Meta-analysis of Guided Bronchoscopy for the Evaluation of the Pulmonary Nodule

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Background: The detection of pulmonary nodules (PNs) is likely to increase, especially with the release of the National Lung Screen Trials. When tissue diagnosis is desired, transthoracic needle aspiration (TTNA) is recommended. Several guided-bronchoscopy technologies have been developed to improve the yield of transbronchial biopsy for PN diagnosis: electromagnetic navigation bronchoscopy (ENB), virtual bronchoscopy (VB), radial endobronchial ultrasound (R-EBUS), ultrathin bronchoscope, and guide sheath. We undertook this meta-analysis to determine the overall diagnostic yield of guided bronchoscopy using one or a combination of the modalities described here.

Methods: We performed a MEDLINE search using “bronchoscopy” and “solitary pulmonary nodule.” Studies evaluating the diagnostic yield of ENB, VB, R-EBUS, ultrathin bronchoscope, and/or guide sheath for peripheral nodules were included. The overall diagnostic yield and yield based on size were extracted. Adverse events, if reported, were recorded. Meta-analysis techniques incorporating inverse variance weighting and a random-effects meta-analysis approach were used.

Results: A total of 3,052 lesions from 39 studies were included. The pooled diagnostic yield was 70%, which is higher than the yield for traditional transbronchial biopsy. The yield increased as the lesion size increased. The pneumothorax rate was 1.5%, which is significantly smaller than that reported for TTNA.

Conclusion: This meta-analysis shows that the diagnostic yield of guided bronchoscopic techniques is better than that of traditional transbronchial biopsy. Although the yield remains lower than that of TTNA, the procedural risk is lower. Guided bronchoscopy may be an alternative or be complementary to TTNA for tissue sampling of PN, but further study is needed to determine its role in the evaluation of peripheral pulmonary lesions.

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Abbreviations: ENB = electromagnetic navigation bronchoscopy; NLST = National Lung Screening Trial; PN = pulmonary nodule; R-EBUS = radial endobronchial ultrasound; TTNA = transthoracic needle aspiration; VB = virtual bronchoscopy

The pulmonary nodule (PN) is becoming an increasingly common radiographic finding among patients in the United States. Nearly 45 million CT scan examinations are performed each year, and 11% to 30% (4.5–14 million) of those include an examination of

the chest.¹ In the recently released National Cancer Institute-sponsored National Lung Screening Trial (NLST), > 25% of the group who underwent low-dose CT scans of the chest had examinations that were

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suspicious for lung cancer.² With the findings of the NLST indicating a reduction in lung-cancer-specific mortality with CT scanning in at-risk people, the number of patients diagnosed with a PN could increase substantially if screening for lung cancer is broadly

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accepted by the medical community. The prevalence of malignancy in studies evaluating patients with noncalcified nodules ranges from 2% to 82%,³ and health-care providers are often faced with the diagnostic dilemma of how to manage these patients. The goal is to diagnose malignant nodules promptly, to permit timely surgical resection, while avoiding invasive testing or surgery in patients with benign nodules.

Practice guidelines offer recommendations for the diagnosis and management of the PN.⁴ The three general management categories based on the patient's probability of malignancy are watchful waiting with serial CT scans, tissue biopsy for pathologic diagnosis, and direct surgical excision. When biopsy is recommended, transthoracic needle aspiration (TTNA) is currently preferred because it has a diagnostic yield of 90%; however, TTNA also has a pneumothorax rate of about 25%, of which at least 15% requires chest tube insertion (overall chest tube rate of 5%).^{4,5} Flexible bronchoscopy is another diagnostic option, but the sensitivity of traditional transbronchial biopsy ranges from 14% to 63%, depending on the size and location of the PN.^{5,6} Bronchoscopy with guidance has evolved as a viable option "if the operator has expertise in newer guided techniques."⁴

Within the past decade, new techniques have emerged that offer guidance through the tracheobronchial tree during bronchoscopy to help reach and biopsy PN. Electromagnetic navigation bronchoscopy (ENB) and virtual bronchoscopy (VB) are able to create a virtual bronchoscopic image and a pathway to the PN (Fig 1). ENB can give additional real-time directions to the PN, much like a car's global positioning system for driving to a destination. Using an ultrathin bronchoscope combined with radial endobronchial ultrasound (R-EBUS) through a guide sheath allows the practitioner to visualize the sixth- to eighth-generation bronchi (whereas a traditional bronchoscope can only reach the fourth-generation bronchi), verify that the lesion has been reached, and maintain the position in the periphery for biopsy.

