Technology Assessment Unit of the McGill University Health Centre (MUHC)

A Mini-Health Technology Assessment of Linear and Radial Endobronchial Ultrasound (EBUS) and Electromagnetic Navigation Bronchoscopy (ENB) in the Diagnosis and Staging of Lung Cancer in Adults:

(Note: A mini health technology assessment (mini-HTA) report consists of two parts. The first is completed by TAU together with the applicant at the time of requesting the evaluation. The second consists of a commentary and possibly additional evidence provided by TAU)

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List of abbreviations: *CADTH: Canadian Agency for Drugs and Technologies in Health, CT-TTNA: Computed Tomography Guided - Transthoracic Needle Aspiration, DY: Diagnostic Yield, ENB: Electromagnetic Navigation Bronchoscopy, HTA: Health Technology Assessment, INESSS: Institut national d'excellence en santé et en services sociaux, MED: Mediastinoscopy, MUHC: McGill University Health Centre, NPV: Negative Predictive Value, NSCLC: Non-small Cell Lung Cancer, PET Positron Emission Tomography, PPT: Pulmonary Peripheral Tumor, PPV: Positive Predictive Value, QALY: Quality Adjusted Life Year, R: Radial / L: Linear EBUS - TBNA: Endobronchial Ultrasound –Trans Bronchial Needle Aspiration, RCT: Randomized Controlled Trial, ROSE: Rapid On Site Evaluation, SCLC: Small Cell Lung Cancer, SPN: Solitary Pulmonary Nodule, TAU: Technology Assessment Unit, TBB: Transbronchial Biopsy; VATS: Video-assisted Thoracic Surgery.*

Part I – Request for HTA (Completed by the applicant)

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Date request received	April, 14th 2015
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Technology (Name, Description, Indication for use at MUHC)

Three different bronchoscopic devices are of interest for this evaluation. All three extend the view of the operator beyond the airway wall and therefore are useful in the diagnosis and staging of lung cancer. All three techniques allow the operator to take biopsies for histological analysis[1-3].

Convex probe or Linear Endobronchial Ultrasound (L-EBUS) is preferred for central, hilar and mediastinal lesions. It allows real-time ultrasound-guided sampling of thoracic lymph nodes, using the technique of trans-bronchial needle aspiration, thus eliminating the need for more invasive diagnostic procedures such as mediastinoscopy.

Radial probe or Radial Endobronchial ultrasound (R-EBUS) is preferred for sampling nodules and masses within the lung periphery. It uses a flexible catheter and a radial probe transducer that produces a 360 degree ultrasound image; surrounding the bronchial wall and allowing the operator to visualize the different layers of the airway wall in greater detail.

Electromagnetic navigation bronchoscopy (ENB) This procedure allows real-time guidance during bronchoscopy, providing 3D-navigation through the bronchial tree, and allowing sampling of smaller and more peripheral lung nodules. In some cases, the diagnostic yield of ENB is improved when it is used in combination with radial EBUS.

Reason for use at the MUHC:

- To facilitate the process of biopsy of the lung and mediastinum with the greatest possible accuracy and safety.
- To permit an early accurate diagnosis of pulmonary pathologies; and an appropriate staging of intrathoracic tumors, decreasing time to initiation of treatment in case of malignancy.
- To avoid complications (such as pneumothorax, massive bleeding, infections, respiratory failure, and open surgery) and increased length of stay associated with more invasive alternatives.

Why is the current evaluation being requested?

These three technologies have been used at the Montreal Chest Hospital with financial support from the Montreal Chest Hospital Foundation. The assumption of all costs of these technologies by the MUHC is currently under consideration. Therefore, an evaluation has been requested to determine whether the additional expense to the MUHC is justified.

Has it been used at the MUHC? What is the alternative?

Linear and radial EBUS have been used at the MUHC since 2009 and ENB since 2014. They have replaced more invasive alternatives that have been used for several years and continue to be used in some cases depending on patient and clinical characteristics. The most commonly used alternative technologies include:

- Mediastinoscopy: Mediastinoscopy is the alternative to linear EBUS. It involves passing a mediastinoscope through the neck and the trachea in order to visualize the mediastinum and to sample the tissue and nodes as desired. It is used for lung cancer staging or for diagnosing other conditions affecting structures in the mediastinum such as sarcoidosis or lymphoma[2].
- Transthoracic needle aspiration (TTNA): TTNA is a biopsy technique that involves passing a cutting needle from the skin to a thoracic target in order to aspirate a core of tissue for histologic analysis. It is done mainly to evaluate peripheral lung nodules or masses and pleural abnormalities; but also undiagnosed infiltrates or pneumonias when bronchoscopy is contraindicated or nondiagnostic[4]. It is usually guided by computerized tomography and is an alternative to R-EBUS and ENB. It is rarely used to evaluate mediastinum and hilar lesions.
- Thoracoscopy (Video assisted thoracoscopic surgery (VATS)): VATS is a surgical procedure where surgeons access the thoracic cavity using a small video camera that is introduced into the patient's chest. The surgeon is able to see and manually operate different kinds of tools and instruments that are placed through several small holes (ports), made in between the ribs. The

surgeon is thus able to search and take samples for further histopathological analysis or, to remove the tumor which means that it can be therapeutic. VATS is an alternative to R-EBUS and ENB.

