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Comparative effectiveness of radial probe endobronchial ultrasound versus CT-guided needle biopsy for evaluation of peripheral pulmonary lesions: A randomized pragmatic trial

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Summary
In many patients the optimal method of investigation of peripheral pulmonary lesions (PPL) is not clear. We performed a prospective randomized pragmatic trial to determine the comparative effectiveness of endobronchial ultrasound-guided transbronchial lung biopsy (EBUS-TBLB) and CT-guided percutaneous needle biopsy (CT-PNB) for the investigation of PPL. Overall complication rates were higher in those undergoing CT-PNB (27% v 3%, $p = 0.03$), while diagnostic accuracy of EBUS-TBLB was shown to be non-inferior to that of CT-PNB.

Expected diagnostic accuracy and complication rates are likely to differ for individual patients on the basis of specific complex clinicoradiologic factors, which will influence the cost-benefit analysis between EBUS-TBLB and CT-PNB for individual patients. Further studies are required to examine the effect of these factors on clinical decision-making.

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Introduction

Peripheral pulmonary lesions (PPL) are focal radiographic opacities that may be characterized as nodules (≤3 cm) or masses (>3 cm). While referral for lobectomy in patients with a PPL with a very high pre-test probability of

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malignancy is suggested by some guidelines,[1] resectional biopsy is not risk-free and may not be necessary in a significant number of patients with such lesions.[2] CT screening studies show that up to 34% of such operations are performed for benign nodules.[3–5]

Non-invasive tests such as FDG-PET or dynamic Computerized Tomography (CT) with nodule enhancement cannot distinguish benign from malignant disease with sufficient accuracy.[2] Consequently, attempts at minimally invasive diagnosis are strongly favored. The two modalities most commonly used to investigate PPLs are CT-guided percutaneous needle biopsy/aspiration (CT-PNB) or bronchoscopy. Bronchoscopy may be limited by poor diagnostic yield,[6,7] though sensitivity is improved by guidance techniques such as fluoroscopy,[7,8] virtual bronchoscopy,[9] endobronchial ultrasound (EBUS),[8] or electromagnetic navigation (EMN).[10]

Clinical acumen may determine the choice of initial investigation in many patients with PPL. For example, those with radiographic evidence of probable mediastinal or extra-thoracic metastases are best served by sampling the metastatic disease site.[11] Conversely, PPL with endobronchial involvement are best evaluated via bronchoscopy.[11,12] Alternatively, expert review of imaging in patients referred for evaluation of PPL may demonstrate that invasive biopsy is not warranted, while in other patients, severe comorbid disease renders tissue diagnosis unnecessary.

However, in a proportion of patients who require tissue diagnosis, the optimal investigation remains unclear. This may be influenced by diagnostic accuracy, complication rates, and costs of individual procedures. Although the individual diagnostic characteristics of both EBUS-guided TBLB (EBUS-TBLB) and CT-PNB are well described, no study has previously directly compared the two tests.

Comparative effectiveness research (CER) was recently defined by the Institute of Medicine as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to diagnose, treat or monitor a clinical condition".[13] We performed a randomized trial of EBUS-TBLB versus CT-PNB for the investigation of solitary PPLs, in patients who had no clinical features to mandate or exclude either procedure. We compared the benefits (diagnostic accuracy) and harms (complications) of the two methods in order to guide clinicians in selection of the optimal investigation.

Methods

Institutional review board approval was granted for the performance of this study. All patients provided informed written consent.

