RADIAL PROBE EBUS VERSUS CT-GUIDED NEEDLE BIOPSY
FOR EVALUATION OF PERIPHERAL PULMONARY LESIONS:
AN ECONOMIC ANALYSIS

Daniel P Steinfot\textsuperscript{1,2*}, Danny Liew\textsuperscript{3}, Louis B Irving\textsuperscript{1}

1. Department of Respiratory Medicine, Royal Melbourne Hospital. Parkville 3050 Australia.
2. Department of Medicine (RMH/WH), University of Melbourne. Parkville 3010 Australia.
3. Department of Medicine (St Vincent’s Hospital), University of Melbourne. Parkville 3052, Australia

*corresponding author details
Dr Daniel P Steinfot
Department of Respiratory Medicine.
Level 1, Centre for Medical Research
Royal Melbourne Hospital
Parkville
Victoria 3050
Australia
Email: daniel.steinfort@mh.org.au
Ph: +61 3 9342 7708
Fax: +61 3 9342 8493
Abstract

BACKGROUND: Selection of the optimal procedure for minimally invasive diagnosis of peripheral pulmonary lesions (PPLs) may be based on clinical factors however selection of diagnostic strategy may also be influenced by cost. Economic analysis of minimally invasive diagnosis of PPL has not been performed previously.

METHODS: Decision-tree analysis was applied to compare downstream costs of endobronchial ultrasound-guided transbronchial lung biopsy (EBUS-TBLB) with CT-guided percutaneous needle biopsy (CT-PNB). Calculations were based on real costs derived from patient data. Sensitivity analyses, and probabilistic sensitivity analysis, were undertaken to identify the more cost-beneficial approach, for varying input parameter values. Cost-effectiveness calculations were based on estimated disutility, according to the wait-tradeoff technique.

RESULTS: For base-case analysis, initial evaluation with CT-PNB was cost-beneficial (CT AU$2,724 v. EBUS-TBLB AU$2,748). The variable which exerted the most influence on cost-benefit outcomes was the cost of managing complications. CT-PNB remained the more cost-effective procedure at base-case parameters, though thresholds were identified during sensitivity analysis where EBUS-TBLB became more cost-effective.

CONCLUSIONS: The costs of EBUS-TBLB and CT-PNB to evaluate PPL appear to be equivalent, but specific clinicoradiologic factors known to influence procedural outcomes will influence cost-benefit outcomes. Further evaluation of patient preferences and their influence on cost-effectiveness are required.
Key words

cost analysis

Endobronchial ultrasound

complications

Non-small cell lung cancer
Peripheral pulmonary lesions (PPL) are focal radiographic opacities that may be characterized as nodules (≤3cm) or masses (>3cm). While referral for lobectomy in patients with a PPL with a very high pre-test probability of 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] Screening studies using computed tomography (CT) show that up to 34% of such operations are performed for benign nodules.[3-5]

Non-invasive tests such as fluorodeoxyglucose positron emission tomography (FDG-PET) or dynamic CT with nodule enhancement cannot distinguish benign from malignant disease with sufficient accuracy.[2] Consequently, attempts at minimally invasive diagnosis are strongly favoured. This may be achieved by either bronchoscopic or percutaneous approaches.

Percutaneous sampling is generally performed under CT-fluoroscopic guidance. Bronchoscopy may be aided by guidance methods such as fluoroscopy,[6, 7] virtual bronchoscopy,[8] endobronchial ultrasound (EBUS),[7] or electromagnetic navigation (EMN).[9] The highest diagnostic yield is associated with EBUS and/or EMN guidance.[9] Availability of EMN remains very limited, partly owing to the significant expense associated with the technology and ongoing consumable costs.

The performance characteristics of EBUS bronchoscopy and CT-guided percutaneous needle biopsy (CT-PNB) have been well described, although only one study has
previously compared the two modalities head-to-head.[10] This study concluded that the overall diagnostic accuracy of EBUS was non-inferior to CT-PNB, but that the complication rate following EBUS-guided transbronchial lung biopsy (EBUS-TBLB) was significantly lower. In addition to clinical ‘performance’, the optimal test for diagnosis of PPLs may also be influenced by the costs of individual procedures. Costs for EBUS-TBLB and CT-PNB have not been previously reported. In particular, the cost of managing complications, and the influence of this on procedural cost outcomes, is unknown. Such information is highly relevant to clinical decision making.