Risks/complications

Risks and complications associated with L- and R-EBUS and ENB are similar. Main complications reported for R-EBUS and ENB are pneumothorax and minor bleeding. Less frequent complications include major bleeding, respiratory failure and infection. In the case of L-EBUS, infectious complications include mediastinitis, pericarditis and sepsis. Death is very rare for all three technologies and is usually the result of major bleeding.

Part II: Commentary by the Technology Assessment Unit

Background

Linear EBUS (L-EBUS), radial EBUS (R-EBUS) and ENB were first carried out in early 2000s and were acquired at the MUHC in 2009 and 2014 to enable biopsy of intrathoracic pathologies with use of less invasive procedures. An extensive literature[1 5-19] has now accrued evaluating these devices in terms of diagnostic yield, accuracy, safety and other relevant outcomes; as well as comparisons with more invasive alternatives.

Objective

The objective of this mini HTA is to review and summarize the most recent evidence on efficacy and safety of all three technologies for the diagnosis and staging of lung cancer. We also report on the budget impact of these technologies to the MUHC.

For each of the three technologies of interest, there are different indications for use and different comparator technologies to consider as summarized below in Table 1.

Table 1*: The three technologies of interest; indications for use, comparator technologies and possible outcome measures.*

Technology of interest	Type of tumors examined	Used for Diagnosis or Staging	Comparator technology	Outcome measures of interest
Linear EBUS	Central lung tumors	Diagnosis	Mediastinoscopy	Diagnostic Yield Diagnostic Accuracy Sensitivity Specificity PPV NPV Complications Time to treatment Length of stay Cost Effectiveness
	Hilar/mediastinal nodes	Staging & Restaging		
Radial EBUS	Peripheral and central lung tumors	Diagnosis	CT-TTNA / Thoracoscopy	
Radial EBUS + ENB	Peripheral and central lung tumors	Diagnosis	CT-TTNA / Thoracoscopy	

Literature search

Given that the technologies of interest are well established, we focused our literature search on the most recent (last 3 years) lung cancer and pulmonary nodule clinical practice guidelines and HTA reports for L- and R- EBUS and ENB. We also considered systematic reviews, meta-analyses and selected RCTs of the three technologies within the last 10 years. Other types of studies such as observational and economic evaluations were considered for non-clinical outcomes, such as time to treatment, cost effectiveness and linear EBUS safety.

We searched the National Guideline Clearing house for clinical practice guidelines, the Centre for Review and Dissemination database of York University for HTA reports and economic evaluations, and Pubmed for research articles. The search terms used in the different databases were: *EBUS, Endobronchial Ultrasound, ENB, Electromagnetic Navigation Bronchoscopy, (Lung cancer AND diagnosis OR staging), pulmonary nodule.*

We included documents related to staging or diagnosis of lung cancer. We excluded documents related to screening for lung cancer. Reports combining EBUS with E-US (endoscopic ultra sound) were also excluded because this combination is not performed at the MUHC for staging or diagnosis of lung cancer. We limited the search to articles in English or French. Both authors reviewed all selected articles.

Summary of the evidence on efficacy:

Given that the purpose of all three technologies (L- or R-EBUS and ENB) is diagnostic (rather than therapeutic) their efficacy is typically reported in the literature in terms of diagnostic accuracy and related metrics (rather than in terms of clinical outcomes). We summarize in the text below and in **Table 2**, the results from the most relevant meta-analyses (and one RCT for R-EBUS + ENB) for each technology for each indication.

Linear EBUS

A recent meta-analysis by Ge et al[20], compared L-EBUS with video assisted mediastinoscopy (VAM) for **lung cancer staging**. The reference standard was open thoracotomy and VATS. Since false positives by L-EBUS and VAM are rarely seen they were assumed to have perfect specificity. They obtained a pooled sensitivity of 0.83 (0.79 – 0.87) for L-EBUS and 0.86 (0.82 – 0.90) for video assisted mediastinoscopy**.**

In 2009 Gu et al[18] systematically reviewed 11 studies of 1299 patients that evaluated L-EBUS for **lung cancer staging.** Histopathology analysis of surgical samples and/or close clinical follow-up for at least six months were used as the reference standard. They reported that L-EBUS had a pooled sensitivity of 0.93 (95% Confidence Interval (CI), 0.91–0.94) and a pooled specificity of 1.00 (95% CI, 0.99–1.00). It should be noted that the pooled specificity estimate is based on two studies that carried out a surgical confirmation of positive results. Furthermore, sensitivity of EBUS was found to be higher in patients with positive CT or PET scans compared with unselected patients [0.94 (0.93 – 0.96) vs. 0.76 (0.65 – 0.85)] respectively and further improved from 0.92 (0.89 – 0.94) to 0.97 (0.94 – 0.99) if rapid on site cytopathology evaluation (ROSE) was performed.