Trial design

This study was a prospective randomized pragmatic trial. The continuum between pragmatic and explanatory trials has been previously elucidated, with pragmatic trials noted to be primarily designed to determine the effects of an intervention under the usual conditions in which it will be applied.[14] Given our intention to provide evidence to guide clinicians in selection the optimal investigation of patients with PPLs, the trial was designed according to the PRECIS tool in order to simulate "usual-care" conditions.[14] Such trial designs are well aligned with the purpose of CER.[15] We have adhered to the CONSORT guidelines for optimal reporting of randomized trials of non-pharmacologic treatment,[16,17] and the STARD guidelines for reporting studies of diagnostic accuracy.[18]

We hypothesized that the diagnostic accuracy of EBUS-TBLB was non-inferior to that of CT-PNB, but that the complication rate of EBUS-TBLB would be significantly lower than CT-PNB. Non-inferiority was defined *a priori* as diagnostic accuracy differing by not greater than 10%. Primary study outcomes were procedural complication rates and diagnostic accuracy.

Participants

All consecutive patients referred to our multidisciplinary lung cancer service for initial evaluation of solitary PPL, suspicious for lung cancer, were considered for inclusion in the study. The multidisciplinary service is based at Royal Melbourne Hospital, a tertiary referral centre and university teaching hospital. All patients were reviewed in a multidisciplinary meeting (MDM) to ensure that consensus opinion is that investigation is warranted *and* that either CT-PNB or EBUS would be acceptable modes of initial investigation of the lesion. Clinicians could exclude patients from the study if clinical acumen (on the basis of clinicoradiologic features) suggested a higher diagnostic accuracy or lower complications rate for one of the two procedures, thus making the alternate procedure unacceptable. The following exclusion criteria were applied only to exclude those with PPLs *not* requiring investigation:

- clinical condition precludes investigation
- lesion <1 cm diameter anywhere in lung fields
- Evidence on CT scan of central (endobronchially visible) lesion
- Other clinical site of disease more amenable to tissue diagnosis
- Tissue diagnosis considered unnecessary by MDM

Randomization to either procedure was performed using a computer-based random sequence generator (www.randomization.com). Both subjects and clinicians were unblinded to the randomization outcome. Subsequent investigation in the event of a non-diagnostic procedure was determined by the primary clinician.

Recorded data included patient demographics (age, gender), clinicoradiologic information (lesion size, lobar position, lesion distance from hilum and pleural, final diagnosis) and procedural information (date, diagnostic (Y/N), complications). All data was recorded prior to performance of the diagnostic test.

Performance of EBUS-TBLB

Bronchoscopy with EBUS guidance was an established technique at our institution for the investigation of peripheral pulmonary lesions,[19–21] with approximately 150 procedures completed in the 12 months prior to commencement of the trial. Procedures were performed

with topical lignocaine 2% and intravenous sedation, as previously described.[20] All procedures were performed by a single physician (DPS) using a standard video-bronchoscope (BF-P160, Olympus, Tokyo, Japan), with a 20-MHz radial EBUS probe (UM-BS20—26R; Olympus, Tokyo, Japan) and guide sheath.

Visible bronchial segments were sequentially examined until the characteristic ultrasound signal indicating presence of solid lesions was demonstrated. The EBUS probe was then removed and sampling instruments (biopsy forceps, cytology brush) introduced through the guide sheath, with sampling performed under fluoroscopic vision. Bronchial washings were taken after performance of TBLB and bronchial brushings. In the event that a PPL was not located, only bronchial washings were performed.

Performance of CT-PNB

Computed tomography-guided percutaneous needle biopsy of lung lesions was performed using CT fluoroscopy using a 64 detector CT scanner (Siemens Sensation 64, Siemens Healthcare. Erlangen, Germany). Twelve biopsies were performed by consultant radiologists (JMV, SH) and four were performed by radiology registrars/fellows.

The lung lesion was localized by a limited CT scan through the chest. Lignocaine 1% was injected into the skin and soft tissues to the pleural surface. A coaxial needle (Bard Tru-Guide needle, Bard Biopsy Systems. Tempe, AZ, USA) was introduced to the periphery of the PPL and multiple core biopsies (Bard Biopy-Cut needle and Bard Magnum biopsy instrument. Bard Biopsy Systems. Tempe, AZ, USA) were obtained. In fourteen of the fifteen biopsies a 19 g coaxial needle and 20 g core needle were used. In one patient a 17 g coaxial needle and 18 g core needle were used.