A number of studies have been published using a variety of these technologies to guide the bronchoscopist to the nodule for biopsy. Most have been small, single-institution case series that reported the diagnostic accuracy of the new technology being investigated. We undertook this meta-analysis to assess the overall diagnostic yield and adverse event rate of these technologies in studies that evaluated any one or a combination of these guidance mechanisms for the tissue biopsy of peripheral lung lesions and to compare and contrast these findings with the reported diagnostic yields of traditional bronchoscopy and TTNA.

MATERIALS AND METHODS

Data Sources

An Ovid MEDLINE (1950 through October 2010) and PubMed database search was performed using "bronchoscopy" and "pulmonary nodule" as terms to identify studies. The search was limited to human subjects. Although the search was not limited to English language studies, no non-English language studies met the inclusion criteria. The reference lists of included studies and review articles were searched manually for other relevant studies.

Study Selection

Review articles and commentaries were excluded from the meta-analysis, but the manuscript and the reference lists of relevant review articles were examined to find other studies. Both prospective and retrospective studies were evaluated for inclusion. The remaining studies were reviewed for relevance. All studies that reported the use of any of the following technologies to evaluate PN were considered for inclusion: ENB or superDimension, VB, endobronchial ultrasound (specifically R-EBUS), ultrathin bronchoscope, and guide sheath. All included studies documented the diagnostic yield of guided bronchoscopy using one or more of the methods described here. Case reports and studies with fewer than five patients were excluded. Studies were excluded if the linear endobronchial ultrasound was used instead of R-EBUS or if guidance was performed with CT scan-fluoroscopy alone. Studies that were performed on inanimate models or on patients without radiographic evidence of nodules to evaluate feasibility were excluded.

Data Synthesis

The articles were reviewed by two investigators (J. W. M. and G. S.). Many of the studies were pilot or feasibility studies undertaken to determine the diagnostic yield of a new technology. The primary technology used and the addition of other methods (eg, VB with R-EBUS) were recorded. The number of lesions and the number of diagnoses made were extracted. The overall diagnostic yield was calculated from the extracted data and compared with the reported diagnostic yield. Although the majority of diagnoses were malignant (primary lung or metastatic disease), other benign causes of the PN (eg, TB, sarcoidosis) were also considered diagnostic if found. If reported in the study, the yield by size (>20 mm or ≤ 20 mm) was recorded. The type of study (prospective vs retrospective) was recorded. All adverse events of pneumothorax, respiratory failure, and severe hemorrhage were extracted if reported.

Statistical Analysis

The reported diagnostic yield proportions from each study were aggregated via meta-analysis techniques that incorporated an inverse variance weighting technique and allowed us (via the *Q* statistic) to determine whether there was significant between-study variation (heterogeneity).⁷ We also used a random-effects meta-analysis approach that yielded similar findings (results not presented). These processes account for the study sample size and study heterogeneity. Inverse-variance weighted means of the studies' diagnostic yields and their 95% CIs were computed across all studies. Studies that used a specific method of biopsy were grouped (ie, all studies that used VB were grouped even if a combination of technologies was evaluated in an individual study), and the same computations for inverse variance weighted means were performed for each group. Because diagnostic yield for study *i* is

FIGURE 1. A, Chest CT image of a right lower lobe pulmonary lesion in a 78-year-old smoker. B, 3-D reconstruction of the tracheobronchial tree with the nodule outlined. C, Airway reconstruction of the pathway to the peripheral lesion. (Figure created and provided by Broncus Technologies, Inc.) Gen = generation; LMB = left mainstem bronchus; MLB = middle lobe bronchus; RB = right bronchial; RLLB = right lower lobe bronchus; RMB = right mainstem bronchus; RULB = right upper lobe bronchus.

a percentage ($Yield_i$) out of the study sample size (n_i), its variance is simply

$$\sigma_i^2 = \frac{Yield_i \times (1 - Yield_i)}{n_i}$$

using standard binomial theory.⁸ The reciprocal of this variance measure

$$w_i = \frac{1}{\sigma_i^2}$$

served as a weight within the calculation of the weighted mean diagnostic yield for this meta-analysis:

$$\text{Inverse variance weighted diagnostic yield} = \frac{\sum_{i=1}^N w_i \times Yield_i}{\sum_{i=1}^N w_i}$$

where N reflects the total number of eligible studies.