A meta-analysis by Dong et al[11] in 2013 focused on the accuracy of L-EBUS for **non-small cell lung cancer staging**. Data from nine studies with a total of 1066 patients was pooled. Different reference techniques were used in each study (mediastinoscopy, surgery and clinical follow up) to confirm positive L-EBUS results. The pooled sensitivity was estimated at 0.90 (95% CI 0.84 to 0.96), the pooled specificity at 0.99, accuracy of 0.96, PPV was 0.99 and pooled NPV was 0.93 (no confidence intervals were provided). No adjustment was made in the analysis for the variation in reference tests in each study.

A meta-analysis by Chandra et al. in 2012[21], pooled data across 1658 patients from 14 prospective studies to determine the **diagnostic** performance of L-EBUS in **mediastinal and hilar** lymphadenopathy

(malignant and non-malignant conditions), by computing pooled sensitivity, specificity and likelihood ratios. The reference test was defined as a combination of clinical follow-up, positive index test results, video-assisted thoracoscopy (VATS), mediastinoscopy and open thoracotomy. The pooled specificity was estimated at 100% (95% CI 0.90 –1.00). The pooled sensitivity was 92% (95% CI 0.91– 0.93). The pooled positive likelihood ratio was 5.1 (95% CI 2.7–9.7) and the pooled negative likelihood ratio was 0.13 (95% CI 0.09–0.19). No adjustment was made in the analysis for the different reference tests in each study.

It has been reported that the sensitivity of L-EBUS can be improved when it is combined with rapid on site evaluation[22] (ROSE). Oki et al[23] carried out an RCT in which patients were randomized to being evaluated by L-EBUS with the ROSE technique (N=55) or without the ROSE technique (N=53). They found that there was no improvement in test accuracy or bronchoscopy time due to the ROSE technique. However, it was associated with a reduced number of punctures [2.2 vs. 3.1 punctures (p < 0.001)] and the need for additional procedures other than the main target [11% vs. 57% (p < 0.001)] when EBUS is used for the **diagnosis of lung cancer**.

Comparator technology: As a comparator of L-EBUS and gold standard for **lung cancer staging**, mediastinoscopy sensitivity has been reported in the literature with ranges between 32 – 92% and a median of 83% for stages of CN0-3[5][13].

Radial EBUS
Wang Memoli et al.[16] published a systematic review of various guided bronchoscopy techniques for the evaluation of **pulmonary nodules.** They identified 20 studies of radial EBUS. Based on a meta-analysis of these studies, the authors estimated that the diagnostic yield of R-EBUS with guide sheath was 73.2% (64.4-81.9), the highest among the technologies considered. The yield was found to depend on size of the lesion. Based on the numbers they reported we estimated that the pooled diagnostic yield of R-EBUS was 0.54 (0.38, 0.70) in lesions ≤ 20mm and 0.79 (0.73, 0.84) in lesions > 20mm. In their discussion they commented that this is much higher than the yield of traditional bronchoscopy. However, it is lower compared to TTNA. A reference standard technique was not mentioned in the meta-analysis but clinical follow up, VATS and TTNA were some of the reference techniques used across the included RCTs.

In a meta-analysis published in 2011, Steinfort et al. aimed to determine the sensitivity and specificity of R-EBUS for the **diagnosis** of **peripheral lung cancer**[24]. A total of 13 studies of 1420 patients were included. The reference standard was confirmation by histology of surgically obtained specimens or close clinical follow-up for at least 6 months. The range of malignancy across studies was 50 – 84%. R-EBUS sensitivity for detection of malignancy varied considerably across individual studies from 49% to 88%. The pooled sensitivity was 0.73 (95% CI 0.70–0.76). The pooled specificity was 1.00 (95% CI 0.99–1.00).

ENB
A recent meta-analysis conducted by Zhang et al[6] in 2015, aimed to determine the **accuracy** and **diagnostic** yield of ENB for **lung nodules** based on 15 studies of 892 patients. They estimated a pooled sensitivity and specificity of 0.82 (0.78 – 0.85) and 1.00 (0.98 – 1.00) respectively. The diagnostic yield ranged from 59.9% to 94% across these studies.

In 2014, Gex[1] published a meta-analysis based on 15 studies of 1033 patients. They reported a pooled diagnostic yield of 64.9% (59.2; 70.3) and sensitivity for malignancy of 71.1% (64.6; 76.8). Specificity was not mentioned.

Comparator technology: TTNA is an alternative for R-EBUS and ENB for the evaluation of **peripheral pulmonary nodules** with a reported diagnostic yield of 90%. [15][16]

R-EBUS + ENB

A randomized controlled trial (RCT) published in 2007, which compared R-EBUS alone, ENB alone and R-EBUS+ENB combined (3 arms)[19], observed that the use of EBUS with ENB had better results in terms of diagnostic yield (88%) for the evaluation of peripheral lesions when compared with ENB or R-EBUS alone; 59% and 69%, respectively. Some guidelines[12 15 25] suggest that diagnostic yield could be further improved by combining ENB and R-EBUS in patients appropriately selected depending on clinical characteristics such as the size and the anatomic location of the lesion. Nevertheless, this RCT was the only relevant evidence in support of joint use of R-EBUS and ENB.