Following each diagnostic procedure, all patients underwent routine CXR. CT screening of patients following PNB was not performed, and diagnosis of pneumothorax was only made by CXR. Final diagnoses in patients in whom procedures were non-diagnostic were determined either on the basis of a subsequent invasive biopsy procedure, or were presumed benign on the basis of either regression of the PPL during radiologic surveillance, or stability during surveillance of a minimum 12 months duration.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, with comparison performed using an unpaired *t*-test (Welch-corrected). The Mann—Whitney test was used to compare non-parametric values. Categorical variables are presented as simple proportions and compared using Fisher's exact test. All reported confidence intervals are two-sided. Sensitivity, specificity, and accuracy of the two methods were calculated according to standard definitions, with comparison performed using Fisher's exact test. Comparison between groups was performed on an as-treated basis. A *p*-value of less than 0.05 was considered significant. Analyses were performed using GraphPad InStat 3 for Macintosh (GraphPad Software, La Jolla, CA. USA).

Results

From February 7th 2008 until January 22nd 2010, 358 patients were referred to our multidisciplinary lung cancer service for initial evaluation of a PPL. A flowchart illustrating the progression of consecutive unselected patients referred for evaluation of PPL is presented in Fig. 1. At least one exclusion criteria was met by 259 (72%) patients (see Fig. 1).

Clinical acumen resulted in exclusion of 28 patients from the trial. Two patients were preferentially referred for CT-PNB as they had pleurally based PPLs felt to be more amenable to percutaneous sampling. Twenty-six patients were referred preferentially for EBUS-TBLB. Two of these patients were refused by interventional radiologists concerned at the risk of complications from CT-PNB (see Fig. 2). The remaining 24 patients were declined by their primary clinician; 23 due to concern regarding the risk of pneumothorax complicating CT-PNB in patients with severe COPD or bleeding complicating CT-PNB in patients on anticoagulation, and one on the basis of an expected diagnostic result for EBUS-TBLB in a patient with a perihilar pulmonary nodule with a bronchus sign.

Eleven patients also declined to undergo randomization to either procedure. Ten declined CT-PNB due to the risk of

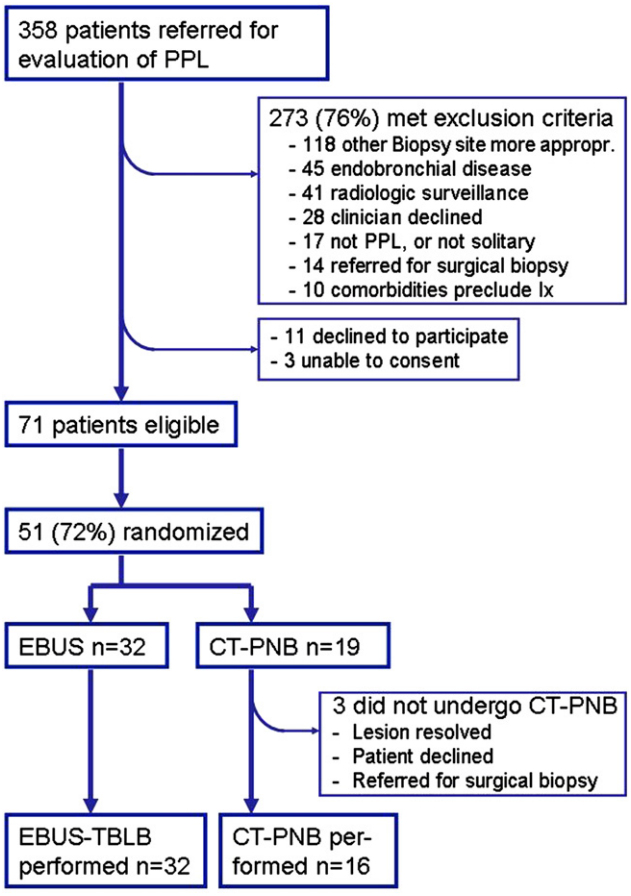

Figure 1 Flow diagram illustrating progression of all patients referred for evaluation of PPL to our multidisciplinary service during the study period.