In this study, we undertook a cost-benefit and cost-effectiveness analysis of EBUS-TBLB for management of PPLs, compared to CT-PNB.

METHODS

Study site
The Royal Melbourne Hospital in Melbourne, Australia, is a tertiary referral centre for the diagnosis, staging and management of lung cancer, with substantial experience in both EBUS-TBLB and CT-PNB. The hospital serves a catchment of over 600,000 people. Patients with suspected/known lung cancer are managed by a multidisciplinary team comprising respiratory physicians, thoracic radiologists, thoracic surgeons, medical oncologists and radiation oncologists. The MDT manages approximately 300 patients with lung cancer per year.
Modelling approach

Decision analysis [11] using specialized software (TreeAge Pro 2009, Excel module. TreeAge Software Inc., Williamstown, MA) was applied to compare the downstream costs of EBUS-TBLB and CT-PNB (Figure 1). The pathway demonstrating lower health care costs (ie. cost minimization) is identified as the more cost-beneficial pathway. The analysis accounted for costs of each procedure as well as costs incurred as a result of extra procedures required in the event of a negative result from either modality.

An advantage of decision tree analysis is its capacity to simulate even complex clinical algorithms, such as that for evaluation of PPL. Furthermore, it can explicitly capture the uncertainty that is inherent in modelling of any type.[12]

Model population

The modeled population comprised hypothetical patients referred to a multidisciplinary team for evaluation of PPL, for whom the team felt investigation was warranted and that either CT-PNB or EBUS would be acceptable modes of initial investigation of the lesion. This therefore excluded patients with the following features:

- clinical condition precluded investigation
- lesion <1cm diameter anywhere in lung fields
- evidence on CT scan of central (endobronchially visible) lesion
- other clinical site of disease more amenable to tissue diagnosis
**Health care costs**

Unit cost estimates, in Australian dollars (AU$), were based on recorded hospital costs for patients undergoing the above-mentioned procedures at the Royal Melbourne Hospital between 7 February 2008 and 22 January 2010. All patients had provided written consent for inclusion in a randomized pragmatic trial comparing EBUS-TBLB with CT-PNB.[10]

EBUS-TBLB and CT-PNB are performed on an outpatient basis at the Royal Melbourne Hospital. EBUS-TBLB is performed in a day procedure unit, with sedation administered by resident staff from the Respiratory Unit, as previously described.[13] The procedure itself has previously been described [14], using a 20-MHz radial EBUS probe (UM-BS20–26R; Olympus, Tokyo, Japan) and guide sheath. CT-PNB is performed using a coaxial needle (Bard TruGuide needle, Bard Biopsy Systems. Tempe, AZ, USA) and core biopsy instrument (Bard Biopy-Cut needle and Bard Magnum biopsy instrument. Bard Biopsy Systems. Tempe, AZ, USA).

Costs were derived from actual patient data at the Royal Melbourne Hospital, and includes both direct care costs (eg. physician, nursing, radiology, pathology costs) as well as indirect costs such as equipment sterilization & repair costs, and non-clinician staff costs (eg. clerical or cleaning staff). Costing data for each patient admission was obtained from cost weight analysis compiled according to guidelines from the Clinical Costing Standards Association of Australia.[15] Hospital and median costs for EBUS-TBLB and CT-PNB were calculated based upon all patients included in a recently published randomized pragmatic trial. Table 1 records summary data for all
uncomplicated procedures. Costs for patients in whom complications occurred are recorded in Table 2. Costs for thoracoscopic resection were established following an audit of all patients undergoing thoracoscopy/thoracotomy for resection of lung lesions at Royal Melbourne Hospital from 1 July 2007 to 30 June 2008. All costs were updated to 2010/11 levels according to the locally recorded Health Price Index, which reported an increase of 3% per year.[16]

Other input parameters

Other input parameters applied to the decision tree analysis are described in Table 3. Sensitivity and specificity of EBUS-TBLB for evaluation of PPL was based on our own institutional experience, and a published meta-analysis[10, 17] while data for CT-PNB was based on our reported experience, and on published guidelines.[2, 10]

Sensitivity analysis

Calculations based on the above data constituted a ‘base-case’ analysis, as defined by NICE guidelines.[18] We recognized that model input values may vary significantly across different institutions. For example, diagnostic sensitivity of EBUS-TBLB differs considerably between institutions,[17] and there is significant discrepancy in reported complication rates following CT-PNB.[2] Therefore, a series of one-way sensitivity analyses were undertaken within the range of each parameter recorded in Table 3, based on data from recent pooled analyses. The values of these key inputs were varied one at a time, while maintaining the other inputs at ‘base case’ values. Subsequent analysis was undertaken to determine the threshold above which the most cost-beneficial approach remained in comparison to other diagnostic modalities.
Cost may also alter, depending on the severity of the condition, and institutional approaches to management (eg. in- versus out-patient care, frequency of intercostal catheter insertion). Sensitivity analysis was performed to determine if a threshold cost for complications existed, above which the alternate investigation modality proved more cost-beneficial.

