DIAGNOSTIC APPROACHES TO SOLITARY PULMONARY NODULE

EXECUTIVE SUMMARY
(Adapted from the report by SYFUL AZLIE MD FUZI)

Authors:
Syful Azlie Md Fuzi
Dr. Erni Zurina Romli

Information Specialist:
Rosnani Abdul Latip

Expert Committee:
Dr. Jamalul Azizi Abdul Rahman
Dr. Tie Siew Teck
Dr. Mona Zaria Nasaruddin
Dr. Aida Abdul Aziz
Dr. Siti Rohani Mohd Yakop
Dr. Ridzuan Abdul Rahim
Dr. Izzuna Mudla Mohamed Ghazali
Dr. Roza Sarimin

External Reviewer:
Dr. Irfhan Ali Hyder Ali
Dr. Kunji Kannan a/l Sivaraman Kannan
Dr. Zuhanis Abdul Hamid
Dr. Mohd Arif Mohd Zim
Associate Professor Dr. Mohamed Faisal Abd Hamid

For further information please contact:

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590 Putrajaya.

Tel: 603 8883 1229

Available at the following website:
http://www.moh.gov.my

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Background

Solitary pulmonary nodule (SPN) 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 and conclusion:

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).

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.