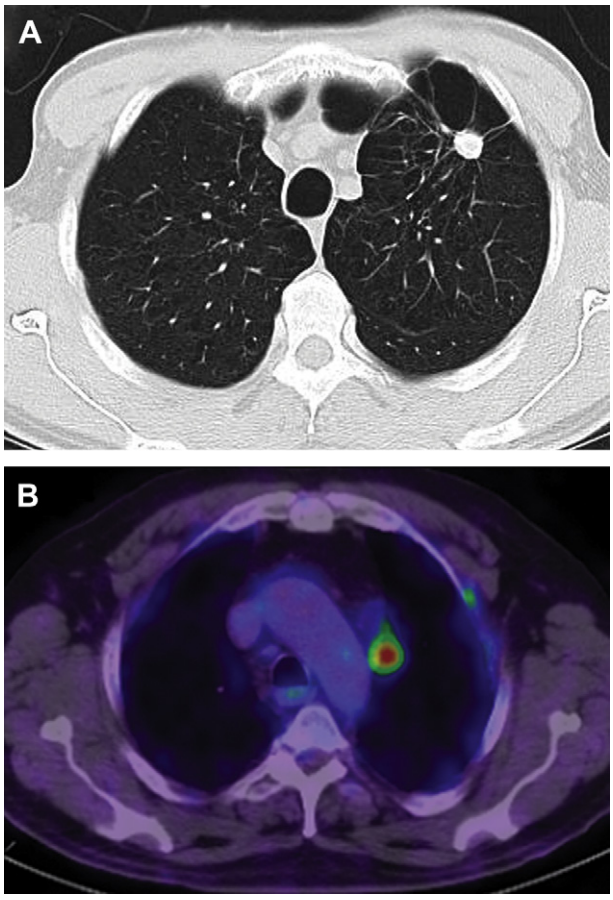

Figure 2 Clinicians were able to exclude patients from randomization if they felt there was an unduly high risk of complications associated with one procedure. Two patients were declined from CT-PNB by interventional radiologists on the basis of a high risk of complications suggested by radiologic appearances. A) CT chest demonstrates a left upper lobe nodule adjacent to an emphysematous bullus, suggesting a high risk of pneumothorax. B) CT/PET demonstrates FDG-avid lesion within the left upper lobe abutting the aortic arch, raising concern regarding of vascular trauma complicating the procedure.

pneumothorax, and one patient declined EBUS as CT-PNB could be performed with shorter delay. Three patients were not able to provide consent for inclusion in the trial.

Of the remaining 71 patients, 51 (72%) were randomized. Demographic and clinicoradiologic data for the 51 randomized patients is recorded in Table 1.

Diagnostic performance

Final diagnoses in all patients undergoing EBUS-TBLB or CT-PNB are recorded in Table 2. Three patients randomized to CT-PNB did not undergo biopsy: in one, the lesion had resolved by the time of biopsy, a second patient subsequently declined invasive biopsy, and a third patient was referred directly to surgery without biopsy after randomization. Outcome data for all subjects is recorded in Table 3. Diagnostic accuracy was similar for both EBUS-TBLB and CT-PNB (87.5% v. 93.3% respectively, $p = 1.0$). The 95% confidence interval for diagnostic accuracy of EBUS-TBLB is within the confidence interval for CT-PNB, therefore our results indicate that EBUS-TBLB is non-inferior to CT-PNB for the diagnosis of PPLs.[22]

