procedure. For the comparison between TBNA and PET, the lymph nodes were grouped into carinal (station 7) and right and left paratracheal (stations 2 and 4) [1].

A decision to perform mediastinoscopy or curative surgical resection with complete lymph node dissection was taken at the weekly multidisciplinary meeting between the pulmonologist, radiologist, thoracic surgeon, pathologist, oncologist and the nuclear medicine physician held at the University Hospital Basel. In patients who underwent mediastinoscopy or surgery, allowing definitive histopathological diagnosis, the current authors calculated the sensitivity, specificity, positive predictive value, the negative predictive value and the overall accuracy of TBNA, PET and combined TBNA and PET. These values were calculated excluding the TBNA samplings that resulted in an inadequate specimen.

RESULTS
TBNA for mediastinal lymph nodes were positive for malignancy in 29 out of the 113 (26%) patients (24 had N2
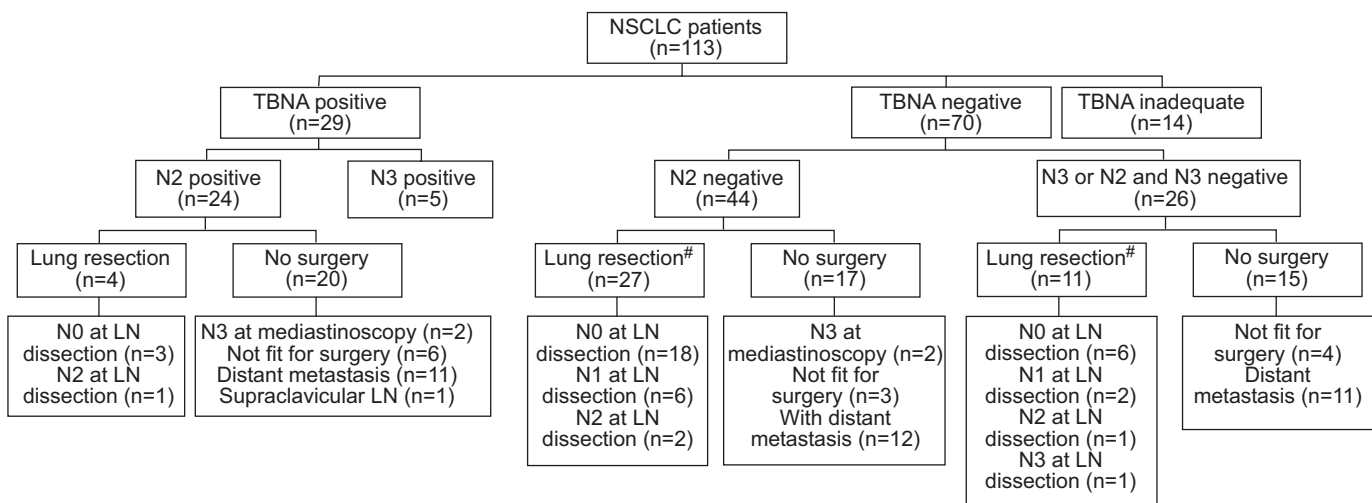
FIGURE 1. Overview of 113 nonsmall cell lung cancer (NSCLC) patients undergoing mediastinal transbronchial needle aspiration (TBNA) for lymphadenopathy. LN: lymph node. #: no LN dissection results in one patient each. n is the number of patients.

station and five had N3 station; fig. 1). A total of 60 patients did not undergo surgical lymph node dissection (47 patients had >Stage IIIA and 13 patients were not fit enough for surgery). Amongst these patients 23 had TBNAs that were positive (five patients had N3 station and 18 patients had N2 station). A total of 53 patients underwent mediastinoscopy (seven patients), mediastinoscopy followed by thoracotomy (nine patients) or only a thoracotomy (37 patients) with lymph node dissection (fig. 1). In one patient, who underwent surgery, mediastinal lymph node dissection was not performed, due to an intra-operative death. In another patient, complete histological data, regarding mediastinal lymph node dissection, were not available. Comparison of TBNA with histopathology and PET was available in 51 patients who had undergone surgery. The final mediastinal staging after mediastinoscopy or surgery was as follows: 38 patients had N0 and N1, 10 patients had N2 and three patients had N3. In 14 patients TBNA samplings were inadequate, as no lymphocytes were found. Six patients underwent lung resection (one patient had N0, three patients had N1 and two patients had N2) and eight patients did not undergo lung resection (seven patients had >Stage IIIA and one patient had poor lung function).