***Table 2*:** *Summary of efficacy results by technology and indication[†].*

Technology of interest	Type of tumors examined	Used for Diagnosis or Staging	Performance / accuracy indicator[†]						Ref
			Specificity %	Sensitivity %	Positive likelihood ratio	Negative likelihood ratio	NPV %	DY %	
Linear EBUS	Central lung tumors	Diagnosis	100%	92%	5.1	0.13	NA	NA	21
	Hilar / mediastinal nodes	Staging & Restaging	99-100%	89-93%	NA	NA	93%	96%	7 11 18
Radial EBUS	Central and peripheral lung tumors	Diagnosis	100%	73%*	26.8	0.28	NA	71-73%	16 26
ENB	Central and peripheral lung tumors	Diagnosis	100%	71%*- 82%	18.6	0.22	52%	65-75%	1 6
R-EBUS + ENB	Central and peripheral lung tumors	Diagnosis	NA	NA	NA	NA	NA	88%	19

* Only for malignancy   NA: Data not available

† Values are point estimates. Corresponding confidence intervals are reported in the text. A range indicates minimum and maximum point estimates across studies.

Cost effectiveness

Linear EBUS

The accuracy of L-EBUS is comparable to mediastinoscopy[5 8 27]. Therefore, cost-effectiveness analyses of L-EBUS tend to focus on savings due to avoiding mediastinoscopy, which is a more invasive procedure.

A 2010 economic evaluation by Ang et al[28] compared L-EBUS vs. mediastinoscopy using a decision tree model using local data and considering only direct costs such as the fees for facilities, manpower and consumables incurred (without government subsidies). Linear EBUS showed savings of around 874$ USD (1214 Singapore Dollars) per positive staging when comparing with mediastinoscopy. However, since clinicians' salaries were considered among the costs in this analysis, the results cannot be readily generalized to the MUHC context.

In a 2009 report on L-EBUS by CADTH[17], it was estimated that the technology could reduce the cost of lung cancer staging by 24% per patient when used as a first line diagnostic intervention compared with conventional TBNA (transbronchial needle aspiration). Additionally, the strategy of L-EBUS – TBNA as first line and mediastinoscopy following a negative L-EBUS is safer and likely to be a cost effective alternative for the staging of non-small cell lung cancer[17 29].

Radial EBUS

It is of interest to compare the cost-effectiveness of R-EBUS to TTNA for peripheral lesions. As summarized in **Table 2**, R-EBUS has a diagnostic yield of roughly 73.2% compared to a 90% for TTNA. However, there is a trade-off in terms of safety with TTNA being associated with a much higher risk of pneumothorax.

A cost benefit analysis of radial EBUS vs. TTNA for the management of peripheral pulmonary lesions performed in 2013 found TTNA more cost beneficial by a difference of 24 Australian Dollars (AU$). Sensitivity analysis showed that EBUS could be cost beneficial if cost of complications exceeds 501 AU$ per episode or if sensitivity of TTNA drops below 91%. In the cost utility analysis the cost per QALY with TTNA was 2278 AU$ compared with 2816 AU$ with Radial EBUS[26]. A cost-effectiveness analysis by Ang et al. in 2010[28] showed similar results: 3335$ SGD (Singapore Dollars) for TTNA vs. 4857$ SGD for R-EBUS per diagnosis of lung cancer. These results should be interpreted keeping in mind that R-EBUS is safer than TTNA for central and peripheral lesions, and TTNA diagnostic yield decreases as the lesion size is less than 20 mm[12].

No economic data were found comparing the combination of R-EBUS and ENB with TTNA.

ENB

Dale et al[30] presented a cost consequence model and a decision tree analysis comparing ENB vs. TTNA in 2012. Based on this model, use of ENB resulted in an important decrease in pneumothorax and chest tubes, but an increase in costs of $3719 USD on average per patient when comparing with TTNA. The main cost driver was the sensitivity of TTNA, followed by the cost of VATS. It should be noted that the intervention evaluated by this model does not reflect the current practice at the MUHC where ENB is typically used with R-EBUS.

No models or economic approaches were found that examined the combined use of **R-EBUS + ENB.**

Time-to-treatment:

Though most articles evaluating EBUS and ENB have focused on accuracy, the reduction in time to treatment is a clinically relevant outcome of interest. This is because an early diagnosis could result in a faster treatment impacting long-term survival. In a 2015 randomized controlled trial[8], Navani et al. compared the time to treatment between EBUS-TBNA and the conventional techniques (bronchoscopy, PET-CT, and mediastinoscopy) as an independent variable and estimated that the time to start treatment with EBUS was 50% shorter (14 days, CI 95% 14–15 days) compared with the time taken with conventional diagnostic and staging approaches: 29 days (95% CI 23–35).

Safety:

Generally, all 3 technologies had a low risk of complications as explained below and summarized in Tables 3a and 3b.

Linear EBUS

A recent meta-analysis by Ge et al[20] compared L-EBUS with video assisted mediastinoscopy. The complications reported for L-EBUS are 4 minor complications out of 999 (0.4%), and 17 for mediastinoscopy out of 915 (1.8%) **Table 3a**. No deaths were reported.