No clinical factors were noted to influence the diagnostic performance of CT-PNB. For subjects undergoing EBUS-TBLB, multiple factors were associated with improved diagnostic sensitivity (Table 4). Diagnostic sensitivity was significantly higher in patients in whom the PPL was located by the probe (22 of 22 v. 5 of 10, $p = 0.001$). Ability to locate the PPL with the radial EBUS probe was significantly associated with a diagnosis of primary lung cancer (19 of 28 patients with lung cancer *v.* 0 of 4 patients with non-lung cancer diagnoses, $p = 0.020$). EBUS was significantly more likely to be diagnostic in patients with lung cancer compared to patients with alternate diagnoses (24 of 28 v. 1 of 3, respectively, $p = 0.025$). Among patients with primary lung cancer, the ability to locate the PPL with the probe was significantly associated with a positive diagnosis ($p = 0.006$).

A trend toward significance was seen for difference in sensitivity for PPL $\leq$6 cm from the pulmonary hilum compared to PPL $>$6 cm from the hilum (20 of 21 v. 5 of 8 respectively, $p = 0.058$). Lesion size, lobar location, and presence/absence of the CT-bronchus sign were not observed to influence diagnostic performance of EBUS-TBLB (data not shown).

Complications

There was a significant difference in the overall complication rate between the groups (EBUS 3% v. CT-PNB 27%, $p = 0.03$). Pneumothorax was noted in 1 subject in the EBUS group. This was small and self-limiting. Significant hemoptysis and pulmonary hemorrhage, as well as pain, was noted in one subject in the CT-PNB group. This patient required management in hospital and was discharged home after 3 days. Biopsy in this patient was performed using a 17-gauge coaxial needle, with pathologic examination confirming nodular lymphoid hyperplasia. Both the large needle size and the nature of the underlying lesion (CT-PNB confirmed nodular lymphoid hyperplasia) may have contributed to the risk of hemorrhage in this patient. Two further patients undergoing CT-PNB experienced small self-limiting pneumothoraces, and one patient experienced a hydropneumothorax. All complications were managed conservatively, with no patients requiring intercostal catheter insertion.

All complications following CT-PNB were noted in patients in whom the biopsy needle traversed aerated lung, with biopsy of PPLs with pleural contact ($n = 5$) associated with no complications. Complications were seen in two of four procedures performed by radiology registrars/fellows. Comparison with rate of complications in procedures performed by radiology consultants was non-significant ($p = 0.24$).

Discussion

This is the first randomized controlled trial to directly compare CT-PNB and EBUS-TBLB for the investigation of PPLs. Our results confirm that both procedures are able to

Table 1 Demographic and clinicoradiologic data for randomized patients.

	EBUS-TBLB	CT-PNB	*p*-value
Subjects	32	19	
Age (mean + SD)	71 + 11	67 + 12	0.193
Gender (F/M)	16/16	7/12	0.36
Size[a] (cm)			
Mean	2.8 + 1.4	4.1 + 2.1	0.026
≤2 cm	12	4	
>2 cm	20	12	
Lobar position[a]			
RUL	9	6	NS
RML	2	0	
RLL	5	5	
LUL	10	2	
LLL	6	3	
Distance[a] (cm)			
from pleura	3.2 + 2.5	1.6 + 1.7	0.017
from hilum	4.5 + 2.5	4.9 + 2.5	0.536
pleural contact	4	5	0.138

[a] of patients undergoing biopsy ($n = 16$ for CT-PNB).

accurately diagnose PPLs. The diagnostic accuracy of the two modalities were comparable, with our results indicating non-inferiority of EBUS-TBLB in comparison to CT-PNB. Inherent in comparative effectiveness research is comparison of both the benefits *and* harms between the two procedures. Importantly, the complication rate following CT-PNB was significantly higher than that observed following EBUS-TBLB (27% v. 3%, $p = 0.03$).

