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DIAGNOSTIC APPROACHES TO SOLITARY PULMONARY NODULE (SPN)

MaHTAS
Malaysian Health Technology Assessment Section

MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH

DIAGNOSTIC APPROCHES TO *SOLITARY PULMONARY NODULE (SPN)*

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HTA Report

MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION (MaHTAS)
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH

HEALTH TECHNOLOGY ASSESSMENT REPORT

DISCLAIMER

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DISCLOSURE

EXECUTIVE
SUMMARY

Background

Solitary pulmonary nodule remain challenging for accurate localization and diagnosis in lung cancer management. Once identified, there are many strategies for diagnosis but implications rest on whether the lesion is benign or malignant. Conventional bronchoscopy have poor performance in locating and acquiring the required tissue. While percutaneous computed tomography (CT) guided biopsy or computerized-assisted transthoracic needle aspiration (TTNA) are currently the favoured diagnostic procedure, it was associated with complications such as pneumothorax and haemorrhage. Video-assisted thoracoscopic surgery (VATS) and open surgical biopsy are invasive, require general anaesthesia, and are therefore not a first-line approach. Fortunately, the last decade has been a game-changer in the arena of diagnostic bronchoscopy. The field of interventional pulmonary has blossomed with significant improvement in the guidance technology defined as guided bronchoscopy techniques for bronchoscopic sampling of SPN. This has the added benefit of simultaneous diagnosis and staging of lung cancer during a single procedure with lower risk of complications. Currently, there are still debates about which method to choose while cost is also an issue. It is necessary to know what type of SPN needs which type of bronchoscopic approaches since some of those techniques are limited to centres with expertise and require specific training for their use. Therefore, this HTA report was prepared in corresponding to the request made by Senior Consultant Pulmonologist from Serdang Hospital to assess the overall diagnostic performance of minimally invasive guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer in Malaysia.

Technical features

Development of guided bronchoscopy biopsy techniques has been a boon for the bronchoscopists. It is not a single technology but comprising of several technologies including virtual bronchoscopy (VB), navigation bronchoscopy (NB), and complementary technologies such as radial probe or radial endobronchial ultrasound (r-EBUS), ultrathin bronchoscopy (UTB), bronchoscopic transparenchymal nodule access (BTPNA), and electromagnetic transthoracic needle aspiration (ETTNA). In addition, the now commercially available robotic bronchoscopy platform has the potential to overcome the limitations of individual techniques while transbronchial lung biopsy with a cryoprobe, or cryobiopsy is a promising new bronchoscopic biopsy technique capable of obtaining larger and better-preserved samples than previously possible using traditional biopsy forceps.

Policy question

What is the appropriate biopsy approaches to SPN in the management of lung cancer in Malaysia?

Objective

   i.   To assess the diagnostic accuracy/ performance of using guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer.
   ii. To assess the safety aspect, particularly its adverse events (AEs) or complications.
   iii. To assess the organisational aspects and economic implication related to guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer.

Research questions

i.   How accurate is guided bronchoscopy techniques compared to conventional method for tissue biopsy of SPN?
ii. Is guided bronchoscopy biopsy techniques safe?
iii. What is the organisational issue and economic implication related with guided bronchoscopy biopsy techniques?

Methods

Literature search was conducted by an *Information Specialist* who searched for published articles pertaining to guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to January 2020, EBM Reviews - Health Technology Assessment (4th Quarter 2016), EBM Reviews - Cochrane Database of Systematic Review (2005 to January 2020), EBM Reviews - Cochrane Central Register of Controlled Trials (December 2019), and EBM Reviews - NHS Economic Evaluation Database (1st Quarter 2016). Parallel searches were run in PubMed, US FDA and INAHTA database. No limits were applied to the search. Detailed search strategy is as in **Appendix 3**. The last search was performed on 2nd March 2020. Additional articles were identified from reviewing the references of retrieved articles.

Results:

A total of **569** records were identified through the Ovid interface and PubMed while **18** were identified from references of retrieved articles. After removal of **seven** duplicates, **580** titles were found to be potentially relevant and were screened using the inclusion and exclusion criteria. Of these, **47** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the **47** full text articles, **25** full text articles were included. The **25** full text articles finally selected for this review comprised of **five** systematic review and meta-analysis, **one** systematic review, **six** randomised controlled trials (RCTs), **four** pre- and post-interventional studies, **six** case series, and **three** economic evaluation studies. The studies were conducted mainly in Japan, China, Korea, Malaysia, Australia, United States, Germany, Belgium, and Costa Rica.

Diagnostic accuracy/ performance

Overall, a diagnostic yield at 70.6% for r-EBUS showed promising results with a pooled sensitivity and specificity of 73% and 100%, respectively. When used in combination with VBN or UTB, the yield increased to 83.6% and 74.0%, respectively. When combined with ENB, diagnostic yield ranged from 60.0% to 94.0% with sensitivity of 82.0% and specificity of 100%. The diagnostic odds ratio (DOR) value of 97.36 and area under the receiver operator characteristic (ROC) curve was higher to 0.98 suggesting an overall high diagnostic accuracy by ENB-guided diagnosis in peripheral pulmonary nodules (PPLs). However, r-EBUS alone or combined with VBN or UTB had lower diagnostic yield as compared to CT-guided percutaneous needle biopsy (CT-PNB; 86.1%) or CT-guided transthoracic needle biopsy (CT-TNB; 96.0%). Apart from that, BTPNA procedure of SPNs was feasible with 83% successful rate. The diagnostic yield for ETTNA alone was 83% and increased to 87% when ETTNA was combined with ENB (p=0.0016). When ETTNA and ENB were performed with r-EBUS for complete staging, the yield increased further to 92% (p=0.0001). Navigation success was also achieved with those using robotic bronchoscopy which demonstrated an overall diagnostic yield between 69.1% and 93.0%, with sensitivity and specificity of 88.2% and 63.6%, respectively. Cryobiopsy on the other hand significantly increased the diagnostic yield between 69.0% and 74.2% as compared to conventional forceps or standard transbronchial biopsy (TBB), with sensitivity

and specificity of 61% and 100%, respectively. The size of the tissue samples obtained with the cryoprobe was significantly larger than those acquired with conventional forceps (11.17 mm^2 versus 4.69 mm^2; p<0.001).

Safety

Compared to percutaneous CT-guided biopsy or computerized-assisted TTNA, guided bronchoscopic biopsy techniques are generally well-tolerated with reported complication rates ranging from 0.0% to 5.0%. Similar to standard bronchoscopy, the spectrum and rate of complications are procedure-related with no severe or moderate AEs except for two main complications, pneumothorax and haemorrhage while less frequent complications include bleeding and respiratory failure. Most of AEs reported could be resolved by standard care and no deaths were related to the procedure, device or associated tools.

Organisational

Total procedure or operation time (median) varied widely based on the guided bronchoscopic biopsy techniques, ranging from 21.0 to 24.0 minutes in the VBN and 46.0 to 52.0 minutes for ENB. In any case, ETTNA seemed to have the longest procedure time of 72.5 minutes as compared to BTPNA (39.8 minutes), while it was between 58.6 and 63.9 minutes for those obtained using robotic bronchoscopy. Cryobiopsy recorded a significantly longer duration at 50.0 minutes compared to 40.5 minutes in forceps biopsy. Patients were discharged within one day with a mean length of stay ranged from five to six hours following the robotic bronchoscopy procedure. As for learning curve, procedure time of BTPNA is comparable to either transthoracic CT-guided biopsy or standard TBB after only eight procedures. Meanwhile, the mean procedure time of the first and last five cases using robotic bronchoscopy was approximately 95.0 and 61.0 minutes, respectively.

Economic implication

There were three studies on cost-analysis retrieved. The first revealed that an ENB with biopsy was more expensive than CT-guided biopsy strategy (mean costs per biopsy were USD$6,633 [95% CI: USD$1,518, USD$18,511] versus USD$2,913 [95% CI: USD$1,248, USD$18,241]). However, costs were decreased in both arms in the serial biopsy strategy; the average cost of the ENB biopsy strategy falls to USD$2,406 (95% CI: USD$1,518, USD$19,759) whereas the average cost decreases to USD$1,934 (95% CI: USD$1,248, USD$19,759) in CT-guided biopsy strategy. Second study reported the costs of r-EBUS-guided transbronchial lung biopsy (r-EBUS-TBLB) and CT-PNB appear to be equivalent. Initial evaluation with CT-PNB was cost-beneficial in comparison to r-EBUS-TBLB by a margin of AU$24 (CT-PNB AU$2,724 versus r-EBUS-TBLB AU$2,748). Finally, the third study indicated that NB and CT-fine needle aspiration (CT-FNA) diagnostic strategies were more cost-effective than VATS biopsy or ^{18}F-fluoro-deoxyglucose positron emission tomography (FDG-PET) in populations with lung cancer prevalence greater than 50% (incremental cost-effectiveness ratio [ICER] per quality adjusted life year [QALY]: NB=USD$4,602; CT-FNA=USD$3,998; VATS=USD$43,578).

Conclusion

The availability of evidence differs between guided bronchoscopy biopsy techniques, and most was related to the use of r-EBUS. There was fair to good level of retrievable evidence to suggest that the combined use of navigation bronchoscopy (virtual or electromagnetic) with r-EBUS improves overall test performance characteristics beyond either technique alone but lower than percutaneous CT-guided biopsy or computerized-assisted TTNA; typically varying with lesion size, location, and equipment used as well as other factors including the presence of a bronchus sign, biopsy technique, and institution expertise or learning curve of the operator. The major strength of guided bronchoscopic biopsy techniques is clearly its safety profile, especially regarding the risk of procedure-related pneumothorax and haemorrhage, which is about 10 times lower than conventional bronchoscopy or CT-guided biopsy. Given the existing evidence, cost of managing complications was the main factor that influenced cost-analysis results. For this reason, guided bronchoscopy biopsy techniques was found to be cost-effective when a sequential diagnostic strategy were applied and when cancer prevalence was high.

Recommendation

Based on the above review, guided bronchoscopy techniques mainly using a combination of VBN or ENB with r-EBUS are an appropriate biopsy approaches to SPN and may be used for management of patients with lung cancer in selected centres in MOH hospitals, provided local expertise is available. Although other techniques appears promising and has the potential to be considered as valuable option, they are rarely used and their role remains largely investigational while cost implication should also be considered. Refinement of selection criteria for the respective techniques may have a significant impact on the results for the patient and close cooperation between bronchoscopists, pulmonologists, and radiologist is an essential step in achieving this aim.

TABLE OF **CONTENTS**

Abbreviations

3-D	Three-dimensional
AEs	Adverse events or adverse effects
AUC	Area under the curve
BR	Bronchoscopic
BTPNA	Bronchoscopic transparenchymal nodule access
CASP	Critical Appraisal Skills Programme
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CT-FNA	CT-guided fine-needle aspiration
CT-PNB	CT-guided percutaneous needle biopsy
CT-TNB	CT-guided transthoracic needle biopsy
CXR	Chest radiography
DOR	Diagnostic odds ratio
EBUS-GS	Endobronchial ultrasonography with a guide sheath
ENB	Electromagnetic navigation bronchoscopy
ETTNA	Electromagnetic transthoracic needle aspiration
FDG-PET	^{18}F-fluoro-deoxyglucose positron emission tomography
GS	Guide sheath
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
LR+	Positive likelihood ratio
LR-	Negative likelihood ratio
MaHTAS	Malaysian Health Technology Assessment Section
MNCR	Malaysia National Cancer Registry
MOH	Ministry of Health
NB	Navigation bronchoscopy
NLST	National Lung Screening Trial
NPV	Negative predictive value
PC	Percutaneous
PL	Pulmonary lesion
POE	Point of entry
PPL	Peripheral pulmonary nodules/ peripheral lung lesions
PPV	Positive predictive value
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
r-EBUS	Radial probe or radial endobronchial ultrasound
RES	Robotic Endoscopy System
SPN	Solitary pulmonary nodule
TB	Thin bronchoscope
TBLB	Transbronchial lung biopsy
TBLC	Transbronchial lung cryobiopsy
TTNA	Transthoracic needle aspiration
US FDA	United States Food and Drug Administration
UTB	Ultrathin bronchoscopy
VATS	Video-assisted thoracoscopic surgery
VB	Virtual bronchoscopy
VBN	Virtual bronchoscopy navigation
WHO	World Health Organization

HEALTH TECHNOLOGY ASSESSMENT (HTA)
DIAGNOSTIC APPROACHES TO SOLITARY PULMONARY NODULE (SPN)

1.0   BACKGROUND

Epidemiology

Worldwide, lung cancer is the most common malignancy and continues to be the leading cause of cancer-related deaths in the past few decades. In 2018, a total of 2.1 million new cases were estimated, contributing about 11.6% of the total cancer incidence burden.[1-2] According to the most recent data by Malaysia National Cancer Registry (MNCR) for the incidence year of 2012-2016, lung cancer was the third (9.8%) most common cancer in the country, the second (14.9%) most common cancer in males, and the fifth (5.6%) most common in females.[3] Despite advances in diagnostic approaches, staging and treatment, and also the fact that early-detected lung cancer is curable in patients with good performance status, the overall 5-year survival for lung cancer has not significantly changed and is estimated to be around 17.8%. Lack of early detection and accurate localization of lesion for tissue acquisition remains one of the biggest challenges in lung cancer management.[4]

Pathophysiology

A solitary pulmonary nodule or *coin lesion* has been defined on imaging as a round or oval opacity ≤3 cm in diameter that is completely surrounded by pulmonary parenchyma, does not touch the hilum or mediastinum, and not associated with atelectasis, lymphadenopathy or pleural effusion. Peripheral pulmonary nodules (also known as peripheral lung lesions, PPLs) with a diameter >3 cm are classified as pulmonary masses and differ from SPN. The prevalence of malignancy in SPNs depends on the clinical setting, ranging from 2.0% to 86.0% for incidentally discovered nodules both on chest radiography (CXR) (**Figure 1**) and computed tomography (CT) (**Figure 2**), and from 1.1% to 12.0% for those that are screen detected.[5-10]
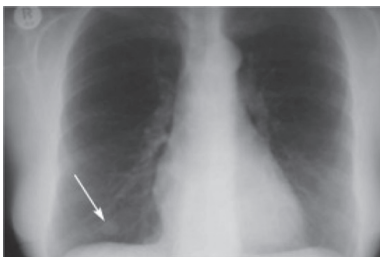
Figure 1: A SPN (arrow) identified in the right lower zone on a CXR.

Figure 2: A SPN (arrow) identified in the left upper lobe on a thoracic CT scan with a background of fibrotic changes.

Management of SPN

The major question that follows detection of a pulmonary nodule is a diagnostic dilemma faced by many clinicians. The differential diagnosis may be broad, but implications rest on whether the lesion is benign or malignant. Indeed, a recently published multicentre National Lung Screening Trial (NLST) has shown the benefit of early detection in a selected high-risk cohort of patients (current and former smokers). The trial revealed that screening with low-dose CT scan results in a relative reduction of 20% cancer-specific mortality; however, 96.4% of nodules detected are false positive and 90.4% of those required further diagnostic investigations.[11] Similarly, among 12,029 nodules found in a large Canadian study, only 144 (1.1%) were malignant.[12] Therefore, the management of a SPN should aim to identify malignancy as fast as possible in order to provide the option of potentially curative surgical treatment, whilst avoiding invasive diagnostic procedures in case of benign lesions.[9, 13-14]

Diagnosis

The gold standard of lung cancer diagnosis is to collect a specimen from the lesion and diagnose it pathologically, an approach for which surgical biopsy, transthoracic needle aspiration (TTNA), and transbronchial biopsy are available for selection. Choosing the most appropriate biopsy technique for suspected peripheral nodule, however, can be a challenging clinical risk–benefit decision and factors such as lesion size, location, patient co-morbidities including emphysematous changes around the lesion, respiratory function, and the pre-test probability (prevalence) of malignancy must be taken into account. Although routine flexible bronchoscopy has been a conventional method to evaluate peripheral lung nodule, it is of limited diagnostic value [15] in locating and acquiring the required tissue with the diagnostic yield ranging from 20% to 84%.[16-18] Success is further compromised if the lesion is <2 cm, due to the inability to go beyond the subsegmental level and to steer endobronchial accessories directly into the lesion.[18] Similarly, while percutaneous CT-guided biopsy or computerized-assisted TTNA are currently the favoured diagnostic procedure, it was associated with complications (pneumothorax and haemorrhage) and are highly operator-dependent. Video-assisted thoracoscopic surgery (VATS) and open surgical biopsy are the most reliable; however, there are invasive, require general anaesthesia, and therefore not a first-line approach for patients with lung nodules suspicious for cancer.[19]

To overcome such problems, several innovative navigation methods that offer guidance through the tracheobronchial tree during bronchoscopy to help reach and biopsy the SPN have recently been developed. The result has been the development of a platform broadly defined as guided bronchoscopy techniques. It is not a single technology but comprising of several technologies including virtual bronchoscopy (VB), navigation bronchoscopy (NB), and complementary technologies such as radial probe or radial endobronchial ultrasound (r-EBUS), ultrathin bronchoscopy (UTB), bronchoscopic transparenchymal nodule access (BTPNA), and electromagnetic transthoracic needle aspiration (ETTNA). On top of that, the now commercially available robotic bronchoscopy platform has the potential to overcome the limitations of individual techniques while transbronchial lung biopsy with a cryoprobe, or cryobiopsy is a promising new bronchoscopic biopsy technique capable of obtaining larger and better-preserved samples than previously possible using traditional biopsy forceps.[20-22]

With so many tools available, there are still debates about which method to choose while cost is also an issue. Therefore, it is necessary to know what type of SPN needs which type of bronchoscopic approaches since some of those techniques are limited to centres with expertise and require specific training for their use. This HTA report was prepared in corresponding to the request made by Senior Consultant Pulmonologist from Serdang Hospital to assess the overall diagnostic performance of minimally invasive guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer in Malaysia.

2.0 TECHNICAL FEATURES

2.1 Virtual bronchoscopy (VB)

Virtual bronchoscopy is a non-invasive form of bronchoscopy. It is not an endoscopic procedure, but rather an imaging modality that uses non-contrast-enhanced CT images to reconstruct the airways in a three-dimensional (3-D) manner producing images that appear similar to those visualized during real-time bronchoscopy. While VB itself cannot acquire samples, it can be used to pre-plan future procedures or as a navigational tool for biopsy.[19, 23]

2.2 Navigation bronchoscopy (NB)

Navigation bronchoscopy uses a navigational system to guide instruments such as flexible or ultrathin bronchoscope through the airways to a target lesion for biopsy. Navigational systems can be virtual (virtual bronchoscopy navigation, VBN) or electromagnetic (electromagnetic navigation bronchoscopy, ENB): [19, 23]

2.2.1 Virtual bronchoscopy navigation (VBN)

Virtual bronchoscopy navigation is a technique for guiding a bronchoscope using VB images along the bronchial route to a peripheral target lesion in the lung. Usually, VBN is combined with fluoroscopy, CT scan, or endobronchial ultrasonography with a guide sheath (EBUS-GS) to confirm the arrival of the biopsy instrument at the lesion.[19, 23]

2.2.2 Electromagnetic navigation bronchoscopy (ENB)

An ENB is a relatively new navigation method that utilizes electromagnetism. An electromagnetic field is prepared around the patient's chest, and biopsy instruments are guided to a pulmonary lesion based on the positional information of the electromagnetic micro-centre and CT information acquired beforehand. The most widely used and reported system is superDimensions® (Covidien, Mansfield, MA, USA) which acquired European CE certification as an electromagnetic navigation system in 2002 and approval from the US Food and Drug Administration (US FDA) in 2004. Two other navigation systems are commercially available, namely The LungPoint Virtual Bronchoscopic Navigation System (Bronchus Technologies, Inc., Mountain View, CA, USA) and the SpiNDrives® (Veran Medical Technologies, Inc., St. Louis, MO, USA).[19, 24]

2.3 Radial probe or radial endobronchial ultrasound (r-EBUS)

Radial probe or radial endobronchial ultrasound is preferred for sampling nodules and masses within the lung periphery since many SPN lesions are located outside bronchial lumen. There are two main types of EBUS: while linear or convex EBUS is used for sampling mediastinal and hilar lymph nodes, r-EBUS is used for PPLs. The technique involves driving the bronchoscope close to the lesion through the maze of airways as planned based on the CT scan. Once the tip of bronchoscope is in vicinity of the PPL and cannot be advanced any further, the r-EBUS probe covered with the guide sheath (GS) is advanced through the working channel of the bronchoscope towards the lesion. The r-EBUS provides a high resolution 360-degree view of the surrounding lung. The characteristic ultrasound features of normal and abnormal lung tissue help identify the lesion. At this point, the r-EBUS probe is withdrawn while the GS is left in place as an extended working channel. Biopsy instruments are then advanced through the GS to the lesion to obtain tissue samples.[19, 25-26]

2.4 Ultrathin bronchoscopy (UTB)

In general, the use of UTB is fairly uncommon since the working channels are small and thus can only accommodate smaller biopsy instruments. Although there is no clear definition of UTB, those with a 3-mm or smaller outer diameter are called ultrathin. These can be used similarly to normal-size bronchoscopes, but should be carefully operated because they are readily broken due to their thinness. Compared with normal-size bronchoscopes, an UTB can be advanced to the peripheral bronchus under direct vision and is useful for cases difficult to diagnose by conventional bronchoscopy.[19, 27-28]

2.5 Bronchoscopic transparenchymal nodule access (BTPNA)

In this techniques, the nodules are accessed through a transparenchymal "off-road" approach that is not dependent on the need to have an airway leading into the lesion. A computer software-generated tunnelled path is created from the bronchial segments through the lung parenchyma directly to the PPLs. Bronchoscopic transparenchymal nodule access relies on the operator experience and the software to ensure that no major vessels are injured while tunneling through the lung parenchyma.[19]

2.6 Electromagnetic transthoracic needle aspiration (ETTNA)

This technology incorporates a unique electromagnetic guidance system allowing clinicians to track SPN and target them for ETTNA without utilizing real time CT in the operating room or bronchoscopy suite. Providing this capability allows the pulmonologist to perform initial lymph node staging with EBUS in the same procedural setting. This approach may provide a much needed intervention allowing physicians to utilize a multimodality approach in a single procedural setting to optimize diagnostic yield and limit complications.[29]

2.7 Robotic bronchoscopy

There are currently two systems available; one in development and other with FDA approval in 2018. These systems use a small robotic endoscope controlled by robotic steering devices under direct visualization by the operator. The bronchoscopes are advanced and steered using a separate control device. The system still requires thin slice CT scan data to plan the pathway and navigate to the desired target. Theoretical advantages of such technology include continuous endobronchial visualization and greater maneuverability of the tip of the bronchoscope with the ability to lock into a desired position.[19]

2.8 Transbronchial cryobiopsy

Transbronchial cryobiopsy, hereafter referred to simply as cryobiopsy, refers to the use of a cryoprobe to obtain larger tissue samples of peripheral lung tissue with the frozen tip allowing biopsy in a 360° direction, thus potentially achieving more effective biopsy in eccentrically and adjacently orientated lesions. The cryoprobe is advanced through the working channel of the bronchoscope into the peripheral lung and then activated for several seconds, causing surrounding parenchyma to rapidly freeze and adhere to the cryoprobe tip. Cryoprobe tip with frozen biopsy are then submerged in saline to rapidly thaw and release the biopsy from the cryoprobe, which is then removed from the working channel as the bronchoscope is re-introduced into the airway.[30]

3.0 POLICY QUESTION

What is the appropriate biopsy approaches to SPN in the management of lung cancer in Malaysia?

4.0 OBJECTIVE

4.1 To assess the diagnostic accuracy/ performance of using guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer.

4.2 To assess the safety aspect, particularly its adverse events (AEs) or complications.

4.3 To assess the organisational aspects and economic implication related to guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer.

The following research questions will be addressed:

  i. How accurate is guided bronchoscopy techniques compared to conventional method for tissue biopsy of SPN?

  ii. Is guided bronchoscopy biopsy techniques safe?

  iii. What is the organisational issue and economic implication related with guided bronchoscopy biopsy techniques?

5.0 METHODS

5.1. Literature search strategy

Literature search was conducted by an *Information Specialist* who searched for published articles pertaining to guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to January 2020, EBM Reviews - Health Technology Assessment (4th Quarter 2016), EBM Reviews - Cochrane Database of Systematic Review (2005 to January 2020), EBM Reviews - Cochrane Central Register of Controlled Trials (December 2019), and EBM Reviews - NHS Economic Evaluation Database (1st Quarter 2016). Parallel searches were run in PubMed, US FDA and INAHTA database. No limits were applied to the search. Detailed search strategy is as in **Appendix 3**. The last search was performed on 2nd March 2020. Additional articles were identified from reviewing the references of retrieved articles.

5.2. Study selection

Based on the policy question, the following inclusion and exclusion criteria were used:-

5.2.1 Inclusion criteria

a.	**Population**	Patients with solitary pulmonary nodule (SPN) or *coin lesion*, patients with or suspected lung cancer

b.	**Intervention**	Guided bronchoscopy biopsy techniques:
		  i. Virtual bronchoscopy (VB)
		  ii. Navigation bronchoscopy (NB): virtual bronchoscopy navigation (VBN) and electromagnetic navigation bronchoscopy (ENB)
		  iii. Radial probe or radial endobronchial ultrasound (r-EBUS)
		  iv. Ultrathin bronchoscopy (UTB)
		  v. Bronchoscopic transparenchymal nodule access (BTPNA)
		  vi. Electromagnetic transthoracic needle aspiration (ETTNA)
		  vii. Robotic bronchoscopy
		  viii. Transbronchial cryobiopsy

c.	**Comparator**	i. Conventional bronchoscopy
		  ii. Percutaneous CT-guided biopsy
		  iii. Video-assisted thorascopic surgery (VATS) or open surgical biopsy

d.	Outcomes	i. Diagnostic accuracy: *diagnostic yield, detection rate, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic odds ratio (DOR), receiver operator characteristic (ROC) curve, and area under the ROC curve (AUC)* ii. Safety: *mortality, AEs, complications* iii. Organisational issues: *hospital utilization (readmission, length of stay, general or local anaesthesia), procedural time points and training or learning curve* iv. Economic implications: *cost, cost-benefit, cost-effectiveness, cost-utility analysis*
e.	Study design	HTA reports, systematic review with/out meta-analysis, randomised controlled trial (RCT), pre-post intervention, diagnostic, cross-sectional, case series, economic evaluation studies
f.	Full text articles published in English	

5.2.2 Exclusion criteria

a.	Study design	Cohort, case-control, case report, animal study, laboratory study, narrative review
b.	Non English full text articles	

Based on the above inclusion and exclusion criteria, study selection were carried out independently by two reviewers. The titles and abstracts of all studies were assessed for the above eligibility criteria. If it was absolutely clear from the title and/or abstract that the study was not relevant, it was excluded. Full text article was retrieved for those title and abstract considered as relevant and if it was unclear from the title and/or abstract whether the study was relevant or not. Two reviewers assessed the content of the full text articles. Disagreement was resolved by discussion.