A massive retrospective survey conducted by the society for respiratory endoscopy of Japan[31] aimed to assess the safety of L-EBUS for the staging and diagnosis of lung cancer involved 455 health care facilities for a total of 7345 EBUS-TBNA procedures. Complications were seen in 90 cases (1.23%; 95% CI 0.97%-1.48%) and in 32 facilities. Most frequent event was bleeding in 50 cases (0.68%). Infectious complications such as mediastinitis, pneumonia, pericarditis, cyst infection and sepsis were seen in 14 procedures (0.19%; 95% CI, 0.09%-0.29%) 7 mediastinitis, 4 cases of pneumonia, 1 case of pericarditis, cyst infection and sepsis. Respiratory failure developed in 5 cases (0.07%). 2 cases of pneumothorax

(0.03%) 1 of them required tube drainage. Other complications are events with rates of 0.05% and under such as fever and hyperventilation, among others.

Radial EBUS
Steinfort et al[24] reported in their meta-analysis that out of 1090 patients in 14 studies, the pooled rate of pneumothorax was 1% and the pooled rate of patients requiring a chest tube was 0.4%. Self-limited minor bleeding was reported in few cases and no intervention was required.
Hayama et cols[32] reported a complication rate of 1.3% among 965 patients who underwent radial EBUS - 0.8% for pneumothorax and 0.5% for infection. No other relevant events were reported.

ENB
In a 2014 meta-analysis by Gex et al.[1] ENB caused 32 pneumothoraces out of 1033 procedures (a proportion of 3.1%, 95% CI 2.1–4.3) in 15 studies. Half of those required chest tube drainage (1.6%, 95% CI 1.0–2.6) and 9 cases of minor self-limited bleeding (0.9%, 95% CI 0.4–1.6) were reported.

Table 3a: Complications following L-EBUS and mediastinoscopy[†].

Complication	Technologies appraised	
	Linear EBUS (999)	Mediastinoscopy (915)
Infection	0.19%	0.11%
Hoarseness	0%	0.22%
Vascular lesions	0.01%	0.44 - 2.5%
Perioperative bleeding	0%	0.22 - 2.3%
Laryngeal injury	0%	0.44 - 3.1%
Esophagus injury	0%	0.11%
Chyle leak	0%	0.11%
Pneumothorax	0.03 - 3%	0.22%
Atrial fibrillation	0.04%	0%
Cough	0.20%	0%
Unspecified complication / morbidity	1.23%	1.4 - 5.3%
Mortality	0%	0.2%
references	*20 31 33 34*	

[†] Values are point estimates. A range indicates minimum and maximum point estimates across studies.

Table 3b: Complications following R-EBUS, ENB, TTNA and VATS[†].

Complication	Technologies appraised			
	R- EBUS	ENB	TTNA	VATS
Infection	0.5%	0%	NA	6.3%
Pneumo	0.8 - 1%	3.1%	15-60%	5%**
Bleeding	0%	0.9*%	4-27%	8-12%
Chest tube	0.3%	1.6%	1-15%	not reported
Mortality	0%	0%	0%	0.07-2%
Reference	*24 32*	*1*	*16 35*	*36*

[†] Values are point estimates. A range indicates minimum and maximum point estimates across studies. NA: No data available.
*Minor or moderate bleeding that do not require any treatment. **Air leak.

Comparator technologies

In the case of TTNA, the pneumothorax risk has been estimated between 25-40% and the risk of need for chest tube insertion is roughly 5%[16][35]. For mediastinoscopy, complications are surgery related: hemorrhage, recurrent nerve palsy, tracheal laceration and pneumothorax; but also anesthesiology related: cardiac arrest, respiratory hypoxia and arrhythmias. In general, occurrence for complication is 0.6% - 3.7% and a 0.2% for mortality[33][34][37].

Budget impact

In 2014, the respiratory division at the MUHC performed around 270 EBUS (approximately 70% linear and 30% radial) and around 20 ENB procedures. The forecast for 2015/16 is 400 EBUS (around 70% linear and 30% Radial) and 35 ENB procedures. These numbers are estimates taking into account the increasing number of patients with lung cancer at the MUHC; explained by the redirection of patients from other affiliated institutions to the MUHC as part of the regionalization of lung cancer care. "(Personal communication from Dr. Stéphane Beaudoin)".

Based on cost estimates provided by the respiratory division and by the Department of Therapeutic and Allied Services[1], the cost per procedure (only supplies) is $270 for EBUS (either linear or radial) and $1130 for ENB. The annual equipment service cost is $15,000 for all three devices. The estimated annual cost for a respiratory therapist time (devoted to these procedures) is $13,500. The total budget anticipated for the 2015/2016 period is CAD$176,050. Acquisition costs are not included.

Clinical practice guidelines

Seven clinical practice guidelines (CPGs)[9][12][13][15][38][39] were identified to determine the current guidance on usage of EBUS and ENB (table 4 a & b). We found that all guidelines were consistent in their recommendations regarding the use and indications of EBUS and ENB for the evaluation and staging of pulmonary nodules and lung cancer. Therefore, we focused our summary on three of the most recent and complete guidelines for the purposes of this mini-HTA.