Comparison of transbronchial needle aspiration with surgical histology

A histological confirmation of TBNA, at either mediastinoscopy or surgery, was available for 74 lymph node stations in 51 patients (fig. 2a). TBNA was positive for malignancy in 6/74

(8%), negative for malignancy in 58/74 (78%) and inadequate in 10/74 (14%) samples. In the adequate TBNA samples, the sensitivity was 6/11 (54%), specificity was 53/53 (100%), positive predictive value was 6/6 (100%), negative predictive value was 53/58 (91%) and the accuracy was 59/64 (92%). The sensitivity of PET in this subgroup was 9/11 (81%), specificity was 50/53 (94%), positive predictive value was 9/12 (75%), negative predictive value was 50/52 (96%) and accuracy was 66/74 (89%).

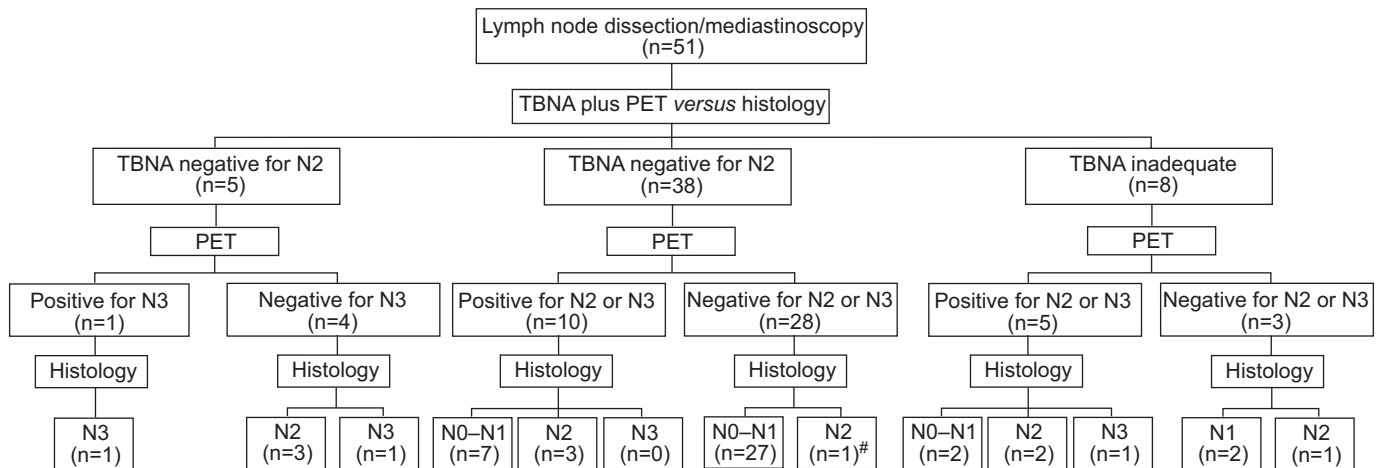### Comparison of positron emission tomography with surgical histology

In the 51 patients undergoing mediastinoscopy or lymph node dissection, 153 lymph node stations were available for comparison of PET results with histology (fig. 2b). The sensitivity of PET scan was 13/19 (68%), specificity was 119/134 (89%), positive predictive value was 13/28 (46%), negative predictive value was 119/125 (95%) and the accuracy was 132/152 (86%).