5.3 Quality assessment strategy

The methodological quality of all the relevant full text articles retrieved was assessed using the *Critical Appraisal Skills Programme (CASP)* [31] tool depending on the type of study design, and was conducted by two reviewers. *The Cochrane Collaboration's tool* for assessing risk of bias of RCT is an example of a component approach which is also use by MaHTAS. It is a two-part tool, addressing the six specific domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues). All full text articles were graded based on guidelines from the *U.S. / Canadian Preventive Services Task Force* (**Appendix 1**).[32-33]

5.4   Data extraction strategy

Data were extracted from included studies by a reviewer using a pre-designed data extraction form (*Evidence Table* as shown in **Appendix 4**) and checked by another reviewer. Disagreements were resolved by discussion and the extracted data was presented and discussed with the *expert committee*. The data extracted was as follows:

   i.   Details of methods including study design
   ii. Study population characteristics including age, trial inclusion and exclusion criteria
   iii. Details of intervention and comparator
   iv. Types of outcome measures including diagnostic accuracy of guided bronchoscopy biopsy techniques (diagnostic yield, detection rate, sensitivity, specificity, PPV, NPV, DOR, ROC curve, and AUC), safety (adverse events or complications related to guided bronchoscopy biopsy techniques), organisational issues (hospital utilization, procedural time points and training or learning curve), and economic implications of using guided bronchoscopy biopsy techniques (cost, cost-benefit, cost-effectiveness, and cost-utility).

5.5   Methods of data synthesis

Data on the diagnostic accuracy, safety, organizational, and economic implication of guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

6.0   RESULTS

Search results

An overview of the search is illustrated in **Figure 3.** A total of **569** records were identified through the Ovid interface and PubMed while **18** were identified from references of retrieved articles. After removal of **seven** duplicates, **580** titles were found to be potentially relevant and were screened using the inclusion and exclusion criteria. Of these, **47** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the **47** full text articles, **25** full text articles were included. A total of **22** full text articles were excluded since the studies were already included in systematic review and meta-analysis (n=17), irrelevant study design (n=1) and irrelevant intervention (n=4). The excluded articles are listed in **Appendix 5**.

The **25** full text articles finally selected for this review comprised of **five** systematic review and meta-analysis, **one** systematic review, **six** RCTs, **four** pre- and post-interventional studies, **six** case series, and **three** economic evaluation studies.

The studies were conducted mainly in Japan, China, Korea, Malaysia, Australia, United States, Germany, Belgium, Switzerland, and Costa Rica.
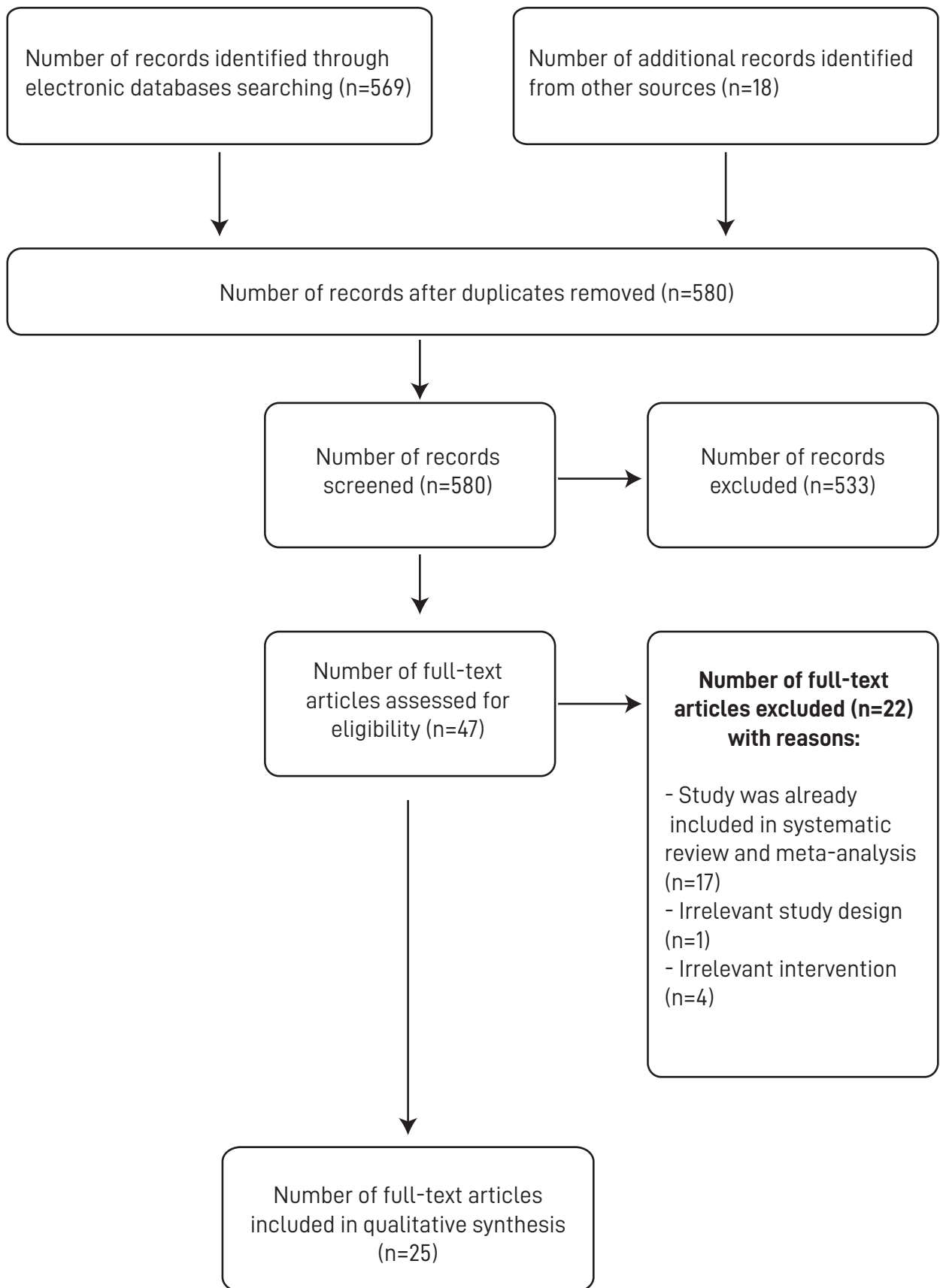
Number of records identified through electronic databases searching (n=569)

Number of addtional records identified from other sources (n=18)

Number of records after duplicates removed (n=580)

Number of records screened (n=580)

Number of records excluded (n=533)

Number of full-text articles assessed for eligibility (n=47)

Number of full-text articles excluded (n=22) with reasons:

- Study was already included in systematic review and meta-analysis (n=17)
- Irrelevant study design (n=1)
- Irrelevant intervention (n=4)

Number of full-text articles included in qualitative synthesis (n=25)

Figure 3: Flow chart of retrieval of articles used in the results

Risk of bias assessment:

The risk of bias in the included studies were assessed using domain-based evaluation. For RCT, Cochrane Collaboration Tool for assessing risk of bias comprising of six domain was used whereas for other studies, the tools that are being used by MaHTAS to assess the risk of bias are adapted from the CASP checklist. This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates low risk of bias
?	indicates unclear risk of bias
-	Indicates high risk of bias

Overall, the risk of bias were low for SRs, RCTs, and economic evaluation studies. Although some of the RCTs and the pre- and post- interventional studies in this review were non-blinded due to the nature of the interventions under investigation, there were not leading to bias or classified as being at a high risk of performance bias. Besides, most of the studies were limited by the sample size or small case number. The results of risk of bias of included studies are summarised in **Figure 4.1 to 4.4**

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Gex G 2014 [37]	+	+	+	+
Zhang W 2015 [38]	+	+	+	+
Steinfort DP 2011 [40]	+	+	+	+
Ali MS 2017 [41]	+	+	+	+
Wang Memoli JS 2012 [43]	+	+	**-**	+
Han Y 2018 [44]	+	+	+	+

Figure 4.1: Assessment of risk of bias of systematic review (CASP)

Criteria assessed	Adequate sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)	Free of other bias
Ishida T 2011 [33]	+	+	+	+	+	+
Asano F 2013 [34]	+	+	+	+	+	+
Bo L 2019 [35]	+	+	+	+	+	+
Xu C 2019 [36]	+	?	?	+	+	+
Wang W 2018 [42]	+	+	?	+	+	+
Oki M 2015 [45]	+	+	?	+	+	+

Figure 4.2: Assessment of risk of bias of RCT

Criteria assessed	Folch EE (NAVIGATE) 2018 [39]	Herth F 2015 [46]	Harzheim D 2016 [47]	Yarmus L 2016 [29]
Question or objective clearly stated?	+	+	+	+
Eligibility/selection criteria for study population clearly described?	+	+	+	+
Were participants representative for those who would be eligible for the test/service/intervention in the population of interest?	+	+	+	+
Were all eligible participants that met the prespecified entry criteria enrolled?	+	+	+	+
Sample size sufficiently large to provide confidence in findings?	+	-	-	-
Test/service/intervention clearly described or delivered consistently?	+	+	+	+
Outcome measures prespecified, valid, reliable, and assessed consistently?	+	+	+	+
People assessing the outcome measures blinded to participants exposure/interventions?	-	-	-	-
Loss to follow-up ≤ 20%? Accounted for in the analysis?	+	+	+	+
Statistical methods examine changes in outcome measures from before to after intervention? P value?	+	?	?	+
Outcome measures taken multiple times before and after intervention? Use interrupted time-series design?	?	?	?	?
If intervention conducted at group level, did statistical analysis take into account of individual level data to determine effects at group level?	?	?	?	?

Figure 4.3: Assessment of risk of bias of pre- and post-interventional studies with no control (NIH)

Criteria assessed	Dale CR 2012 [56]	Steinfort DP 2013 [57]	Deppen S 2014 [58]
A well-define question posed?	+	+	+
Comprehensive description of competing alternative given?	+	+	+
Effectiveness established?	+	+	+
Effects of intervention identified, measured and valued appropriately?	+	+	+
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	+	+	+
Costs and consequences adjusted for different times at which they occurred (discounting)?	+	+	+
Results of the evaluation?	+	+	+
Incremental analysis of the consequences and costs of alternatives performed?	+	+	+
Sensitivity analysis performed?	+	+	+

Figure 4.4: Assessment of risk of bias of economic evaluation (CASP)

6.1 DIAGNOSTIC ACCURACY/ PERFORMANCE OF GUIDED BRONCHOSCOPY BIOPSY TECHNIQUES:

6.1.1 Navigation bronchoscopy: virtual bronchoscopy navigation (VBN)

To demonstrate the usefulness of VBN system, three multicentre RCTs have been performed. Ishida T et al. (2011) randomly allocated 200 patients with PPLs ≤3 cm to a VBN-assisted (VBNA) and a non-VBN-assisted (NVBNA) group, according to lesion size and the skill of the operators. A thin bronchoscope (TB) with an outer diameter of 4 mm was guided by a VBN system in the VBNA group and using axial CT images as a reference in the NVBNA group. Biopsy was performed concomitantly with r-EBUS with a guide sheath (r-EBUS-GS) under x-ray fluoroscopy. They found that the diagnostic yield was significantly higher for the VBNA group than for the NVBNA group (80.4% versus 67.0%; p=0.032).[33, level I]

Asano F et al. (2013) further evaluated the value of VBN system by randomly assigned 350 patients with PPLs ≤3 cm into two groups: an ultrathin bronchoscope (UTB) with an outer diameter of 2.8 mm was guided using a VBN system in the VBNA group, and using axial CT images as a reference in the NVBNA group. Since the working channel of the UTB was thin (1.2 mm), r-EBUS probe could not be inserted. Thus, the investigators performed biopsy under fluoroscopy in both groups. There was no significant difference in the diagnostic yield between the VBNA group (67.1%) and the NVBNA group (59.9%; p=0.173). The subgroup analysis, however, showed that the diagnostic yield was significantly higher in the VBNA group than in the NVBNA group for right upper lobe lesions (81.3% versus 53.2%; p=0.004); lesions invisible on posterior–anterior radiographs (63.2% versus 40.5%; p=0.043); and lesions in the peripheral third of the lung field (64.7% versus 52.1%; p=0.047).[34, level I]

In another multicentre, multi-arm RCT by Bo L et al. (2019), a total of 1,010 patients were randomly divided into one of three groups: a traditional non-guided bronchoscopy biopsy (NGB group), r-EBUS-GS guided bronchoscopy biopsy (r-EBUS-GS group), and a guided bronchoscopy biopsy that combined r-EBUS-GS with VBN (combined group). The study indicated that the r-EBUS-GS and combined groups (r-EBUS-GS + VBN) had a significantly higher diagnostic yield (72.3% and 74.3%) than the NGB group (41.2%) (p<0.01). The ultrasonic probe location significantly affected the diagnostic yields in the r-EBUS-GS and combined groups. The diagnostic yield was approximately 86.8% if the probe was internal to the nodule before the biopsy and when the probe was near or outside the nodule, the diagnostic yields were only 64.5% and 37.0%, respectively. The diagnostic yield for PPLs >20 mm in diameter in this trial was significantly higher than that for those <20 mm in diameter.[35, level I]

Most recently, Xu C et al. (2019) conducted a small RCT to compare a combination of VBN and r-EBUS guided bronchoscopy with r-EBUS alone among 115 patients with SPN. Overall diagnostic yield between the VBN + r-EBUS group and the r-EBUS group were 83.6% and 66.7%, respectively. In subgroup analysis, diagnostic yield of both groups were lower in lesions diameter <20 mm than ≥20 mm. However, the diagnostic yield was higher in the r-EBUS + VBN group for lesions ≤20 mm in diameter than the r-EBUS group (80.0% versus 53.6%, respectively, p=0.041). There were also no significant difference in diagnosis rate between the two groups with regards to malignant lesions, benign lesions, and different location lesions.[36, level II-1]

6.1.2   Navigation bronchoscopy: electromagnetic navigation bronchoscopy (ENB)

To date there have been two systematic reviews and one clinical trial published on the role of ENB in diagnosis lung nodules. In 2014, Gex G et al. performed a meta-analysis which included 15 trials with 1,033 lung nodules or masses in 971 patients. Analysis of all studies demonstrated an accessibility rate or successful navigation toward PPLs with ENB of 97.4% (95% confidence interval [CI]: 95.4, 98.5). The pooled diagnostic yield was 64.9% (95% CI: 59.2, 70.3) while diagnostic accuracy was analysable in 14 trials and reached 73.9% (95% CI: 68.0, 79.2). The overall sensitivity of ENB to detect cancer was 71.1% (95% CI: 64.6, 76.8). The accuracy to determine the correct malignancy status ranged from 66.7% to 98.0%, leading to a pooled accuracy for malignancy of 78.6% (95% CI: 72.8, 83.4). The NPV of ENB for cancer was 52.1% (95% CI: 43.5, 60.6). Univariate analyses identified six statistically significant variables: location of the lower lobe correlated with decreased yields whereas greater nodule size, presence of a bronchus sign, lower registration error (AFTRE), nodule visualization with r-EBUS, and catheter suction technique were associated with increased yields.[37, level II-2]

Zhang W et al. (2015) updated the meta-analysis by Gex G et al. by looking at 17 studies consisting of 1,106 patients with PPLs. They found that the diagnostic yield ranged from 60% to 94%. The pooled sensitivity, specificity, positive likelihood ratios (LRs+), negative likelihood ratios (LRs-), and diagnostic odds ratios (DORs) of ENB was 82%, 100%, 18.67, 0.22, and 97.36, respectively. The area under the curve (AUC) for the summary receiver operating characteristic curves (SROC) was 0.9786, suggesting an overall high diagnostic accuracy by ENB-guided diagnosis in PPLs. Like the previous meta-analysis, similar statistically significant variables were identified.[38, level II-2]

NAVIGATE is a large multicentre, single arm study that evaluated ENB using the superDimension® navigation system. A total of 1,215 consecutive subjects were enrolled at 29 academic and community sites in the United States. Follow-up was completed in 98.9% subjects (1,202 of 1,215) at 1-month and 80.3% (976 of 1,215) at 12 months. Among the 1,157 lung lesion biopsy cases, navigation was successful and tissue was obtained in 94.4% (1,092 of 1,157). The 12-month diagnostic yield was 72.9%. Pathology results of the ENB-aided tissue samples showed malignancy in 44.3% (484 of 1,092) and were negative in 55.7% (608 of 1,092). As of 12 months, 284 initially negative outcomes were considered true negative and 220 were false negative. Hence, sensitivity, specificity, PPV, and NPV for malignancy were 69%, 100%, 100%, and 56%, respectively. Multivariate predictors of increased diagnostic yield were procedure time <60 minutes, use of <3 biopsy tools, lymph node sampling during the ENB procedure, biopsy of multiple lesions, and presence of a bronchus sign.[39, level II-2]

6.1.3   Radial probe or radial endobronchial ultrasound (r-EBUS)

The diagnostic yield and factors affecting the performance of r-EBUS have been extensively evaluated, although most of these studies have been small. The first meta-analysis specifically evaluating r-EBUS was published by Steinfort DP et al. in 2011. They aimed to determine point sensitivity and specificity for the diagnosis of peripheral lung cancer. A total of 16 studies with 1,420 patients were included. The reference standard was confirmation by histology of surgically obtained specimens or close clinical follow-up for at least six months. Based on meta-analysis, r-EBUS had point sensitivity of 0.73 (95% CI: 0.70, 0.76) and point specificity of 1.00 (95% CI: 0.99, 1.00). Diagnostic odds ratio was 103.75 (95% CI: 46.4, 231.7), correspond to a LR+ of 26.84 (95% CI: 12.60, 57.20) and a LR- of 0.28 (95% CI: 0.23, 0.36). The yield of the technique improves as the prevalence of malignancy and the size of the nodule increase (77.7% for >20 mm versus 56.3% for ≤20 mm).[40, level II-2]

Ali MS et al. (2017) conducted the largest meta-analysis to date, assessing the performance of r-EBUS for diagnosing PPLs using data from previously published r-EBUS studies. Fifty-seven studies with a total of 7,872 lesions were included. Overall weighted diagnostic yield for r-EBUS was 70.6% (95% CI: 68.0, 73.1). Four factors were shown to impact the diagnostic yield: size of PPL (75.7% for >2 cm versus 60.5% for ≤2 cm), its nature (72.4% for malignant versus 60.2% for benign), presence of a bronchus sign on CT scan (76.5% if present versus 52.4% if absent), and position of the r-EBUS probe with regards to the lesion (78.7% when the probe reached within the lesion versus 52.0% when the probe was adjacent to the lesion). However, there was no significant difference in the diagnostic yields based on the lobar location.[41, level II-2]

Direct comparison between r-EBUS and CT-guided percutaneous needle biopsy (CT-PNB) have been relatively rare. In order to provide more reasonable choices in evaluating SPNs, Wang W et al. (2018) conducted an RCT to compare the diagnostic yield, complications, and influencing factors between the two methods. A total of 215 patients with SPN detected by spiral CT were consecutively enrolled at the Endoscopic Centre of Nanjing Chest Hospital. According to the inclusion and exclusion criteria, 160 eligible patients were randomly allocated into either r-EBUS or CT-PNB group. All patients were followed up for at least one year. The study revealed that sensitivity of r-EBUS for malignancy was 73.7% (42/57) and for benign was 43.5% (10/23); overall diagnostic accuracy was 65.0% (52/80). In CT-PNB group, sensitivity was 87.9% (51/58) for malignancy and 81.0% (17/21) for benign; overall diagnostic accuracy was 85.0% (68/80). Factors affecting diagnostic yield of r-EBUS were size of SPNs (76.6% for >20 mm and ≤30 mm versus 50.0% for >10 mm and ≤20 mm; p=0.027), the distance from the SPN lesion to pleura (the longer the distance the higher the diagnostic yield; p=0.031), and the location of the probe to lesions (probe located within the SPNs had higher diagnostic yield than those probes adjacent or invisible to the SPNs; p=0.009). However, these factors were not observed to influence the diagnostic yield in CT-PNB group.[42, level II-1]

6.1.4 Multimodality-guided bronchoscopy

Wang Memoli JS et al. (2012) published a systematic review of various guided bronchoscopy techniques for the evaluation of PPLs. Studies evaluating the diagnostic yield of any one or a combination of ENB, VB, r-EBUS, UTB, and GS were assessed. A total of 3,004 patients with 3,052 lesions from the 39 studies performed between 2002 and 2010 were finally included in the meta-analysis. They reported an overall pooled diagnostic yield of 70.0% (95% CI: 67.1, 72.9%). The yield of VB (72.0% 95% CI: 65.7, 78.4%) and r-EBUS (71.1% 95% CI: 66.5, 75.7%) were higher than the overall weighted diagnostic yield, whereas the highest yield was seen with the use of a GS (73.2% 95% CI: 64.4, 81.9%) to maintain the position for biopsy after the localization of the nodule. The yield was also found to depend on size of the lesion. For nodules measuring ≤20 mm in diameter, the diagnostic yield was 60.9% (95% CI: 54.0, 67.7%) and 82.5% (95% CI: 78.6, 86.4%) in nodules >20 mm.[43, level II-2]

Recently, Han Y et al. (2018) compared the efficacy and safety of transbronchial lung biopsy using r-EBUS plus VBN with CT-guided transthoracic needle biopsy (CT-TNB) for tissue diagnosis of small pulmonary lesions (PLs) up to 3 cm. From 7,345 records, nine articles on the bronchoscopic (BR) approach and 15 articles on the percutaneous (PC) approach were included in the meta-analysis. For lesion of the same size (≤3 cm), CT-TNB exhibited a higher diagnostic yield than r-EBUS plus VBN. The pooled diagnostic yield was 75% (95% CI: 69, 80) using the BR approach and 93% (95% CI: 90, 96) using the PC approach. For both techniques, diagnostic yield improved with increasing lesion size. For tissue biopsy of PLs ≤2 cm, the PC approach was superior to the BR approach (pooled diagnostic yield: 92% [95% CI: 88, 95] versus 66% [95% CI: 55, 76]). However, for PLs >2 cm but ≤3 cm, the diagnostic yield using the BR approach was improved to 81% (95% CI: 75, 85).[44, level II-2]

The combination of r-EBUS and navigation provides higher diagnostic yield than each method alone as previously reported [33, 35-36]; thus, the addition of UTB with navigation devices and r-EBUS seems to be promising. Oki M et al. (2015) performed a randomised multicentre controlled study to evaluate the diagnostic ability of bronchoscopic biopsy with a 3.0-mm UTB directed by an r-EBUS, VBN, and fluoroscopy (UTB group). They used the bronchoscopic technique with a conventional 4.0-mm thin bronchoscope (TB), r-EBUS-GS, VBN, and fluoroscopy as a reference arm (TB-GS group). A total of 310 patients with suspected PPLs ≤30 mm were enrolled; 150 in the UTB group and 155 in the TB-GS group were finally analysed. The study demonstrated that the histologic diagnostic yield in the UTB group and TB-GS group were 74% (111/150) and 59% (92/155) (p=0.007), respectively. When divided based on the final histologic diagnosis, the diagnostic yields of the UTB method and the TB-GS method were 81% and 70% (p=0.040) in malignant lesions and 42% and 36% (p=0.622) in benign lesions, respectively. Comparison of both groups revealed that the UTB method provided a higher diagnostic yield for lesions located within the outer third elliptical lung region (p=0.002) and lesions with bronchus sign (p=0.001) than the TB-GS method. However, there was no significant difference in the visibility on r-EBUS (p=0.080). The UTB could reach more distal bronchi than the TB (median, 5th-generation bronchi versus 4th-generation bronchi; p<0.001).[45, level II-1]

6.1.5   Bronchoscopic transparenchymal nodule access (BTPNA)

The BTPNA technology was developed with the intention of overcoming the constraint of guidance technologies that depend on the need to have an airway leading into the lesion. A pilot study in a human population by Herth F et al. (2015) reported the feasibility and safety of the BTPNA procedure. Twelve patients with a SPN detected on CT imaging suspicious for lung cancer and suitable for surgical resection were enrolled. A tunnel tract was created from the point of entry (POE) to the nodule using a set of catheter-based tools under fused fluoroscopy guidance. The patients proceeded to surgical resection immediately after the biopsy. The procedure was successfully completed in 10 patients (83%), and a positive biopsy was successfully obtained in all 10 cases in which a tunnel was successfully created from the POE to the SPN. The histological findings from the biopsies obtained by BTPNA correlated with the final pathology in all the surgically resected nodules.[46, level II-2]

Another prospective single arm interventional study by Harzheim D et al. (2016) evaluated the feasibility and safety of the BTPNA procedure among six patients with a SPN detected on CT imaging, which was suspicious for malignancy in a standard endoscopy suite. This is the first evaluation of the technique being performed outside an operation theatre, followed by a clinical observation of at least 72 hours. A positive biopsy was obtained in all five cases (83%) in which the BTPNA procedure could be successfully completed. Adequate histological sampling sufficient for a histological diagnosis was successfully attained in five patients. The biopsies obtained by BTPNA correlated with the final pathology in all four surgically resected nodules.[47, level II-2]

6.1.6   Electromagnetic transthoracic needle aspiration (ETTNA)

Recently, ETTNA procedure which can be combined with navigation bronchoscopy and EBUS in a single setting has become available. This approach may provide a much needed intervention allowing physicians to utilize a multimodality approach in a single procedural setting to optimize diagnostic yield and limit complications. A study of a different system is limited to a single report in 2016 by Yarmus L et al. In this first human pilot prospective single arm study, they evaluated the safety, feasibility, and diagnostic yield of ETTNA, ENB, and r-EBUS in a single procedural setting. Twenty-four patients undergoing lymph node sampling for lung cancer staging were enrolled. An additional diagnostic yield analysis was performed using a cohort analysis of combined interventions (r-EBUS + ENB + ETTNA). A total of 24 r-EBUS and ENB procedure were performed, and ETTNA was feasible in 96% of cases (23/24). The diagnostic yield for ETTNA alone was 83% and increased to 87% when ETTNA was combined with ENB (p=0.0016). When ETTNA and ENB were performed with r-EBUS for complete staging, the diagnostic yield increased further to 92% (p=0.0001). Additional larger studies will be needed to further evaluate this ETTNA system.[29, level II-2]