Table 4a: Summary of the indications for which L-EBUS is recommended by clinical practice guidelines.

Indication	Clinical practice guidelines		
	2014 European Society of Thoracic Surgeons*[9]	2014 INESSS[39]	2013 American College of Chest Physicians*[13]
As the best first test for confirming mediastinal enlarged lymph nodes on CT or PET positive.	Recommended	Recommended	Recommended
As the best first test for central lesions, suspected N1 nodes	Recommended	Recommended	AND: N2,3 involvement suspected
As the best first test for lesions with high uptake on the PET scan and no metastasis	Recommended	Recommended	Recommended
As the best first test when suspicious N2,3 node involvement either by node enlargement or PET uptake	Mediastinoscopy also recommended. Both are not limited to N2,3 but to tumors of more than 3 cm.	Recommended	Recommended

* Dedicated for NSCLC. 75 - 80 % of lung cancer cases.

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[1] Antoinette Di Re.

Table 4b: Summary of the indications for which R-EBUS and ENB is recommended by clinical practice guidelines.

Indication	Clinical practice guidelines		
	2015 British Thoracic Society guidelines[38]	2014 INESSS[39]	2013 American College of Chest Physicians[12][15]
In patients for whom a non-imaging and non-surgical approach to diagnosis of pulmonary nodules is needed	Recommend R-EBUS or ENB.	Pulmonary nodules not considered in this guideline	Recommends R-EBUS and ENB when: nodule of 8 mm or more in diameter, probability of malignancy low to moderate. Benign disease that requires treatment. Proof of malignancy in high surgical risk patients. Or discordant imaging findings and suggestive pre-test probability of malignancy.
For lesions found in the lung periphery with bronchus sign	Recommend R-EBUS or ENB.	Suggests R-EBUS as an alternative due to the complications with TTNA.	
Nodule with evidence of malignant growth	Recommend R-EBUS or ENB.	Pulmonary nodules not considered in this guideline	
Suspected SCLC. It is recommended to confirm the diagnosis by the least invasive method available	Recommend R-EBUS or ENB.	Suggests R-EBUS as an alternative for lesions found in the lung periphery	
In peripheral lung lesions that are hard to reach	Indication not considered in this guideline	ENB not mentioned in this guideline	Guidance with ENB is recommended if the equipment and the expert are available

In summary, L-EBUS is the first choice for mediastinal staging of non-small cell lung cancer. When L-EBUS is negative, mediastinoscopy is recommended. R-EBUS and ENB are recommended for indications related to diagnosis of peripheral lung lesions. ENB seems to improve the navigation across the bronchial tree but no guideline mentioned the combination of both.

In general, all guidelines note that the particular technology selected should be determined in accordance with the indication, nodule size, location and proximity to a patent airway; patient's risk assessment (surgical and procedure risks), clinical probability of cancer and the availability of expertise for using the technology.

Health Technology Assessments

Seven different HTA[17][29][40-44] reports from five different countries were identified - one on radial EBUS, three on linear EBUS and four on both, linear and radial EBUS.

In keeping with our purpose for this mini-HTA, we reviewed the most recent reports from HAS (Haute autorité de santé), the 2010 NICE (National Institute for Health and Care Excellence) report and the CADTH (Canadian Agency for Drugs and Technologies in Health) report. In summary, these reports also supported the use of EBUS for the indications described by the clinical practice guidelines.

Discussion

Our review found that endobronchial ultrasound (both L-EBUS and R-EBUS) and electromagnetic navigation bronchoscopy are emerging technologies that have already gained a place in diagnosis, staging and management of lung cancer. We found a considerable body of evidence on their efficacy and safety, which has led to their being recommended by a number of clinical practice guidelines. However, the evidence on their clinical impact and cost-effectiveness is limited.

Mediastinoscopy has traditionally been considered the gold standard for lung cancer staging and diagnosis, but is an invasive procedure. Research studies have now shown that the less invasive linear EBUS technology has comparable sensitivity to mediastinoscopy, is associated with a low risk of complications and a shorter time to commencement of treatment.

The preferred technique for diagnosis of lung cancer in peripheral pulmonary nodules is TTNA, though it is associated with a relatively high risk of pneumothorax. Our review identified meta-analyses of radial EBUS and ENB showing that these technologies have a comparatively better safety profile. They have a relatively high diagnostic yield, which may be higher or lower than that for TTNA depending on different variables: bronchus sign, lesion size, distance of lesion from the thorax, expertise and learning curve of the operator. In practice, clinicians rely on these variables and the probability of malignancy to determine which technology to use to assess a lesion.
There is little evidence on efficacy supporting the combined use of R-EBUS with ENB and no data was found regarding safety. However, this technique is performed at the McGill University Health Centre.