Diagnostic sensitivity for both procedures in our study is consistent with previously published studies.[2,23] A recent meta-analysis confirmed a point sensitivity for detection of lung cancer of 0.73 for EBUS-TBLB in investigation of PPLs, and sensitivity in studies where prevalence of malignancy was greater than 75% was 0.83.[23] No systematic review of CT-PNB for investigation of PPLs has been published but evidence-based clinical practice guidelines observe that sensitivity for detection of malignancy using CT-PNB in most studies exceeds 90%. However, approximately 20% of procedures were non-diagnostic,[2] reflecting the lower yield of CT-PNB in benign conditions.

Table 2 Final diagnoses in all patients undergoing minimally invasive biopsy.

Procedure			Method diagnosis established
Diagnostic			
EBUS ($n = 25$)	Adenocarcinoma	14	
	Squamous cell lung carcinoma	3	
	Small cell lung carcinoma	3	
	Large cell lung carcinoma	2	
	Non-small cell lung carcinoma	2	
	Mycobacterium tuberculosis	1	
CT-PNB ($n = 13$)	Adenocarcinoma	7	
	Squamous cell lung carcinoma	4	
	Non-small cell lung carcinoma	1	
	Nodular lymphoid hyperplasia	1	
Non-diagnostic			
EBUS ($n = 7$)	Squamous cell lung carcinoma	2	VATS
	Adenocarcinoma lung	1	CT-PNB
	Adenosquamous carcinoma lung	1	VATS
	Chondroid hamartoma	1	VATS
	Inflammatory mass	1	Radiologic surveillance[a]
	Metastatic breast carcinoma	1	VATS
CT-PNB ($n = 3$)	Inflammatory mass	2	Radiologic surveillance[a]
	Squamous cell carcinoma	1	Bronchoscopy

EBUS — endobronchial ultrasound, CT-PNB — CT-guided percutaneous needle biopsy, VATS — Video-assisted thoracoscopic surgery.
[a] all lesions were observed to have resolved on subsequent CT chest.

Table 3 Diagnostic performance for detection of lung cancer, and complication rates for the two study groups.

	EBUS-TBLB	CT-PNB	*p*-value
Diagnostic accuracy % (95%CI)	87.5% (71—96)	93.3% (68—99)	1.0
Sensitivity[a] % (95%CI)	86% (68—95)	92% (62—99)	1.0
Complications			
Overall	1 (3%)	4 (27%)	0.03
pneumothorax	1 (3%)	3 (20%)	
admission	0 (0%)	1 (7%)	
ICC	0	0	
deaths	0	0	

[a] sensitivity for the detection of lung cancer.

Our findings suggest that neither modality is uniformly preferable in the investigation of PPLs. If non-inferior in diagnostic accuracy, EBUS-TBLB would be the preferred procedure due to the lower complication rate. While non-inferiority of EBUS-TBLB in evaluation of PPL is demonstrated in our study, this applies only to clinicoradiologically similar PPLs. Clinical and radiologic features affecting diagnostic and complication rates are well described for both EBUS-TBLB and CT-PNB (Table 5). Individual randomized or cross-over trials examining the effect on diagnostic accuracy of variation in each of these individual factors is not feasible given the virtually infinite permutations of these factors.

These results add to data from previous studies regarding the effect of specific clinicoradiologic factors on diagnostic sensitivity or complication rates. Such information may be used to inform a clinical decision-making algorithm to assist clinicians in selection of the most appropriate test. The presence of features that predict a lower diagnostic sensitivity for EBUS-TBLB may lead clinicians to refer patients for evaluation with CT-PNB. Alternatively, clinicoradiologic factors predicting a higher rate of pneumothorax complicating CT-PNB may result in selection of EBUS-TBLB as the primary investigation modality. A significant number of eligible patients excluded by referring physicians in our study were excluded on the basis of such clinicoradiologic factors, suggesting that many clinicians already make such assessments intuitively.

