Combining Bronchoscopy and Positron Emission Tomography for the Diagnosis of the Small Pulmonary Nodule ≤ 3 cm*

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Aim: **To assess the role of bronchoscopy and positron emission tomography (PET) scanning in an integrated approach for the diagnosis of noncalcified, small, chest radiologic lesions (≤ 3 cm).**
Methods: **Seventy-four consecutive patients (29 men; mean age, 64 years) with a pulmonary nodule ≤ 3 cm undergoing both combined PET and bronchoscopy were included. When bronchoscopy and PET findings were negative, a multidisciplinary decision was taken to perform further invasive diagnostics or follow-up.**
Results: **Malignancy was diagnosed in 51 patients (69%), and a positive benign diagnosis was made in 9 patients (12%). Six patients (8%) had endobronchial lesions. Bronchoscopy was diagnostic in 53% patients (cancer, n = 35; benign, n = 4). PET findings were positive in 19 of 35 patients with a nondiagnostic bronchoscopy. In these 19 patients, malignant diagnosis was made in 14 patients (CT-fine needle aspiration [FNA], n = 3; thoracoscopic biopsy, n = 3; resection, n = 7; FNA of PET-positive supraclaviclar lymph node, n = 1), and a benign diagnosis was made in 5 patients (CT-FNA, n = 1; thoracoscopic biopsy, n = 1; resection, n = 1; follow-up, n = 2). In 16 patients with nondiagnostic bronchoscopy and negative PET findings, 5 patients had a tissue diagnosis (cancer, n = 2 [< 1 cm]; benign, n = 3) and 11 patients were followed up. Sixty-seven patients had a lesion 11 mm to 3 cm; among these, all 12 patients who were bronchoscopy negative and PET negative had benign lesions. In 24 patients without mediastinal adenopathy (solitary pulmonary nodule), bronchoscopy was diagnostic in 12 patients (cancer, n = 11; bronchiolitis obliterans organizing pneumonia, n = 1). In the remaining 12 patients, PET findings were positive in 6 patients (cancer, n = 3; resection, n = 2; CT-FNA, n = 1) and negative in 6 patients (benign, n = 2, both on resection; follow-up, n = 4).**
Conclusion: **Combining bronchoscopy and PET scanning has an useful role in the diagnosis of noncalcified chest radiologic lesions ≤ 3 cm in size. Bronchoscopy has a diagnostic yield of > 50% and also allows the diagnosis of endobronchial lesions. If bronchoscopy is nondiagnostic, a PET scan should be performed.** ***(CHEST 2005; 128:3558–3564)***

Key words: bronchoscopy; positron emission tomography; small pulmonary nodule

Abbreviations: BOOP = bronchiolitis obliterans organizing pneumonia; ELCAP = Early Lung Cancer Action Project; FNA = fine-needle aspiration; PET = positron emission tomography; TBB = transbronchial biopsy; TBNA = transbronchial needle aspiration; VATS = video-assisted thoracoscopic surgery

Patients with resected malignant nodules have a high 5-year survival of up to 80%. In contrast, the 5-year survival in patients with advanced lung malignancy remains below 5%.[1,2] The incidence of cancer in patients with solitary pulmonary nodule ranges from 10 to 70%.[1,3,4] A risk-stratification approach to a patient with a pulmonary nodule has been suggested based on an estimate of the probability of cancer, determined according to the size of the nodule, the presence or absence of a history of smoking, the patient's age, and the characteristics of the margins of the module on CT.[1] Positron emission tomography (PET) scanning has a sensitivity of 96% and a specificity of 77%.[5] For these reasons, a biopsy is required to make a definitive diagnosis. Transthoracic needle aspiration has a sensitivity of 62 to 99%

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and a specificity of 93 to 100% but is associated with a considerable risk of pneumothorax.[5,6] A definitive diagnosis for a small pulmonary nodule can be obviously achieved by surgery. However, in case of benign lesions, the procedure might be futile.[7] Surgery for both benign and malignant lung nodules is known to be associated with morbidity and mortality.[1,8,9] Video-assisted thoracoscopic surgery (VATS) has a lower perioperative morbidity compared to open thoracotomy but a conversion rate to thoracotomy of 25%.[7] The sensitivity of bronchoscopy for detecting a malignant process in a small pulmonary nodule ranges from 20 to 80%.[1,10,11]