Combined transbronchial needle aspiration and positron emission tomography

The combined sensitivity of TBNA and PET in the detection of mediastinal lymph node involvement was 11/11 (100%), specificity was 50/53 (94%), positive predictive value was 11/14 (79%), negative predictive value was 50/50 (100%) and accuracy was 61/64 (95%). The combined TBNA and PET scan approach identified 27/51 (53%) patients with negative TBNA samplings of enlarged lymph nodes and a physiological mediastinal uptake on PET, which were confirmed to be free
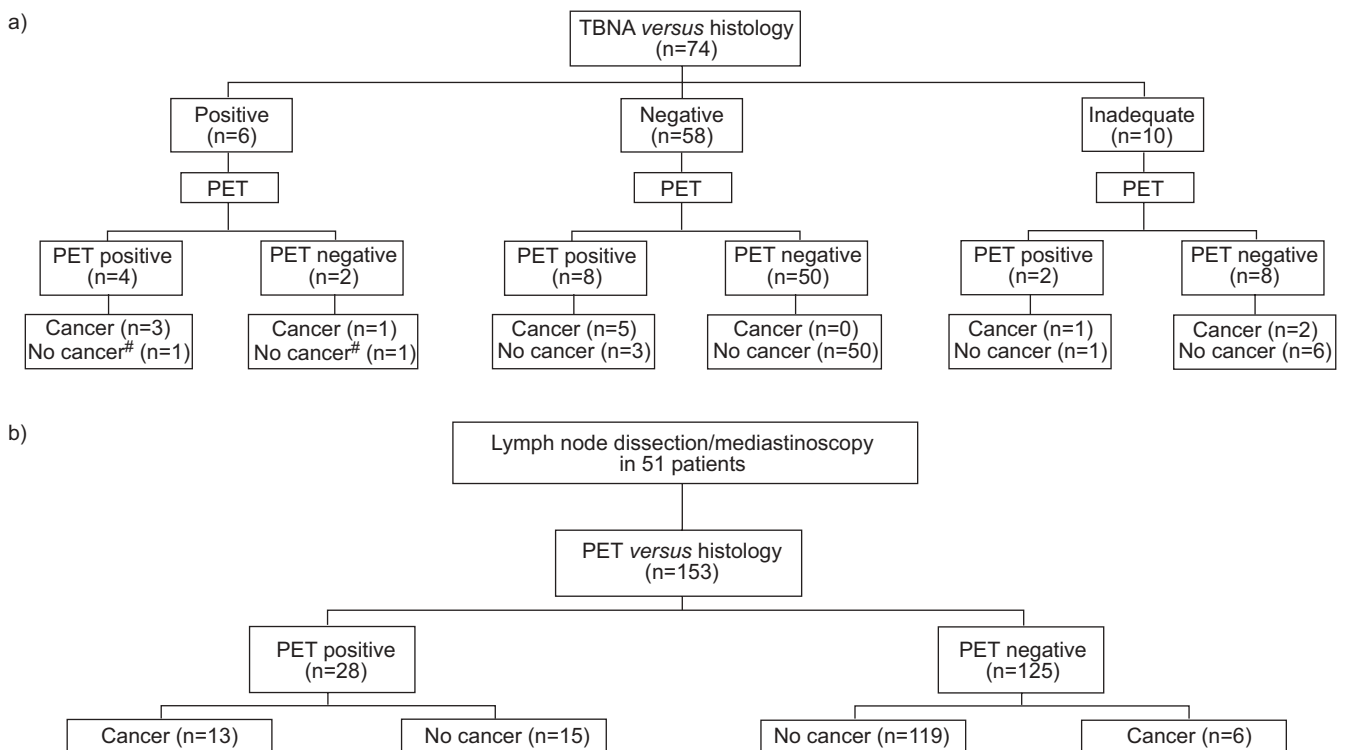
FIGURE 2. a) Comparison of transbronchial needle aspiration (TBNA) with histology in 74 lymph node stations, of 51 patients, who underwent surgical lymph node dissection and/or mediastinoscopy. #: TBNA positive for lymph node involvement, subsequently resulted negative at curative resection after neoadjuvant chemotherapy (successful down staging). b) Comparison of positron emission tomography (PET) with histology in 51 patients who underwent surgical lymph node dissection and/or mediastinoscopy. n is the number of lymph nodes.

FIGURE 3. Diagnostic value of combined transbronchial needle aspiration (TBNA) and positron emission tomography (PET) in the mediastinal staging of potentially operable patients with nonsmall cell lung cancer and lymphadenopathy. #: one patient, with a left upper lobe tumour, PET negative, subaortic lymph node station (not accessible to TBNA and cervical mediastinoscopy), was found to be positive at thoracotomy and lymph node dissection. n is the number of patients.

of tumour at mediastinal lymph node exploration (fig. 3). In one patient, with a left upper lobe tumour that was TBNA and PET negative for ipsilateral paratracheal mediastinal lymph node, a PET negative subaortic lymph node station (not accessible to TBNA sampling and cervical mediastinoscopy) was found to be positive at thoracotomy and lymph node dissection (fig. 3). In another patient, PET was found to be a false negative for a non-enlarged lymph node at N3 station, which was diagnosed at surgical staging.