6.1.7   Robotic bronchoscopy

Two bronchoscopic robotic systems have been reported: Robotic Endoscopy System (RES, Auris Health Inc., CA) and The Intuitive Robotic Bronchoscope System (Intuitive Surgical, Sunnyvale, CA). In clinical studies, the RES was first reported by Rojas-Solano JR et al. (2018) among 15 patients with suspicious central lesion or bronchus-sign positive peripheral nodules. All procedures were performed in an operating room under general intravenous anaesthesia. This feasibility study showed that the RES performed without malfunctions in 14 of 15 (93%) cases. The lesions (12 peripheral and three central) were located in the right lower lobe (33%), right upper lobe (27%), left upper lobe (27%), and left lower lobe (13%). Cancer was confirmed in 60% (9/15) of patients whereas benign features were found in five out of six (83%) patients.[48, level III]

A recent study on the RES system was reported by Chaddha U et al. in 2019. They retrospectively reviewed medical records of consecutive patients who were considered to require a guided bronchoscopy (ENB, VB with or without r-EBUS) and underwent RES to diagnose lung lesions at four centres in the United States (academic and community). One hundred and sixty-seven lesions in 165 patients were included in the analysis, with an average follow-up of 185 ± 55 days. The average size of targeted lesions was 25.0 ± 15.0 mm and 71% were located in the peripheral third of the lung. In this case series, tissue samples were successfully obtained in 161 (97.6%) patients with overall diagnostic yield ranged from 69.1% to 77.0%. The yield was 81.5%, 71.7%, and 26.9% for concentric, eccentric and absent r-EBUS views, respectively (p<0.001). Diagnostic yield was also higher for lesions with a bronchus sign (78.3% versus 54.1%; p=0.001) but not effected by lesion size, density, lobar location or centrality.[49, level III]

In the first-in-human study for a new shape-sensing Intuitive Robotic Bronchoscope System, Fielding D et al. (2019) evaluated its safety and feasibility to bronchoscopically approach and facilitate the sampling of small PPLs of 1–3 cm. The study included 29 subjects with a mean lesion size of 12.2 ± 4.2 mm, 12.3 ± 3.3 mm, and 11.7 ± 4.1 mm in the axial, coronal, and sagittal planes, respectively. Similarly, procedures were performed under general anaesthetic and endotracheal intubation. In 28 of 29 cases (96.6%), the target was reached and tissue sample was obtained. Early performance trends through the six month follow-up demonstrated an overall diagnostic yield of 79.3% (95% CI: 60.3, 92.0%), with a diagnostic yield for malignancy (sensitivity) trending towards 88.2% (95% CI: 63.6, 98.5%) and specificity trending towards 63.6% (95% CI: 30.8, 89.1%).[50, level III]

6.1.8   Transbronchial cryobiopsy

There is interest in the potential role of cryobiopsy for peripheral nodules, not only to allow increased tissue sample size, but also to potentially allow sampling of lesions adjacent to a bronchus because of a deeper effect across the bronchus wall to include some adjacent tissue. The majority of published literature describes case series of PPLs biopsied with cryobiopsy. Schuhmann M et al. first reported a method for this in 2014, using a 1.2 mm cryoprobe with 1.7 mm outer sheath. They assessed the safety, feasibility and efficacy of the cryoprobe in 39 consecutive patients with a solid pulmonary lesion of ≤40 mm. After identifying the lung lesion by r-EBUS, patients were randomised to receive either the forceps or the cryobiopsies first according to a randomisation list. One patient was excluded due to visible endobronchial tumour. The remaining 38 patients had a lung lesion of 29.7 ± 7.3 mm, of which 31 were malignant and seven were benign. The overall diagnostic yield including lesions not biopsied as they unable to detect by r-EBUS was 60.5% (23 out of 38 patients) whereas in the lesions reached by r-EBUS, it was 74.2% (23 out of 31 patients). In 19 cases, both techniques established a diagnosis. Additionally, four cases that were non-diagnostic with forceps biopsy were successfully diagnosed with cryobiopsy resulting in a diagnostic yield of 61.3% (19 out of 31) for forceps and 74.2% (23 out of 31) for cryobiopsy, respectively (p=0.42). The size of the samples obtained with the cryoprobe were significantly larger than those acquired with conventional forceps (11.17 mm^2 versus 4.69 mm^2; p<0.001).[51, level III]

The study by Taton O et al. (2018) used transbronchial lung cryobiopsy (TBLC) in order to obtain as large as possible tissue samples and compared the diagnostic yield with standard transbronchial biopsy (TBB) among 32 patients with pulmonary nodules <2 cm. Both methods were guided with fluoroscopy, r-EBUS, and ENB in order to accurately reach the target nodules. Pathological analysis of the surgical specimen and CT follow-up were considered as the independent methods of reference for establishing the final diagnosis. Among the 29 patients in whom both TBLC and TBB could be obtained, their overall diagnostic yield was 69% (20/29) and 38% (11/29), respectively (p=0.017). The sensitivity and specificity of TBLC for the diagnosis of a malignant nodule were 61% and 100%, respectively, whereas 35% and 100% for TBB (p=0.008 and p>0.999, respectively). As compared to TBB, TBLC provides larger tissue samples (mean diameters 5.3 ± 0.7 mm versus 1.1 ± 0.6 mm; p<0.001).[52, level III]

Most recently, a retrospective single centre local study by Kho SS et al. (2019) evaluated the performance and safety of transbronchial cryobiopsy versus forceps biopsy in eccentrically and adjacently orientated r-EBUS lesions over 17 months at Respiratory Care Unit, Sarawak General Hospital. During the study period, a total of 114 r-EBUS scans were included for analysis. Forceps biopsy was performed in 76 (66.7%) cases and cryobiopsy in 38 (33.3%) cases; 65 out of 114 (57%) of the lesions demonstrated eccentric and adjacent orientations to the r-EBUS, with only 43% (49/114) in concentric orientations. This study indicated that orientation remained an important factor affecting diagnostic yield. Overall diagnostic yield was 67.5% (77 out of 114) while the yields for concentrically (n=49), eccentrically (n=47) and adjacently (n=18) orientated lesions were 79.6%, 63.8% and 44.4%, respectively. For concentric lesions, cryobiopsy did not increase the diagnostic yield significantly compared to the forceps biopsy group (85.7% versus 77.1%; p=0.501). However, cryobiopsy significantly increased the diagnostic yield in eccentrically and adjacently orientated lesions to 75.0% (18 out of 24), compared to 48.8% (20 out of 41) obtained via forceps biopsy (p<0.05).[53, level III]

Summary of studies related to diagnostic accuracy for each technology are shown in **Table 1**.

Table 1: Diagnostic accuracy/ performance of guided bronchoscopy biopsy technique reported by the included studies

Study	Design	Technology of interest	Comparator	Diagnostic yield (%)												Diagnostic accuracy (%)				
				Overall	Nature Malign	Nature Benign	Size ≤2 cm	Size ≥2 cm	Size >2 cm; ≤3 cm	Size ≤3 cm	Size ≥3 cm	Probe Within	Probe Adjacent	Bronchus Present	Bronchus Absent	Sens Malign	Sens Benign	Spec Malign	Spec Benign	Overall
Ishida T 2011		VBN + r-EBUS	non-VBN + r-EBUS	80.4 vs 67.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Asano F 2013	RCT	VBN + UTB	non-VBN + UTB	67.1 vs 59.9	-	-	64.9 vs 56.4	-	71.7 vs 66.7	-	-	-	-	69.1 vs 62.8	50.0 vs 46.7	-	-	-	-	-
		NGB		41.2	43.9	23.1	20.9	-	56.8	-	-	NA	NA	-	-	-	-	-	-	-
Bo L 2019	RCT	r-EBUS-GS	Between intervention	72.3	81.8	52.0	47.1	-	89.5	-	-	85.2	68.1	-	-	-	-	-	-	-
		VBN + r-EBUS-GS		74.3	85.9	56.3	50.4	-	88.9	-	-	88.4	60.7	-	-	-	-	-	-	-
Xu C 2019	RCT	VBN + r-EBUS	r-EBUS	83.6 vs 66.7	85.7 vs 67.5	80.0 vs 65.0	80.0 vs 53.6	-	86.7 vs 78.1	-	-	-	-	-	-	-	-	-	-	-
Gex G 2014	SR & MA	ENB	-	64.9	-	-	-	-	-	-	-	-	-	-	-	71.1	-	-	-	73.9
Zhang W 2015	SR & MA	ENB	-	60.0-94.0	-	-	-	-	-	-	-	-	-	-	-	82.0	-	100.0	-	-
NAVIGATE 2019	Intv	ENB	-	72.9	-	-	-	-	-	-	-	-	-	-	-	69.0	-	100.0	-	-
Steinfort DP 2011	SR & MA	r-EBUS	-	-	-	-	56.3	77.7	-	-	-	-	-	-	-	73.0	-	100.0	-	-
Ali MS 2017	SR & MA	r-EBUS	-	70.6	72.4	60.2	60.5	75.7	-	58.7	68.4	78.7	52.0	76.5	52.4	-	-	-	-	-
Wang W 2018	RCT	r-EBUS	CT-PNB	-	-	-	50.0 vs 83.3	-	76.6 vs 86.1	-	-	76.5	44.8	-	-	73.7 vs 87.9	43.5 vs 81.0	-	-	65.0 vs 85.0
Wang Memoli JS 2012	SR & MA	ENB, VBN, UTB, r-EBUS, GS	-	70.0	-	-	60.9	82.5	-	-	-	-	-	-	-	-	-	-	-	-
Han Y 2018	SR & MA	r-EBUS + VBN	CT-TNB	-	-	-	66.0 vs 92.0	-	81.0 vs 96.0	75.0 vs 93.0	-	-	-	-	-	-	-	-	-	-
Oki M 2015	RCT	UTB	TB-GS	74.0 vs 59.0	81.0 vs 70.0	42.0 vs 36.0	65.0 vs 49.0	-	84.0 vs 71.0	-	-	78.0 vs 66.0	17.0 vs 26.0	82.0 vs 63.0	49.0 vs 43.0	-	-	-	-	-
Herth F 2015	Intv	BTPNA	-	83.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Study	Design	Technology of interest	Comparator	Diagnostic yield (%)												Diagnostic accuracy (%)				
				Overall	Nature		Size of SPNs					Probe position to lesions		Bronchus sign		Sensitivity		Specificity		Overall
					Malign	Benign	≤2 cm	≥2 cm	>2 cm; ≤3 cm	≤3 cm	≥3 cm	Within	Adjacent	Present	Absent	Malign	Benign	Malign	Benign	
Harzheim D 2016	Intv	BTPNA	-	83.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Yarmus L 2016	Intv	ETTNA	-	83.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		ETTNA + ENB	Between intervention	87.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		ETTNA + ENB + r-EBUS		92.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rojas-Solano JR 2018	Case series	Robotic bronchoscopy	-	93.0	60.0	83.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chaddha U 2019	Case series	Robotic bronchoscopy	-	69.1-77.0	-	-	-	-	-	68.5	77.1	-	-	78.3	54.1	-	-	-	-	-
Fielding D 2019	Case series	Robotic bronchoscopy	-	79.3	-	-	-	-	-	-	-	-	-	-	-	88.2	-	63.6	-	-
Schuhmann M 2014	Case series	Transbronchial cryobiopsy	Forcep biopsy	74.2 vs 61.3	68.0 vs 56.0	100.0 vs 83.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Taton O 2018	Case series	Transbronchial cryobiopsy	Standard TBB	69.0 vs 38.0	61.0 vs 35.0	67.0 vs 50.0	54.0 vs 45.0	78.0 vs 33.0	-	-	-	-	-	73.0 vs 27.0	67.0 vs 44.0	61.0 vs 35.0	-	100.0 vs 100.0	-	-
Kho SS 2019	Case series	Transbronchial cryobiopsy	Forcep biopsy	67.5	-	-	-	-	-	56.7	60.0	-	-	-	-	-	-	-	-	-

SPNs, solitary pulmonary nodules; RCT, randomised controlled trial; SR & MA, systematic review & meta-analysis; Intv, pre-post intervention study; VBN, virtual bronchoscopy navigation; r-EBUS, radial probe or radial endobronchial ultrasound; UTB, ultrathin bronchoscopy; NGB, non-guided bronchoscopy biopsy; GS, guide sheath; ENB, electromagnetic navigation bronchoscopy; CT-PNB, CT-guided percutaneous needle biopsy; CT-TNB, CT-guided transthoracic needle biopsy; TB, thin bronchoscope; BTPNA, bronchoscopic transparenchymal nodule access; ETTNA, electromagnetic transthoracic needle aspiration; TBB, transbronchial biopsy

6.2 SAFETY OF GUIDED BRONCHOSCOPY BIOPSY TECHNIQUES:

6.2.1 Navigation bronchoscopy: virtual bronchoscopy navigation (VBN)

No deaths were related to the VBN device or associated tools. In an RCT by Ishida T et al. (2011), there was no severe or moderate AEs associated with bronchoscopy except for mild pneumothorax that did not require chest drainage in a patient from the NVBNA group.[33, level I] In another trial by Asano F et al. (2013), the incidence of complications (pneumothorax not requiring drainage, haemorrhage, xylocaine intoxication, pneumonia, and transient bradycardia) did not differ between the two groups (p=0.500), and no severe AEs were observed in either group.[34, level I] Recently, Bo L et al. (2019) found that the two major complications (pneumothorax and haemorrhage) did not vary among the groups (NGB, r-EBUS-GS, and VBN + r-EBUS-GS), and no severe AEs occurred. Every case that developed a pneumothorax after surgery was admitted for inpatient observation, and all recovered following treatment. Regarding haemorrhage, the bleeding stopped following treatment and none of the patients required therapeutic intervention.[35, level I] Xu C et al. (2019) also reported that the incidence of complications did not differ between the two groups in a small randomised study to compare a combination of VBN and r-EBUS guided bronchoscopy with r-EBUS alone among 115 patients with SPN. One case in VBN + r-EBUS group was complicated with pneumothorax (compressed 15%), and was healed after five days of oxygen inhalation. In the r-EBUS group, there was haemorrhage in one case, with the bleeding amount about 20 ml, and stopped after local injection of thrombin and epinephrine.[36, level II-1]

6.2.2 Navigation bronchoscopy: electromagnetic navigation bronchoscopy (ENB)

In a 2014 meta-analysis by Gex et al., ENB caused 32 pneumothoraxes out of 1,033 procedures (a proportion of 3.1%, 95% CI: 2.1, 4.3). Half of those required chest tube drainage (1.6%, 95% CI: 1.0, 2.6) and nine cases of minor self-limited bleeding (0.9%, 95% CI: 0.4, 1.6) were reported.[37, level II-2] Zhang W et al. (2015) updated the previous meta-analysis by Gex G et al. and found 40 pneumothoraces in 681 procedures (5.8%), in which two cases were induced using transbronchial biopsy, otherwise, none pneumothorax was ENB procedure-related. In addition, minor or moderate bleeding was reported in seven cases and two of post-procedure respiratory failure were recorded; none of them requiring specific treatment.[38, level II-2] The pneumothorax risk (grade 2 or higher) in NAVIGATE trial was low (4.3% overall and 2.9% requiring admission or chest tube placement) and was not increased in subjects with chronic obstructive pulmonary disease (COPD) or poor pulmonary function.[39, level II-2] No deaths were reported in any studies.

6.2.3 Radial probe or radial endobronchial ultrasound (r-EBUS)

Steinfort DP et al. (2011) reported in their meta-analysis (involving 1,090 patients from 14 studies) that the only major complication was pneumothorax, which is very rare (pooled rate of 1.0%) with only 0.4% requiring chest tube placement. Self-limited minor bleeding was reported in few cases and no intervention was required.[40, level II-2] In the largest meta-analysis performed to date by Ali MS et al. (2017), overall complication rate of 2.8% from 54 studies with a total of 7,872 lesions were reported. Most r-EBUS complications included self-limited bleeds and small pneumothoraces which required no further intervention. Rate of chest tube insertion was 0.2%.[41, level II-2] Recent trial by Wang W et al. (2018) revealed the incidence of complications in CT-PNB group were higher than those in r-EBUS group (p=0.002). The overall incidence of pneumothorax and haemorrhage was 17.5% (14/80) and 7.5% (6/80), respectively in CT-PNB group whereas in r-EBUS group were 1.3% (1/80) and 5.0% (4/80), respectively.[42, level II-1] No deaths were related to r-EBUS procedure.

6.2.4   Multimodality-guided bronchoscopy

In a meta-analysis assessing the overall performance of guided-bronchoscopy in the evaluation of peripheral nodules, Wang Memoli JS et al. (2012) reported overall adverse event rate of 1.5% with the majority reporting pneumothorax. Only one third (0.6%) of which required chest tube placement. The incidence of respiratory failure requiring intubation was 0.1%, and there were no deaths or significant bleeding reported.[43, level II-2] Most of the studies included in the meta-analysis by Han Y et al. (2018) reported complications associated with the procedure. In the r-EBUS + VBN group, pneumothorax occurred in 2.3% while chest tube insertion and haemoptysis occurred in less than 1.0%. In contrast, the rate of complications in the CT-TNB group was quite high. The pooled complication rate for pneumothorax was 26.0% (95% CI: 21.0, 32.0) and among these cases, the pool incidence rate of severe pneumothorax requiring chest tube insertion was 3.0% (95% CI: 1.8, 4.8). Pulmonary haemorrhage and haemoptysis were reported with pooled incidence rate of 16.0% (95% CI: 10.0, 25.0) and 7.1% (95% CI: 6.0, 8.4).[44, level II-2] Regarding UTB with multimodal device for PPLs (under r-EBUS, VBN, and fluoroscopic guidance), Oki M et al. (2015) found no significant difference in complication rate between UTB group and TB-GS group (p=0.595). The incidence of pneumothorax, bleeding, chest pain, and pneumonia has been reported to be 3.0% and 5.0% in the respective groups.[45, level II-1]

6.2.5   Bronchoscopic transparenchymal nodule access (BTPNA)

This first in human trial of BTPNA procedure by Herth F et al. (2015) for sampling SPNs has demonstrated that it is a safe approach with no significant AEs observed at the time of the procedure or in the follow-up period. There was no evidence of significant immediate bleeding or pneumothoraces, which were the primary safety concerns for this approach. The only AE observed was a transient rise in troponin levels in one patient post-BTPNA and surgical resection. Clinical follow-up at 6-month did not discover any unanticipated AEs.[46, level II-2] Similarly, Harzheim D et al. (2016) found no evidence of pneumothoraces or significant immediate bleeding during the procedure. However, a chest x-ray, performed 2-hour after the procedure, revealed two patients who had developed a pneumothorax. One subject was managed with the insertion of an intercostal drain while in the other subject, the pneumothorax was small and did not need any further intervention. There were no other complications within the 72-hour hospitalization following the BTPNA procedure.[47, level II-2]

6.2.6   Electromagnetic transthoracic needle aspiration (ETTNA)

A pilot study by Yarmus L et al. (2016) using navigational systems and/or r-EBUS to perform ETTNA resulted with an acceptable safety profile. No bleeding, haemoptysis or respiratory events were encountered. There were five (5/24, 21%) pneumothoraces of which only two (2/24, 8%) subjects required chest tube placement. None of the chest tube placements were emergent. In the five cases with a pneumothorax, four (4/5, 80%) had a diagnosis from the procedure (ETTNA sample alone).[29, level II-2]

6.2.7 Robotic bronchoscopy

The robotic bronchoscopy performed with the RES appears to be safe as reported by Rojas-Solano JR et al. (2018). The absent of serious AEs (pneumothorax or significant bleeding requiring intervention) while three minor unrelated complications that resolved within 6-hour such as fever sensation, anaesthesia-related nausea, and back pain are encouraging.[48, level III] A recent study by Chaddha U et al. (2019) on the RES system revealed that pneumothorax occurred in six (3.6%) cases, requiring chest tube placement in four (2.4%). Significant bleeding post-biopsies was reported in four (2.4%) cases. There was no need for blood transfusion, open thoracotomy or use of endobronchial blockers in any case. There were also no reports of respiratory failure, deaths or any other procedure-related complications.[49, level III] Fielding D et al. (2019) conducted the first-in-human study for a new shape-sensing Intuitive Robotic Bronchoscope System. During this study, there were no instances of pneumothorax or bleeding requiring intervention observed and no airway injury was reported. No instances of unexpected bleeding, which included any type of bleeding that required prolonged or continuous suction were reported. Regarding procedure-related complications, two subjects experienced adverse reaction to anaesthesia and contralateral pneumonia.[50, level III]

6.2.8 Transbronchial cryobiopsy

Schuhmann M et al. first reported a method for this with the guidance of r-EBUS in 2014 and no severe complications were observed during the study. There was one case of moderate bleeding at the end of all six biopsies that required no further procedures other than prolonged suction with the bronchoscope. No pneumothorax was detected on chest radiography.[51, level III] In another study comparing TBLC with standard TBB, AEs consisted in 15 mild or moderate bleeding (grade 1 and 2) while pneumothorax needing pleural drainage for three days was observed in one patient. No other AE was observed and no mortality was recorded.[52, level III] The local study by Kho SS et al. (2019) showed that only one pneumothorax occurred in the forceps biopsy group whereas none in the cryobiopsy group; hence, the overall pneumothorax rate was 0.8% (1/114) in the current cohort. Mild and moderate bleeding complications were more common in the cryobiopsy group compared to forceps biopsy group (47.4% versus 7.9%; p<0.001). However, most bleeding episodes in cryobiopsy were mild (39.5%), requiring only suction with local adrenaline instillation; while moderate bleeding occurred in three (7.9%) patients. There was no occurrence of severe life-threatening bleeding event.[53, level III]

Summary of studies related to safety for each technology are shown in **Table 2**.

Table 2: Mortality/ adverse event/ complication rates of guided bronchoscopy biopsy technique reported by the included studies

Study	Design	Technology of interest	Comparator	Death (%)	Pneumothorax (%) Require chest tube	Pneumothorax (%) Not require chest tube	Haemorrhage (%) Require specific treatment	Haemorrhage (%) Not require specific treatment	Bleeding (%)	Haemoptysis (%)	Pneumonia (%)	Chest pain (%)	Respiratory failure (%)	Minor (%) Fever sensation	Minor (%) Anaesthesia-related nausea	Minor (%) Back pain
Ishida T 2011	RCT	VBN + r-EBUS	non-VBN + r-EBUS	0.0	-	0.0 vs 1.0 (1/97)	-	-	-	-	-	-	-	-	-	-
Asano F 2013	RCT	VBN + UTB	non-VBN + UTB	0.0	-	0.6 (1/167) vs 0.6 (1/167)	-	1.2 (2/167)	-	-	0.6 (1/167)	-	-	-	-	-
Bo L 2019	RCT	NGB	Between intervention	0.0	0.6 (2/340)	1.8 (6/340)	-	1.2 (4/340)	-	-	-	-	-	-	-	-
Bo L 2019	RCT	r-EBUS-GS	Between intervention	0.0	0.3 (1/336)	2.1 (7/336)	-	1.2 (4/336)	-	-	-	-	-	-	-	-
Bo L 2019	RCT	VBN + r-EBUS-GS	Between intervention	0.0	0.9 (3/334)	1.5 (5/334)	-	0.9 (3/334)	-	-	-	-	-	-	-	-
Xu C 2019	RCT	VBN + r-EBUS	r-EBUS	0.0	-	1.8 (1/55)	-	1.7 (1/60)	-	-	-	-	-	-	-	-
Gex G 2014	SR & MA	ENB	-	0.0	1.6 (17/1,033)	3.1 (32/1,033)	-	-	0.9 (9/1,033)	-	-	-	0.1 (1/1,033)	-	-	-
Zhang W 2015	SR & MA	ENB	-	0.0	0.0	3.6 (40/1,106)	-	-	0.6 (7/1,106)	0.1 (4/1,106)	-	0.5 (5/1,106)	0.2 (2/1,106)	0.3 (3/1,106)	0.1 (4/1,106)	-
NAVIGATE 2019	Intv	ENB	-	0.0	2.9 (35/1,215)	4.3 (52/1,215)	-	2.5 (30/1,215)	-	-	-	-	0.7 (9/1,215)	-	-	-
Steinfort DP 2011	SR & MA	r-EBUS	-	0.0	0.4 (4/1,090)	1.0 (11/1,090)	-	-	0.3 (3/1,090)	-	-	-	-	-	-	-
Ali MS 2017	SR & MA	r-EBUS	-	0.0	0.2 (15/7,872)	1.0 (82/7,872)	-	-	0.8 (61/7,872)	-	0.2 (17/7,872)	-	-	-	-	-
Wang W 2018	RCT	r-EBUS	CT-PNB	0.0	-	1.3 (1/80) vs 17.5 (14/80)	-	5.0 (4/80) vs 7.5 (6/80)	-	-	-	-	-	-	-	-
Wang Memoli JS 2012	SR & MA	ENB, VBN, UTB, r-EBUS, GS	-	0.0	0.6 (14/2,156)	1.5 (33/2,156)	-	-	-	-	-	-	0.1 (1/2,156)	-	-	-
Han Y 2018	SR & MA	r-EBUS + VBN	CT-TNB	0.0	1.0 (3/305) vs 3.3 (87/2,611)	2.3 (10/426) vs 25.2 (660/2,611)	-	0.0 vs 14.9 (230/1,545)	-	0.7 (2/305) vs 6.8 (126/1,865)	-	-	-	-	-	-

Study	Design	Technology of interest	Comparator	Death (%)	Pneumothorax (%)		Haemorrhage (%)		Bleeding (%)	Haemoptysis (%)	Pneumonia (%)	Chest pain (%)	Respiratory failure (%)	Minor (%)		
					Require chest tube	Not require chest tube	Require specific treatment	Not require specific treatment						Fever sensation	Anaesthesia-related nausea	Back pain
Oki M 2015	RCT	UTB	TB-GS	0.0	-	2.0 (3/150) vs 3.2 (5/155)	-	-	0.0 vs 1.3 (2/155)	-	0.7 (1/150) vs 0.0	0.7 (1/150) vs 0.0	-	-	-	-
Herth F 2015	Intv	BTPNA	-	0.0	-	-	-	-	-	-	-	-	-	-	-	-
Harzheim D 2016	Intv	BTPNA	-	0.0	16.7 (1/6)	16.7 (1/6)	-	-	-	-	-	-	-	-	-	-
Yarmus L 2016	Intv	ETTNA / ETTNA + ENB / ETTNA + ENB + r-EBUS	Between intervention	0.0	8.3 (2/24)	12.5 (3/24)	-	-	-	-	-	-	-	-	-	-
Rojas-Solano JR 2018	Case series	Robotic bronchoscopy	-	0.0	-	-	-	-	-	-	-	-	-	6.7 (1/15)	6.7 (1/15)	6.7 (1/15)
Chaddha U 2019	Case series	Robotic bronchoscopy	-	0.0	2.4 (4/165)	3.6 (6/165)	-	-	2.4 (4/165)	-	-	-	-	-	-	-
Fielding D 2019	Case series	Robotic bronchoscopy	-	0.0	-	-	-	-	-	-	3.4 (1/29)	-	-	-	3.4 (1/29)	-
Schuhmann M 2014	Case series	Transbronchial cryobiopsy	Forcep biopsy	0.0	-	-	-	-	2.6 (1/38)	-	-	-	-	-	-	-
Taton O 2018	Case series	Transbronchial cryobiopsy	Standard TBB	0.0	3.1 (1/32)	-	-	-	46.9 (15/32)	-	-	-	-	-	-	-
Kho SS 2019	Case series	Transbronchial cryobiopsy	Forcep biopsy	0.0	0.0 vs 0.9 (1/114)	-	-	-	47.4 (54/114) vs 7.9 (9/114)	-	-	-	-	-	-	-

SPNs, solitary pulmonary nodules; RCT, randomised controlled trial; SR & MA, systematic review & meta-analysis; Intv, pre-post intervention study; VBN, virtual bronchoscopy navigation; r-EBUS, radial probe or radial endobronchial ultrasound; UTB, ultrathin bronchoscopy; NGB, non-guided bronchoscopy biopsy; GS, guide sheath; ENB, electromagnetic navigation bronchoscopy; CT-PNB, CT-guided percutaneous needle biopsy; CT-TNB, CT-guided transthoracic needle biopsy; TB, thin bronchoscope; BTPNA, bronchoscopic transparenchymal nodule access; ETTNA, electromagnetic transthoracic needle aspiration; TBB, transbronchial biopsy

6.3   ORGANISATIONAL

Though most articles have focused on accuracy, the procedure time or duration of navigational bronchoscopy is another clinically relevant outcome of interest. This is because an early diagnosis could result in a faster treatment impacting long-term survival and reduce treatment cost as well.