To our knowledge, there are no data regarding an integrated approach using bronchoscopy and PET for the evaluation of noncalcified pulmonary nodules ≤ 3 cm in size. The definition of the solitary pulmonary nodule has not been used consistently in literature and has been referred to lesions with size ranging from 1 to 6 cm; some authors do not clearly mention adenopathy, and others have used it synonymous with bronchoscopic peripheral lesions.[12–17] The aims of this study were therefore to assess the role of flexible bronchoscopy and PET in an integrated approach for the diagnosis of noncalcified chest radiologic lesions ≤ 3 cm in size and if this combined approach allows to better select patients for surgical resection.

Materials and Methods

This study was approved by the institutional ethics committee. Seventy-four consecutive patients with a small radiologic lesion ≤ 3 cm in diameter on CT scan of the chest and who underwent combined diagnostic flexible bronchoscopy and PET scanning over a period of 3 years were included in this retrospective study. Patients with a classical benign calcification pattern on CT were not included in the study.[1] The flexible bronchoscopic procedures performed included brushings, BAL, transbronchial needle aspiration (TBNA) and transbronchial lung biopsy (TBB) of the radiologic lesion. Bronchoscopic brushings, TBNA, and TBB were performed using uniplanar fluoroscopic assistance.[18,19] BAL was performed as described earlier.[20] When flexible bronchoscopy was nondiagnostic, a consensus decision to perform transthoracic needle aspiration, VATS lung biopsy, resection, or follow-up was taken at the weekly multidisciplinary meeting between the pulmonologist, radiologist, thoracic surgeon, oncologist, pathologist, and the nuclear medicine physician held at our institution. The factors that were considered in such a decision-making process included clinical profile of the patient (age, tobacco smoking, geographic origin, history of malignancy), radiologic characteristics (size, pattern of the nodule margin, growth rate, increased attenuation on contrast-enhanced CT scan), and PET results.[1] Transthoracic needle aspiration was performed under CT guidance (CT-guided fine-needle aspiration [FNA]). Those patients who were deemed acceptable for follow-up and did not undergo surgery were evaluated at the outpatient clinic in our hospital or by the referring physician for at least 2 years.

PET scanning was performed 60 min after IV injection of 5 MBq/kg of body weight of ^{18}F-2-fluoro-2-desoxy-glucose (ECAT EXACT PET scanner; Siemens Medical Solutions; Knoxville, TN). Patients had to fast for at least 12 h prior to ^{18}F-2-fluoro-2-desoxy-glucose administration in order to minimize insulin activity. Scanning itself encompassed an emission scan (1 min) using ^{68}Ge line sources and iterative image reconstruction. Images were read by two experienced nuclear medicine physicians blinded to the pathology results, and their consensus was classified as follows: (1) no typical uptake for malignancy: negative; or (2) typical uptake for malignancy (standardized uptake value ≥ 2.5): positive.

Results

The mean age of the 74 patients (29 men and 45 women) was 64 ± 12 years (± SD). Seventy-nine percent of patients were smokers (38% current smokers and 31% previous smokers), and 21% had never smoked. A history of a nonpulmonary cancer was present in 10 patients. One fourth of the patients also had COPD. Twelve percent of patients were investigated for a small pulmonary nodule that was an incidental radiologic finding. Endobronchial lesions on flexible bronchoscopy were present in 6 of 74 patients (8%), and the diagnoses were non-small cell carcinoma (4 patients), neuroendocrine tumor (1 patient), and metastasis from renal cell carcinoma (1 patient). Overall, a diagnosis of malignancy was made in 51 of 74 patients (69%), a positive benign diagnosis was made in 9 of 74 patients (12%), and a benign diagnosis based on follow-up was made in 14 of 74 patients (19%).