In order to assess the impact of uncertainty more accurately, probabilistic sensitivity analysis was performed using Monte Carlo simulations.[19] With this method, input parameters are assigned a distribution to reflect the nature of uncertainty. Multiple model simulations are then run. Monte Carlo Simulation was performed using triangular distributions of values (lowest – likeliest – highest) as recorded in Table 4. With each simulation, one value from every input range is randomly sampled from within a specified data range according to its probability distribution. Multiple outputs are thus generated, and uncertainty ranges are derived from the distributions of these. In our analysis, 10,000 simulations were undertaken.

Cost-effectiveness

The above methodology is used to assess the comparative cost-benefit of competing diagnostic strategies for assessment of PPL. Cost-effectiveness requires consideration of quality-of-life measures. Patient preferences with regard to the impact of procedural complications or anxiety related to waiting for test results have been shown to influence cost-effectiveness analyses for patients with PPL.[20]

Cost-effectiveness outcomes are expressed in cost per quality-adjusted life year ($/QALY), with utility being the measure on which quality adjustment is based.
Utility allows adjustment of life-years gained by an intervention when those gained years would be lived in less than perfect health. Extra life-years are given a utility value of between 0 and 1 to account for this. This method is suitable for assessment of chronic health/disease states, although it is not able to assess the cost impact of short-term disease states, such as pain or complications arising from a diagnostic procedure, or the anxiety resulting from a non-diagnostic procedure.[21]

Multiple methods for assessment of the impact of transient disease states have been described. With the time-tradeoff (TTO) technique, a patient decides between a longer period of time in less optimal health versus a shorter period in good health. A variation, the wait-tradeoff (WTO) technique, quantifies patients’ preference for undergoing a particular test or treatment that has associated discomfort or restrictions that the patient may dislike. The patient is asked to trade off extended time with the condition being diagnosed or treated in order to avoid the noxious effects of the test or treatment in favor of a similarly effective test or treatment but one not having side effects.[22] A QALY toll is reflected in the WTO by an individual’s willingness to wait longer to avoid more noxious experiences.[23] and may be measured by disutility, being a the fraction of a year of perfect health a patient would be willing to give up to avoid having to undergo a diagnostic test and to avoid its short-term morbidity.[24] This tool was originally designed for use in states related to diagnostic screening and testing.[25]

Sensitivity analysis was performed for disutility, starting at a theoretical disutility of 0 for both the procedure itself (that is no utility penalty), as well as disutility attributable to complications arising from the procedure. One-way sensitivity analysis was
performed to identify theoretical thresholds that may influence cost-effectiveness outcomes.

Assumptions
As sensitivity analysis is based on theoretical patients, we were required to make some specific assumptions regarding the theoretical model population. Key assumptions in the analysis were:

- There was a well-defined outcome in each arm of our decision model; that is, pathologic diagnosis of PPL.
- The long-term outcomes (measures of effectiveness) were equivalent in each model arm; that is, treatment and outcomes of all patients was similar regardless of how the diagnosis was determined. As previously recognized [26], a cost-benefit analysis that assumes competing diagnostic strategies have equivalent outcomes and focuses thereafter only on cost outcomes is the most appropriate form of economic analysis to use in this setting.
- Once a diagnosis has been made, the downstream costs of medical care were the same, regardless of how diagnosis was achieved.
- Thoracotomy/thoracoscopy had a diagnostic accuracy of 100% in the evaluation of PPL.
- Pathology costs were identical regardless of method of acquisition of tissue.

RESULTS

Base-case analysis
Costs of each procedure based on base-case parameters are recorded in Table 5. For the base-case analysis, initial evaluation with CT-PNB was cost-beneficial in comparison to EBUS-TBLB by a margin of $24 (CT $2,724 v. EBUS-TBLB $2,748).