Patients with positive N2 lymph node stations

TBNA was positive for N2 lymph node involvement in five patients. Two of these patients had enlarged lymph nodes on contralateral side (N3 station) and were negative at TBNA. However, one patient was PET positive and was confirmed as having malignancy at lymph node dissection. The other patient was PET negative and was confirmed as having malignancy at lymph node dissection. The remaining three patients with TBNA positive at N2 station did not have significant lymph node enlargement at N3 station and were also PET negative. Of these, one patient had N3 disease at lymph node dissection and the remaining two did not have malignancy.

Impact of combined transbronchial needle aspiration and positron emission tomography in avoiding mediastinoscopy

Applying the approach of combining a negative TBNA and a negative PET result in patients with enlarged lymph nodes, it can be estimated that mediastinoscopy could be avoided in 29/51 (57%) patients (both TBNA and PET negative in 28 patients at N2 lymph node station and a positive TBNA for N2 and negative for N3 lymph node station in one patient).

DISCUSSION

The role of PET scanning for mediastinal lymph node staging has been debated [10–12]. PET scanning has been reported to significantly improve the rate of detection of mediastinal lymph node involvement in patients with NSCLC and also has a high negative predictive value [10]. Cervical mediastinoscopy has been recommended as a standard for lymph node

staging of NSCLC [7, 11]. The sensitivity of PET scan in the current study was 68%, specificity was 89% and the positive predictive value was 46%. Furthermore, the negative predictive value was 95%. The findings of the present study concur with the literature, which states that the PET scan, in itself, is incomplete in the mediastinal lymph node staging of NSCLC and needs to be supplemented by pathological confirmation of PET positive lymph nodes or PET negative enlarged lymph nodes.

TBNA is a minimally invasive staging procedure, which is able to preclude the need for additional staging for the mediastinum [4], and is cost-effective if performed during the first diagnostic bronchoscopy in all patients with suspected lung cancer [13]. It is an underused technique, despite its indisputable advantages [14]. This study is a novel step forward in highlighting its benefits [6, 14]. In the current study, TBNA diagnosed inoperable disease (TBNA of contralateral mediastinal lymph node) in five patients precluding other diagnostic procedures. The sensitivity of TBNA in patients who underwent a surgical lymph node exploration was 54%. Some studies, have reported a higher sensitivity of TBNA [15]. However, the sensitivity of TBNA has consistently been reported as high in studies with a high prevalence of involvement of N2 and N3 mediastinal lymph node stations, whereas it is low in those with a lower prevalence [7]. This finding has also been confirmed in a very recent meta-analysis [16]. Therefore, the relatively low sensitivity of TBNA in the present study may be attributed to the nature of the patients analysed, which the current authors restricted to those who were considered potentially eligible for curative resection. Introduction of real-time endobronchial ultrasound-guided TBNA might enhance the diagnostic yield of this approach [17]. The current data set is unique as the diagnostic value of a combined staging approach was analysed based on a non-invasive procedure (PET scan) and a very specific minimally invasive procedure (TBNA), which can be performed along with routine diagnostic bronchoscopy. The findings of the present study clearly show that both these diagnostic tools are complementary and are able to enhance the diagnostic value of the individual modality for a specific lymph node station. In
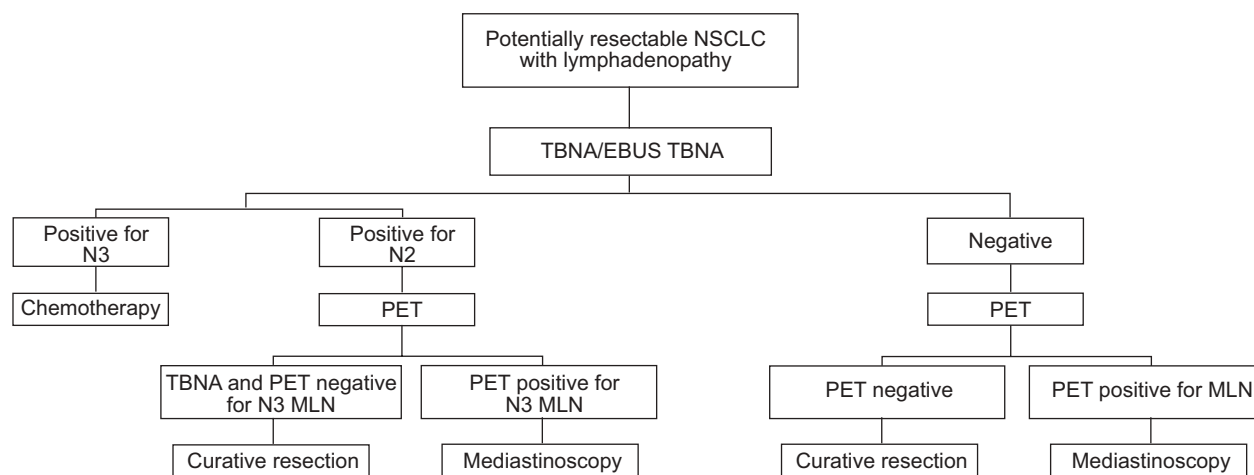
FIGURE 4. Bronchoscopic Algorithm for Staging of Mediastinal Lymphadenopathy in nonsmall cell lung cancer (NSCLC-BASEL algorithm). TBNA: transbronchial needle aspiration; EBUS: endobronchial ultrasound; PET: positron emission tomography; MLN: mediastinal lymphadenopathy.