A positive diagnosis (both malignant and benign) was made using flexible bronchoscopy in 39 of 74 patients (53%) [Fig 1]. PET findings were positive in 36 of 39 patients (92%). Thirty-five patients (47%) had a diagnosis of malignancy (including 1 patient with small cell lung cancer [SCLC]) using bronchoscopic methods (TBNA, n = 17; BAL, n = 16; brushings, n = 8; TBB, n = 7) including 1 PET-negative patient. A positive benign diagnosis was made in four patients (two PET positive and two PET negative), which included bronchiolitis obliterans organizing pneumonia (BOOP) [TBB], sarcoidosis (TBB), eosinophilic pneumonia (BAL), and infection (BAL). In 35 of 74 patients (47%), flexible bronchoscopy was not diagnostic (Fig 1). Of these cases, in 19 patients who were PET positive, a diagnosis of malignancy (including 1 patient with SCLC) was made in 14 patients (74%) using CT-FNA,[3] VATS lung biopsy,[3] resection,[7] and FNA of a PET-positive supraclavicular lymph node.[1] A benign diagnosis was made in five patients based on CT-FNA (n = 1), VATS lung biopsy (n = 1), resection (n = 1), and follow-up (n = 2). A consensus decision to perform further invasive diagnostics to obtain a tissue diagnosis was taken at the multidisciplinary

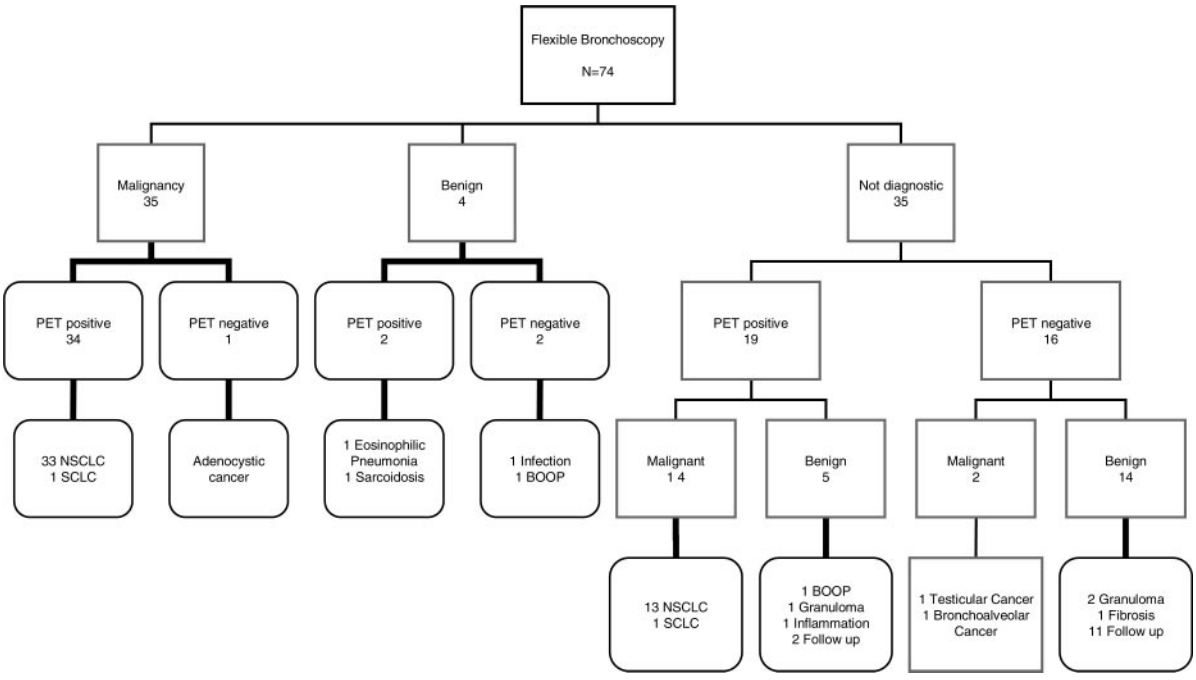

FIGURE 1. Yield of flexible bronchoscopy and PET for radiologic lesions ≤ 3 cm in diameter. NSCLC = non-small cell lung cancer.