**Sensitivity analysis**

One-way sensitivity analysis identified threshold values at which EBUS-TBLB became more cost-beneficial, which included cost of managing complications exceeding $501 per episode, complication rate of CT-PNB exceeding 40% and sensitivity of CT-PNB for detection of malignancy falling below 91%. Prevalence of malignancy had no effect on cost-benefit during one-way analysis. Variation in diagnostic yield for benign disease had negligible effect on outcomes for both procedures. The variable which exerted the most influence on cost outcomes was the cost of managing complications. The influence of this is illustrated in Figure 2.

Two-way sensitivity analysis was undertaken to explore the interaction between two specific parameters. Threshold values are altered when two parameters are varied making identification of specific values impossible. The variation in cost-outcome with variation in both cost of complications as well as complication rate of CT-PNB is illustrated in Figure 3a. Significant interaction was seen in two-way analysis with variation of prevalence of malignancy and sensitivity of EBUS-TBLB for detection of benign disease (Figure 3b), and with variation of sensitivity for detection of malignancy for both procedures (Figure 3c).

Given the influence of diagnostic sensitivity and complication rates on costs for procedures, we have modelled cost comparisons for hypothetical patient scenarios,
with results presented in Table 5. Input data for each scenario is presented in parentheses (EBUS-TBLB sensitivity, CT-PNB sensitivity, CT-PNB complication rate) and is based on published studies presented in Table 6.

- Scenario 1: Right lower lobe (RLL) pleurally based nodule (0.5, 0.97, 0.03)
- Scenario 2: Peri-hilar Right middle lobe nodule (0.88, 0.85, 0.43)
- Scenario 3: 6cm Right upper lobe mass with ‘bronchus sign’ (0.9, 0.8, 0.2)
- Scenario 4: 1.5cm proximal RLL nodule, FEV1 800mL (0.7, 0.7, 0.4)

As expected, differing clinical scenarios resulted in different outcomes from cost comparisons. An increase in cost of managing complications above $327 as used for these calculation would result in increasing cost-benefit towards EBUS-TBLB due to the lower complication rate seen with this procedure.

**Probabilistic sensitivity analyses**

Outcomes of probabilistic sampling demonstrate the negligible difference in net costs between the two procedures (Table 5). The two procedures differ by a maximum of $132 when comparison of mean, median and 10th and 90th centile values are made.

**Cost-effectiveness analysis**

Cost-effectiveness analysis was performed to examine the effect of disutility resulting from two potential adverse outcomes of the procedures – a non-diagnostic procedure (meaning further anxiety, and the need for additional procedures), and; a procedural complication (eg. pneumothorax, hospital admission).
Using a theoretical WTO for a non-diagnostic procedure of 20 days (0.05 years), CT-PNB remained the more cost-effective procedure at base-case parameters. One-way sensitivity analysis in the range of values recorded in Table 3 revealed that EBUS-TBLB became the more cost-effective procedure if sensitivity of EBUS-TBLB for benign disease exceeded 71%, if sensitivity of CT-PNB (malignancy) was below 89%, or if cost of managing complications exceeded $560. Unlike cost-benefit analyses, no threshold was observed for the complication rate of CT-PNB.

Using a theoretical WTO for a procedural complication of 20 days (0.05 years), CT-PNB remained the more cost-effective approach (CT = $2,778/QALY v. EBUS = $2,816/QALY) at base-case parameters. One-way sensitivity analyses demonstrated that EBUS-TBLB became the more cost-effective approach if the cost of complications exceeded $489, if the complication rate for CT-PNB exceeded 40%, and if the sensitivity of EBUS-TBLB for detection of benign disease exceeded 65%. The effect in alteration of these two parameters (two-way sensitivity analysis) is demonstrated in Figure 4.

As was demonstrated for cost-benefit calculations, the cost of managing complications was the input parameter that most heavily influenced the results of cost-effectiveness comparisons.

**DISCUSSION**

Our study was conducted in order to determine the most cost-beneficial and cost-effective diagnostic procedure in the evaluation of PPL. Our analysis indicates that the two minimally invasive approaches used in evaluation of PPL differ in cost by
negligible amounts, both in evaluation of the base-case scenario and following Monte Carlo probabilistic simulation.