RESULTS

The MEDLINE and PubMed searches identified 140 and 309 potential studies, respectively. A thorough review of the reference lists of related studies uncovered an additional 29 studies. From these, a total of 39 studies met the inclusion criteria and were included in the analysis (Fig 2). The included studies were published between 2002 and October 2010. All studies reported the diagnostic yield of bronchoscopic biopsy of PN using at least one of five guidance techniques: VB, ENB, R-EBUS, guide sheath, or ultrathin bronchoscope. Six of the studies were retrospective. A total of 3,004 patients with 3,052 lesions from the 39 studies were included in this meta-analysis. Table 1⁹⁻⁴⁷ lists the study characteristics and summarizes the findings for each of the studies (Fig 3).

The inverse variance weighted diagnostic yield was 70.0% with a 95% CI of 67.1% to 72.9% (Table 2). Across the studies, the diagnostic yield ranged from 46.0% to 86.2% (Fig 2), and the Q statistic ($\chi^2_{[30df]} = 119.4$) indicated that there was significant ($P < .0001$) variation in the diagnostic yield estimates. Table 2 lists the pooled diagnostic yield estimates for groups of studies that used various technologies, along with group-specific heterogeneity test results. Diagnostic yield appeared to be highest (73.2% [95% CI, 64.4% to 81.9%]) when a guide sheath was used, although there was significant variation across studies (Q statistic = 63.8, $P < .0001$). The yields for VB (72.0% [95% CI, 65.7% to 78.4%]) and R-EBUS (71.1% [95% CI, 66.5% to 75.7%]) were also higher than the overall weighted diagnostic yield.

FIGURE 2. Literature search and selection. fluoro = fluoroscopy; PN = pulmonary nodule; TTNA = transthoracic needle aspiration.

Twenty-two studies evaluated the effect of size on the diagnostic yield (Table 3). Of these, 20 studies reported the diagnostic yields for lesions ≤ 20 mm and > 20 mm (in two studies, 30 mm was used as the size criteria, and those were excluded from this sub-analysis). From these, the weighted diagnostic yields of the 629 lesions ≤ 20 mm and the 767 lesions > 20 mm were 60.9% (95% CI, 54.0% to 67.7%) and 82.5% (95% CI, 78.6% to 86.4%), respectively. The weighted difference in diagnostic yield for these two measurement groups is 19.6% (95% CI, 11.7% to 27.6%; $P < .001$).

Of the studies included in the meta-analysis, 28 (2,156 total patients) reported on the rate of adverse events. The overall adverse event rate from those reported is 1.5% ($n = 33$) with the majority reporting pneumothorax. Thirty-two patients (1.5%) developed a pneumothorax (range 0.0% to 7.5% across studies) and, of these, 14 (0.6%) required placement of a chest tube and one underwent aspiration without placement of a chest tube. One patient (0.1%) developed respiratory failure requiring intubation. No episodes of significant bleeding or death were reported.

DISCUSSION

This study has several important findings that may influence our current practice and approach to the evaluation and management of PN. First, the pooled diagnostic yield of 70% is much higher than yields reported previously using traditional bronchoscopic techniques.^{5,6} Second, although the diagnostic yield for guided bronchoscopic techniques is lower than that reported for TTNA, the adverse event rate is also significantly lower. Third, the yield is dependent on the size of the lesion. Finally, the use of VB, R-EBUS, and a guide sheath may have a greater influence on the diagnostic yield of bronchoscopic evaluation of PN.

The current algorithms for management of PN rely heavily on TTNA when a pathologic diagnosis is desired.^{4,48} TTNA does have a 90% chance of confirming a diagnosis (range, 76% to 90%), but some report a pneumothorax rate as high as 40%.^{4,5,49-57} Additionally, the diagnostic yield is influenced by the size of the lesion, the size of the needle, the number of passes, and the presence of rapid on-site evaluation.^{4,5,53-56} The location of the lesion in the lungs, peripheral vs central, may also influence the diagnostic yield of TTNA.