meeting in 5 of 16 patients who were bronchoscopy negative as well as PET negative. Of these, a diagnosis of malignancy was obtained in two patients by surgical resection, both of whom had a radiologic lesion < 1 cm in diameter. One patient had a history of testicular carcinoma. Overall, a diagnosis of malignancy was made in 2 of 16 patients (13%) who were bronchoscopy negative and PET negative. Both these patients had a lesion < 1 cm in size. In the remaining 14 patients who were PET negative, a benign diagnosis was based on CT-FNA (n = 1), resection (n = 2), and follow-up (n = 11). A single, combined diagnostic and therapeutic lung resection procedure was carried out in 16 of 74 patients (22%) [Fig 2]. Among patients with lesions size 11 mm to 3 cm, all 12 patients who were bronchoscopy negative and PET negative had a benign diagnosis (Fig 2, *top*, *A*).

Most of the nodules were > 1 cm in diameter (91%) [Fig 2]. The smallest size of a nodule in this study was 7 mm. PET results were false-positive for malignancy in seven patients and false-negative in three patients. The sensitivity, specificity, positive predictive value, and negative predictive value of PET scanning for tumor were 94% (48 of 51 patients), 70% (16 of 23 patients), 87% (48 of 55 patients), and 84% (16 of 19 patients), respectively.

Twenty-four of the total 74 patients showed no lymphadenopathy, the solitary pulmonary nodule (Fig 3). Flexible bronchoscopy was diagnostic in 12 of 24 patients (50%). A diagnosis of malignancy was made in 11 patients (BAL, n = 7; TBNA, n = 6; brushings, n = 5; TBB, n = 3). A benign diagnosis of BOOP was made in one patient using TBB. In the remaining 12 patients in whom flexible bronchoscopy was negative for malignancy, PET was positive in 6 patients. The group of patients in whom flexible bronchoscopy was nondiagnostic and PET was positive, a diagnosis of malignancy was made in three patients (CT-FNA, n = 1; resection, n = 2). A benign lesion was diagnosed in the remaining three patients in whom flexible bronchoscopy was negative for malignancy and PET was positive based on resection (granuloma), VATS lung biopsy (BOOP), and early regression on follow-up. A benign diagnosis was made in all six patients in whom flexible bronchoscopy was negative for malignancy and were PET negative (hamartoma and fibrosis, n = 1 each on surgical resection; follow-up, n = 4).

DISCUSSION

The risk-stratification approach for the management of solitary pulmonary nodules has been discussed as an inexact science.[21] Flexible bronchoscopy has been suggested to have a limited usefulness in the evaluation of the small pulmonary nodule.[22] As many literature reports are inconsistent with defining the solitary pulmonary nodule, our data set is