6.3.1   Navigation bronchoscopy: virtual bronchoscopy navigation (VBN)

The duration of the examination and time elapsed until the start of sample collection were significantly shorter in the VBNA compared with the NVBNA group as mentioned by Ishida T et al. (2011) (median [range]: 24.0 minutes [8.7-47.0] versus 26.2 minutes [11.6-58.6]; p=0.016) and 8.1 minutes (2.8-39.2) versus 9.8 minutes (2.3-42.3; p=0.045, respectively).[33, level I] Asano F et al. (2013) reported total bronchoscopic examination and total fluoroscopy time did not differ between the groups. However, the interval to starting the specimen collection and the duration of x-ray fluoroscopy before the sample collection were significantly shorter in the VBNA group than in the NVBNA group (median [range]: 6.4 minutes [2.4-24.0] versus 6.8 minutes [2.5-27.8]; p=0.021, and 1.2 minutes [0.2-11.5] versus 2.2 minutes [0.1-10.1]; p<0.001, respectively).[34, level I] Another RCT by Bo L et al. (2019) found the required time to reach the biopsy position was significantly less in the combined group, r-EBUS-GS + VBN (7.96 ± 1.18 minutes) when compared with r-EBUS-GS alone (11.92 ± 5.37 minutes; p<0.01). However, the bronchoscope operation time was the same in the r-EBUS-GS and combined groups.[35, level I] Recent study by Xu C et al. (2019) also revealed that the total examination time was not significantly different between VBN + r-EBUS and r-EBUS groups (20.59 ± 2.12 minutes versus 21.53 ± 1.62 minutes, p=0.236). However, the time for positioning lesions in VBN + r-EBUS group was less than that in r-EBUS group (5.67 ± 2.48 minutes versus 8.65 ± 2.23 minutes; p=0.015).[36, level II-2]

6.3.2   Navigation bronchoscopy: electromagnetic navigation bronchoscopy (ENB)

A meta-analysis by Grex G et al. (2014) indicated that the mean duration of the entire ENB procedure ranged from 25.7 to 70.0 minutes with a median of 46.0 minutes.[37, level II-2] NAVIGATE trial reported the median total procedure time (bronchoscope in to bronchoscope out) was 52.0 (35.0-71.0) minutes, which included 25.0 (14.0-40.0) minutes of ENB-specific navigation and sampling time (first entry to last exit of the locatable guide or extended working channel).[39, level II-2]

6.3.3   Multimodality-guided bronchoscopy

Oki M et al. (2015) indicated that although the use of UTB during navigational endosonographic bronchoscopy improved the diagnostic yield as compared to the TB-GS method, no significant difference in procedural time were observed (median 27.5 minutes in UTB group and 28.5 minutes in TB-GS group; p=0.101).[45, level II-1]

6.3.4   Bronchoscopic transparenchymal nodule access (BTPNA)

In this early report with BTPNA, Herth F et al. (2015) recorded a mean procedure time of 39.8 minutes, with the planning stage accounting for 18.0 minutes (range 10.0–30.0 minutes), and nodule access time (creation of the tunnelled pathway) was 21.8 minutes (range 12.0–40.0 minutes). A learning curve was demonstrated with the first four, second four, and third four tunnel creation times averaging 35.0, 21.5, and 13.3 minutes, respectively. Hence, after only eight procedures, the procedure time of BTPNA is comparable to either transthoracic CT-guided biopsy or standard TBB. The fluoroscopy time was 5.5 minutes (range 1.8–11.6 minutes).[46, level II-2] Harzheim D et al. (2016) reported mean procedure planning time of 14.4 minutes and with a nodule access time

averaging 18.8 minutes, the procedure could be carried out three minutes faster than previous study [46], which implies a learning curve. The fluoroscopy time was 3.7 minutes (range 1.8–7.5 minutes).[47, level II-2]

6.3.5 Electromagnetic transthoracic needle aspiration (ETTNA)

Using navigational systems and/or r-EBUS to perform ETTNA, total procedural time as defined by the time the EBUS bronchoscope was inserted into the oropharynx until the time the ETTNA needle was removed was 72.5 minutes. Yarmus L et al. (2016) also revealed that the additional time to perform the ETTNA (18.3 minutes) was shorter than either r-EBUS (20.5 minutes) or ENB (22.9 minutes) and more importantly, the additional procedure time was not associated with any anaesthesia related complications.[29, level II-2]

6.3.6 Robotic bronchoscopy

The robotic bronchoscopy performed with the RES resulted in quick recover of direct visualization while advancing and articulating the bronchoscope as mentioned in study by Rojas-Solano JR et al. (2018). The total median time to biopsy location was 21.0 (7.0 to 84.0) minutes and the median time to biopsy location reduced from 45.0 (21.0 to 84.0) minutes in first five cases to 20.0 (7.0 to 47.0) minutes in last nine cases; p=0.039). All patients were discharged within six hours following the procedure.[48, level III] A recent study on the RES system by Chaddha U et al. (2019) revealed that the average navigation and procedure time were 17.8 ± 19.1 minutes and 58.6 ± 31.4 minutes, respectively.[49, level III]

Fielding D et al. (2019) conducted the first-in-human study for a new shape-sensing Intuitive Robotic Bronchoscope System and found that the procedure time was 63.9 ± 24.4 minutes. Mean procedure time of the first and last five cases was approximately 95.0 and 61.0 minutes, respectively. Most subjects (25/26, 86.2%) were discharged the same day with a mean length of stay of 5.2 ± 0.6 hours.[50, level III]

6.3.7 Transbronchial cryobiopsy

Schuhmann M et al. first reported a method for this with the guidance of r-EBUS in 2014. All 31 positive patients received three transbronchial forceps biopsies and three transbronchial cryobiopsies according to the study protocol. The study showed that the duration or average time required of the cryobiopsies was significantly longer in comparison with forceps biopsy (11.6 ± 4.4 minutes versus 5.1 ± 2.75 minutes; p<0.0001). The longer time was due to the need to remove the GS for each biopsy, requiring repeat localisation of the lesion with r-EBUS prior to repeat sampling. A prolonged procedure time may be acceptable in order to obtain larger samples.[51, level III] Kho SS et al. (2019) also performed cryobiopsy for PPL under r-EBUS guidance in 114 patients. Overall median procedure time was 45.0 (35.8–60.0) minutes, with cryobiopsy recording a significantly longer duration at 50.0 (45.0-60.0) minutes compared to 40.5 (35.0-51.5) minutes in forceps biopsy (p<0.01).[53, level III]

Summary of studies related to organizational issues for each technology are shown in **Table 3**.

Table 3: Organizational issues of guided bronchoscopy biopsy technique reported by the included studies

Study	Design	Technology of interest	Comparator	Total procedure/ examination/ operation/ bronchoscopic time (min)			Initial sampling/ interval to starting sample collection/ biopsy initial time/ time of arrival at the nodule/ time for positioning lesion/ time to biopsy location/ nodule access time/ time require for biopsy/ creation of the tunnelled pathway/ navigation time (min)		Total fluoroscopy time (min)	Training/ learning curve (min)	Hospital discharge/ length of stay
				Median (range)	Mean ± SD	Planning stage (range)	Median (range)	Mean ± SD	Median (range)		
Ishida T 2011	RCT	VBN + r-EBUS	non-VBN + r-EBUS	-24.0 (8.7–47.0) vs 26.2 (11.6–58.6)	-	-	8.1 (2.8–39.2) vs 9.8 (2.3–42.3)	-	9.7 (1.5–22.7) vs 11.0 (1.3–31.0)	-	-
Asano F 2013	RCT	VBN + UTB	non-VBN + UTB	21.1 (8.9–45.1) vs 20.8 (6.3–72.4)	-	-	-	-	6.9 (1.3–22.7) vs 6.9 (1.2–20.8)	-	-
		NGB		-	18.40 ± 5.19	-	-	NA	-	-	-
Bo L 2019	RCT	r-EBUS-GS	Between intervention	-	29.06 ± 6.40	-	-	11.92 ± 5.37	-	-	-
		VBN + r-EBUS-GS		-	28.34 ± 5.65	-	-	7.96 ± 1.18	-	-	-
Xu C 2019	RCT	VBN + r-EBUS	r-EBUS	-	20.59 ± 2.12 vs 21.53 ± 1.62	-	-	5.67 ± 2.48 vs 8.65 ± 2.23	-	-	-
Gex G 2014	SR & MA	ENB	-	46.0 (25.7–70.0)	-	-	-	-	-	-	-
NAVIGATE 2019	Intv	ENB	-	52.0 (35.0–71.0)	-	5.0 (4.0–9.0)	-	-	-	-	-
Oki M 2015	RCT	UTB	TB-GS	27.5 (12.0–77.0) vs 28.5 (15.0–81.0)	-	-	-	-	-	-	-
Herth F 2015	Intv	BTPNA	-	-	39.8	18.0 (10.0–30.0)	-	21.8 (12.0–40.0)	5.5 (1.8–11.6)	Tunnel creation times: 1st four: 35.0 2nd four: 21.5 3rd four: 13.3	-
Harzheim D 2016	Intv	BTPNA	-	-	-	14.4 (8.0–20.0)	-	18.8 (8.0–25.0)	3.7 (1.8–7.5)	-	-

Study	Design	Technology of interest	Comparator	Total procedure/ examination/ operation/ bronchoscopic time (min)			Initial sampling/ interval to starting sample collection/ biopsy initial time/ time of arrival at the nodule/ time for positioning lesion/ time to biopsy location/ nodule access time/ time require for biopsy/ creation of the tunnelled pathway/ navigation time (min)		Total fluoroscopy time (min)	Training/ learning curve (min)	Hospital discharge/ length of stay
				Median (range)	Mean ± SD	Planning stage (range)	Median (range)	Mean ± SD	Median (range)		
Yarmus L 2016	Intv	ETTNA	Between intervention	-	-	-	-	-	-	-	-
		ETTNA + ENB		-	72.5	-	-	-	-	-	-
		ETTNA + ENB + r-EBUS		-	-	-	-	-	-	-	-
Rojas-Solano JR 2018	Case series	Robotic bronchoscopy	-	-	-	-	21.0 (7.0–84.0)	-	-	Time to biopsy location: 1st 5 cases: 45.0 Last 9 cases: 20.0	Same day; 6.0 hours
Chaddha U 2019	Case series	Robotic bronchoscopy	-	-	58.6 ± 31.4	-	-	17.8 ± 19.1	-	-	-
Fielding D 2019	Case series	Robotic bronchoscopy	-	-	63.9 ± 24.4	-	-	-	11.0 (2.0–22.0)	Mean procedure time: 1st 5 cases: 95.0 Last 5 cases: 61.0	Same day; 5.2 ± 0.6 hours
Schuhmann M 2014	Case series	Transbronchial cryobiopsy	Forcep biopsy	-	-	-	-	11.6 ± 4.4 vs 5.1 ± 2.75	-	-	-
Kho SS 2019	Case series	Transbronchial cryobiopsy	Forcep biopsy	50.0 (45.0–60.0) vs 40.5 (35.0–51.5)	-	-	-	-	-	-	-

SPNs, solitary pulmonary nodules; RCT, randomised controlled trial; SR & MA, systematic review & meta-analysis; Intv, pre-post intervention study; VBN, virtual bronchoscopy navigation; r-EBUS, radial probe or radial endobronchial ultrasound; UTB, ultrathin bronchoscopy; NGB, non-guided bronchoscopy biopsy; GS, guide sheath; ENB, electromagnetic navigation bronchoscopy; CT-PNB, CT-guided percutaneous needle biopsy; CT-TNB, CT-guided transthoracic needle biopsy; TB, thin bronchoscope; BTPNA, bronchoscopic transparenchymal nodule access; ETTNA, electromagnetic transthoracic needle aspiration; Min, minutes; SD, standard deviation; NA, not applicable

Data are presented as median (range) or mean ± SD

6.4 ECONOMIC IMPLICATION

Selection of the optimal procedure for minimally invasive diagnosis of PPLs may be based on clinical factors; however, selection of diagnostic strategy may also be influenced by cost. Economic evaluation of navigational bronchoscopy with biopsy has been very limited and to date, three cost-analysis have been undertaken:

6.4.1 Electromagnetic navigation bronchoscopy (ENB) with biopsy versus CT-guided biopsy

Dale CR et al. (2012) presented a cost consequence model and a decision tree analysis with values from the literature to evaluate the clinical consequences and societal costs of an ENB biopsy strategy versus CT-guided biopsy strategy for the diagnosis of a SPN. The serial use of ENB after non-diagnostic CT-guided biopsy and CT-guided biopsy after non-diagnostic ENB biopsy were tested as alternate strategies. In a hypothetical cohort of 100 patients, the base case was 65 year-old with a >40 pack-year smoking history with a 2 cm SPN. The costs were obtained from the literature, the American Medical Association and private coding websites and are national Medicare reimbursement rates expressed in 2011 USD. The inflation rate was estimated at 3%. One-way sensitivity analysis were plotted on a tornado diagram. All analyses were carried out in TreeAge Pro 2011. Results from the base case analysis and the alternate serial testing scenarios are both shown in **Table 4** below:

Table 4: Estimates based on a Monte Carlo simulation of costs and consequences of ENB with biopsy versus CT-guided biopsies of a SPN

Base Case (VATS after non-diagnostic biopsy)

Estimates per 100 cases	Navigational bronchoscopy strategy	CT-guided biopsy strategy
Total Cost ($), mean (SD)	663, 278 (779,457)	291,343 (505,227)
Pneumothorax/100 cases, n	1.6	15.0
Chest tube/100 cases	0.7	6.6
Significant hemorrhage/100 cases	0.1	1.0
Respiratory failure/100 cases	0.1	0.7
VATS cases/100 cases	30.0	10.0

Serial Biopsy Strategy (ENB biopsy after non-diagnostic CT-guided biopsy and CT-guided biopsy after negative ENB biopsy)

Estimates per 100 cases	Navigational bronchoscopy strategy	CT-guided biopsy strategy
Total Cost ($), mean (SD)	240,621 (311,637)	193,494 (322,257)
Pneumothorax/100 cases, n	6.1	15.2
Chest tube/100 cases	2.7	6.7
Significant hemorrhage/100 cases	0.4	1.0
Respiratory failure/100 cases	0.3	0.7
VATS cases/100 cases	3.0	3.0

In the base case scenario, the ENB with biopsy strategy was associated with a 20% increased rate of VATS surgery compared with the CT-guided biopsy strategy. The ENB biopsy strategy, however, was associated with fewer complications. For every 100 ENB procedures, 13.4 fewer pneumothoraces were produced and 5.9 fewer chest tubes were placed compared to CT-guided biopsy. Additionally, 0.9 fewer haemorrhages and 0.6 fewer cases of respiratory failure occurred. The sequential diagnostic strategy that combines CT-guided biopsy after non-diagnostic ENB biopsy and vice-versa decreases the rate of VATS procedures to 3%. As expected, the rate of other complications increases in both arms with a sequential approach. For example, the rate of pneumothorax in the ENB-first arm increases by 4.5 per 100 patients to 6.1 from 1.6 per 100 patients. The costs were greater in the ENB biopsy strategy. In the base case scenario, the ENB with biopsy strategy was on average USD$3,719 per patient more expensive than the CT-guided biopsy strategy. Mean costs per biopsy were USD$6,633 (95% CI: USD$1,518, USD$18,511) versus USD$2,913 (95% CI: USD$1,248, USD$18,241) in the ENB and CT-guided arms, respectively. Costs are decreased in both arms in the serial biopsy strategy. The average cost of the ENB biopsy strategy falls to USD$2,406 (95% CI: USD$1,518, USD$19,759) from USD$6,633 (95% CI: USD$1,518, USD$18,511), a savings of USD$4,227 or 64%. Similarly, the average cost of the CT-guided biopsy strategy decreases by USD$978 or 34% to USD$1,934 (95% CI: USD$1,248, USD$19,759) from USD$2,913 (95% CI: USD$1,248, USD$18,241). Based on the tornado diagram of the univariate sensitivity analyses, the main cost driver was the sensitivity of the CT-guided biopsy followed by the cost of VATS, highlighting its direct role in overall costs.[54]

6.4.2 Radial probe EBUS guided transbronchial lung biopsy (r-EBUS-TBLB) versus CT-percutaneous needle biopsy (CT-PNB)

Steinfort DP et al. (2013) undertook a cost-benefit and cost-utility analysis between r-EBUS-TBLB and CT-PNB for management of PPLs by applying a decision-tree analysis using TreeAge Pro 2009 software. The modelled population comprised hypothetical patients referred to a multidisciplinary team for evaluation of PPL at the Royal Melbourne Hospital. Unit cost estimates, in Australian dollars (AU$), were based on recorded hospital costs (direct and indirect) and were updated to 2010/2011 levels according to the locally recorded Health Price Index, which reported an increase of 3% per year. Sensitivity analysis and probabilistic sensitivity analysis were undertaken to identify the more cost-beneficial approach for varying input parameter values. Cost-utility analysis on the other hand was performed to examine the effect of disutility (according to the wait-trade-off technique) resulting from two potential adverse outcomes: a procedural complication (pneumothorax or hospital admission) and a non-diagnostic procedure (anxiety related to waiting for test results). Cost-utility outcomes are expressed in cost per quality adjusted life year (QALY). For the base-case analysis, the costs of r-EBUS-TBLB and CT-PNB to evaluate PPL appear to be equivalent. Initial evaluation with CT-PNB was cost-beneficial in comparison to r-EBUS-TBLB by a margin of AU$24 (CT-PNB AU$2,724 versus r-EBUS-TBLB AU$2,748). Sensitivity analyses revealed that cost of managing complications was the factor that most influenced cost-benefit results. A higher cost of complications favoured r-EBUS-TBLB in cost comparisons, due to the lower complication rate associated with this procedure: r-EBUS-TBLB became more cost-beneficial if cost of complications exceeding AU$501 per episode, a complication rate of CT-PNB exceeding 40%, and sensitivity of CT-PNB for detection of malignancy falling below 91%. In the cost-utility analysis, CT-PNB remained the more cost-effective approach (AU$2,778 per QALY versus r-EBUS-TBLB AU$2,816 per QALY) at base-case parameters. However, sensitivity analyses demonstrated that r-EBUS-TBLB became the more cost-effective approach if the cost of complications exceeded AU$489, the complication rate for CT-PNB exceeded 40%, and if the sensitivity of r-EBUS-TBLB for detection of benign disease exceeded 65%.[55]

6.4.3 Navigation bronchoscopy (NB) compared with computed tomography fine needle aspiration (CT-FNA), ^{18}F-fluoro-deoxyglucose positron emission tomography (FDG-PET), and video-assisted thoracoscopic surgery (VATS)

Using a decision analysis model (TreeAge Pro 2013 software), Deppen S et al. (2014) studied the costs and outcomes of four initial diagnostic strategies for diagnosis of pulmonary nodule with either a 50% or 65% pre-test probability (prevalence) of cancer. Compared strategies included NB, CT-FNA, FDG-PET, and VATS. The base case is a 60 year old male with a 15 pack year smoking history, no prior history of lung cancer, and a 1.5 cm to 2.0 cm nodule in an upper lobe incidentally observed on a CT scan. Medicare hospital reimbursable rate for the indicated inpatients procedure using a base year of 2011 were used for societal costs. Quality adjusted life years were estimated using patient survival based on pathologic staging and utilities derived from the literature. Sensitivity analyses were performed to assess changes in cost-effectiveness of modeled strategies and to identify potential thresholds where the preferred treatment option would change. Incremental cost-effectiveness ratio (ICER) was used to compare the cost-effectiveness of different treatments and indicates the additional cost required to gain one additional QALY. Based on the model, when cancer prevalence was 65%, tissue acquisition strategies of NB and CT-FNA had higher QALYs compared to either FDG-PET or VATS. The FDG-PET had the lowest expected cost for diagnosing patients whereas diagnosis by VATS had both higher expected cost and a lower effectiveness. The other two biopsy strategies provided higher QALYs at a lower cost than VATS biopsy (**Table 5**; ICER per QALY: NB=USD$4,602; CT-FNA=USD$3,998; VATS=USD$43,578). Navigation bronchoscopy, CT-FNA, and FDG-PET had similar cost-effectiveness when cancer prevalence was 50%. In sensitivity analysis of individual model components, CT-FNA or NB were the preferred diagnostic strategies (more cost-effective) when FDG-PET sensitivity was fixed at 87% and the specificity fell below 72%. When the sensitivity of FDG-PET was greater than 94% and specificity was fixed at 77%, then FDG-PET was less costly than tissue biopsy or surgery and similarly effective. In two-way sensitivity analysis, FDG-PET remained the least costly diagnostic strategy across all combinations of sensitivity between 80% and 100% and specificity between 60% and 90%. The authors concluded that NB and CT-FNA diagnostic strategies were more cost-effective than VATS biopsy or FDG-PET strategies in the work up of a 1.5 cm to 2.0 cm nodule in populations with lung cancer prevalence greater than 50%. The FDG-PET scan for diagnosis of lung cancer may not be cost-effective in regions of the country where specificity is low.[56]

Table 5: Results of Decision Tree Analysis

Strategy	Total Cost ($)	Incremental Cost ($)	QALYs	Incremental Effectiveness	ICER[a] ($ per QALY)
Base case scenario—65% prevalence of cancer					
FDG-PET	10,411		14.12		
CT-FNA	10,603	193	14.17	0.05	3,998
NB	10,601	191	14.17	0.04	4,602
VATS	11,720	1,294	14.15	0.03	43,578
Base case scenario—50% prevalence of cancer					
FDG-PET	9,256		15.55		
CT-FNA	9,542	286	15.58	0.03	9,533
NB	9,476	220	15.58	0.03	7,333
VATS	11,623	2,367	15.54	−0.02	−118,350

[a] Incremental cost-effectiveness ratio is the ratio of the differences in the cost of decisions divided by the increase in QALY, where FDG-PET is the reference decision (Cost$_{decision}$ − Cost$_{FDG-PET}$)/(QALY$_{decision}$ − QALY$_{FDG-PET}$).

7.0   DISCUSSION

Although our review was designed to compare the overall diagnostic performance of different guided bronchoscopy biopsy techniques, r-EBUS is the most common reported technique being used, considering its role as an adjunctive imaging tool and can be used together with conventional bronchoscopy as well as with navigational tools (virtual or electromagnetic) to facilitate tissue biopsy of SPN. Other techniques including UTB, BTPNA, ETTNA, robotic bronchoscopy, and cryobiopsy are rarely used and their role remains largely investigational.

Overall, findings indicated a wide variation in diagnostic accuracy among studies, which may be due to the differences in 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. A diagnostic yield at 70.6% for r-EBUS showed promising results with a pooled sensitivity and specificity of 73% and 100%, respectively. When used in combination with VBN or UTB, the yield increased to 83.6% and 74.0%, respectively. When combined with ENB, diagnostic yield ranged from 60.0% to 94.0% with sensitivity of 82.0% and specificity of 100%. The DOR value of 97.36 and AUC was higher to 0.98 suggesting an overall high diagnostic accuracy by ENB-guided diagnosis in PPLs. However, r-EBUS alone or combined with VBN or UTB had lower diagnostic yield as compared to CT-guided percutaneous needle biopsy (CT-PNB; 86.1%) or CT-guided transthoracic needle biopsy (CT-TNB; 96.0%). The reason is that the guidance of CT scanning could make clear whether puncture needle had entered into SPN lesion before biopsy, whereas r-EBUS's guidance can hardly perform such real-time supervision. Apart from that, BTPNA procedure of SPNs was feasible with 83% successful rate. Although promising, additional studies documenting superior outcomes and higher yield are required before these techniques ready for prime time. The diagnostic yield for ETTNA alone was 83% and increased to 87% when ETTNA was combined with ENB. When ETTNA and ENB were performed with r-EBUS for complete staging, the yield increased further to 92%. The biopsies obtained by both BTPNA and ETTNA were correlated with the final pathology. Navigation success was also achieved with those using robotic bronchoscopy which demonstrated an overall diagnostic yield between 69.1% and 93.0%, with a diagnostic yield for malignancy (sensitivity) trending towards 88.2%. Cryobiopsy on the other hand significantly increased the diagnostic yield between 69.0% and 74.2% as compared to conventional forceps or standard TBB, with sensitivity and specificity of 61% and 100%, respectively. The size of the tissue samples obtained with the cryoprobe were significantly larger than those acquired with conventional forceps or standard TBB.