While reviewing the meta-analyses selected for this report, we noticed that most individual studies of diagnostic accuracy were considered to be of either poor or moderate quality based on the QUADAS score[45]. In general, the score for studies of linear EBUS was higher than for studies of radial EBUS and ENB. A frequent bias found in L-EBUS studies was that L-EBUS was interpreted only after seeing the reference standard, which could exaggerate the agreement between the two tests. Another commonly reported bias, was that all positive EBUS results were classified as true positive irrespective of the reference standard results, which can potentially lead to an over estimation of EBUS sensitivity. In R-EBUS and ENB studies, the lack of an appropriate reference standard in most studies was the most frequent concern for bias. Also a poor description of the selection criteria limits the generalisability of these studies.

Though we found numerous studies on the efficacy and cost effectiveness of EBUS and ENB, very few have directly compared these technologies with the relevant alternatives. More research in comparative effectiveness is needed to fill these evidence gaps. Different economic analyses comparing R-EBUS or ENB with TTNA do not reach a consistent conclusion due to the variability in their assumptions and the scenario considered. On the other hand, most studies of L-EBUS concluded that it was a cost effective first line strategy for staging of NSCLC.

Finally, the efficacy and clinical impact of EBUS and ENB can vary across institutions based on variables previously mentioned. Therefore, it is necessary to gather local data in order to measure the real impact (in clinical, humanistic and monetary terms) of these technologies at the McGill University Health Centre.

In summary, L-EBUS, R-EBUS and ENB are generally safe and effective in the diagnosis and staging of lung cancer. Future studies on cost-effectiveness, clinical impact and quality of life, may further clarify the effectiveness of these technologies compared to current gold-standards.

Recommendations:

- There is sufficient evidence supporting the use of linear EBUS as a first-line approach for lung cancer staging.
- For investigation of peripheral nodules suspected of lung cancer, radial EBUS should be available for use at the clinician's discretion.
- There is very limited evidence supporting the usage of ENB together with R-EBUS. Therefore, this technology should be judiciously used only when the yield of radial EBUS is felt to be lower than usual and TTNA is best avoided.
- Given the residual uncertainty in patient selection and the low quality of evidence on efficacy, particularly for R-EBUS and ENB technologies, it is recommended that a prospective database be maintained that will allow the study of patient characteristics and patient outcomes that can aid decision making. Such a database has been commenced for ENB at the MUHC and should be extended to include R-EBUS and L-EBUS.

Acknowledgement

References:

1. 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; international review of thoracic diseases 2014;87(2):165-76.
2. Jalil BA, Yasufuku K, Khan AM. Uses, limitations, and complications of endobronchial ultrasound. Proceedings (Baylor University Medical Center) 2015;28(3):325-30.
3. Kokkonouzis I, Strimpakos AS, Lampaditis I, et al. The role of endobronchial ultrasound in lung cancer diagnosis and staging: a comprehensive review. Clinical lung cancer 2012;13(6):408-15.
4. Lechtzin N. Transthoracic Needle Biopsy http://www.merckmanuals.com/professional/pulmonary-disorders/diagnostic-pulmonary-procedures/transthoracic-needle-biopsy: Merck manuals; June 2013
5. Um SW, Kim HK, Jung SH, et al. Endobronchial ultrasound versus mediastinoscopy for mediastinal nodal staging of non-small-cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 2015;10(2):331-7.
6. Zhang W, Chen S, Dong X, et al. Meta-analysis of the diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules. Journal of thoracic disease 2015;7(5):799-809.
7. Murgu SD. Diagnosing and staging lung cancer involving the mediastinum. Chest 2015;147(5):1401-12.
8. Navani N, Nankivell M, Lawrence DR, et al. Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: an open-label, pragmatic, randomised controlled trial. The Lancet Respiratory medicine 2015;3(4):282-9.
9. De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2014;45(5):787-98.
10. Deppen SA, Davis WT, Green EA, et al. Cost-effectiveness of initial diagnostic strategies for pulmonary nodules presenting to thoracic surgeons. The Annals of thoracic surgery 2014;98(4):1214-22.
11. Dong X, Qiu X, Liu Q, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in the mediastinal staging of non-small cell lung cancer: a meta-analysis. The Annals of thoracic surgery 2013;96(4):1502-7.

12. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e142S-65S.

13. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e211S-50S.

14. Dincer HE. Linear EBUS in staging non-small cell lung cancer and diagnosing benign diseases. Journal of bronchology & interventional pulmonology 2013;20(1):66-76.

15. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e93S-120S.

16. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. Chest 2012;142(2):385-93.

17. CADTH. Endobronchial ultrasound for lung cancer diagnosis and staging: a review of the clinical and cost-effectiveness. CADTH technology overviews 2010;1(2):e0115.

18. Gu P, Zhao YZ, Jiang LY, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. European journal of cancer 2009;45(8):1389-96.

19. Eberhardt R, Anantham D, Ernst A, et al. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. American journal of respiratory and critical care medicine 2007;176(1):36-41.

20. Ge X, Guan W, Han F, et al. Comparison of Endobronchial Ultrasound-Guided Fine Needle Aspiration and Video-Assisted Mediastinoscopy for Mediastinal Staging of Lung Cancer. Lung 2015;193(5):757-66.