particular, the negative predictive value of a specific enlarged lymph node station, in which both TBNA and PET results are available, is 100%. Therefore, a lymph node station, which is both TBNA and PET negative, does not need further invasive diagnostic investigation. Furthermore, PET was falsely negative in two patients in whom TBNA was positive (fig. 2a). Both these patients had adenocarcinoma, which is known to have a low sensitivity with PET scanning [18]. The sensitivity of combined TBNA and PET scanning for enlarged lymph nodes was 100%, thus highlighting the value of an integrated approach. Due to the restrospective nature of the current study and the relatively limited patient numbers, the present authors believe that these results generate a strong hypothesis and form a good basis for a prospective trial.

The potential direct clinical impact of a combined approach using TBNA and PET can be assessed as follows. First, TBNA alone allows the reduced need for mediastinoscopy, by diagnosing N3 involvement at time of diagnosis. Secondly, TBNA may also yield a positive result for an enlarged lymph node, which might be PET negative. Thirdly, the combination of TBNA and PET might identify the patients with N2 disease. Fourthly, the combined approach also identifies patients who can be referred directly to surgery without the need of mediastinoscopy (N0, N1 TNM stages). One patient who was staged as having N2 disease on TBNA and N3 location showing no lymph node enlargement, nor a PET hotspot, eventually had N3 lymph node involvement for cancer. PET scan is known to have a low sensitivity for lesions <1 cm [19]. The issue of sampling mediastinal lymph nodes, which are <1 cm in NSCLC, might be potentially addressed using direct endobronchial ultrasound-guided TBNA [17, 20]. Thus, patients with N2 lymph node involvement who have an N3 mediastinal lymph node station, which is both TBNA and PET negative for enlarged mediastinal lymph node, might be referred directly for neoadjuvant chemotherapy to be followed by surgery. Furthermore, all patients who had a physiological mediastinal uptake at PET scanning and negative TBNA for enlarged mediastinal lymph node were confirmed to have operable disease (fig. 3). Based on the approach of combining a negative TBNA and a negative PET, it can be estimated that

mediastinoscopy could be potentially obviated in 57% of patients (figs. 3 and 4). This number of avoided mediastinoscopies using combined TBNA and PET scan might be markedly increased with the use of real-time endobronchial ultrasound TBNA or esophageal ultrasound-guided fine-needle aspiration plus a rapid, onsite cytology to adequately reach the lymph nodes and to avoid inadequate sampling [17, 21, 22]. Furthermore, it is possible to have malignancy in non-enlarged lymph nodes and PET negative lymph nodes (fig. 3). Recently, real-time endobronchial ultrasound-guided TBNA has been shown to detect advance mediastinal disease in patients with NSCLC having non-enlarged lymph nodes <1 cm [23].

In conclusion, transbronchial needle aspiration is useful in making an initial diagnosis of N3 disease and also has the potential to identify malignant mediastinal lymph nodes that are negative for a positron emission tomography scan. The high negative predictive value (100%) of combined transbronchial needle aspiration and positron emission tomography for enlarged lymph nodes on computed tomography scan, has the potential to significantly reduce the need of mediastinoscopy by correctly identifying patients for neoadjuvant chemotherapy or direct surgical resection. The current authors propose the Bronchoscopic Algorithm for Staging of Mediastinal Lymphadenopathy (BASEL algorithm) in nonsmall cell lung cancer as a rational approach to the optimal use of transbronchial needle aspiration, positron emission tomography and mediastinoscopy for mediastinal staging and therapy of patients with nonsmall cell lung cancer with lymphadenopathy.

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