Several factors were shown to impact the diagnostic performance of guided bronchoscopy biopsy techniques: size of nodule or lesion, its nature (malignant versus benign), presence of a bronchus sign on CT scan, location of the lesions, and position of the r-EBUS probe with regards to the lesion. At a 2-cm cut-off, the diagnostic yield was higher for larger lesions. The yield was also higher for malignant than benign lesion, which is consistent with the prior reports. This might be because malignant lesions grow faster and tend to be larger at the time of diagnosis, although most studies did not report sizes separately for benign and malignant lesions. When a bronchus leads straight into a lesion (positive bronchus sign), the diagnostic yield is higher than if the bronchus is adjacent or at a distance away from the nearest bronchus. The addition of UTB to either VBN or r-EBUS had significantly increases the diagnostic yield when nodules are located in the peripheral one third of the lung or in the right upper lobe. However, 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 nodule. Not to mention, the distance from the SPN lesion to pleura was a significant predictor of r-EBUS visualization yield; the longer the distance the higher positive diagnostic rate could be obtained. The possible reason may be that the shorter the distance to pleura was, the SPN is nearer to the peripheral distal bronchus. Therefore, when the biopsy forceps were sent forward under the guidance of r-EBUS, the tip of forcep often could

hardly fully open the narrowed lumen, so that invalid sampling and poor diagnostic yield might be resulted in. Finally, position of the r-EBUS probe within the lesion was associated with a significantly higher diagnostic yield as compared with the lesions where the r-EBUS probe was adjacent but not exactly in the lesion. However, these factors were not observed to influence the diagnostic yield in CT-guided biopsy.

The biggest advantage of guided bronchoscopic biopsy techniques compared to percutaneous CT-guided biopsy or computerized-assisted TTNA is its superior safety profile. The spectrum of AEs associated with guided bronchoscopic biopsy techniques are generally well-tolerated with reported complication rates ranging from 0.0% to 5.0%. There was no severe or moderate AEs except for two main complications - pneumothorax and haemorrhage. Less frequent complications include bleeding and respiratory failure. Anyhow, robotic bronchoscopy was a safe approach with no evidence of significant immediate bleeding and pneumothoraces. Mild and moderate bleeding were more common in the cryobiopsy compared to forceps biopsy or standard TBB. Most of AEs reported could be resolved by standard care and no deaths were related to the procedure, device or associated tools.

Total procedure or operation time varied widely based on the guided bronchoscopic biopsy techniques, ranging from 21.0 to 24.0 minutes (median) in the VBN and 46.0 to 52.0 minutes for ENB. Compared to ENB, VBN has the significant advantages of not requiring specific training because the technique is similar to conventional bronchoscopy and not needing a sensor or a specific biopsy instrument other than the system. In any case, ETTNA seemed to have the longest procedure time of 72.5 minutes as compared to BTPNA (39.8 minutes), while it was between 58.6 and 63.9 minutes for those obtained using robotic bronchoscopy. Cryobiopsy recorded a significantly longer duration at 50.0 minutes compared to 40.5 minutes in forceps biopsy. Regarding time to biopsy location or nodule access time, it was shorter in the VBN (5.67 to 7.96 minutes) as compared to BTPNA (18.8 to 21.8 minutes), robotic bronchoscopy (17.8 minutes), and cryobiopsy (11.6 minutes). All patients were discharged within one day following the robotic bronchoscopy procedure with a mean length of stay ranged from five to six hours. As for learning curve, procedure time (tunnel creation times) of BTPNA is comparable to either transthoracic CT-guided biopsy or standard TBB after only eight procedures. Robotic bronchoscopy when performed with the RES reduced the median time to biopsy location from 45.0 minutes in first five cases to 20.0 minutes in last nine cases. Meanwhile, the mean procedure time of the first and last five cases using Intuitive Robotic Bronchoscope System was approximately 95.0 and 61.0 minutes, respectively.

There were three studies on cost-analysis retrieved. The first revealed that an ENB with biopsy strategy is associated with decreased pneumothorax rate but increased costs and increased use of VATS. Combining CT-guided biopsy and ENB with biopsy serially, however, can decrease costs and complications. Second study reported the costs of r-EBUS-TBLB and CT-PNB to evaluate PPL appear to be equivalent, but specific clinical radiologic factors known to influence procedural outcomes will influence cost-benefit outcomes. Finally, the third study indicated that NB and CT-FNA diagnostic strategies were more cost-effective than VATS biopsy or FDG-PET in populations with lung cancer prevalence greater than 50%.

In keeping with our purpose for this review, two different HTA reports were identified and both assessing r-EBUS. For other guided-bronchoscopy biopsy techniques, no HTA were retrieved. In summary, our review are in line with the Canadian Agency for Drugs and Technologies in Health (CADTH) [57] report and previous HTA report by MaHTAS in 2008.[58] Over and above, two clinical practice guidelines (The American College of Chest Physicians 2013 [9, 59] and British Thoracic Society Guidelines 2015 [60]) were consistent with our findings, particularly regarding the use and indications of r-EBUS and ENB for the evaluation and staging of pulmonary nodules and lung cancer.

Limitations

We acknowledge some limitations in our review and these should be considered when interpreting the results. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited our study numbers. One of the important limitations was the methodological quality of the included studies, particularly in terms of heterogeneity and risk of bias. Most individual studies of diagnostic accuracy from the meta-analysis reported in this review were considered to be of either poor or moderate quality, as determined by the low overall QUADAS scores. This could be because of the differences in the baseline characteristics of the study participants, differences in the inclusion and exclusion criteria, disparity in the sampling or procedural techniques, assessment of outcomes, variation in expertise of the physicians, and the geographic locations in which the studies were conducted. As a consequence, random effects model was applied to account for the between-study variance. In addition, the number of subjects in most study was small thereby decreasing the power of the studies to detect a meaningful difference. Since most of the studies were follow-up between three to 12 months, more trials with longer follow-up period are needed. On the other hand, different economic analyses do not reach a consistent conclusion due to the variability in their assumptions and the scenario considered. This include a lack of primary patient-level data and a reliance on literature values that might not be generalize to all patient populations. Besides, cost are given as Medicare costs and might not generalize to other countries, nor do they represent the cost to individual patients or health care systems.

8.0 CONCLUSION

The availability of evidence differs between guided bronchoscopy biopsy techniques, and most was related to the use of r-EBUS. There was fair to good level of retrievable evidence to suggest that the combined use of navigation bronchoscopy (virtual or electromagnetic) with r-EBUS improves overall test performance characteristics beyond either technique alone but lower than percutaneous CT-guided biopsy or computerized-assisted TTNA; typically varying with lesion size, location, and equipment used as well as other factors including the presence of a bronchus sign, biopsy technique, and institution expertise or learning curve of the operator. The major strength of guided bronchoscopic biopsy techniques is clearly its safety profile, especially regarding the risk of procedure-related pneumothorax and haemorrhage, which is about 10 times lower than conventional bronchoscopy or CT-guided biopsy. Given the existing evidence, cost of managing complications was the main factor that influenced cost-analysis results. For this reason, guided bronchoscopy biopsy techniques was found to be cost-effective when a sequential diagnostic strategy that combines CT-guided biopsy and ENB were applied, whereas r-EBUS and CT-PNB differ in cost by negligible amounts. When cancer prevalence was high, tissue acquisition of NB and CT-FNA was the most cost-effective strategies.

9.0 RECOMMENDATION

Based on the above review, guided bronchoscopy techniques mainly using a combination of VBN or ENB with r-EBUS are an appropriate biopsy approaches to SPN and may be used for management of patients with lung cancer in selected centres in MOH hospitals, provided local expertise is available. Although other techniques appears promising and has the potential to be considered as valuable option, they are rarely used and their role remains largely investigational while cost implication should also be considered. Refinement of selection criteria for the respective techniques may have a significant impact on the results for the patient and close cooperation between bronchoscopists, pulmonologists, and radiologist is an essential step in achieving this aim.

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11.0   APPENDICIES

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I   Evidence obtained from at least one properly designed randomized controlled trial.

II-I   Evidence obtained from well-designed controlled trials without   randomization.

II-2   Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3   Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III   Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL DIAGNOSTIC APPROACHES TO SOLITARY PULMONARY NODULE (SPN)

1.0 BACKGROUND INFORMATION

Worldwide, lung cancer is the most common malignancy and continues to be the leading cause of cancer- related deaths in the past few decades. In 2018, a total of 2.1 million new cases were estimated, contributing about 11.6% of the total cancer incidence burden.[1-2] According to the most recent data by Malaysia National Cancer Registry (MNCR) for the incidence year of 2012-2016, lung cancer was the third (9.8%) most common cancer in the country, the second (14.9%) most common cancer in males, and the fifth (5.6%) most common in females.[3] Despite advances in diagnostic approaches, staging and treatment, and also the fact that early-detected lung cancer is curable in patients with good performance status, the overall 5-year survival for lung cancer has not significantly changed and is estimated to be around 17.8%. Lack of early detection and accurate localization of lesion for tissue acquisition remains one of the biggest challenges in lung cancer management.[4]

A solitary pulmonary nodule or *coin lesion* has been defined on imaging as a round or oval opacity < 3 cm in diameter that is completely surrounded by pulmonary parenchyma and does not touch the hilum or mediastinum. In contrast, peripheral pulmonary nodules/ lesions (PPLs; also known as peripheral lung lesions, PLLs) with a diameter > 3 cm are classified as pulmonary masses and differ from SPN. The prevalence of malignancy in SPNs depends on the clinical setting, ranging from 2.0% to 86.0% for incidentally discovered nodules both on chest radiography (CXR) and computed tomography (CT) and from 1.1% to 12.0% for those that are screen detected.[5-10]

The major question that follows detection of a pulmonary nodule is a diagnostic dilemma faced by many clinicians. The differential diagnosis may be broad, but implications rest on whether the lesion is benign or malignant. A recently published multicentre National Lung Screening Trial (NLST) has shown the benefit of early detection in a selected high-risk cohort of patients (current and former smokers). The trial revealed that screening with low-dose CT scan results in a relative reduction of 20% cancer-specific mortality; however, 96.4% of nodules detected are false positive and 90.4% of those required further diagnostic investigations.[11] Similarly, among 12,029 nodules found in a large Canadian study, only 144 (1.1%) were malignant.[12] Therefore, the management of a SPN should aim to identify malignancy as fast as possible in order to provide the option of potentially curative surgical treatment, whilst avoiding invasive diagnostic procedures in case of benign lesions.[9, 13-14]

Choosing the most appropriate biopsy technique for suspected peripheral nodule, however, can be a challenging clinical risk–benefit decision and factors such as tumour size, location, patient co-morbidities including emphysematous changes around the lesion, respiratory function, and the pre-test probability of malignancy must be taken into account. Although routine flexible bronchoscopy has been a conventional method to evaluate peripheral lung nodule, it is of limited diagnostic value [15] in locating and acquiring the required tissue with the diagnostic yield ranging from 20% to 84%.[16-18] Success is further compromised if the lesion is < 2 cm, due to the inability to go beyond the subsegmental level and to steer endobronchial accessories directly into the lesion.[18] Similarly, while percutaneous CT-guided biopsy or computerized-assisted transthoracic needle aspiration biopsy (TNAB) are currently the favoured diagnostic procedure, it was associated with complications (pneumothorax and haemorrhage) and are highly operator-dependent. Other methods such as video-assisted thoracoscopic surgery (VATS) and open surgical biopsy are invasive, require general anaesthesia and are therefore not a first-line approach for patients with lung nodules suspicious for cancer.[19]

In order to achieve better results in the management algorithm of SPN, several innovative navigation methods that offer guidance through the tracheobronchial tree during bronchoscopy to help reach and biopsy the SPN have recently been developed. The result has been the development of a platform broadly defined as image-guided bronchoscopy techniques. It is not a single technology but comprising of several technologies including virtual bronchoscopy (VB), navigation bronchoscopy (virtual or electromagnet), and complementary technologies such as radial probe endobronchial ultrasound (r-EBUS), ultrathin bronchoscopy (UB), bronchoscopic transparenchymal nodule access (BTNA), and electromagnetic transthoracic needle aspiration (ETNA). The now commercially available robotic bronchoscopy platform has the potential to overcome the limitations of individual techniques.[20-22]

Technical Description:

1.1   Virtual bronchoscopy (VB)

Virtual bronchoscopy is a non-invasive form of bronchoscopy. It is not an endoscopic procedure, but rather an imaging modality that uses non-contrast-enhanced CT images to reconstruct the airways in a three-dimensional (3-D) manner producing images that appear similar to those visualized during real-time bronchoscopy. While VB itself cannot acquire samples, it can be used to preplan future procedures or as a navigational tool for biopsy.[19, 23]

1.2   Navigation bronchoscopy

Navigation bronchoscopy uses a navigational system to guide instruments (flexible or ultrathin bronchoscope) through the airways to a target lesion for biopsy. Navigational systems can be virtual (virtual bronchoscopy navigation, VBN; also known as virtual navigation bronchoscopy, VNB) or electromagnetic (electromagnetic navigation bronchoscopy, ENB):[19,23]

1.2.1   Virtual bronchoscopy navigation (VBN)

Virtual bronchoscopy navigation is a technique that utilizes VB CT imaging to guide the bronchoscope to a peripheral target lesion in the lung. First, CT scan images are acquired with a specialized CT protocol and transferred to a computer workstation where specific software is used to create a virtual bronchoscopic pathway to the target lesion (planning phase). It is done usually on the same day or a few days ahead of the planned biopsy procedure. During the guidance phase, the acquired virtual images of the airway pathway are displayed and synchronized with real-time images from the bronchoscope or until the target lesion is reached. This allows the bronchoscope to be advanced branch-by-branch through the airway to the target lesion.[19, 23]

1.2.2   Electromagnetic navigation bronchoscopy (ENB)

Electromagnetic navigation bronchoscopy is an exciting new bronchoscopic technique that incorporates VB imaging with an additional navigational tool, an electromagnetic field using technology similar to a car global positioning system unit (GPS). In the planning phase, CT scans of the patient's chest are loaded into proprietary software that reconstructs the patient's airways in multiple 3-D images. The physician utilizes these images to mark target locations and plan pathways to these target locations within the lungs. Using the planned pathway created in the planning phase and real-time guidance, the physician navigates the steerable sensor probe and extended working channel to the desired target location(s). Once at the desired location, the physician locks the extended working channel in place and the steerable sensor probe is removed. The extended working channel provides access to the target lesion for standard bronchoscopic tools or catheters.[19, 24-25]

1.3   Radial probe or radial endobronchial ultrasound (r-EBUS)

Radial probe endobronchial ultrasound comprises a miniature (20 or 30 MHz) ultrasound probe that can fit through the working channel of a flexible bronchoscope to provide a 360 degree view of the lung parenchyma. Its small size allows it to extend distally into subsegmental bronchi so that PPLs can be visualized. The r-EBUS is itself not a navigational tool, rather, it is typically used as an adjunctive imaging tool to confirm that the lesion has been reached. It can be used with the following biopsy modalities: [23]

- Standard flexible bronchoscopy with or without a designated guide sheath
- Computed tomographic reconstruction with bronchoscopic fluoroscopy
- Navigational techniques, most commonly ENB

1.4   Ultrathin bronchoscopy (UB)

Ultrathin bronchoscopy are smaller variants of a flexible bronchoscope ranging in diameter from approximately 2.8 mm to 3.5 mm. Compared with a standard flexible bronchoscope, the smaller size of ultrathin bronchoscopes allows for better maneuverability and greater ability to reach much smaller airways beyond the typical reach of conventional bronchoscopes. Ultrathin bronchoscopy is not a form of image-guided bronchoscopy but it is usually combined with image guidance (e.g., CT VBN or r-EBUS) to reach PPLs for biopsy. In general, the use of UB is fairly uncommon since the working channels are small and thus can only accommodate smaller biopsy instruments.[19, 23]

1.5   Bronchoscopic transparenchymal nodule access (BTNA)

One of the limitations of ENB is the challenge of accessing the nodules, which are eccentrically positioned and may not have the airway directly leading to them. To overcome this, BTNA has been recently developed whereby the nodules are accessed through a transparenchymal "off-road" approach that is not dependent on the need to have an airway leading into the lesion. A computer software-generated tunneled path is created from the bronchial segments through the lung parenchyma directly to the PPLs.[19]

1.6   Electromagnetic transthoracic needle aspiration (ETNA)

This technology incorporates a unique electromagnetic guidance system allowing clinicians to track SPN and target them for ETNA without utilizing real time CT in the operating room or bronchoscopy suite. Providing this capability allows the pulmonologist to perform initial lymph node staging with EBUS in the same procedural setting. This approach may provide a much needed intervention allowing physicians to utilize a multimodality approach in a single procedural setting to optimize diagnostic yield and limit complications.[26]

1.7   Robotic bronchoscopy

Robotic bronchoscopy allows physicians to visualize and biopsy remote parts of the lung that were previously inaccessible. Physicians use a hand-held controller to very precisely navigate a small, flexible endoscope into the lung. An endoscope is a hollow tube fitted with a camera-like lens and light source. The new robotic platform has an innovative telescoping endoscope attached to flexible robotic arms that allow greater dexterity, reach, vision, and control.[27]

Integrated software combines traditional endoscopic views of the lung with computer-assisted navigation, all based on 3-D models of the patient's own lung anatomy. Physicians are able to visualize the lung continuously throughout the entire procedure. The consistency and reproducibility achieved far exceed traditional bronchoscopy, allowing rapid, accurate diagnosis. It is crucial to navigate the airways quickly and safely to get accurate answers.[27]

In Malaysia, some of those techniques are limited to centres with expertise and require specific training for their use. With so many tools available, there are still debates about which method to choose while cost is also an issue. Therefore, it is necessary to know what type of SPN needs which type of bronchoscopic approaches. This HTA report was prepared in connection to the request made by Senior Consultant Pulmonologist from Serdang Hospital to assess the overall diagnostic accuracy/ performance of minimally invasive image-guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer.

2.0   POLICY QUESTION

What is the appropriate biopsy approaches to SPN in the management of lung cancer in Malaysia?

3.0   OBJECTIVES

The objective of this report is to assess the clinical and economic implications of image-guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer.

The following research questions will be addressed:

3.1   The diagnostic accuracy/ performance of using image-guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer.
3.2   The safety aspect, particularly its adverse events or complications.
3.3   The cost-effectiveness and organisational aspects related to image-guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer.

4.0   METHODS

4.1.   Search Strategy

Electronic database will be searched for published literatures pertaining to image-guided bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer.

4.1.1   Databases as follows; MEDLINE, EMBASE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning, INAHTA Database, HTA database and FDA database will be searched.
4.1.2   Additional literatures will be identified from the references of the retrieved articles.
4.1.3   General search engine will be used to get additional web-based information if there is no retrievable evidence from the scientific databases.
4.1.4   There will be no limitation applied in the search such as year and language.
4.1.5   The search strategy will be included in the appendix.

4.2   Inclusion and Exclusion Criteria

4.2.1   Inclusion criteria

a) Population**:**

Patients with solitary pulmonary nodule (SPN) or coin lesion, patients with lung cancer or suspected lung cancer

b)Intervention**:**

Image-guided bronchoscopy techniques:
  i.   Virtual bronchoscopy (VB)
  ii.   Navigation bronchoscopy: virtual bronchoscopy navigation (VBN) and electromagnetic navigation bronchoscopy (ENB)
  iii.   Radial probe endobronchial ultrasound (r-EBUS)
  iv.   Bronchoscopic transparenchymal nodule access (BTNA)
  v.   Electromagnetic transthoracic needle aspiration (ETNA)
  vi.   Robotic bronchoscopy

c) Comparator**:**

  i.   Conventional bronchoscopy
  ii.   Percutaneous CT-guided biopsy
  iii.   Video-assisted thorascopic surgery (VATS) and open surgical biopsy

d) Outcome**:**

  i.   Diagnostic accuracy: diagnostic yield, detection rate, positive rate, sensitivity, specificity, predictive value (positive and negative), diagnostic odds ratio, receiver operator characteristic curve and area under the curve
  ii.   Safety: mortality, adverse events, complications
  iii.   Economic impacts: cost-effectiveness, cost-utility analysis
  iv.   Organisational issues: hospital utilisation (readmission, length of stay, general or local anaesthesia), procedural time points and training or learning curve

e) Study design:

HTA reports, systematic review with meta-analysis, systematic review, randomised controlled trial (RCT), diagnostic accuracy, case series, and economic evaluation studies

f)English full text articles

4.2.2   Exclusion criteria

a) Study design:
Animal study, laboratory study, cohort, case-control, case report, narrative review

b) Non English full text articles

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3   Critical Appraisal of Literature

The risk of bias of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP) and The Cochrane Collaboration's tool for RCT**.**

4.4   Analysis and Synthesis of Evidence

4.4.1   Data extraction strategy

The following data will be extracted:
- i.   Details of methods and study population characteristics
- ii.   Detail of intervention and comparators
- iii.   Details of individual outcomes specified

Data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion.

4.4.2   Methods of data synthesis

Data on the accuracy, safety and cost-effectiveness associated with image-guided bronchoscopy techniques will be presented in tabulated format with narrative summaries. Meta-analysis may be conducted for this HTA.

5.0   REPORT WRITING

6.0   REFERENCES

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SEARCH STRATEGY:

Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® <1946 to January 28, 2020>

1. SOLITARY PULMONARY NODULE/ (3930)
2. (Pulmonary coin adj2 lesion*).tw. (115)
3. (Solitary pulmonary adj2 nodule*).tw. (1555)
4. 1 or 2 or 3 (4582)
5. BRONCHOSCOPY/ (24764)
6. (Bronchoscopic adj2 (surger* or surgical procedure*)).tw. (41)
7. Bronchoscop*.tw. (25575)
8. Virtual bronchoscopy.tw. (300)
9. IMAGING, THREE-DIMENSIONAL/ (69567)
10. ((3 d or 3-d) adj 2 imag*).tw. (0)
11. ((computer assisted three dimensional or computer-assisted three-dimensional) adj4 imag*).tw. (11)
12. ((computer-generated or computer generated) adj3 imag*).tw. (365)
13. ((three dimensional or three-dimensional) adj2 imag*).tw. (10669)
14. Virtual bronchoscopy navigation.tw. (5)
15. Vbn.tw. (123)
16. Electromagnetic navigation bronchoscopy.tw. (118)
17. Enb.tw. (486)
18. ENDOSONOGRAPHY/ (12380)
19. ((echo or ultrasonic) adj1 endoscop*).tw. (278)
20. (Endoscopic adj1 ultrasonograph*).tw. (4116)
21. Echo-endoscop*.tw. (152)
22. Endosonograph*.tw. (2495)
23. IMAGE-GUIDED BIOPSY/ (3324)
24. ((image guided or image-guided) adj2 biops*).tw. (868)
25. Radial probe endobronchial ultrasound.tw. (55)
26. Radial probe Ebus.tw. (20)
27. Bronchoscopy Bronchoscopic transparenchymal nodule access.tw. (1)
28. BTPNA.tw. (8)
29. Electromagnetic Transthoracic Needle Aspiration.tw. (1)
30. EMTTNA.tw. (1)
31. BIOPSY, NEEDLE/ (48690)
32. ((aspiration or needle or puncture) adj1 biops*).tw. (26435)
33. ROBOTIC SURGICAL PROCEDURES/ (7107)
34. (Robotic surgical adj2 procedure*).tw. (54)
35. Robotic Endoscopy System.tw. (1)
36. Robotic bronchoscopy.tw. (4)
37. Ultrathin bronchoscopy.tw. (33)
38. Transbronchial cryobiopsy.tw. (94)
39. or/5-38 (199569)
40. Conventional bronchoscopy.tw. (119)
41. TOMOGRAPHY, X-RAY COMPUTED/ (372390)
42. CT X ray*.tw. (187)
43. Cine ct.tw. (160)
44. cine-ct.tw. (160)

45. ((computed X ray or computed x ray or electron beam computed or electron beam) adj2 tomography).tw. (1473)
46. tomodensitometry.tw. (636)
47. ((x-ray or X ray) adj3 (CAT scan* or ct scan* or computed tomography or computer assisted tomography or computerized axial tomography)).tw. (7284)
48. Percutaneous CT-guided biopsy.tw. (42)
49. THORACIC SURGERY, VIDEO-ASSISTED/ (6717)
50. VATs*.tw. (4786)
51. ((video assisted or video-assisted) adj3 (thoracic surger* or thoracoscopic surger*)).tw. (5790)
52. BIOPSY/ (171617)
53. Biops*.tw. (386297)
54. Open surgery biopsy.tw. (4)
55. or/40-54 (824305)
56. 39 and 55 (75740)
57. 4 and 56 (696)
58. limit 57 to (English language and humans) (561)

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#12   Add   Search ((((SOLITARY PULMONARY NODULE[MeSH Terms]) OR Pulmonary Coin Lesion*[Title/Abstract]) OR Solitary Pulmonary Nodule*[Title/Abstract])) AND (((((((Conventional bronchoscopy[Title/Abstract]) OR Percutaneous CT-guided biopsy[Title/Abstract]) OR Open surgery biopsy[Title/Abstract])) OR ((((((THORACIC SURGERY, VIDEO-ASSISTED[MeSH Terms]) OR Video-Assisted Thoracic Surg*[Title/Abstract]) OR Video-Assisted Thoracoscopic Surg*[Title/Abstract]) OR Video Assisted Thoracic Surg*[Title/Abstract]) OR Video Assisted Thoracoscopic Surg*[Title/Abstract]) OR VATS*[Title/Abstract]))) AND ((((((((((((Virtual bronchoscopy[Title/Abstract]) OR Virtual bronchoscopy navigation[Title/Abstract]) OR VBN[Title/Abstract]) OR Electromagnetic navigation bronchoscopy[Title/Abstract]) OR ENB[Title/Abstract]) OR Radial probe endobronchial ultrasound[Title/Abstract]) OR Radial probe EBUS[Title/Abstract]) OR Bronchoscopic transparenchymal nodule access[Title/Abstract]) OR BTPNA[Title/Abstract]) OR Electromagnetic Transthoracic Needle Aspiration[Title/Abstract]) OR EMTTNA[Title/Abstract]) OR Robotic bronchoscopy[Title/Abstract]) OR Ultrathin bronchoscopy[Title/Abstract]) OR Transbronchial cryobiopsy[Title/Abstract])) Filters: English **(9)**

#9   Add   Search ((((SOLITARY PULMONARY NODULE[MeSH Terms]) OR Pulmonary Coin Lesion*[Title/Abstract]) OR Solitary Pulmonary Nodule*[Title/Abstract])) AND (((((((Conventional bronchoscopy[Title/Abstract]) OR Percutaneous CT-guided biopsy[Title/Abstract]) OR Open surgery biopsy[Title/Abstract])) OR ((((((THORACIC SURGERY, VIDEO-ASSISTED[MeSH Terms]) OR Video-Assisted Thoracic Surg*[Title/Abstract]) OR Video-Assisted Thoracoscopic Surg*[Title/Abstract]) OR