In contrast, the sensitivity of the traditional bronchoscopic biopsy is only 34% for nodules ≤ 2 cm, and has been found to be as low as 14%.^{5,6} The sensitivity increases to 63% when nodules are > 2 cm in size, but decreases as the distance from the hilum increases. A lesion having a bronchus sign (the finding of a bronchus leading to the lesion) increases the success of transbronchial biopsy and brushing.⁵⁸ Recently, technology

Table 1—List of Studies and Results Included in Meta-analysis

No.	Study	Year	Pro/Retro	Technology	No. Lesions	No. Diagnosed	Yield, %	Adverse
1	Herth et al ⁹	2002	Pro	R-EBUS	50	40	80	1 PTX (1 CTI)
2	Shirakawa et al ¹⁰	2004	Pro	R-EBUS, GS	51	42	82.4	No report
3	Yang et al ¹¹	2004	Retro	R-EBUS	122	80	65.6	None
4	Shinagawa et al ¹²	2004	Pro	U, VB	26	17	65.4	No report
5	Yamamoto et al ¹³	2004	Pro	U	35	21	60	No report
6	Kikuchi et al ¹⁴	2004	Pro	R-EBUS, GS	24	14	58.3	1 PTX (1 CTI)
7	Kurimoto et al ¹⁵	2004	Pro	R-EBUS, GS	150	116	77.3	None
8	Becker et al ¹⁶	2005	Pro	R-EBUS, ENB	29	20	68.9	1 PTX (1 CTI)
9	Hautmann et al ¹⁷	2005	Pro	ENB	5	3	60	None
10	Asahina et al ¹⁸	2005	Pro	U, VB, R-EBUS, GS	30	19	63.3	None
11	Paone et al ¹⁹	2005	Pro	R-EBUS	87	66	75.8	None
12	Herth et al ²⁰	2006	Pro	R-EBUS, GS	54	38	70.4	1 PTX (1 CTI)
13	Schwarz et al ²¹	2006	Pro	ENB	13	9	69.2	None
14	Gildea et al ²²	2006	Pro	ENB	54	40	74.1	2 PTX (2 CTI)
15	Asano et al ²³	2006	Pro	U, VB	38	31	81.6	No report
16	Shinagawa et al ²⁴	2007	Pro	U, VB	71	50	70.4	No report
17	Shinagawa et al ²⁵	2007	Pro	U, VB	85	56	65.9	No report
18	Dooms et al ²⁶	2007	Pro	R-EBUS	50	34	68	None
19	Makris et al ²⁷	2007	Pro	ENB	40	25	62.5	3 PTX (1 CTI)
20	Eberhardt et al ²⁸	2007	Pro	R-EBUS, ENB, GS	118	85	72	7 PTX (4 CTI, 1 aspiration)
21	Tachihara et al ²⁹	2007	Pro	U, VB	96	60	62.5	None
22	Yoshikawa et al ³⁰	2007	Pro	R-EBUS, GS	123	106	86.2	1 PTX (0 CTI)
23	Eberhardt et al ³¹	2007	Pro	ENB	92	62	67.4	2 PTX (0 CTI), 1 intub
24	Yamada et al ³²	2007	Retro	R-EBUS, GS	158	106	67.1	No report
25	Wilson et al ³³	2007	Retro	ENB	279	167	59.9	3 PTX (0 CTI)
26	Asano et al ³⁴	2008	Pro	U, VB, R-EBUS, GS	32	27	84.4	No report
27	Fielding et al ³⁵	2008	Pro	R-EBUS, GS	140	93	66.4	2 PTX (0 CTI)
28	Oki et al ³⁶	2008	Pro	U	98	68	69.4	None
29	Lamprecht et al ³⁷	2009	Retro	ENB	13	10	76.9	None
30	Huang et al ³⁸	2009	Retro	R-EBUS	83	44	53	2 PTX (0 CTI)
31	Weiner et al ³⁹	2009	Pro	VB	50	29	58	No report
32	Eberhardt et al ⁴⁰	2009	Pro	R-EBUS, GS	100	46	46	3 PTX (2 CTI)
33	Bertoletti et al ⁴¹	2009	Pro	ENB	53	41	77.3	2 PTX (1 CTI)
34	Chao et al ⁴²	2009	Pro	R-EBUS	182	126	69.2	No report
35	Oki et al ⁴³	2009	Pro	U, R-EBUS	71	49	69	None
36	Iwano et al ⁴⁴	2011	Retro	VB	122	96	78.7	No report
37	Seijo et al ⁴⁵	2010	Pro	ENB	51	34	66.7	None
38	Disayabutr et al ⁴⁶	2010	Pro	R-EBUS	152	101	66.4	None
39	Eberhardt et al ⁴⁷	2010	Pro	U, VB	25	20	80	1 PTX (0 CTI)