21. Chandra S, Nehra M, Agarwal D, et al. Diagnostic accuracy of endobronchial ultrasound-guided transbronchial needle biopsy in mediastinal lymphadenopathy: a systematic review and meta-analysis. Respiratory care 2012;57(3):384-91.

22. Cardoso AV, Neves I, Magalhaes A, et al. The value of rapid on-site evaluation during EBUS-TBNA. Revista portuguesa de pneumologia 2015;21(5):253-8.

23. Oki M, Saka H, Kitagawa C, et al. Rapid on-site cytologic evaluation during endobronchial ultrasound-guided transbronchial needle aspiration for diagnosing lung cancer: a randomized study. Respiration; international review of thoracic diseases 2013;85(6):486-92.

24. Steinfort DP, Khor YH, Manser RL, et al. Radial probe endobronchial ultrasound for the diagnosis of peripheral lung cancer: systematic review and meta-analysis. The European respiratory journal 2011;37(4):902-10.

25. Du Rand IA, Barber PV, Goldring J, et al. British Thoracic Society guideline for advanced diagnostic and therapeutic flexible bronchoscopy in adults. Thorax 2011;66 Suppl 3:iii1-21.

26. Steinfort DP, Liew D, Irving LB. Radial probe EBUS versus CT-guided needle biopsy for evaluation of peripheral pulmonary lesions: an economic analysis. The European respiratory journal 2013;41(3):539-47.

27. Ernst A, Anantham D, Eberhardt R, et al. Diagnosis of mediastinal adenopathy-real-time endobronchial ultrasound guided needle aspiration versus mediastinoscopy. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 2008;3(6):577-82.

28. Ang SY, Tan RW, Koh MS, et al. Economic analysis of endobronchial ultrasound (EBUS) as a tool in the diagnosis and staging of lung cancer in Singapore. International journal of technology assessment in health care 2010;26(2):170-4.

29. MSAC. Endobronchial ultrasound - guided procedures. MSAC application 1108. http://www.msac.gov.au/: Australian Medical Services Advisory Committee, 2008.

30. 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. Journal of bronchology & interventional pulmonology 2012;19(4):294-303.

31. Asano F, Aoe M, Ohsaki Y, et al. Complications associated with endobronchial ultrasound-guided transbronchial needle aspiration: a nationwide survey by the Japan Society for Respiratory Endoscopy. Respiratory research 2013;14:50.
32. Hayama M, Izumo T, Matsumoto Y, et al. Complications with Endobronchial Ultrasound with a Guide Sheath for the Diagnosis of Peripheral Pulmonary Lesions. Respiration; international review of thoracic diseases 2015;90(2):129-35.
33. Zakkar M, Tan C, Hunt I. Is video mediastinoscopy a safer and more effective procedure than conventional mediastinoscopy? Interactive cardiovascular and thoracic surgery 2012;14(1):81-4.
34. Leschber G, Sperling D, Klemm W, et al. Does video-mediastinoscopy improve the results of conventional mediastinoscopy? European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2008;33(2):289-93.
35. Winokur RS, Pua BB, Sullivan BW, et al. Percutaneous lung biopsy: technique, efficacy, and complications. Seminars in interventional radiology 2013;30(2):121-7.
36. Lochowski MP, Kozak J. Video-assisted thoracic surgery complications. Wideochirurgia i inne techniki maloinwazyjne = Videosurgery and other miniinvasive techniques / kwartalnik pod patronatem Sekcji Wideochirurgii TChP oraz Sekcji Chirurgii Bariatrycznej TChP 2014;9(4):495-500.
37. Paleru C, Danaila O, Bolca C, et al. [Complications of mediastinoscopy]. Pneumologia (Bucharest, Romania) 2009;58(1):39-40, 42.
38. Baldwin DR, Callister ME. The British Thoracic Society guidelines on the investigation and management of pulmonary nodules. Thorax 2015;70(8):794-8.
39. Rédigé par Gino Boily JB, Stéphanie Goulet et Marie-Christine Paquin. Algorithmes d'investigation, de traitement et de suivi Cancer du poumon. Institut national d'excellence en santé et en services sociaux (INESSS), 2014:269p.
40. HAS. Echo-endoscopie bronchique avec ponction transbronchique à l'aiguille. www.has-sante.fr: Haute Autorité de santé, 2014.
41. NICE. Endobronchial ultrasound guided transbronchial biopsy for peripheral lung lesions. NICE interventional procedure guidance 337: National institute for health and clinical excellence. , 2010:7.
42. NICE. Endobronchial ultrasoundguided transbronchial needle aspiration for mediastinal masses. National institute for health and clinical excellence, 2008.
43. MSAC. Endoscopic ultrasound guided fine-needle aspiration for the staging of non-small cell lung cancer and the diagnosis of mediastinal masses. MSAC application 1104. http://www.msac.gov.au/: Australian Medical Services Advisory Committee, 2007.
44. Sabirin J TN. Endobronchial ultrasound in Malaysia: Health Technology Assessment http://www.moh.gov.my: Ministry of Health Malaysia, 2008:89.
45. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine 2011;155(8):529-36.