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#10 Add Search ((((SOLITARY PULMONARY NODULE[MeSH Terms]) OR Pulmonary Coin Lesion*[Title/Abstract]) OR Solitary Pulmonary Nodule*[Title/Abstract])) AND (Conventional bronchoscopy[Title/Abstract]) OR Percutaneous CT-guided biopsy[Title/Abstract]) OR Open surgery biopsy[Title/Abstract]) OR ((THORACIC SURGERY, VIDEO-ASSISTED[MeSH Terms]) OR Video-Assisted Thoracic Surg*[Title/Abstract]) OR Video-Assisted Thoracoscopic Surg*[Title/Abstract]) OR Video Assisted Thoracic Surg*[Title/Abstract]) OR Video Assisted Thoracoscopic Surg*[Title/Abstract]) OR VATS*[Title/Abstract]))) AND ((Virtual bronchoscopy[Title/Abstract]) OR Virtual bronchoscopy navigation[Title/Abstract]) OR VBN[Title/Abstract]) OR Electromagnetic navigation bronchoscopy[Title/Abstract]) OR ENB[Title/Abstract]) OR Radial probe endobronchial ultrasound[Title/Abstract]) OR Radial probe EBUS[Title/Abstract]) OR Bronchoscopic transparenchymal nodule access[Title/Abstract]) OR BTPNA[Title/Abstract]) OR Electromagnetic Transthoracic Needle Aspiration[Title/Abstract]) OR EMTTNA[Title/Abstract]) OR Robotic bronchoscopy[Title/Abstract]) OR Ultrathin bronchoscopy[Title/Abstract]) OR Transbronchial cryobiopsy[Title/Abstract])) Filters: Humans **(8)**

#8 Add Search (Conventional bronchoscopy[Title/Abstract]) OR Percutaneous CT-guided biopsy[Title/Abstract]) OR Open surgery biopsy[Title/Abstract]) OR ((THORACIC SURGERY, VIDEO-ASSISTED[MeSH Terms]) OR Video-Assisted Thoracic Surg*[Title/Abstract]) OR Video-Assisted Thoracoscopic Surg*[Title/Abstract]) OR Video Assisted Thoracic Surg*[Title/Abstract]) OR Video Assisted Thoracoscopic Surg*[Title/Abstract]) OR VATS*[Title/Abstract]) AND (Virtual bronchoscopy[Title/Abstract]) OR Virtual bronchoscopy navigation[Title/Abstract]) OR VBN[Title/Abstract]) OR Electromagnetic navigation bronchoscopy[Title/Abstract]) OR ENB[Title/Abstract]) OR Radial probe endobronchial ultrasound[Title/Abstract]) OR Radial probe EBUS[Title/Abstract]) OR Bronchoscopic transparenchymal nodule access[Title/Abstract]) OR BTPNA[Title/Abstract]) OR Electromagnetic Transthoracic Needle Aspiration[Title/Abstract]) OR EMTTNA[Title/Abstract]) OR Robotic bronchoscopy[Title/Abstract]) OR Ultrathin bronchoscopy[Title/Abstract]) OR Transbronchial cryobiopsy[Title/Abstract]) **(82)**

#7 Add Search (Conventional bronchoscopy[Title/Abstract]) OR Percutaneous CT-guided biopsy[Title/Abstract]) OR Open surgery biopsy[Title/Abstract])) OR ((THORACIC SURGERY, VIDEO-ASSISTED[MeSH Terms]) OR Video-Assisted Thoracic Surg*[Title/Abstract]) OR Video-Assisted Thoracoscopic Surg*[Title/Abstract]) OR Video Assisted Thoracic Surg*[Title/Abstract]) OR Video Assisted Thoracoscopic Surg*[Title/Abstract]) OR VATS*[Title/Abstract]) **(10841)**

#6 Add Search (Conventional bronchoscopy [Title/Abstract]) OR Percutaneous CT-guided biopsy [Title/Abstract]) OR Open surgery biopsy [Title/Abstract] **(166)**

#5   Add   Search ((THORACIC SURGERY, VIDEO-ASSISTED [MeSH Terms]) OR Video-Assisted Thoracic Surg*[Title/Abstract]) OR Video-Assisted Thoracoscopic Surg*[Title/Abstract]) OR Video Assisted Thoracic Surg*[Title/Abstract]) OR Video Assisted Thoracoscopic Surg*[Title/Abstract]) OR VATS*[Title/Abstract] **(10677)**

#4   Add   Search (Virtual bronchoscopy[Title/Abstract]) OR Virtual bronchoscopy navigation[Title/Abstract]) OR VBN[Title/Abstract]) OR Electromagnetic navigation bronchoscopy[Title/Abstract]) OR ENB[Title/Abstract]) OR Radial probe endobronchial ultrasound[Title/Abstract]) OR Radial probe EBUS[Title/Abstract]) OR Bronchoscopic transparenchymal nodule access[Title/Abstract]) OR BTPNA[Title/Abstract]) OR Electromagnetic Transthoracic Needle Aspiration[Title/Abstract]) OR EMTTNA[Title/Abstract]) OR Robotic bronchoscopy[Title/Abstract]) OR Ultrathin bronchoscopy[Title/Abstract]) OR Transbronchial cryobiopsy[Title/Abstract] **(1186)**

#3   Add   Search ((SOLITARY PULMONARY NODULE [MeSH Terms]) OR Pulmonary Coin Lesion*[Title/Abstract]) OR Solitary Pulmonary Nodule*[Title/Abstract] **(4634)**

Evidence Table : Diagnostic accuracy/ safety/ organisational **(VBN-assisted r-EBUS versus non-VBN-assisted r-EBUS)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. Ishida T, Asano F, Yamazaki K et al . Virtual bronchoscopic navigation combined with endobronchial ultrasound to diagnose small peripheral pulmonary lesions: a randomised trial. Thorax 2011; 66: 1072-1077.	**Randomised controlled trial** This prospective multicentre study randomly allocated 200 cases of peripheral pulmonary lesions (≤3 cm) into VBN-assisted (VBNA) and non-VBN-assisted (NVBNA) groups in consideration of the lesion size and operators and performed biopsy under fluoroscopy in combination with r-EBUS-GS. Bronchoscopic insertion was assisted using the VBN system in the VBNA group. The bronchoscope was introduced into the bronchus of the NVBNA group without VBN support and with reference only to CT axial images. They analysed the diagnostic yield and safety of the entire intent-to-treat population. Data from the per-protocol population that included all randomised patients with planned bronchoscopic procedures for peripheral lesions were also statistically analysed. The key secondary end point was total examination duration, which was calculated as the interval between the moments the endoscope passed the vocal cords until its withdrawal from the trachea. Other secondary end points were the interval until the start of sample collection, duration of x-ray fluoroscopy and the generation number of the inserted bronchi.	I	A total of 199 patients who were referred to three Japanese medical centres between April 2006 and August 2007 with peripheral pulmonary lesions (mean diameter ≤3 cm calculated from axial CT images) suspected to be cancer that were not pathologically confirmed. Among bronchoscopically undiagnosed patients, 23 of 52 (44.2%) underwent video-assisted thoracoscopy and/or surgery and 8 (15.4%) were diagnosed by CT-guided FNA or repeated bronchoscopy. Twenty of the 21 patients who refused further intervention were followed up for two years.	VBN-assisted r-EBUS (VBNA) (n=102)	non-VBN-assisted (NVBNA) (n=97)	≤2 years	**Diagnostic accuracy** Diagnostic yield was significantly higher for the VBNA than for the NVBNA groups in both the intent-to-treat (80.4% versus 67.0%; p=0.032) and per-protocol (80.8% versus 67.4%; p=0.032) populations. In the VBNA group, virtual bronchoscopic images could be prepared up to the 6th-generation bronchus (median; range: 4th–12th generations), and the concordance rate with the real image was 98%. The endoscope was also accurately positioned in the VBNA group, with more targets being confirmed by EBUS (VBNA versus NVBNA: 92/99 (92.9%) versus 77/95 (81.1%) (p=0.014). **Safety** No severe or moderate adverse events were associated with bronchoscopy except for mild pneumothorax that did not require chest drainage in a patient from the NVBNA group. **Organisational** Total examination duration was significantly shorter in the VBNA than in the NVBNA group (median [range]: 24.0 minutes [8.7–47.0] versus 26.2 minutes [11.6–58.6]; p=0.016). The interval to starting sample collection was significantly shorter in the VBNA versus the NVBNA group (8.1 minutes [2.8–39.2] versus 9.8 minutes [2.3–42.3]; p=0.045). The duration of x-ray fluoroscopy exposure did not differ significantly between the groups.	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(VBN-assisted UTB versus non-VBN-assisted UTB)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Asano F, Shinagawa N, Ishida T et al. Virtual bronchoscopic navigation combined with ultrathin bronchoscopy. A randomized clinical trial. Am J Respir Crit Care Med. 2013; 188:327–333	**Randomised controlled trial** This prospective multicentre study randomly allocated 350 cases of ≤3 cm peripheral pulmonary lesions to two groups: an ultrathin bronchoscope (UTB) with an outer diameter of 2.8 mm was guided using a VBN system in the VBNA group, and it was guided using axial CT images as a reference in the NVBNA group. Since the working channel of the UTB was thin (1.2 mm), r-EBUS probe could not be inserted. Thus, the investigators performed biopsy under fluoroscopy in both groups. The primary endpoint was the diagnostic yield and was analysed in subgroups classified according to the following items: lesion size, lung lobe containing the lesion, whether the lesion was detected by posterior–anterior radiographs, presence or absence of bronchus sign, and lesion location. The safety endpoints of interest included haemorrhage, pneumothorax, hypoxemia, lidocaine intoxication, arrhythmia, pneumonia, and other serious adverse events. A retrieved blood loss of >50 ml mixed with or without saline lavage was defined as significant. As for the secondary endpoint, the following items were evaluated: total bronchoscopic examination time; biopsy initiation time (the time required to reach the target lesion); total fluoroscopy time; and fluoroscopy time before sample collection.	I	Subjects for analysis included 334 patients who were referred to five Japanese medical centres between December 2008 and March 2011 with peripheral pulmonary lesions (mean diameter ≤30 mm calculated from axial CT images) suspected to be cancer but were not pathologically confirmed. Among the bronchoscopically undiagnosed patients, 62 of 122 (50.8%) underwent video-assisted thoracoscopy or surgery, and the conditions of 31 patients (25.4%) were diagnosed by CT-guided transthoracic needle aspiration or repeated bronchoscopy. Twenty-nine patients (23.8%) who refused further intervention were followed-up for two years.	VBN-assisted UTB (VBNA) (n=167)	non-VBN-assisted UTB (NVBNA) (n=167)	≤2 years	**Diagnostic accuracy** There was no significant difference in the diagnostic yield between the VBNA group (67.1%) and the NVBNA group (59.9%; p=0.173). The subgroup analysis, however, showed that the diagnostic yield was significantly higher in the VBNA group than in the NVBNA group for right upper lobe lesions (81.3% versus 53.2%; p=0.004); lesions invisible on posterior–anterior radiographs (63.2% versus 40.5%; p=0.043); and lesions in the peripheral third of the lung field (64.7% versus 52.1%; p=0.047). In the VBNA group, virtual bronchoscopic images could be prepared up to the 6th-generation bronchus (median; range: 1st–11th generations), and the concordance rate with the real image was 93.4%. The percentage of patients in whom the forceps reached the lesion under fluoroscopy was significantly higher in the VBNA group than in the NVBNA group (92.8% versus 83.8%; p=0.011). **Safety** There were four complications in the VBNA group (pneumothorax not requiring drainage, n=1; haemorrhage, n=2; and transient bradycardia, n=1), and three complications in the NVBNA group (pneumothorax not requiring drainage, n=1; xylocaine intoxication, n=1; and pneumonia, n=1). The incidence of complications did not differ between the two groups (p=0.500), and no severe adverse effects were observed in either group. **Organisational** The total bronchoscopic examination and total fluoroscopy time did not differ significantly between the groups. The interval to starting the specimen collection and the duration of x-ray fluoroscopy before the sample collection were significantly shorter in the VBNA group than in the NVBNA group (median [range]: 6.4 minutes [2.4–24.0] versus 6.8 minutes [2.5–27.8]; p=0.021, and 1.2 minutes [0.2–11.5] versus 2.2 minutes [0.1–10.1]; respectively).	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(NGB versus r-EBUS-GS versus r-EBUS-GS + VBN versus NGB)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
3. Bo L, Li C, Pan L et al. Diagnosing a solitary pulmonary nodule using multiple bronchoscopic guided technologies: A prospective randomized study. Lung Cancer. 2019;129: 48-54	**Randomised controlled trial** This was a prospective, multicentre, multi-arm, RCT involving 1,095 subjects underwent a chest CT scan which found SPNs that needed to be diagnosed. The subjects were randomly divided into one of three groups by the computer (according to the ratio 1:1:1): a traditional, non-guided, bronchoscopy biopsy group (NGB group), an r-EBUS-GS guided bronchoscopy biopsy group (r-EBUS-GS group), and a guided bronchoscopy biopsy group that combined r-EBUS-GS with VBN (combined group). The primary endpoint was to investigate the differences between the diagnostic yields of the three groups. A secondary endpoint was calculation of the mean bronchoscope operation time and the time of arrival at the nodule in the three groups. Histological diagnosis was recorded to calculate the diagnostic yield. If the diagnosis was unclear, fibrosis, normal or inflammation, the patients underwent further examination such as repeat transbronchial biopsy, transthoracic needle biopsy, positron emission computed tomography (PET/CT), surgery, or follow-up for two years to clarify and confirm the diagnosis. The bronchoscope operation time and the time of arrival at the nodule were recorded separately. The bronchoscope operation time was defined as the time from the insertion of the bronchoscope into the trachea until the time of completion of the operation. The time of arrival at the nodule was defined as the time from the insertion of the bronchoscope into the trachea until the time of confirmation of the location of the SPNs.	I	A total of 1,010 patients met the inclusion criteria and were recruited into this trial between January 2014 and December 2016. The age, sex, lobar distribution of nodules, nodule size, and spectrum of disease at baseline were similar among the groups.	NGB (n=340) r-EBUS-GS (n=336) r-EBUS-GS with VBN (n=334)	Between intervention	2-year	**Diagnostic accuracy** The r-EBUS-GS and combined groups (r-EBUS-GS + VBN) had a significantly higher diagnostic yield (72.3% and 74.3%) than the NGB group (41.2%; p<0.01). No matter the mode of analysis whether by lobar distribution, by pathology, or by nodule size, the r-EBUS-GS and the combined groups always had a heightened yield. However, the diagnostic yield of the combined group was not significantly different from that of the r-EBUS-GS-only group. In addition, the ultrasonic probe location significantly affected the diagnostic yields in the r-EBUS-GS and combined groups; the diagnostic yield was approximately 86.8% if the probe was internal to the nodule before the biopsy. However, when the probe was near or outside the nodule, the diagnostic yields were only 64.5% and 37%, respectively. As in many former trials, the diagnostic yield for PPLs >20 mm in diameter in this trial was significantly higher than that for those <20 mm in diameter. **Safety** There were two major complications: pneumothorax and haemorrhage. The incidence of complications did not vary among the groups, and no severe adverse events occurred. Every case that developed a pneumothorax after surgery was admitted for inpatient observation, and all recovered following treatment. Regarding haemorrhage, the bleeding stopped following treatment and none of the patients with bleeding required therapeutic intervention. **Organisational** Although r-EBUS-GS + VBN did not increase the diagnostic yield when compared with r-EBUS-GS alone, the required time to reach the biopsy position was significantly less in the combined group (7.96 ± 1.18 minutes in the combined group versus 11.92 ± 5.37 minutes in the r-EBUS-GS group; p<0.01). However, the bronchoscope operation time was the same in the r-EBUS-GS and combined groups, and that in NGB group was one third shorter compared with the other groups. This was because that the biopsy procedure took up the greatest part of the operation time.	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(VBN + r-EBUS versus r-EBUS)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
4. Xu C, Yuan Q, Wang Y et al. Usefulness of virtual bronchoscopic navigation combined with endobronchial ultrasound guided transbronchial lung biopsy for solitary pulmonary nodules. Medicine. 2019; 98: 7(e14248)	**Randomised controlled trial** A total of 115 patients with suspected SPN who underwent transbronchial lung biopsy were evaluated. The patients were randomly divided into an r-EBUS and VBN + r-EBUS groups. The diagnostic yield and examination time were compared. If pulmonary lesions are not diagnosed by the bronchoscopy, other further diagnostic methods were considered, including CT-guided percutaneous puncture or surgical intervention. Patients were followed up for six months if they refused further examination. *Time required for r-EBUS to location: from the bronchoscope reaching the carina to ultrasonogram of the lesions attained. *Total operating time: from the bronchoscope reaching the carina to exiting the glottis.	II-1	A total of 115 patients (average age 56.7 ± 11.8 years old) with SPN (lesion diameter was 27 ± 2 mm) was recruited at the Endoscopy Centre of Nanjing Chest Hospital from January 2015 to December 2017.	VBN + r-EBUS (n=55)	r-EBUS (n=60)	6-month	**Diagnostic accuracy** Overall diagnostic yield between the VBN + r-EBUS group and the r-EBUS group were 83.6% and 66.7%, respectively. Diagnostic yield of both the r-EBUS group and VBN + r-EBUS group were lower in lesions diameter <20 mm than the diameter ≥20 mm with statistically significant difference. However, in the SPN with diameter <20 mm, the diagnostic yield was higher in the VBN + r-EBUS group than in the r-EBUS group (80.0% versus 53.6%, p=0.041). The diagnosis yield of benign lesions in r-EBUS group and VBN + r-EBUS group was 65% and 80% respectively (p=0.240), and malignant lesions was 67.5% and 85.7% respectively (p=0.057). However, there was no significant difference in diagnosis rate between r-EBUS and VBN + r-EBUS group in different location lesions. **Safety** The incidence of complications did not differ between the two groups. One case in VBN + r-EBUS group was complicated with pneumothorax (compressed 15%), and was healed after five days of oxygen inhalation. In the r-EBUS group, there was haemorrhage in one case, with the bleeding amount about 20 ml, and stopped after local injection of thrombin and epinephrine. **Organisational** The time for positioning lesions in VBN + r-EBUS group was less than that in r-EBUS group (5.67 ± 2.48 minutes versus 8.65 ± 2.23 minutes; p=0.015). However, the total examination time was not significantly different between the two groups (20.59 ± 2.12 minutes versus 21.53 ± 1.62 minutes, p=0.236).	

Evidence Table　:　Diagnostic accuracy/ safety/ organisational **(ENB)**
Question　　:　What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
5. Gex, G, Pralong JA, Combescure C et al. Diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules: A systematic review and meta-analysis. Respiration. 2014; 87(2):165-176	**Systematic review and meta-analysis** The MEDLINE and EMBASE databases were systematically searched for studies reporting electromagnetic navigation bronchoscopy (ENB)'s yield for peripheral lung lesions. The quality of included studies was further assessed with the QUADAS tool. Publication bias was explored by using the Egger test and the trim and fill method. Clearly defined performance outcomes were reconstructed and meta-analysed. Subgroup analysis and meta-regression were used to identify possible sources of study heterogeneity. Diagnostic certainty was achieved by surgical resection, alternative biopsy techniques or extended follow-up.	II-2	A total of 15 trials with 1,033 lung nodules or masses in 971 patients (37.6% females, mean age 64.2 years) were included. The median number of nodules per study was 50 (range 13–271), with a median diameter of 25 mm and a median distance to the pleural surface of 11 mm. Thirty-eight percent of nodules were located in the lower lobes. The overall pooled prevalence was 76.5% (95% CI: 70.2, 81.8).	ENB with additional techniques or strategies	-	-	**Diagnostic accuracy** Several studies relied on additional techniques or strategies to enhance performance such as fluoroscopy, r-EBUS, rapid on-site cytological evaluation (ROSE) and general anaesthesia. In one study comparing three different endoscopic techniques (ENB alone, ENB with r-EBUS, and r-EBUS alone). The methodological quality of the studies included in this meta-analysis was poor, as determined by the low overall QUADAS scores. No significant publication bias was identified. Meta-analysis of all studies demonstrated an accessibility rate or successful navigation toward peripheral lung lesions with ENB of 97.4% (95% CI: 95.4, 98.5). The pooled diagnostic yield was 64.9% (95% CI: 59.2, 70.3). Diagnostic accuracy was analysable in 14 trials and reached 73.9% (95% CI: 68.0, 79.2). Fourteen studies were suitable for evaluation of outcomes regarding malignancy status. The overall sensitivity of ENB to detect cancer was 71.1% (95% CI: 64.6, 76.8). The accuracy to determine the correct malignancy status ranged from 66.7% to 98.0%, leading to a pooled accuracy for malignancy of 78.6% (95% CI: 72.8, 83.4). The negative predictive value of ENB for cancer was 52.1% (95% CI: 43.5, 60.6). Univariate analyses identified six statistically significant variables. Location of the lower lobe correlated with decreased yields, whereas greater nodule size, presence of a bronchus sign, lower registration error (AFTRE), nodule visualization with r-EBUS, and catheter suction technique were associated with increased yields. Heterogeneity exploration revealed that studies using general anaesthesia was associated with better diagnostic yields as compared with conscious sedation (69.2% versus 57.5%, p=0.02) while sensitivity for cancer was better in trials using ROSE (80.2% versus 66.3%; p=0.006). **Safety** Electromagnetic navigation bronchoscopy of peripheral nodules caused 32 pneumothoraces in 1,033 procedures (3.1%, 95% CI: 2.1, 4.3), but only 17 patients required chest tube drainage (1.6%, 95% CI: 1.0, 2.6). Minor or moderate bleeding was reported in nine cases (0.9%, 95% CI: 0.4, 1.6), none of them requiring specific treatment. Additional complications included one self-limited hematoma and one episode of hypercapnic respiratory failure attributed to sedation. **Organisational** The mean duration of the entire ENB procedure ranged from 25.7 to 70.0 minutes with a median of 46.0 minutes.	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(ENB)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
6. Zhang W, Chen S, Dong X et al. Meta-analysis of the diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules. J Thorac. 2015; 7: 799–809	**Systematic review and meta-analysis** A systematic search in PubMed database from 2000 to 2015 was performed to update the previous meta-analysis to assess the diagnosis accuracy and safety of ENB for the peripheral lung nodules. The quality of included studies was assessed with the QUADAS tool while test performance characteristics with the use of forest plots, summary receiver operating characteristic curves (SROCs) and bivariate random effects were summarized using Meta-Disc software. Adverse events and complications were recorded if reported. Diagnostic certainty was achieved by surgical resection, alternative biopsy techniques or extended follow-up	II-2	A total of 17 studies (1,106 patients with peripheral lung lesions) were included in this analysis.	ENB with additional techniques or strategies such as fluoroscopy, r-EBUS, ROSE	-	-	**Diagnostic accuracy** The overall low QUADAS scores indicated that the methodological quality of the enrolled studies was poor. Since none of the included studies compared ENB to surgery as a gold standard, QUADAS scores were only evaluated in 6 of the 14 domains. The pooled sensitivity, specificity, positive likelihood ratios (LRs+), negative likelihood ratios (LRs−), and diagnostic odds ratios (DORs) of ENB was 82%, 100%, 19.36, 0.23, and 97.62, respectively. The area under the curve (AUC) for the SROC was 0.9786. Six statistically significant variables were identified by univariate analyses. Two trials reported that location of lower lobe was correlated with decreased yields, while greater nodule size, nodule visualization with r-EBUS, presence of bronchus sign, lower registration error (AFTRE), and catheter suction technique were associated with increased yields. **Safety** A total of 40 pneumothoraces occurred in 681 procedures, in which two cases were induced using transbronchial biopsy, otherwise, none pneumothorax was ENB procedure-related. In addition, minor or moderate bleeding was reported in seven cases, and two of post-procedure respiratory failure were recorded, none of them requiring specific treatment. Other adverse events included two of chest drainage, five of chest pain, three of fever, seven of sore throat, four of haemoptysis, and four of emesis, attributed to sedation or biopsy procedure.	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(ENB)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
7. Folch EE, Pritchett MA, Nead MA et al. Electromagnetic navigation bronchoscopy for peripheral pulmonary lesions: one-year results of the prospective, multicenter NAVIGATE study. J Thorac Oncol. 2019; 14: 445–458	**Prospective single arm interventional study** NAVIGATE is a prospective, multicentre, global, single-arm, pragmatic cohort that evaluated the diagnostic yield of ENB with rigorous follow-up to ensure that negative or indeterminate results are truly negative. Follow-up was completed in 98.9% (1,202 of 1215) at 1-month and 80.3% (976 of 1215) at 12 months. Diagnostic certainty was achieved by surgical resection, alternative biopsy techniques or extended follow-up. General anaesthesia was used in 81.4% of procedures (989 of 1,215) and moderate sedation was used in 18.6%. One to five lesions were sampled per subject (average: 1.2 lesions).	II-2	In this United States cohort analysis, 1215 consecutive subjects were enrolled at 29 academic and community sites from April 2015 to August 2016. The average age was 67.6 ± 11.3 years; 15% had a history of lung cancer; median lesion size was 20 mm.	ENB with additional techniques or strategies such as fluoroscopy, r-EBUS, ROSE	-	12-month	**Diagnostic accuracy** Among the 1,157 lung lesion biopsy cases, navigation was successful and tissue was obtained in 94.4% (1,092 of 1,157). The 12-month diagnostic yield was 72.9%. ENB-aided biopsy procedures diagnosed malignancy in 44.3% (484 of 1,092) and were negative in 55.7% (608 of 1,092). As of 12 months, 284 initially negative outcomes were considered true-negative and 220 were false-negative. Sensitivity, specificity, positive predictive value, and negative predictive value for malignancy were 69%, 100%, 100%, and 56%, respectively. **Multivariate predictors of diagnostic yield** A personal history of cancer was a significant multivariate predictor of lower diagnostic yield. Use of less than three biopsy tools, lymph node sampling during the ENB procedure, presence of a bronchus sign, biopsy of multiple lesions, and procedure time less than 60 minutes were significant multivariate predictors of higher diagnostic yield. **Safety** ENB-related Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or higher pneumothoraces (requiring admission or chest tube placement) occurred in 2.9%. The ENB-related CTCAE grade 2 or higher bronchopulmonary haemorrhage and grade 4 or higher respiratory failure rates were 1.5% and 0.7%, respectively. There were 233 deaths within 12 months. There was one anaesthesia-related death due to grade 5 hypoxic respiratory failure nine days post-ENB in a subject with multiple comorbidities. No deaths were related to the ENB device or associated tools. **Organisational** The median ENB planning time was 5.0 minutes (Q1, 4.0 minutes – Q3, 9.0 minutes). The median total procedure time (bronchoscope in to bronchoscope out) was 52.0 minutes, which included 25.0 minutes of ENB-specific navigation and sampling time (first entry to last exit of the locatable guide or extended working channel [EWC]). The median ENB-specific procedure time was 30.0 minutes with rapid on-site evaluation (ROSE) and 18.0 minutes without ROSE.	