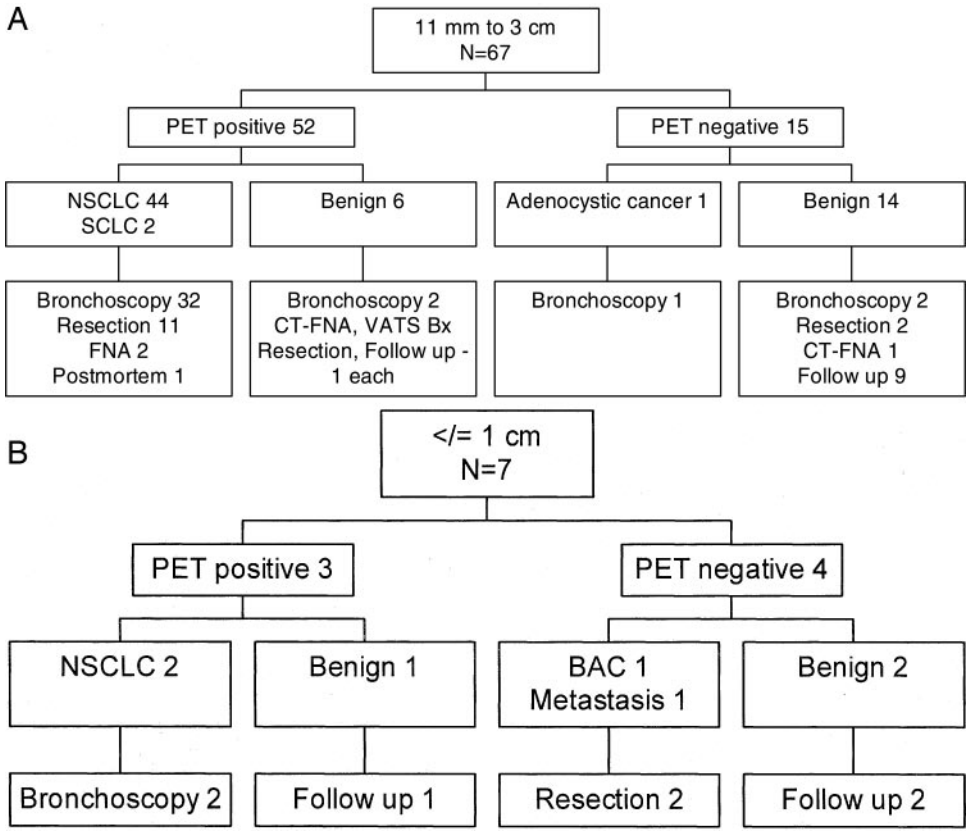

FIGURE 2. *Top*, *A*: PET results for radiologic lesions 11 mm to 3 cm. *Bottom*, *B*: PET results for radiologic lesions < 1 cm. Bx = biopsy; see Figure 1 legend for expansion of abbreviation.

unique because we analyzed all patients with noncalcific radiologic lesions ≤ 3 cm in size and also did a subset analysis of the solitary pulmonary nodule within these patients.[12] The findings of our study support that flexible bronchoscopy should be performed in all patients with a noncalcified chest radiologic lesion ≤ 3 cm in diameter because a significant number of patients will have an endobronchial lesion, and a malignant or a positive benign diagnosis can be made in > 50% patients. In our

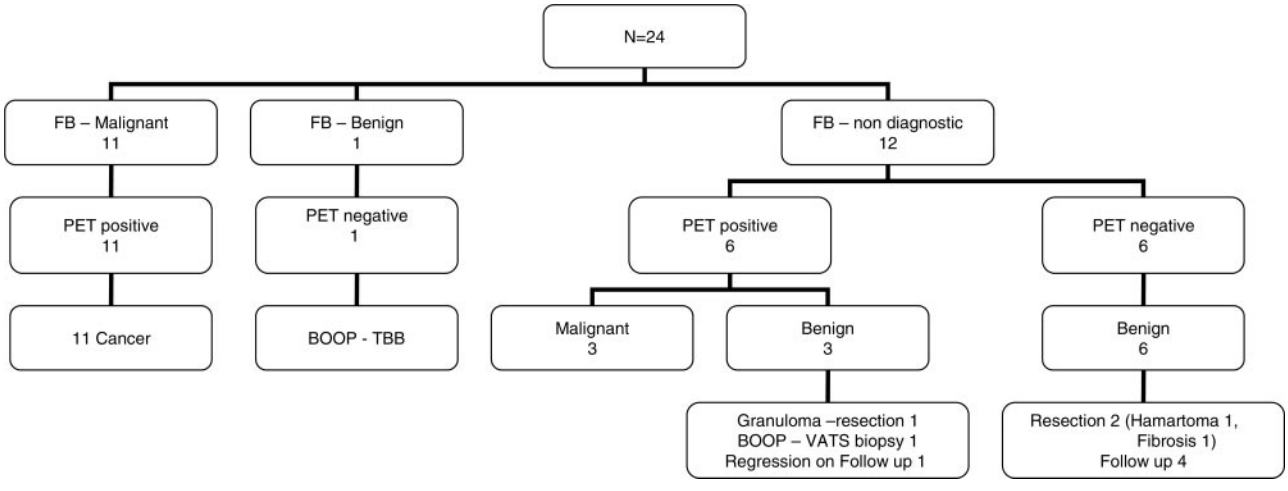

FIGURE 3. Yield of flexible bronchoscopy (FB) and PET for radiologic lesions ≤ 3 cm in diameter without lymphadenopathy.