The minimal differences between the two procedures observed in the base-case and probabilistic sensitivity analyses highlight the importance of clinical acumen in determining the most appropriate procedure. The only previously published randomized trial comparing EBUS-TBLB and CT-PNB found that overall diagnostic accuracy of EBUS-TBLB was non-inferior to CT-PNB.[10] However, numerous studies have demonstrated that both diagnostic accuracy and complication rates for both procedures may vary significantly, based on clinical factors (summarized in Table 6).

At base-case values, CT-PNB enjoys an advantage by having higher diagnostic sensitivity, while EBUS-TBLB has a lower complication rate. Specific clinical features are known to influence clinical outcomes, and therefore will have an effect on cost outcomes. Clinical acumen may suggest to clinicians which procedure may serve a patient better (eg. higher diagnostic sensitivity, lower risk of complications) and these factors will, as demonstrated in Table 5, also predict favourable outcomes from a cost perspective.

Where cost and clinical outcomes may diverge is in assessment of cost-effectiveness. We have used theoretical values to conduct cost-effectiveness analysis using the WTO method. Modelling has previously indicated that cost-effectiveness of competing strategies depends on patient attitudes about taking risks.[20] To our knowledge, no published studies have examined the disutility value patients place on
adverse outcomes, such as complications, or delay in diagnosis due to a non-diagnostic procedure.

Some patients may place a larger ‘cost’ than 20 days (in the WTO methodology) on adverse outcomes, such that thresholds between the two methods may be significantly different that to that recorded in our study. The ‘cost’ of complications versus non-diagnostic procedures may differ considerably, and may be highly dependent on personality type. This also highlights the value of involving the patient in medical decision making, especially when clinical acumen suggests two approaches may be equivalent. Patients may prefer a procedure with higher diagnostic success even at the cost of a higher risk of complications, or more risk averse patients may prefer a procedure with lower morbidity accepting a slightly higher likelihood of a non-diagnostic procedure.

Our analysis has demonstrated some factors that may influence the cost comparison between EBUS-TBLB and CT-PNB. Cost of managing complications was the factor that most influenced cost-benefit results. A higher cost of complications favoured EBUS-TBLB in cost comparisons, due to the lower complication rate associated with this procedure. Cost of complications is likely to vary significantly between institutions, based on clinical practice (eg. admission vs. out-patient care) and cost of delivering care. Individual institutions and health care services may wish to undertake decision tree analysis, based on local clinical and cost data, to determine their specific optimal investigative approach for patients with PPL.

**Strengths and Limitations**
To our knowledge, this is the first cost comparison study of two minimally invasive procedures for evaluation of PPL. It is also the first to describe the cost of specific procedures, and costs associated with complications of these procedures.

Assumptions are required for decision tree analysis, and validity of the analyses is more certain when actual clinical data or variables are used instead of assumptions. Our analyses were well informed by our own local cost and clinical data, and sensitivity analysis allowed us to perform cost comparisons across most clinically realistic values, as described in published literature. We also accounted for the impact that false-negative results and procedural complications might have had.

Bronchoscopic staging of the mediastinum is cost-beneficial in comparison to the previous standard of surgical mediastinoscopy, largely as a minimally invasive approach is supplanting the significantly more expensive surgical procedure.[26] In contrast, we are comparing two minimally invasive procedures which are very similar in cost. Cost-benefit therefore relies on minimizing ‘downstream’ costs and, as illustrated in Table 5, we have emphasized the influence that clinicoradiologic factors known to influence procedural outcomes also strongly influence cost outcomes. Decision tree analysis incorporating such information may assist clinical decision-making, though this requires future study.

Our decision analysis model may aid clinicians in guiding local practice, but outcomes may vary considerably between institutions. Availability of local services, or expertise, may be a more pressing issue in determining clinical practice than our findings. Furthermore, individual patient characteristics may determine which specific
modalities are most appropriate, regardless of cost concerns. Finally, patient preference will also guide clinical decision making. We attempted to account for the influence of patient preferences using measures of disutility to obtain cost-effectiveness values, but disutility has not been examined previously and should be included in future studies.

CONCLUSIONS

The costs of EBUS-TBLB and CT-PNB to evaluate PPL appear to be equivalent, but specific clinicoradiologic factors known to influence procedural outcomes will influence cost comparisons. Use of disutility scores to obtain QALY values did not significantly alter the outcome of cost-comparisons. Cost-minimization relies on minimizing ‘downstream’ care costs. As a result, clinical acumen and incorporation of published data regarding influence of clinicoradiologic factors on procedural outcomes are likely to identify the most cost-beneficial diagnostic strategy. Further evaluation of patient preferences and their influence on cost-effectiveness are required.
Sources of support: DPS is supported by a Post-graduate research scholarship from the National Health & Medical Research Council of Australia.