CTI = chest tube insertion; ENB = electromagnetic navigation bronchoscopy; GS = guide sheath; intub = intubation; pro = prospective; PTX = pneumothorax; R-EBUS = radial endobronchial ultrasound; retro = retrospective; U = ultrathin bronchoscope; VB = virtual bronchoscopy.

has advanced to allow for better visualization of more distal airways with ultrathin bronchoscopes and endobronchial ultrasound. Additionally, virtual re-creation of the airway leading to the peripheral lesions, and navigation using improved CT imaging combined with ENB and VB, allows for direction and guidance to those PN. With the advancement of these new modalities, the recommendations for diagnosing a PN allow for the use of bronchoscopy if newer guidance techniques are available.⁴ Few data, though, exist to determine if guided bronchoscopy is equivalent to TTNA or if these procedures are complementary, depending on the location of the target lesion and an assessment of patient risk.

This meta-analysis includes >3,000 cases of guided bronchoscopy performed for the diagnosis of PN. It establishes that the weighted diagnostic yield is

significantly better than that reported for traditional flexible bronchoscopy, but the yield still remains lower than that of TTNA.⁴ Several studies included reported yields that approached the 90% yield of TTNA. Most notably, the study with the highest diagnostic yield using guided bronchoscopy compared a single method to a combination of technologies. Eberhardt et al²⁸ studied ENB alone, R-EBUS alone, and ENB combined with R-EBUS. The diagnostic yields of ENB, R-EBUS, and the combination of the two were 59%, 69%, and 88%, respectively. Although R-EBUS alone was better than ENB alone, the combination increased the yield to levels comparable to that of TTNA, suggesting that a combination of modalities may improve diagnostic yield.

Our results show wide variation in diagnostic yields among studies, which may be due to the differences

FIGURE 3. Overall summary of the diagnostic yields of the studies included in this meta-analysis.

in the definition of PN; the variability in the location of lesions targeted, which affects biopsy method; and the many options for obtaining a biopsy specimen, which have varying yields and risks. Patient selection was not uniform: Some defined the PN as a well-circumscribed opacity of ≤ 3 cm surrounded by aerated lung, whereas others defined it as a nodule farther than the fourth- or fifth-generation bronchi. The location of the lesion may also affect the ability to reach the lesion, but the location of the PN is not reported in all studies. Additionally, the various techniques used and operator ability can affect yield.

In this meta-analysis, three modalities had a higher diagnostic yield than the overall yield: VB, R-EBUS, and the use of a guide sheath. With R-EBUS, the location of the bronchoscope at the lesion can be verified with real-time visualization, and the guide sheath acts as an extended working channel to maintain that location during biopsy. Using these two technologies may help ensure that the lesion is definitively reached for biopsy. The finding of a higher weighted diagnostic yield with VB is more interesting, especially because it had a higher yield than ENB (Table 2). ENB has a VB component that is simulated prior to the bronchoscopy. In addition, ENB has real-time navigation that subsequently directs the bronchoscopist to the lesion, potentially making it more accurate.

However, the yield of ENB in this meta-analysis was less than that of VB alone. This may have depended on the software that generated the virtual picture, as well as on the operator.

Further subanalysis of the patients included in this meta-analysis supports the previous finding that diagnostic yield increases as the size of the PN increases.⁶ Of the studies that reported the diagnostic yield categorized by size, the yield was significantly higher for larger lesions. We are unable to comment on the effect of location on diagnostic yield because so few studies reported the yield in relation to the lobar location of the PN.

Of the studies that included information on adverse events, the rates of pneumothorax, hemorrhage, and

Table 2—Inverse Weighted Diagnostic Yield Overall and by Modality

Technology	Studies, No.	Weighted Proportion, %	95% CI	Q Statistic	Q P Value
VB	10	72.0	(65.7-78.4)	21.0	.01
ENB	11	67.0	(62.6-71.4)	13.3	.21
GS	10	73.2	(64.4-81.9)	63.8	<.0001
U	11	70.0	(65.0-75.1)	15.2	.12
R-EBUS	20	71.1	(66.5-75.7)	84.2	<.0001
All	39	70.0	(67.1-72.9)	119.4	<.0001

See Table 1 legend for expansion of abbreviations.