study, 8% of patients had an endobronchial lesion. There are also other reports[16,23] in the literature that have reported the finding of an endobronchial lesion when flexible bronchoscopy was performed for the evaluation of small pulmonary nodules. Surgical resection has been suggested as the ideal approach in patients not having a benign appearing calcification, as it is both diagnostic and therapeutic.[6] However, not all benign lesions have calcifications.[7] The findings of our study clearly show that flexible bronchoscopy can obviate the need for surgery by making a positive benign diagnosis or sometimes that of SCLC. Also, having a malignant diagnosis prior to surgery excludes the need to perform a fresh-frozen section analysis during the operation to confirm the tumor and allows the patient to have a definitive indication for the operation. However, a fresh-frozen section analysis may still be performed to confirm the margins of resection to be free of tumor. Therefore, risk stratification in the decision making of noncalcified chest radiologic lesions ≤ 3 cm in diameter should begin after flexible bronchoscopy.

The sensitivity (94%) and specificity (70%) of PET scanning in our study is consistent with literature reports.[5] The negative predictive value of PET depends on the pretest probability of the disease.[9] Furthermore, several prediction rules exist for determining pretest probability of malignancy.[9] In a series[7] of 429 patients in whom VATS resection was performed for solitary pulmonary nodule, a benign diagnosis was made in 86% patients using histopathology. In our study, only 22% patients underwent VATS surgery as a single, combined diagnostic and therapeutic lung resection procedure. In patients who were flexible bronchoscopy negative, a decision to perform further invasive diagnostics was facilitated in those who had a PET-positive lesion. Both the patients with a diagnosis of malignancy who were bronchoscopy and PET negative for malignancy had a radiologic lesion < 1 cm in size. Overall, there were four patients who were PET negative with a lesion size ≤ 1 cm. It is known that pulmonary nodules that are < 1 cm in diameter cannot be evaluated accurately by PET.[24] The decision to evaluate the two patients further was taken at the multidisciplinary meeting. The findings of our study suggest that patients with radiologic lesions ranging 11 mm to 3 cm who are bronchoscopy negative and PET negative do not need further invasive diagnostics. Only selected patients with chest radiologic lesions ≤ 1 cm, which are both bronchoscopy negative and PET negative, risk stratification should be performed to either obtain a pathologic diagnosis or follow-up with serial CT scans as recommended by the Early Lung Cancer Action Project (ELCAP) protocol.[25,26] Furthermore, in solitary pulmonary nodule (lesions without adenopathy) that are both bronchoscopy negative and PET negative further invasive diagnostics or surgery can be avoided.

The ELCAP protocol recommended that if a nodule is ≤ 5 mm in size, a follow-up high-resolution CT scan should be performed 3 months later, and if there has been no growth, repeat high-resolution CT should be performed at 6 months, 12 months, and 24 months.[25,26] None of the patients in the current study had a lesion that was ≤ 5 mm. For nodules 6 to 10 mm in size, the protocol recommended assessment of an individual basis of the possibility of obtaining a biopsy specimen using percutaneous transthoracic CT-guided FNA or video-assisted thoracoscopic biopsy. If biopsy was not possible, then follow-up for growth as described for lesions ≤ 5 mm in size was recommended.[25,26] Four of seven patients (57%) with a nodule size ranging from 7 to 10 mm had a diagnosis of malignancy; of these two patients, both were bronchoscopy negative and PET negative. The findings of the current study highlight the importance of obtaining a histologic diagnosis in this group of patients. Careful risk stratification is needed if the number of biopsies or futile surgeries must be reduced in patients with nodules 6 to 10 mm in size that are both bronchoscopy negative and PET negative. The ELCAP recommended that a biopsy procedure must be performed for nodules ≥ 11 mm in size according to current standards of care by FNA, video-assisted thoracoscopy, bronchoscopy, or a combination of these methods.[25,26] In the current study, 67 patients (91%) had nodules ≥ 11 mm in size. Our approach of including bronchoscopy and PET scanning in a stepwise algorithm is novel because it allows to obtain a positive pathological diagnosis and markedly reduces the risk of malignancy if both bronchoscopy and PET findings are negative for nodules that are 11 mm to 3 cm in size (Fig 2*A*).