Cost-effectiveness models may also influence the development of such a clinical algorithm. While diagnostic accuracy appears equivalent, a lower complication rate suggests that EBUS-TBLB may be the preferable test due to a lower morbidity, and lower costs required to manage these complications.

Strengths and limitations

The study was designed as a randomized pragmatic trial in order to replicate usual conditions in which clinical decision-making regarding the choice of investigation for a PPL occurs. We believe the prospective pragmatic study design results in a high degree of external validity. We also carefully defined patient eligibility in order to examine the group of patients with PPL in whom we feel insufficient evidence exists to inform clinical decision-making and in whom the choice between EBUS-TBLB and CT-PNB is frequently arbitrary. We deliberately excluded patients with suspected lung cancer in whom we believe clinical acumen was sufficient to guide initial investigation (eg. patients with endobronchial disease, or suspected distant metastases).

We recognize some limitations to our study. Diagnostic accuracy and complication rates are reported to vary widely for both procedures.[2,23] The generalizability of our results to other patient cohorts undergoing investigation for PPL is contingent on individual proceduralists having similar diagnostic sensitivity and complication rates to ours. Significant deviation from our observed outcomes may alter the decision regarding the most appropriate initial investigation for PPLs.

While 14 patients eligible for randomization declined, or were unable, to consent, reasons for failure to randomize were unstated in a further 20 patients. The trial design specified that clinicians may exclude patients from randomization if clinical acumen suggested that one procedure was preferred, and 28 patients were excluded on this basis. We suspect that clinical acumen similarly determined the optimal initial investigation in a significant proportion of these 20 patients. Although selection bias

Table 4 Comparison of radiologic features of PPLs between patients with lung cancer in whom EBUS-TBLB was diagnostic, versus those in whom EBUS was non-diagnostic. The only factor predictive for a diagnostic procedure was the ability to locate the lesion with the radial EBUS probe.

	Diagnostic EBUS ($n = 24$)	Non-diagnostic EBUS ($n = 4$)	*p*-value
Lesion size (mean)	30.4	27	0.69
SD	14	10	
Distance from pleura	3.5	2.0	0.27
SD	2.6	2.7	
Distance from hilum	4.0	5.5	0.22
SD	2.6	3.1	
Probe located within lesion	19	0	0.006

Table 5 Evidence-based summary of clinicoradiologic features affecting diagnostic yield & complication rates following invasive biopsy of peripheral pulmonary lesions.

Radiologic characteristic	Pleural contact	Lesion size		Lobar position		Proximity to pulmonary hilum	COPD	Bronchus sign
Effect on procedural outcome:		<2 cm	>5 cm	Apico-posterior left upper lobe	RML, RLL, lingula			
Diagnostic accuracy								
EBUS-TBLB	↓[31,32]	↓[22]	↑[37,38]	↓/—[37]	↑/—[10,42]	↑[31,32]	—	↑/—[43]
CT-PNB	—	↓[33–36]	—/↓[33,39–41]	—	—/↓[41]	—	—	—
Complication rates								
EBUS-TBLB	—	—	—	—	—	—	—	—
CT-PNB	↓↓[31,44]	↑[45–47]	—	—	↑/—[41,48]	↑[45–49]	↑↑[a,44,46,50–52]	—

RML — right middle lobe, RLL — right lower lobe, COPD — chronic obstructive pulmonary disease, EBUS-TBLB — endobronchial ultrasound-guided transbronchial lung biopsy, CT-PNB — CT-guided percutaneous needle biopsy.

[a] as well as a higher complication rate, the rate of intercostal tube insertion in the event of a pneumothorax in patients with COPD is also increased.[44,47,48,53,54]

cannot be fully excluded, such a bias would be expected to *reduce* the observed discrepancy in complication rates. Our findings would therefore remain valid and significant.