Table 3—Studies That Reported on Diagnostic Yield Based on Size

No.	Study/Year	Lesions > 20 mm			Lesions ≤ 20 mm		
		Lesions, No.	Diagnoses Made, No.	Yield, %	Lesions, No.	Diagnoses Made, No.	Yield, %
1	Kikuchi et al ¹⁴ /2004	9	6	66.7	15	8	53.3
2	Kurimoto et al ¹⁵ /2004	69	57	82.6	81	59	72.8
3	Asahina et al ¹⁸ /2005	12	11	91.7	18	8	44.4
4	Schwarz et al ²¹ /2006	11	8	72.7	2	1	50
5	Gildea et al ²² /2006	23	17	73.9	31	23	74.1
6	Asano et al ²³ /2006	12	10	83.3	26	21	80.8
7	Dooms et al ²⁶ /2007	39	32	82.1	11	2	18.2
8	Makris et al ²⁷ /2007	20	15	75	20	10	50
9	Eberhardt et al ²⁸ /2007	30	20	66.7	9	7	77.8
10	Tachihara et al ²⁹ /2007	19	18	94.7	77	42	54.5
11	Yoshikawa et al ³⁰ /2007	86	78	90.7	37	28	75.7
12	Eberhardt et al ³¹ /2007	57	40	70.2	35	22	62.9
13	Yamada et al ³² /2007	84	65	77.4	74	41	55.4
14	Asano et al ³⁴ /2008	17	16	94.1	15	11	73.3
15	Oki et al ³⁶ /2008	75	55	73.3	23	13	56.5
16	Lamprecht et al ³⁷ /2009	9	7	77.8	4	3	75
17	Eberhardt et al ⁴⁰ /2009	0	0		100	46	46
18	Bertoletti et al ⁴¹ /2009	46	37	80.4	7	3	42.9
19	Oki et al ⁴³ /2009	57	44	77.2	14	5	35.7
20	Iwano et al ⁴⁴ /2011	92	74	80.4	30	22	73.3

respiratory failure were very low. Most of the patients who suffered an adverse event had a pneumothorax, but fewer than one-half of those needed management with a chest tube. One other patient developed respiratory failure requiring intubation and mechanical ventilation. Thus, the adverse event rate that required intervention was only 0.7%. When compared with the 25% pneumothorax rate and an overall 5% chest tube rate with TTNA, the pneumothorax (1.5%) and chest tube (0.6%) rates with guided bronchoscopy were significantly lower.⁴

This meta-analysis does not give clear evidence that guided bronchoscopy is an adequate alternative to TTNA in all cases in which a diagnosis of PN is needed. It does show that using guidance when evaluating a PN will increase the yield of bronchoscopy, as will biopsy of lesions > 20 mm. Because patient selection varies for those referred for TTNA compared with those referred for evaluation by bronchoscopy, the diagnostic yield and the adverse event rate of guided bronchoscopy needs to be prospectively compared with those of TTNA. A multicenter, prospective, randomized control trial would provide a direct comparison between guided bronchoscopy and TTNA, which may allow us to determine the most advantageous use of these guided biopsy modalities. As we continue to understand these new technologies better, including their limitations, we may find that the various options to reach and biopsy PN are complementary; the decision may be based on location (center vs periphery), size, and expertise available. Further study may help to determine the appropriate role of these emerging technologies.

CONCLUSIONS

In summary, this meta-analysis, based on 39 studies with > 3,000 patients spanning the past decade, shows that guided bronchoscopy for evaluation of PN provides a reasonably high diagnostic yield with a low side-effect profile. The release of the NLST findings and the continued interest in radiographic lung cancer screening will likely lead to an increase in the number of PN identified. As the current modalities evolve and new technologies are developed, the capability of bronchoscopy to reach peripheral PN for diagnostic and treatment purposes will continue to improve. It has become increasingly important to determine the role of these guided procedures in the evaluation of patients, with the goal of these emerging techniques to be to identify malignancy quickly while limiting risk to the patient.

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Dr Silvestri: contributed to the study concept and design, analysis and interpretation of the data, and drafting of the manuscript.

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