Conflicts of Interest: No authors have any conflicts of interest to disclose
Table 1. Model input data: Hospital costs associated with uncomplicated procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n</th>
<th>Median cost</th>
<th>Updated mean cost (±SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS-TBLB</td>
<td>12</td>
<td>$1,318</td>
<td>$1,572 ± $232</td>
</tr>
<tr>
<td>CT-PNB</td>
<td>12</td>
<td>$1,688</td>
<td>$1,569 ± $244</td>
</tr>
</tbody>
</table>

All procedures completed as day-admission cases

*based on local Health Price Index of 3%/year.[15]
**Table 2. Model input data:** Hospital costs associated with complicated procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>complication</th>
<th>management</th>
<th>Length of stay</th>
<th>Updated cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EBUS-TBLB</strong></td>
<td>Small self-limiting pneumothorax</td>
<td>Conservative#</td>
<td>0</td>
<td>$1,941</td>
</tr>
<tr>
<td><strong>CT-PNB</strong></td>
<td>Small self-limiting pneumothorax</td>
<td>Conservative#</td>
<td>0</td>
<td>$1,952</td>
</tr>
<tr>
<td><strong>CT-PNB</strong></td>
<td>Small self-limiting pneumothorax</td>
<td>Conservative#</td>
<td>0</td>
<td>$1,791</td>
</tr>
<tr>
<td><strong>CT-PNB</strong></td>
<td>Hydropneumothorax</td>
<td>Conservative#</td>
<td>0</td>
<td>$1,905</td>
</tr>
<tr>
<td><strong>CT-PNB</strong></td>
<td>Haemothorax, pulmonary haemorrhage</td>
<td>Admission for analgesia and observation</td>
<td>3</td>
<td>$4,932</td>
</tr>
</tbody>
</table>

# conservative management comprised discharge home if the patient was clinically stable and pneumothorax not enlarging on repeat CXR at 4 hours. Costs include performance of procedure and the cost of next-day CXR and clinical review.

*based on local Health Price Index of 3%/year.[15]*
Table 3. Model input data: Parameter values used for variables in performance of decision tree analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-case value</th>
<th>Range utilized for sensitivity analysis</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS-TBLB sensitivity</td>
<td></td>
<td></td>
<td>[10, 17]</td>
</tr>
<tr>
<td><em>Malignant PPL</em></td>
<td>0.86</td>
<td>0.60 – 0.88</td>
<td></td>
</tr>
<tr>
<td><em>Benign PPL</em></td>
<td>0.50</td>
<td>0.50 – 0.80</td>
<td></td>
</tr>
<tr>
<td>CT-PNB sensitivity</td>
<td></td>
<td></td>
<td>[2, 10]</td>
</tr>
<tr>
<td><em>Malignant PPL</em></td>
<td>0.93</td>
<td>0.65 – 0.94</td>
<td></td>
</tr>
<tr>
<td><em>Benign PPL</em></td>
<td>0.56</td>
<td>0.50 – 0.90</td>
<td></td>
</tr>
<tr>
<td>CT-PNB complication rate</td>
<td>0.27</td>
<td>0.14 – 0.43</td>
<td>[2, 10]</td>
</tr>
<tr>
<td>Prevalence of malignancy</td>
<td>0.87</td>
<td>0.5 – 0.95</td>
<td>[10, 17]</td>
</tr>
<tr>
<td>Mean cost of complications</td>
<td>$327</td>
<td>$300 – $3,363</td>
<td><em>Current study</em></td>
</tr>
</tbody>
</table>
### Table 4. Model input data: Values used in Monte Carlo simulation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values utilized in triangular probabilistic calculation</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lowest</td>
<td>likeliest</td>
</tr>
<tr>
<td>EBUS-TBLB sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant PPL</td>
<td>0.60</td>
<td>0.79</td>
</tr>
<tr>
<td>Benign PPL</td>
<td>0.50</td>
<td>0.75</td>
</tr>
<tr>
<td>CT-PNB sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant PPL</td>
<td>0.82</td>
<td>0.90</td>
</tr>
<tr>
<td>Benign PPL</td>
<td>0.56</td>
<td>0.80</td>
</tr>
<tr>
<td>CT-PNB complication rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.14</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean cost of complications</td>
<td>$300</td>
<td>$654</td>
</tr>
</tbody>
</table>
**Table 5.** Calculated costs of the two diagnostic approaches