Evidence Table : Diagnostic accuracy/ safety/ organisational (**r-EBUS**)

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
8. Steinfort DP, Khor YH, Manser RL et al. Radial probe endobronchial ultrasound for the diagnosis of peripheral lung cancer: systematic review and meta-analysis. Eur Respir J. 2011; 37(4): 902–910	**Systematic review and meta-analysis** A systematic review of published literature (Medline and PubMed) evaluating radial probe endobronchial ultrasound (r-EBUS) accuracy was performed to determine point sensitivity and specificity for the diagnosis of peripheral lung cancer. Sub-group analysis was used to identify possible sources of study heterogeneity. Further examination of included studies was performed using the QUADAS tool to assess study quality. Meta-analysis was performed using Meta-DiSc (Version 1.4). The reference standard was confirmation by histology of surgically obtained specimens or close clinical follow-up for at least six months.	II-2	A total of 16 studies with 1,420 patients fulfilled inclusion criteria (referral for diagnosis of peripheral lung lesion). Only 13 studies (n=1,090) presented data sufficient to allow inclusion in meta-analysis.	r-EBUS with additional guidance devices including guide sheaths (GS), fluoroscopy, virtual bronchoscopy (VB)	-	≤ 6-month	**Diagnostic accuracy** The prevalence of malignancy was reported in 13 studies, and overall pooled prevalence being 72%. The QUADAS tool revealed that there were generally low scores in all of the eligible papers (poor methodology quality). Radial probe EBUS had point sensitivity of 0.73 (95% CI: 0.70, 0.76) and point specificity of 1.00 (95% CI: 0.99, 1.00) for the detection of lung cancer. Diagnostic odds ratio was 103.75 (95% CI: 46.4, 231.7). The results correspond to a positive likelihood ratio of 26.84 (95% CI: 12.60, 57.20) and a negative likelihood ratio of 0.28 (95% CI: 0.23, 0.36). Significant inter-study heterogeneity for sensitivity was observed with prevalence of malignancy and lesion size being possible sources. No heterogeneity in specificity was found. Ten studies reported overall diagnostic yield for lesions ≤20 mm and for lesions ≥20 mm. Pooled statistics demonstrated a diagnostic yield of 56.3% (95% CI: 51.0, 61.0%) and 77.7% (95% CI: 73.0, 82.0%) for lesions ≤20 mm (364 patients) and lesions ≥20 mm (367 patients), respectively. This difference was significant (p=0.007). **Safety** Complication rates were not reported in two studies; in the remaining 14 studies varied from 0% to 7.4%. The highest complication rate was noted in a single study whereby three out of the four patients experienced only minor self-limiting bleeding. No patients in any study experienced bleeding requiring intervention. Pneumothorax rate varied from 0% to 5.1%, with a pooled rate of pneumothorax across 14 studies of 1.0% (11/1,090). The pooled rate of intercostal catheter drainage of pneumothorax was 0.4%. No deaths were reported in any studies.	

Evidence Table   :   Diagnostic accuracy/ safety/ organisational (**r-EBUS**)

Question   :   What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
9. Ali MS, William T, Benjamin T, et al. Radial endobronchial ultrasound for the diagnosis of peripheral pulmonary lesions: A systematic review and meta-analysis. Respirology. 2017; 22(3):443-453	**Systematic review and meta-analysis** An Ovid MEDLINE and PubMed search was performed in September 2016. Studies that employed r-EBUS for diagnosing peripheral pulmonary lesions (PPLs) and provided data regarding its diagnostic yield, factors affecting its performance and associated complications were included. The quality of the eligible studies was assessed using the QUADAS-2 tool. Meta-analysis was performed using MedCalc (Version 16.8, Ostend, Belgium). Inverse variance weighting was used to aggregate diagnostic yield proportions across studies. Publication bias was assessed using funnel plot and Duval and Tweedie's test. The reference standard was confirmation by histology of surgically obtained specimens or close clinical follow-up for at least 6 months.	II-2	Fifty-seven studies with a total of 7,872 lesions were included in this meta-analysis. These studies were published between October 2002 and August 2016.	r-EBUS with additional guidance devices including guide sheaths (GS), fluoroscopy	-	≤ 6 months	**Diagnostic accuracy** The QUADAS-2 tool showed all included studies were low of risk of bias. Funnel plot and Duval and Tweedie's test did not suggest publication bias. Overall weighted diagnostic yield for r-EBUS was 70.6% (95% CI: 68.0, 73.1). Twenty-eight studies reported diagnostic yields separately for lesions ≤2 cm and >2 cm. Weighted diagnostic yields for 1,067 lesions ≤2 cm and 2,107 lesions >2 cm were 60.5% (95% CI: 56.6, 64.4) and 75.7% (95% CI: 72.1, 79.2), respectively (p<0.001). Eight studies reported diagnostic yields based on subgroups of lesions ≤3 cm and >3 cm. Weighted diagnostic yields for 544 lesions ≤3 cm and for 656 lesions >3 cm were 58.7% (95% CI: 46.1, 70.7) and 68.4% (95% CI: 61.7, 74.8), respectively (p=0.107). Subgroup analysis was also performed for benign and malignant lesions. For 1,320 benign lesions, weighted diagnostic yield was 60.2% (95% CI: 54.7, 65.4), whereas for 4,605 malignant lesions the diagnostic yield was 72.4% (95% CI: 69.1, 75.6) (p=0.018). Twelve studies evaluated the impact of r-EBUS probe positioning with regards to the lesion. For 1,026 lesions where the r-EBUS probe was adjacent to the lesion, weighted diagnostic yield was 52.0% (95% CI: 43.3, 60.8). On the other hand, for 2,244 lesions where the r-EBUS probe reached within the lesion, diagnostic yield was 78.7% (95% CI: 72.9, 84.0) (p<0.001). Nine studies reported the impact of bronchus sign on the diagnostic yield of PPLs. For 868 lesions with bronchus sign present on CT scan and 494 lesions with bronchus sign absent on CT scan, the weighted diagnostic yields were 76.5% (95% CI: 65.9, 85.6) and 52.4% (95% CI: 37.6, 67.0), respectively (p=0.008). There was no significant difference in the diagnostic yields based on the lobar location. **Safety** In total, 160 complications (82 pneumothoraces, 61 bleeds and 17 pneumonias) were reported. Overall complication rate was 2.8%. Rate of chest tube insertion was 0.2%.	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(r-EBUS versus CT-PNB)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
10. Wang W, Like Yu L, Wang Y et al. Radial EBUS versus CT-guided needle biopsy for evaluation of solitary pulmonary nodules. Oncotarget. 2018; 9(19):15122–15131	**Randomised controlled trial** To compare the diagnostic yield, complications and influencing factors between r-EBUS and CT-guided percutaneous needle biopsy (CT-PNB) for evaluation of solitary pulmonary nodules (SPNs). According to the inclusion/ exclusion criteria, 160 eligible patients were randomly allocated into either r-EBUS or CT-PNB group by random number selection.	II-1	A total of 215 patients with SPN detected by spiral CT were consecutively enrolled from June 2014 to June 2016 at the Endoscopic Centre of Nanjing Chest Hospital.	r-EBUS (n=80)	CT-PNB (n=80)	≤1-year	**Diagnostic accuracy:** No statistical difference between the mean diameters of SPNs in the two group (2.17 ± 0.31 cm in the r-EBUS and 2.09 ± 0.30 cm in the CT-PNB). **Pathological diagnosis of SPNs** Sensitivity of r-EBUS for malignancy was 73.7% (42/57) and for benign lesions was 43.5% (10/23); overall diagnostic accuracy was 65% (52/80). In CT-PNB group, overall diagnostic accuracy was 85% (68/80), sensitivity for malignancy was 87.9% (51/58), and for benign was 81.0% (17/21), respectively. **Diagnostic yield and influencing factors** Factors affecting diagnostic yield of r-EBUS were size of SPNs, the distance from the SPN lesion to pleura, and the location of the probe to lesions. Those SPN with diameter >20 mm and ≤30 mm had higher diagnostic yield than that those with diameter >10 mm and ≤20 mm cases (76.6% versus 50.0%; p=0.027). The longer the distance between the SPN lesion and pleura, the higher the diagnostic yield (p=0.031). The r-EBUS' probe located within the SPNs had higher diagnostic yield than those probes adjacent or invisible to the SPNs (p=0.009). However, these three factors were not observed to influence the diagnostic yield in CT-PNB group (p=0.984, p=0.778, and p=0.972). Overall, diagnostic yield in CT-PNB group were higher than those in r-EBUS group (p=0.006). **Safety:** **Comparison of incidence of complications and influencing factors between the r-EBUS and CT-PNB** Incidence of complications in CT-PNB group were higher than those in r-EBUS group (p=0.002). In CT-PNB group, the incidence of pneumothorax was 17.5% (14/80); 14 patients encountered pneumothorax including one patient requiring insertion of thoracotomy tube. In R-EBUS group, only one patient had pneumothorax with compressed lung volume <5 % and was relieved in two days through oxygen therapy; the rate of pneumothorax was 1.25% (1/80). The incidence of pneumothorax between these two groups was significant different (p=0.001). Another common complication is haemorrhage. In this study, four patients in r-EBUS group and six patients in CT-PNB group encountered pulmonary haemorrhage with no statistical difference in its incidence between two groups (p=0.900, and p=0.842, respectively). In CT-PNB group, no pneumothorax occurred in the subgroup in which the distance from SPN to pleura was ≤20 mm (0%, 0/24). However, a significant difference was found between the rest two subgroups in which distance from lesion to pleura ranged was 20 mm to 40 mm or >40 mm (p= 0.001). Furthermore, the distance between the lesion and pleura was also another influencing factor for pulmonary haemorrhage (p=0.042). Those SPNs' location was near to great vessels would be more likely to cause pulmonary haemorrhage (p=0.009).	

Evidence Table   :   Diagnostic accuracy/ safety/ organisational **(ENB, VB, r-EBUS, UB, and GS)**

Question   :   What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
11. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. Chest. 2012; 142(2): 385-393	**Systematic review and meta-analysis** An Ovid MEDLINE (1950 through October 2010) and PubMed database search wasperformed. Studies evaluating the diagnostic yield of any one or a combination of ENB, VB, r-EBUS, UB, and 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 approach were used.	II-2	A total of 3,004 patients with 3,052 lesions from the 39 studies were included in the meta-analysis.	ENB, VB, r-EBUS, UB, and GS	Traditional bronchoscopy and transthoracic needle aspiration (TTNA)	-	**Diagnostic accuracy** The pooled diagnostic yield was 70% (95% CI: 67.1, 72.9%; p<0.0001) which is higher than the yield for traditional transbronchial biopsy. Diagnostic yield appeared to be highest (73.2% 95% CI: 64.4, 81.9%) when a guide sheath was used, although there was significant variation across studies (Q statistic=63.8%, p<0.0001). The yields for VB (72.0% 95% CI: 65.7, 78.4%) and r-EBUS (71.1% 95% CI: 66.5, 75.7%) were also higher than the overall weighted diagnostic yield. Twenty studies evaluated the effect of size on the diagnostic yield. 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, 67.7%) and 82.5% (95% CI: 78.6, 86.4%), respectively. **Safety** 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.	

Evidence Table   :   Diagnostic accuracy/ safety/ organisational **(r-EBUS+VBN versus CT-TNB)**

Question   :   What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
12. Han Y, Kim HJ, Kong KA et al. Diagnosis of small pulmonary lesions by transbronchial lung biopsy with radial endobronchial ultrasound and virtual bronchoscopic navigation versus CT-guided transthoracic needle biopsy: A systematic review and meta-analysis. PLoS One. 2018; 13(1): e0191590	**Systematic review and meta-analysis** A systematic literature search was performed in May 2016 for all studies describing biopsy of pulmonary lesions (PLs) using transbronchial lung biopsy (TBLB) with r-EBUS, GS and virtual bronchoscopic navigation (VBN) or CT-guided transthoracic needle biopsy (CT-TNB) among five databases: MEDLINE, EMBASE, the Cochrane Library Central Register of Controlled Trials, Web of Science, and Scopus. The articles were limited to those published after 2000 that studied small PLs ≤3 cm. The quality of the included studies was assessed using the QUADAS-2 tool. Meta-analyses were performed with Comprehensive Meta-Analysis software (version 3.0, Biostat, Englewood NJ, USA). Publication bias was assessed using a funnel plot and Egger's linear regression test. To estimate the diagnostic yields by PL size, a subgroup analysis was performed on PLs ≤2 cm and PLs >2 cm but ≤3 cm in diameter.	II-2	From 7,345 records, nine articles on the bronchoscopic (BR) approach (813 procedures) and 15 articles on the percutaneous (PC) approach (3,463 procedures) were included in the meta-analysis.	r-EBUS & VBN	CT-TNB	≤6 months	**Diagnostic accuracy:** **Quality assessment** The overall methodological quality was low or unclear due to potential bias regarding methodological quality and applicability. The choice between pathological confirmation by surgery or by clinical follow-up was not uniform and had a risk of bias. Most publications in the CT-TNB group used a retrospective study design, making it difficult to evaluate the consistency of patient selection. The funnel plots for PLs ≤3 cm showed general symmetry, and no publication bias was determined by Egger's linear regression test in the r-EBUS & VBN (p=0.17) and CT-TNB (p=0.41) groups. **Test performance: meta-analysis** For lesions with a diameter ≤3 cm, diagnostic yields in 813 procedures from nine r-EBUS & VBN studies ranged from 63% to 85%. The pooled diagnostic yield was 75% (95% CI: 69, 80). Diagnostic yields in 2,578 procedures from nine CT-TNB studies ranged from 86% to 97%, with a pooled diagnostic yield of 93% (95% CI: 90, 96). **Subgroup analysis** In the r-EBUS & VBN group, the diagnostic yields for lesions ≤2 cm in six studies ranged from 44% to 76%, and the pooled diagnostic yield was 66% (95% CI: 55, 76). The diagnostic yields for lesions between 2 and 3 cm in the same six studies were 78% to 97%, and the pooled diagnostic yield was 81% (95% CI: 75, 85). In the CT-TNB group, 12 studies with lesions ≤2 cm reported diagnostic yields of 77% to 98% and a pooled diagnostic yield of 92% (95% CI: 88, 95). Of these studies, six with lesions between 2 and 3 cm reported diagnostic yields of 90% to 98% and a pooled diagnostic yield of 96% (95% CI: 94, 98). **Safety:** Most of the studies included in the analysis reported complications associated with the procedure. **r-EBUS & VBN** In the r-EBUS & VBN group, pneumothorax occurred in 10 subjects with a total of 426 procedures, and chest tube insertion and haemoptysis occurred in less than 1% of all procedures. **CT-TNB** In contrast, the rate of complications in the CT-TNB group (13 studies) was quite high. The incidence of pneumothorax as a post-procedural complication ranged from 15% to 52%, and the pooled complication rate was 26% (95% CI: 21, 32) among 2,611 procedures. Among these cases, the incidence of severe pneumothorax requiring chest tube insertion was 2% to 8%, and the pooled incidence rate was 3% (95% CI: 1.8, 4.8). Pulmonary haemorrhage was reported in nine studies with an incidence rate ranging from 3% to 43%, and the pooled incidence rate was 16% (95% CI: 10, 25) among 1,545 procedures. Haemoptysis was reported in eight studies with an incidence range of 2% to 11%, and the pooled incidence rate was 7.1% (95% CI: 6.0, 8.4) among 1,865 procedures	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(UTB versus TB-GS)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
13. Oki M, Saka H, Ando M et al. Ultrathin bronchoscopy with multimodal devices for peripheral pulmonary lesions: a randomized trial. Am J Respir Crit Care Med. 2015; 192(4): 468-476	**Randomised controlled trial**	II-1	A total of 310 patients were enrolled in this study; 150 in the UTB group and 155 in the TB-GS group were finally analysed.	UTB group (transbronchial biopsy was performed using a 3.0-mm ultrathin bronchoscope under EBUS, VBN, and fluoroscopic guidance) (n=150)	TB-GS group (transbronchial biopsy was performed using a 4.0-mm thin bronchoscope under EBUS with a GS, VBN, and fluoroscopic guidance) (n=155)	1-year	**Diagnostic accuracy: Primary endpoint**	
	In four centres, patients with suspected peripheral pulmonary lesions ≤30 mm in the longest diameter were included and randomised to undergo transbronchial biopsy with r-EBUS, fluoroscopy, and VBN guidance using a 3.0-mm ultrathin bronchoscope (UTB group) or a 4.0-mm thin bronchoscope with a guide sheath (TB-GS group).						The histologic diagnostic yield in the UTB group and TB-GS group was 74% (111/150) and 59% (92/155) (p=0.007), respectively.	
							When divided based on the final histologic diagnosis, the diagnostic yields of the UTB method and the TB-GS method were 42% and 36% (p=0.622) in benign lesions and 81% and 70% (p=0.040) in malignant lesions, respectively.	
	Randomisation was performed by the minimisation method with stratification factors including lesion size, lesion distance from hilum on CT, and examiner experience.		No statistically significant difference in the baseline characteristics in both groups.				**Secondary endpoints**	
							Comparison of both groups revealed that the UTB method provided a higher diagnostic yield for lesions located within the outer third elliptical lung region (p=0.002) and lesions with bronchus sign (p=0.001) than the TB-GS method. However, there was no significant difference in the visibility on EBUS (p=0.080).	
	The final diagnoses were established by pathologic evidence from biopsy including bronchoscopic or surgical procedures, microbiologic analysis, or clinical follow-up.						The UTB could reach more distal bronchi than the TB (median, 5th-generation bronchi versus 4th-generation bronchi; p<0.001).	
							Safety	
	The primary endpoint was the histopathologic diagnostic yield of transbronchial biopsy whereas secondary endpoints were overall diagnostic yield, diagnostic yield according to benign or malignant, lesion size, lesion location, ultrasonic probe location on the EBUS image, level of bronchus reached with bronchoscopes, time of procedure, and safety.						There was no significant difference in complication rate between UTB group and TB-GS group (p=0.595).	
							Complications including pneumothorax, bleeding, chest pain, and pneumonia occurred in 3% and 5% in the respective groups.	
							Organisational	
							There was no significant difference in procedural time (median, 27.5 minutes in UTB group and 28.5 minutes in TB-GS group; p=0.101).	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(BTPNA)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
14. Herth F, Eberhardt R, Sterman D et al. Bronchoscopic transparenchymal nodule access first in human trial of a novel procedure for sampling solitary pulmonary nodules. Thorax. 2015; 70: 326–332	**Prospective single arm interventional study** Using the subject's CT, an optimal airway wall point of entry (POE) and an avascular path through lung tissue from the POE to the SPN was calculated. A tunnel tract was created from the POE to the nodule using a set of catheter-based tools under fused fluoroscopy guidance. The patients proceeded to surgical resection immediately after the biopsy. The primary endpoint of the study was to evaluate the feasibility to access and biopsy the nodule. Safety was evaluated by carefully assessing the subject for any intraprocedural and post-procedural complications. Secondary endpoints included parameters such as the biopsy yield, procedural time points, length of tunnel path created, number and adequacy of the biopsy samples.	II-2	Twelve patients (six men and six women with a median age of 62 years, with a SPN detected on CT imaging, which was suspicious for lung cancer, who were suitable for surgical resection) were enrolled in this study	BTPNA	-	Three and six months after the procedure	**Diagnostic accuracy** The BTPNA procedure was successfully completed in 10 patients (83%), and a positive biopsy was successfully obtained in all 10 cases in which a tunnel was successfully created from the POE to the SPN. An average of 3.3 biopsy samples were obtained (range 0–6) in the 12 patients who underwent BTPNA. The overall yield for BTPNA was 83% (10/12) as the tract could not be created in two patients. The biopsy yield was 100% for procedures where a tunneled pathway was created, and at least one biopsy attempted. Adequate histological sampling sufficient for a histological diagnosis was successfully achieved in 10 of the patients. Inspection at surgery and in the post-resection specimens demonstrated that the tunnel path was created in the correct position and orientation that led directly to the target nodule. The histological findings from the biopsies obtained by BTPNA correlated with the final pathology in all the surgically resected nodules. **Safety** There were no significant intraprocedural adverse events (AEs). Fluoroscopy, after completion of the procedure, did not reveal any occurrence of AEs such as pneumothorax. Inspection during surgical resection and of the resected lobe did not reveal any evidence of localised haemorrhage, bronchial or pulmonary lacerations. The only AE observed was a transient rise in troponin levels in one patient post-BTPNA and surgical resection. Outpatient follow-up conducted at 90 days and 180 days after the procedure did not reveal any AEs attributable to the procedure. **Organisational** The mean procedure time was 39.8 minutes, with the planning stage accounting for 18.0 minutes (range 10.0–30.0 minutes), and the creation of the tunnelled pathway was 21.8 minutes (range 12.0–40.0 minutes). A learning curve was demonstrated with the first four, second four, and third four tunnel creation times averaging 35.0, 21.5, and 13.3 minutes, respectively. Hence, after only eight procedures, the procedure time of BTPNA is comparable to either transthoracic CT-guided biopsy or standard transbronchial biopsy. The fluoroscopy time was 5.5 minutes (range 1.8–11.6 minutes). The mean tunnel length was 47 mm (range 10–90 mm). **Authors conclusion** This first in human study demonstrated that bronchoscopic transparenchymal access of SPNs is feasible.	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(BTPNA)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
15. Harzheim D, Sterman D, Shah P et al. Bronchoscopic transparenchymal nodule access: feasibility and safety in an endoscopic unit. Respiration. 2016; 91:302–306	**Prospective single arm interventional study** To evaluate the safety and feasibility of the BTPNA procedure in a standard endoscopy suite. This is the first evaluation of the technique being performed outside an operation theatre. The subject's CT was employed to calculate an airway wall POE as well as an avascular path through lung tissue from the POE to the SPN. Using a set of catheter-based tools under fused fluoroscopy guidance, a tunnelled tract was created from the POE to the nodule. The primary endpoint was to further evaluate the feasibility and safety of the BTPNA procedure in a standard bronchoscopy suite. Safety was evaluated by assessing any intraprocedural and post-procedural complications. Secondary endpoints included parameters such as the biopsy yield, procedural time points, length of tunnel path created, number and adequacy of the biopsy samples.	II-2	Six patients (three men and three women, median age 68 years) with a SPN detected on CT imaging, which was suspicious for malignancy were enrolled in this study. The mean length of the five tunnels from POE on the airway wall to the nodule was 29 mm (range 11–46 mm). The size of the lesions ranged from 14 to 21 mm in long-axis diameter, with a mean target diameter of 17.5 mm.	BTPNA	-	Two hours after the BTPNA procedure, a chest x-ray was performed and the patients were surveyed for at least 72 hours	**Diagnostic accuracy** A positive biopsy was obtained in all five cases in which the BTPNA procedure could be successfully completed. Adequate histological sampling sufficient for a histological diagnosis was successfully attained in five patients. The biopsies obtained by BTPNA correlated with the final pathology in all four surgically resected nodules. **Safety** There were no significant intraprocedural AEs. Two pneumothoraces were diagnosed by chest x-ray 2-hour after the procedure, with one pneumothorax requiring drainage. There were no other complications within the 72-hour hospitalization following the BTPNA procedure. **Organisational** The mean procedure planning time was 14.4 minutes and the creation of the tunnelled pathway was 18.8 minutes. The fluoroscopy time was 3.7 minutes (range 1.8–7.5 minutes). The mean tunnel length was 28.75 mm (range 11–46 mm).	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(ETTNA)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
16. Yarmus LB, Arias S, Feller-Kopman D et al. Electromagnetic navigation transthoracic needle aspiration for the diagnosis of pulmonary nodules: a safety and feasibility pilot study. J Thorac. 2016; 8(1):186-194	**Prospective single arm interventional study** To evaluate the safety, feasibility and diagnostic yield of electromagnetic navigation transthoracic needle aspiration (ETTNA), ENB, and r-EBUS in a single procedural setting. All patients enrolled underwent r-EBUS for lung cancer staging followed by ENB and ETTNA. Feasibility of performing ETTNA and a safety assessment by recording procedural related complications including pneumothorax or bleeding was performed. Diagnostic yield of ETTNA defined by a definitive pathologic tissue diagnosis was recorded. An additional diagnostic yield analysis was performed using a cohort analysis of combined interventions (r-EBUS + ENB + ETTNA). All non-diagnostic biopsies were either followed with radiographic imaging or a surgical biopsy.	II-2	A total of 594 patients were assessed for eligibility of which 35 met inclusion criteria during the study period. Eleven patients declined consent. Twenty-four subjects were recruited into the study. The mean SPN size was 20.3 mm (range, 12–29 mm) and mean distance from the pleural surface to the edge of the nodule in its shortest path distance was 12.6 mm (1.6–29.5 mm).	ETTNA ETTNA + ENB ETTNA + ENB + r-EBUS	-	All subjects had a post procedural chest radiograph within two hours of the procedure. If chest tube placement was not needed, a four hour follow up chest radiograph was performed. Subjects with a non-malignant diagnosis were followed radiographically for 12 months.	**Diagnostic accuracy** Twenty-four r-EBUS and ENB were performed,and ETTNA was feasible in 96% of cases (23/24). The diagnostic yield for ETTNA alone was 83% and increased to 87% when ETTNA was combined with ENB (p=0.0016). When ETTNA and ENB were performed with r-EBUS for complete staging, the diagnostic yield increased further to 92% (p=0.0001). **Safety** Twenty-four r-EBUS and ENB were performed,and ETTNA was feasible in 96% of cases (23/24). No bleeding, haemoptysis, or respiratory events were encountered. There were five (5/24, 21%) pneumothoraces of which only two (2/24, 8%) subjects required chest tube placement. None of the chest tube placements were emergent. In the five cases with a pneumothorax, 4/5 (80%) had a diagnosis from the procedure. All four of these cases were diagnostic from the ETTNA sample alone. All five samples from patients who experienced a pneumothorax yielded lung tissue on pathologic analysis. **Organisational** Total procedural time as defined by the time the EBUS bronchoscope was inserted into the oropharynx until the time the ETTNA needle was removed was 72.5 minutes. The additional time to perform the ETTNA (18.3 minutes) was shorter than either r-EBUS (20.5 minutes) or ENB (22.9 minutes) and more importantly, the additional procedure time was not associated with any anaesthesia related complications.	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(Robotic bronchoscopy)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
17. Rojas-Solano JR, Ugalde-Gamboa L, Machuzak M. Robotic bronchoscopy for diagnosis of suspected lung cancer: a feasibility study. J Bronchology Interv Pulmonol. 2018; 25:168-175	**Single centre, prospective, case series** To assess complication rate and technical feasibility of robotic bronchoscopy performed with the Robotic Endoscopy System (RES). Adult patients from a single institution underwent bronchoscopy of suspected lesions with a bronchus sign with the RES. The primary outcome was complication rate, as assessed by the incidence of related serious adverse events (SAE). The secondary endpoint was the technical success defined as the ability of the RES to complete the intended procedure. The ability to directly visualize deployment of the biopsy instruments and to observe the bronchial tree during bronchoscopy was also assessed. The total procedure time was defined by the time the bronchoscope is inserted into the oropharynx until the time the bronchoscope was removed.	III	Of the 17 screened patients, 15 eligible patients with median age 67 years underwent bronchoscopy with the RES. Of the two excluded patients, one had no lesion identifiable on the pre-procedure CT scan and another showed a lung nodule with no bronchus sign.	Robotic Endoscopy System (RES)	-	All patients completed two prespecified follow up visits (2- and 7-day post-procedure)	**Diagnostic accuracy** Tissue acquisition under direct visualization was performed using the RES in 14 of 15 (93%) patients. In one case, the system required to be restarted during the procedure and the bronchoscope had to be removed for cleaning. After cleaning, the procedure continued. The lesions (12 peripheral and three central) were located in the right lower lobe (33%), right upper lobe (27%), left upper lobe (27%), and left lower lobe (13%). Cancer was confirmed in 60% (9/15) of patients. Benign features were found in five of six patients. **Safety** During the study period, there were no reports of SAE related to the use of the RES such as pneumothorax or significant bleeding requiring intervention. Three minor unrelated complications were reported. One patient reported symptoms of a "fever sensation" four days after the procedure. The symptoms resolved spontaneously and were absent at the 7-day follow-up. Another patient experienced anaesthesia-related nausea and vomiting. These events resolved within six hours. The third patient reported back pain. A physical examination showed no abnormality except for contracture of the paravertebral muscles. **Organisational** The total median time to biopsy location was 21 (7 to 84) minutes. The median time to biopsy location reduced from 45 (21 to 84) minutes (first 5 cases) to 20 (7 to 47) minutes (last 9 cases; p=0.039). All patients were discharged within six hours following the procedure.	