Several approaches have been reported that may have the potential to enhance the yield for bronchoscopy in patients with small pulmonary nodules. Bandoh et al[17] performed flexible bronchoscopy with multiplanar CT images and onsite ultrafast Papanicolaou staining of samples obtained by curette biopsies in patients with circumscribed chest radiologic lesions ≤ 4 cm in diameter. They obtained adequate diagnostic samples in 84% of patients, and a diagnosis of malignancy could be made in 92% of patients during the bronchoscopic examination.[17] The other methods that have been evaluated in the diagnosis of the solitary pulmonary nodule and bronchoscopic peripheral lesions include the radial probe endobronchial ultrasound, ultrathin flexible bronchoscopes, and electromagnetic navigation.[27–30] The results of our study are encouraging even though we

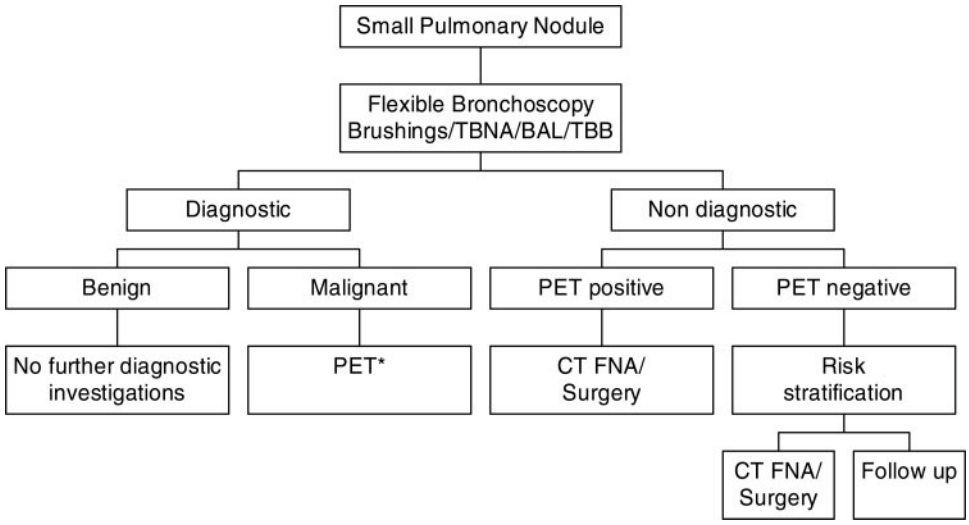

FIGURE 4. The Bronchoscopic Algorithm for Small pulmonary nodule EvaLuation-The BASEL algorithm. *For preoperative assessment of lung cancer.

used conventional bronchoscopic diagnostic methods such as brushings, BAL, TBNA, and TBB. With evolution in technology, the yield of bronchoscopic methods in obtaining a diagnosis in patients with a small pulmonary nodule and bronchoscopic peripheral lesions is geared to increase.

In conclusion, combining flexible bronchoscopy and PET scanning has an useful role in the diagnosis of noncalcified chest radiologic lesions ≤ 3 cm in size. Bronchoscopy has a diagnostic yield of $> 50\%$ and allows the diagnosis of endobronchial lesions. If bronchoscopy is nondiagnostic, then a PET scan should be performed. Based on the findings of our study, we propose the Bronchoscopic Algorithm for Small pulmonary nodule EvaLuation (BASEL algorithm). (Fig 4). Although PET scanning has a higher sensitivity than bronchoscopy, we suggest bronchoscopy as the first step because it allows for a tissue diagnosis, is safe, and is more readily available. This algorithm is valuable in identifying endobronchial lesions, making a malignant as well as a positive benign diagnosis and also proposes a definitive role of PET scanning in the evaluation of the small pulmonary nodule. It might also be used for better selection of patients for a single, combined diagnostic and therapeutic lung resection procedure.

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