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Base case cost</th>
<th>Range*</th>
<th>Monte Carlo simulation results</th>
<th>Patient scenario outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) 10(^{th}) centile Median 90(^{th}) centile</td>
<td>Scenario 1 Scenario 2 Scenario 3 Scenario 4</td>
</tr>
<tr>
<td>EBUS-TBLB</td>
<td>$2,748</td>
<td>$2,719 – $3,534</td>
<td>$2,843 (301) $2,482 $2,814 $3,253</td>
<td>$2,482 $2,482 $2,814 $2,814</td>
</tr>
<tr>
<td>CT-PNB</td>
<td>$2,724</td>
<td>$2,683 – $3,868</td>
<td>$2,935 (340) $2,515 $2,911 $3,385</td>
<td>$2,515 $2,515 $2,911 $2,911</td>
</tr>
</tbody>
</table>

*range of costs based on diagnostic sensitivity (malignancy) range recorded in table 3 for each procedure.

Scenarios outlined in Methods section under ‘Sensitivity analysis’
Table 6. Evidence-based summary of clinicoradiologic features affecting diagnostic yield & complication rates following invasive biopsy of peripheral pulmonary lesions

<table>
<thead>
<tr>
<th>Radiologic characteristic</th>
<th>Pleural contact</th>
<th>Lesion size</th>
<th>Lobar position</th>
<th>Proximity to pulmonary hilum</th>
<th>COPD</th>
<th>Bronchus sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic accuracy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBUS-TBLB</td>
<td>↓ [27, 28]</td>
<td>↓ [37]</td>
<td>↑ [14, 40]</td>
<td>↓/↑ [14]</td>
<td>↑/– [27, 28]</td>
<td>↑/– [32]</td>
</tr>
<tr>
<td>CT-PNB</td>
<td>–</td>
<td>↓ [33, 35, 38, 39]</td>
<td>–/↓ [31, 33, 41, 42]</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Complication rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBUS-TBLB</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CT-PNB</td>
<td>↓↓ [27, 43]</td>
<td>↑ [34, 36, 44]</td>
<td>–</td>
<td>↑/– [31, 45]</td>
<td>↑ [34, 36, 44-46]</td>
<td>↑↑* [30, 36, 43, 47, 48]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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. [34, 43, 45, 49, 50]

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
REFERENCES


36. Heyer CM, Reichelt S, Peters SA, Walther JW, Muller KM, Nicolas V. Computed tomography-navigated transthoracic core biopsy of pulmonary lesions:


Figure 1: Decision tree illustrating possible clinical pathways following selection of one either diagnostic approach.

PPL – peripheral pulmonary lesion

EBUS = endobronchial ultrasound

□ = decision node. *ie.* The clinician may choose any clinical pathway for an individual patient.

○ = chance node. *ie.* Patients may experience either outcome, based on chance. The proportion of patients following each pathway from a chance node is dependent on pre-defined clinical parameters (see table 3).

◇ = terminal node in decision pathway. *ie.* An individual patient has reached a definitive outcome in their diagnostic pathway.
Figure 2: Graphical representation of effect on expected cost of each procedure (Y-axis) during one-way sensitivity analysis (variation) in the cost of managing complications (X-axis) among the modelled population. EBUS-TBLB is cost-beneficial (ie. cheaper) if mean cost of complications exceeds $501 per episode.

Figure 3: Results of two-way sensitivity analysis (ie. alteration of two input parameters) are indicated by the pattern present on the graphs. The most cost-beneficial diagnostic pathway for the combination of the two varied parameters is indicated by the pattern present on the graph. Parameters varied are:

A) Cost of complications versus CT-PNB complication rate
B) Prevalence of malignancy in PPL *versus* diagnostic yield of EBUS-TBLB for benign PPL

C) Sensitivity of EBUS-TBLB for detection of malignancy *versus* sensitivity of CT-PNB for detection of malignancy

**Figure 4:** Disutility may be measured by the wait-tradeoff (WTO) technique. The most cost-effective procedure may then be determined on the basis of $/QALY. This graph illustrates the results of two-way sensitivity analysis, with cost-effectiveness measured according to disutility arising from procedural complications. A dynamic relationship is evident between the cost of complications and the complication rate of CT-PNB.