Evidence Table   :   Diagnostic accuracy/ safety/ organisational **(Robotic bronchoscopy)**

Question   :   What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
18. ..Chaddha U, Kovacs S, Manley C et al. Robot-assisted bronchoscopy for pulmonary lesion diagnosis: results from the initial multicenter experience. BMC Pulm Med. 2019; 19(1): 243	**Multi-centre, retrospective, case series** They retrospectively reviewed data on consecutive cases in which robot-assisted bronchoscopy (RAB) was used to sample lung lesions at four centres in the US (academic and community). The medical records of consecutive patients who were considered to require a guided bronchoscopy (ENB, VB with or without r-EBUS) and underwent RAB to diagnose lung lesions were reviewed and included in the analysis. Endpoints: device or procedure-related complications, successful navigation, diagnostic yield, navigation and procedure time. Multivariable logistic regression was performed to determine the odds ratio of diagnostic yield adjusted for the following characteristics: lesion location, centrality, density and size, bronchus sign, and r-EBUS view.	III	One hundred and sixty-seven lesions in 165 patients (75 females) were included in the analysis. The average age at the time of the procedure was 66.5 ± 10.9 years; 77% were smokers.	Robot-assisted bronchoscopy (RAB)	-	Average 6-month (185 ± 55 days)	**Diagnostic accuracy:** **Lesion characteristics** The average size of targeted lesions based on the largest measurable diameter was 25.0 ± 15.0 mm; 71.3% were ≤30 mm and 70.7% were located in the peripheral third of the lung. Bronchus-sign on the pre-procedure CT scan was observed in 106 (63.5%) lesions, and 68.8% lesions were solid. **Biopsy data** Tissue samples were successfully obtained in 161 (97.6%) patients. Samples were not obtained in four (2.4%) cases; one software failure, three unsuccessful navigation. Navigation was successful in 148 (88.6%) lesions with 69.1% to 77% overall diagnostic yield (conservative and maximum estimate). There were 13 cases in which pathology showed inflammation for which follow-up was not available. The targeted lesions were detected with r-EBUS in 141 (84.4%); eccentric view in 42.5%, and concentric view in 57.5%. The yield was 81.5%, 71.7% and 26.9% for concentric, eccentric and absent r-EBUS views, respectively (p=0.001). Diagnostic yield was higher for lesions with a bronchus sign (78.3% versus 54.1%; p=0.001). Yield was not different for solid versus ground glass nodules (68.8% versus 70.6%; p=0.74), central versus peripheral location (73.5% versus 67.8%; p=0.47) and did not depend upon lesion size (45.5% for <10 mm versus 68.5% for 10–30 mm versus 77.1% for ≥30 mm; p=0.11). **Safety** Pneumothorax occurred in six (3.6%) cases, requiring chest tube placement in four (2.4%). Significant bleeding post-biopsies was reported in four (2.4%) cases. There was no need for blood transfusion, open thoracotomy or use of endobronchial blockers in any case. There were also no reports of respiratory failure, deaths or any other procedure-related complications. **Organisational** The average navigation and procedure time were 17.8 ± 19.1 minutes and 58.6 ± 31.4 minutes, respectively.	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(Robotic bronchoscopy)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
19. Fielding D, Bashirzadeh F, Son H et al. First human use of a new robotic-assisted fiber optic sensing navigation system for small peripheral pulmonary nodules. Respiration. 2019; 98: 142-150	**Single centre, prospective, case series** This first-in-human study evaluated the safety and feasibility of a new shape-sensing robotic bronchoscope system to bronchoscopically approach and facilitate the sampling of small peripheral pulmonary nodules of 1-3 cm. Secondary objectives included evaluating procedural characteristics and early performance trends (overall diagnostic yield and yield for malignancy). Procedure time (defined as catheter insertion to removal) and the mean number of biopsy attempts (characterized by a series of tool passes and subsequent repositioning of the catheter) were also assessed. Disease assessment used pathology from the sample obtained through the study procedure and confirmed through up to six months per standard of care.	III	Thirty subjects underwent a biopsy attempt; one was later found to be ineligible due to previous radiotherapy and was excluded from the analysis. The mean patient age was 63.2 ± 9.7 years, with an almost even distribution of gender. The most commonly reported comorbidities included chronic obstructive pulmonary disease, prior history of extra pulmonary malignancy, and hypertension. Eleven subjects (36.7%) had previously undergone biopsy attempts.	Robotic-assisted bronchoscope system	-	All subjects were required to complete three pre-specified follow-up visits (7-day, 3-month and 6-month)	**Diagnostic accuracy** The study included 29 subjects with a mean lesion size of 12.2 ± 4.2 mm, 12.3 ± 3.3 mm, and 11.7 ± 4.1 mm in the axial, coronal, and sagittal planes, respectively. The CT bronchus sign was absent in 41.4% (12/29) of cases. In 28 of 29 cases (96.6%), the target was reached and tissue sample was obtained (supportive of a histological or cytological assessment with feature other than bronchial epithelial cells or lung parenchyma). Early performance trends through the 6-month follow-up demonstrated an overall diagnostic yield of 79.3% (95% CI: 60.3, 92.0%), with a diagnostic yield for malignancy (sensitivity) trending towards 88.2% (95% CI: 63.6, 98.5%) and specificity trending towards 63.6% (95% CI: 30.8, 89.1%). However, it should be noted that this was not designed as a performance study. **Safety** There were no instances of pneumothorax or bleeding requiring intervention observed and no airway injury was reported. No instances of unexpected bleeding, which included any type of bleeding that required prolonged or continuous suction were reported. Two subjects experienced procedure-related complications: adverse reaction to anaesthesia and contralateral pneumonia. **Organisational** Procedure time was 63.9 ± 24.4 minutes; mean procedure time of the first and last five cases was approximately 95.0 and 61.0 minutes, respectively. The mean number of biopsy attempts was 2.6 ± 1.8. The catheter instrument reached significantly further than the standard bronchoscope used; a comparison of branch points reached yielded a mean difference of 2.21 ± 1.2 (95% CI: 1.76, 2.67; p<0.001). Most subjects (25/26, 86.2%) were discharged the same day with a mean length of stay of 5.2 ± 0.6 hours; with regard to the four overnight hospital admissions, only one was for a clinical observation of the muscle relaxant complication, while the other three admissions were pre-planned.	

Evidence Table   :   Diagnostic accuracy/ safety/ organisational (**Transbronchial cryobiopsy versus forceps biopsies**)
Question   :   What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
20. Schuhmann M, Bostanci K, Bugalho A et al. Endobronchial ultrasound-guided cryobiopsies in peripheral pulmonary lesions: a feasibility study. Eur Respir J. 2014; 43(1): 233-239	**Case series (cross-over)** They assessed the safety, feasibility and efficacy of the cryoprobe for transbronchial biopsies in solitary pulmonary lesions with the guidance of r-EBUS. After identifying the lung lesion by r-EBUS, patients received three transbronchial biopsies of their lung lesion with forceps as well as three with the cryoprobe. Patients were randomised to receive either the forceps or the cryobiopsies first according to a randomisation list with a distribution of 1:1. After six biopsies, the examination was terminated and 2-hour after the procedure, a chest radiograph was performed. The length of time required for the detection of the lesion as well as for the individual biopsy techniques (compared diagnostic yield and sample size) was recorded. Bleeding and complications such as post-interventional pneumothorax, as well as histological outcomes were documented.	III	A total of 39 consecutive patients (mean age 68 years) with a solid pulmonary lesion of ≤40 mm were included in this prospective study. One patient was excluded due to visible endobronchial tumour. The remaining 38 patients had a lung lesion of 29.7 ± 7.3 mm in diameter, of which 31 were malignant and seven were benign.	Transbronchial cryobiopsy	Forceps biopsies	2-hour	**Diagnostic accuracy** The overall diagnostic yield including lesions not biopsied as they unable to detect by r-EBUS was 60.5% (23 out of 38 patients) whereas in the lesions reached by r-EBUS, it was 74.2% (23 out of 31 patients). In 19 cases, both techniques established a diagnosis. Additionally, four cases that were non-diagnostic with forceps biopsy were successfully diagnosed with cryobiopsy resulting in a diagnostic yield of 61.3% (19 out of 31) for forceps and 74.2% (23 out of 31) for cryobiopsy, respectively (p=0.42). Cryobiopsies were significantly obtained larger sample size than forceps biopsies (11.17 mm²versus 4.69 mm²; p<0.001). **Safety** No severe complications were observed during this study. There was one case of moderate bleeding at the end of all six biopsies necessitating prolonged suction with the bronchoscope, but no other intervention. No pneumothorax was detected on chest radiography. **Organisational** The average time required for forceps biopsy was significantly shorter than the time required for the cryobiopsies (5.1 ± 2.75 minutes versus 11.6 ± 4.4 minutes; p<0.0001).	

Evidence Table : Diagnostic accuracy/ safety/ organisational **(Transbronchial cryobiopsy + ENB versus TBB)**

Question : What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
21. Taton O, Bondue B, Gevenois P et al. Diagnostic yield of combined pulmonary cryobiopsies and electromagnetic navigation in small pulmonary nodules. Pulm Med. 2018; 6032974	**Case series** To compare the diagnostic yield of transbronchial lung cryobiopsy (TBLC) with standard transbronchial biopsy (TBB) in pulmonary nodules of less than 2 cm in diameter; both guided by r-EBUS combined with ENB. Adverse events occurring during and after completion of the procedure were also recorded. All samples were analysed by a pathologist (blind for review) with more than 25 years of experience in lung pathology. If the diagnosis based on TBB and TBLC samples was uncertain or inconsistent with the clinical presentation, operable patients were referred for surgical resection and non-operable patients were followed up by CT six months thereafter. Pathological analysis of the surgical specimen and CT follow-up were considered as the independent methods of reference for establishing the final diagnosis.	III	A total of 32 consecutive patients (18 men and 14 women; mean age 68 ± 9 years) were included. Mean diameter of the target nodules was 16 ± 3 mm; 15, 16, and one patient, respectively, had the nodule in their upper, lower, or middle lobe. Eleven patients presented a bronchus sign at CT.	Transbronchial lung cryobiopsy (TBLC)	Standard transbronchial biopsy (TBB)	6-month	**Diagnostic accuracy:** **Final diagnosis** Twenty-five nodules were malignant and 18 were surgically resected. Surgery was avoided in fo Among the 29 patients in whom both TBLC and TBB could be obtained, their overall diagnostic yield was 69% (20/29) and 38% (11/29), respectively (p=0.017). Considering the three patients in whom the target nodule could not be reached with ENB, the diagnostic yield was 63% (20/32) and 34% (11/32), respectively (p=0.024). The sensitivity and specificity of TBLC for the diagnosis of a malignant nodule were 61% and 100%, respectively, as compared to 35% and 100% for TBB (p=0.008 and p>0.999, respectively). The corresponding positive and negative predictive values of TBLC were respectively, 100% and 40% as compared to 100% and 29% for TBB (p>0.999 and p=0.277, respectively). The lobar location of the nodule, the bronchus sign, the nodule size, the malignant versus benign disease, or the technique used (nodule visualization or not with r-EBUS) for visualizing the nodule in addition to ENB had no statically significant impact on the diagnostic performance (p value ranging from 0.073 to 0.934). The mean diameters of the samples obtained by TBLC and TBB were 5.3 ± 0.7 mm and 1.1 ± 0.6 mm, respectively (p<0.001). **Safety** Bleeding was graded 1 and 2 in, respectively, eleven and four patients. Pneumothorax needing pleural drainage for three days was observed in one patient. No other adverse event was observed and no mortality was recorded.	

Evidence Table   :   Diagnostic accuracy/ safety/ organisational **(Transbronchial cryobiopsy versus forceps biopsies)**

Question   :   What is the diagnostic accuracy, safety, and organisational issue related to the use of guided bronchoscopy biopsy techniques?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
22. Kho SS, Chan SK, Yong MC et al. Performance of transbronchial cryobiopsy in eccentrically and adjacently orientated radial endobronchial ultrasound lesions. ERJ Open Res. 2019; 5: 00135-2019	**Case series** A retrospective single centre study at respiratory care unit, Sarawak General Hospital evaluated the performance and safety of transbronchial cryobiopsy versus forceps biopsy in eccentrically and adjacently orientated r-EBUS lesions over 17 months. The target lesion was classified as "concentric" when the probe was within and completely surrounded by the lesion, "eccentric" when the probe was within but largely biased toward one side at the edge of the lesion, and "adjacent" when the probe was not within the lesion and only placed next to the lesion. The procedure was considered to be conclusive if histological, microbiological or cytological studies provided definitive results, allowing specific treatment to be implemented. Procedures were considered to be inconclusive if results failed to provide a definitive answer to the presenting clinical problem, requiring further intervention or biopsy.	III	During the study period, a total of 127 r-EBUS procedures were performed: 114 cases were included for analysis. This study comprised of mainly male patients with overall median age of 58.5 (49.8–68.3) years. Overall lesion size was 3.48 (2.63–4.51) cm with the majority of the lesions located in the outer third of the hemithorax, and more commonly in the upper lobe.	Transbronchial cryobiopsy	Forceps biopsies	--	**Diagnostic accuracy:** **Baseline clinical and target lesion characteristics** Forceps biopsy was performed in 76/114 (66.7%) cases and cryobiopsy in 38/114 (33.3%) cases; 65 out of 114 (57%) of the lesions demonstrated eccentric and adjacent orientations to the r-EBUS, with only 43% (49 out of 114) in concentric orientations. **Overall diagnostic yield** Overall diagnostic yield was 67.5% (77 out of 114). Diagnostic yields for concentrically (n=49), eccentrically (n=47) and adjacently (n=18) orientated lesions were 79.6%, 63.8% and 44.4%, respectively. **Performance of transbronchial cryobiopsy in eccentrically and adjacently orientated r-EBUS lesions (n=65)** For concentric lesions (n=49), cryobiopsy did not increase the diagnostic yield significantly compared to the forceps biopsy group (85.7% [12 out of 14] versus 77.1% [27 out of 35]; p=0.501). For eccentric lesions (n=47), the diagnostic yield was 80% (12 out of 15) in cryobiopsy and 56.3% (18 out of 32) in forceps biopsy (p=0.114). For adjacently orientated lesions (n=18), cryobiopsy increased the diagnostic yield to 66.7% (six out of nine) from 22.2% (two out of nine) in forceps biopsy (p=0.058). Overall, for eccentrically and adjacently orientated lesions, cryobiopsy significantly increased the diagnostic yield from 48.8% (20 out of 41) to 75.0% (18 out of 24) (p<0.05). **Safety** Only one pneumothorax occurred in the forceps biopsy group whereas none in the cryobiopsy group; hence, the overall pneumothorax rate was 0.8% in the current cohort. Mild and moderate bleeding complications were more common in the cryobiopsy group compared to forceps biopsy group (47.4% versus 7.9%; p<0.001). However, most bleeding episodes in cryobiopsy were mild (39.5%), requiring only suction with local adrenaline instillation; while moderate bleeding occurred in three (7.9%) patients. There was no occurrence of severe life-threatening bleeding event. **Organisational** Overall median procedure time was 45 (35.8–60.0) minutes, with cryobiopsy recording a significantly longer duration at 50 minutes compared to 40.5 minutes in forceps biopsy. The majority of procedures (79.8%) were performed without advanced airway. However, advanced airway was used more in the cryobiopsy group to allow placement of prophylactic balloon in high-risk cases. The use of fluoroscopy was more common in the cryobiopsy group. However, guide sheath was used significantly less in the cryobiopsy group at only 57.9% versus 94.7% in the forceps group.	

Evidence Table : Economic implications **(ENB with biopsy versus CT-guided biopsy)**

Question : What is the cost-effectiveness of using guided-bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. Dale CR, Madtes DK, Fan VS et al. Navigational bronchoscopy with biopsy versus computed tomography-guided biopsy for the diagnosis of a solitary pulmonary nodule: a cost-consequences analysis. J Bronchol Interv Pulmonol. 2012; 19(4): 294–303	**Cost-consequences analysis** A decision tree was created with values from the literature to evaluate the clinical consequences and societal costs of a CT-guided biopsy strategy versus an ENB biopsy strategy for the diagnosis of a SPN. The serial use of ENB after non-diagnostic CT-guided biopsy and CT-guided biopsy after non-diagnostic ENB biopsy were tested as alternate strategies. The costs were obtained from the literature, the American Medical Association and private coding websites and are national Medicare reimbursement rates expressed in 2011 dollars. The inflation rate was estimated at 3%. One-way sensitivity analysis were plotted on a tornado diagram. All analyses were carried out in TreeAge Pro 2011.		In a hypothetical cohort of 100 patients, the base case was 65 year-old with a >40 pack-year smoking history with a 2 cm SPN	ENB biopsy strategy	CT-guided biopsy strategy	-	In the base case scenario, the ENB with biopsy strategy was associated with a 20% increased rate of VATS surgery compared with the CT-guided biopsy strategy. The ENB biopsy strategy, however, was associated with fewer complications. For every 100 ENB procedures, 13.4 fewer pneumothoraces were produced and 5.9 fewer chest tubes were placed compared to CT-guided biopsy. Additionally, 0.9 fewer haemorrhages and 0.6 fewer cases of respiratory failure occurred. The costs were greater in the ENB biopsy strategy. In the base case scenario, the ENB with biopsy strategy was on average USD$3,719 per patient more expensive than the CT-guided biopsy strategy. Mean costs per biopsy were USD$6,633 (95% CI: USD$1518, USD$18,511) versus USD$2,913 (95% CI: USD$1,248, USD$18,241) in the ENB and CT-guided arms, respectively. **Serial biopsy strategy** The sequential diagnostic strategy that combines CT-guided biopsy after non-diagnostic ENB biopsy and vice-versa decreases the rate of VATS procedures to 3%. A sequential approach starting with ENB decreases average per case cost relative to CT-guided biopsy followed by VATS, if needed, by USD$4,227; and a sequential approach starting with CT-guided biopsy decreases the cost relative to ENB followed by VATS, if needed, by USD$978. **Univariate sensitivity analyses** Costs were most influenced by the sensitivity of the CT-guided biopsy. Given that a VATS procedure cost USD$16,993, a decrease in the sensitivity of the CT-guided biopsy led to an increase number of VATS procedures and greater costs. In fact, the cost of the VATS procedure itself is the second factor in the tornado diagram, highlighting its direct role in overall costs.	

Evidence Table : Economic implications **(r-EBUS versus CT-PNB)**

Question : What is the cost-effectiveness of using guided-bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Steinfort DP, Liew D, Irving LB. Radial probe EBUS versus CT-guided needle biopsy for evaluation of peripheral pulmonary lesions: an economic analysis. Eur Respir J. 2013; 41(3): 539-547	**Cost-benefit and cost-effectiveness analysis** Decision-tree analysis using TreeAge Pro 2009 software was applied to compare downstream costs of r-EBUS guided transbronchial lung biopsy (r-EBUS-TBLB) with CT-percutaneous needle biopsy (CT-PNB). Unit cost estimates, in Australian dollars (AU$), were based on recorded hospital costs (direct and indirect) for patients undergoing the above mentioned procedures at the Royal Melbourne Hospital. All costs were updated to 2010/2011 levels according to the locally recorded Health Price Index, which reported an increase of 3% per year. Sensitivity analysis and probabilistic sensitivity analysis were undertaken to identify the more cost-beneficial approach for varying input parameter values. Cost-effectiveness analysis was performed to examine the effect of disutility resulting from two potential adverse outcomes: a procedural complication (e.g. pneumothorax or hospital admission) and a non-diagnostic procedure (meaning further anxiety and the need for additional procedures). Cost-effectiveness calculations were based on estimated disutility, according to the wait-trade-off technique.		The modelled 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 r-EBUS would be acceptable modes of initial investigation of the lesion.	r-EBUS-TBLB	CT-PNB	-	**Base-case analysis** At base-case values, CT-PNB enjoys an advantage by a having higher diagnostic sensitivity while r-EBUS-TBLB has a lower complication rate. The costs of r-EBUS-TBLB and CT-PNB to evaluate PPL appear to be equivalent. Initial evaluation with CT-PNB was cost-beneficial in comparison to r-EBUS-TBLB by a margin of AU$24 (CT-PNB AU$2,724 versus r-EBUS-TBLB AU$2,748). **Sensitivity analysis** Cost of managing complications was the factor that most influenced cost-benefit results. A higher cost of complications favoured r-EBUS-TBLB in cost comparisons, due to the lower complication rate associated with this procedure. They identified threshold values at which r-EBUS-TBLB became more cost-beneficial which included the cost of managing complications exceeding AU$501 per episode, a 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 analysis. **Probabilistic sensitivity analyses** Outcomes of Monte Carlo probabilistic simulation demonstrated the negligible difference in net costs between the two procedures. The two procedures differ by a maximum of AU$132 when comparisons of mean, median and 10th and 90th centile values are made. **Cost-effectiveness analysis** Using a theoretical wait-trade-off for a non-diagnostic procedure of 20 days (0.05 yrs), CT-PNB remained the more cost-effective procedure at base-case parameters. Sensitivity analysis, however, revealed that r-EBUS-TBLB became the more cost-effective procedure if sensitivity of r-EBUS-TBLB for benign disease exceeded 71%, if sensitivity of CT-PNB (malignancy) was below 89%, or if cost of managing complications exceeded AU$560. Unlike cost-benefit analyses, no threshold was observed for the complication rate of CT-PNB Using a theoretical wait-trade-off for a procedural complication of 20 days (0.05 yrs), CT-PNB remained the more cost-effective approach (AU$2,778 per QALY versus r-EBUS-TBLB AU$2,816 per QALY) at base-case parameters. However, sensitivity analyses demonstrated that r-EBUS-TBLB became the more cost-effective approach if the cost of complications exceeded AU$489, the complication rate for CT-PNB exceeded 40%, and if the sensitivity of r-EBUS-TBLB for detection of benign disease exceeded 65%.	

Evidence Table : Economic implications **(NB, CT-FNA, FDG-PET, and VATS)**

Question : What is the cost-effectiveness of using guided-bronchoscopy techniques for tissue biopsy of SPN in the management of lung cancer?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
3. Deppen S, Davis W, Green E et al. Cost-effectiveness of initial diagnostic strategies for pulmonary nodules presenting to thoracic surgeons. Ann Thorac Surg. 2014; 98(4): 1214-1222	**Cost-utility analysis** A decision analysis model using TreeAge Pro 2013 software was developed to assess the costs and outcomes of four initial diagnostic strategies for diagnosis of a 1.5 cm to 2.0 cm nodule with either a 50% or 65% pre-test probability (prevalence) of cancer. Compared strategies included ^{18}F-fluoro-deoxyglucose positron emission tomography (FDG-PET), navigation bronchoscopy (NB), computed tomography fine needle aspiration (CT-FNA), and VATS. They used Medicare reimbursable amounts for societal costs representing the mean Medicare hospital reimbursement for the indicated inpatients procedure using a base year of 2011. Sensitivity analyses were performed to assess changes in cost-effectiveness of modeled strategies and to identify potential thresholds where the preferred treatment option would change. Incremental cost-effectiveness ratio (ICER) is used to compare the cost-effectiveness of different treatments and indicates the additional cost required to gain one additional quality adjusted life year (QALY).		The base case is a 60 year old male with a 15 pack year smoking history, no prior history of lung cancer, and a 1.5 cm to 2.0 cm nodule in an upper lobe incidentally observed on a CT scan.	FDG-PET NB CT-FNA VATS	Between intervention	-	When cancer prevalence was 65%, tissue acquisition strategies of NB and CT-FNA had higher QALYs compared to either FDG-PET or VATS, and VATS was the most costly strategy (ICER per QALY: NB=USD\$4,602; CT-FNA=USD\$3,998; VATS=USD\$43,578). The FDG-PET had the lowest expected cost for diagnosing patients (USD\$10,411) with an expected QALY of 14.12. Navigation bronchoscopy, CT-FNA, and FDG-PET had similar cost-effectiveness when cancer prevalence was 50%. **One-way sensitivity analysis** When FDG-PET sensitivity was fixed at 87% and the specificity of a FDG-PET scans fell below 72%, then CT-FNA or NB were the preferred diagnostic strategies (more cost-effective). **Two-way sensitivity analysis** FDG-PET remained the least costly diagnostic strategy across all combinations of sensitivity between 80% and 100% and specificity between 60% and 90%. **Authors conclusion** Navigational bronchoscopy and CT-FNA diagnostic strategies were more cost-effective than VATS biopsy or FDG-PET strategies in the work up of a 1.5 cm to 2.0 cm nodule in populations with lung cancer prevalence greater than 50%. FDG-PET scan for diagnosis of lung cancer may not be cost-effective in regions of the country where specificity is low.	

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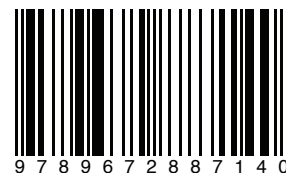
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