We compared CT-PNB with bronchoscopy guided by radial probe EBUS. Other bronchoscopic modalities not included in our study design may be selectively utilized during diagnostic bronchoscopy to further increase diagnostic accuracy. Transbronchial needle aspiration (TBNA) guided by linear probe EBUS may achieve diagnosis via sampling of central parenchymal lesions,[24,25] or mediastinal and hilar lymph node metastases.[24,26,27] EMN is an alternate guidance mechanism however it is very expensive and diagnostic accuracy is not significantly better than EBUS-TBLB.[10] It may be appropriate for selected patients though this remains unclear. Consideration of the potential additional value of these tools should be made when deciding between bronchoscopic and percutaneous approaches to PPL biopsy.

The randomization process resulted in significant differences between the two groups in lesion size (CT-PNB 4.1 ± 2.1 cm *v.* EBUS-TBLB 2.8 ± 1.4 cm, $p = 0.026$) and in the distance from pleura to the PPL (CT-PNB 1.6 ± 1.7 *v.* EBUS-TBLB 3.2 ± 2.5, $p = 0.017$). The discrepancy in both factors would be expected to favor the CT-PNB arm of the study, with smaller lesion size recognized as a factor in lower diagnostic accuracy for both procedures, and shorter distance between pleura and PPL predicting a lower rate of pneumothorax complicating CT-PNB (see Table 5). We believe therefore that this does not alter our finding of non-inferiority.

The number of subjects is relatively small, though is consistent with many published interventional bronchoscopy studies. Sample size calculations were performed in order to avoid a type II error (false negative finding) for the primary outcome of complication rates. Given a statistically significant observed difference in complication rates, our subject number, though small, is sufficient to address the primary outcome of complication rates.

Implications for future research

Randomized trials in the field of interventional pulmonology are rare, and our results highlight the difficulty of performing such studies. The two major difficulties encountered related to the unequal randomization of subjects (both in terms of numbers per study arm as well as clinical features), and the small proportion of patients screened for trial inclusion that were successfully randomized.

There is a significant chance when randomizing small numbers of subjects that imbalances might be seen between groups.[28] Block (or restricted) randomization may be used to ensure equal numbers of subjects per group, and stratified randomization can be utilized to decrease the odds of significant differences between groups. Response-adaptive (Bayesian) randomization may also allow a reduction in required sample size without impairment of statistical power.[29]

The pragmatic study design used resulted in exclusion of a significant number of patients (Fig. 1), including those with clinical stage N2/3 and clinical stage IV disease, as well as those with poor performance status, as we felt the clinical question did not apply to these patient groups. The resultant small proportion of screened patients who were randomized is therefore unsurprising, and is consistent with the proportion of lung cancer patients with localized disease at diagnosis.[30] Future studies may be more effective if performed as multi-centre trials, and may also be required to be more explanatory in design,[14] to optimize subject accrual. Alternatively, further studies examining clinicoradiologic features influencing diagnostic sensitivity and complication rates of EBUS-TBLB and CT-PNB may be more valuable in informing clinical decision-making algorithms. Prospective validation of any such algorithm would be required prior to their adoption in routine clinical practice.

Conclusion

Both modalities examined have very good diagnostic accuracy in the investigation of peripheral pulmonary lesions. Our findings suggest that diagnostic accuracy of EBUS-TBLB in evaluation of PPL is non-inferior to CT-PNB. However, clinicoradiologic factors influencing diagnostic accuracy and complication rates should allow clinicians to determine

which procedure is most appropriate as the initial investigation for individual patients. Complication rates following EBUS-TBLB are significantly lower than following CT-PNB and as a result, if expected diagnostic sensitivity is equivalent, patients should be preferentially referred for EBUS-TBLB for investigation of PPL. Further studies are required to allow clinicians to accurately assess expected diagnostic accuracy, and complication rates, for individual patients on the basis of clinicoradiologic features.

Conflict of interest

No authors have any conflicts of interest to disclose.

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