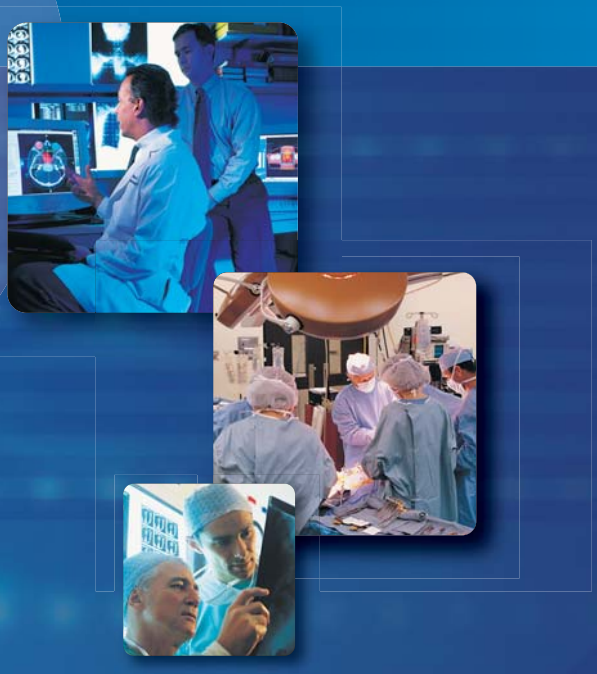
Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

HEALTH TECHNOLOGY ASSESSMENT
RAPID REVIEW

HTA
August 2009

# Endobronchial Ultrasound for Lung Cancer Diagnosis and Staging: A Review of the Clinical- and Cost-Effectiveness



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**Canadian Agency for Drugs and Technologies in Health**

# Endobronchial Ultrasound for Lung Cancer Diagnosis and Staging: A Review of the Clinical- and Cost-Effectiveness

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August 2009

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Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision-making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision-makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.

## Reviewers

These individuals kindly provided comments on this report:

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**Conflict of Interest:** Dr. Alain Tremblay indicated that the University of Calgary has received grants from Olympus Canada for support of an interventional pulmonary medicine training program and for Continuing Medical Education (CME) events on endobronchial ultrasound.

# ACRONYMS AND ABBREVIATIONS

| | |
|---|---|
| CT | Computed tomography |
| EBUS | Endobronchial ultrasound |
| EBUS-TBNA | Endobronchial ultrasound-guided transbronchial needle aspiration |
| EUS | Transesophageal ultrasound |
| EUS-FNA | Transesophageal ultrasound-guided fine needle aspiration |
| HTA | Health technology assessment |
| MRI | Magnetic resonance imaging |
| NSCLC | Non-small cell lung cancer |
| PET | Positron emission tomography |
| TBNA | Transbronchial needle aspiration |

# TABLE OF CONTENTS

# EXECUTIVE SUMMARY

## Context and Policy Issues

Lung cancer is the leading cause of death from malignancies in Canada and worldwide. The accurate diagnosis and staging of lung cancer help to ensure that early and suitable treatment and determination of a prognosis occur. Endobronchial ultrasound (EBUS) involves the use of an ultrasound probe to generate images of pulmonary and mediastinal structures, and allows for minimally invasive sampling of peripheral pulmonary, mediastinal, and hilar lesions. The built-in probe allows for real time guidance during EBUS-transbronchial needle aspiration (TBNA). Because of its recent introduction and increased use in practice, a review of the clinical- and cost-effectiveness of the use of EBUS in the diagnosis and staging of lung cancer is needed.

## Research Questions

1. What is the clinical-effectiveness of endobronchial ultrasound (EBUS) for the diagnosis and staging of lung cancer?
2. What is the cost-effectiveness of EBUS for the diagnosis and staging of lung cancer?

## Methods

Published literature was obtained by cross-searching EMBASE and MEDLINE databases on the Ovid search system between 2004 and April 2009. Regular alerts were established and were current to May 28, 2009. Parallel searches were performed on PubMed and The Cochrane Library (Issue 1, 2009) databases. The websites of regulatory agencies, and health technology assessment and related agencies, were searched, as were specialized databases. The Google™ search engine was used to search for information on the Internet.

## Summary of Findings

One health technology assessment, one meta-analysis, two cost analyses, and three observational studies on the use of EBUS for lung cancer diagnosis and staging were identified.

In the 2009 meta-analysis, the overall diagnostic accuracy of EBUS-TBNA in detecting metastatic mediastinal lymph nodes in patients who were suspected of having lung cancer was assessed. EBUS-TBNA had a pooled sensitivity of 0.93 (95% CI, 0.91 to 0.94) and a pooled specificity of 1.00 (95% CI, 0.99 to 1.00) for lung cancer detection and staging. When compared directly, EBUS-TBNA was found to be more sensitive than conventional TBNA. The findings from recent trials were in agreement with the findings of the meta-analysis on EBUS-TBNA diagnostic accuracy.

The health technology assessment (HTA) examined the effectiveness and safety of EBUS for detection and staging in patients with suspected or established lung cancer. No meta-analysis was performed, and the conclusions that were presented came from individual trials. The HTA found a statistically significantly increased diagnostic yield for mediastinal lymph nodes when EBUS-TBNA was compared to conventional TBNA.

The value of EBUS-guided procedures in the Australian health care system was examined in a 2008 cost-effectiveness analysis. The cost per procedure for EBUS-TBNA was calculated to be A$1,120 (C$996), which represented a savings of A$347 (C$308) per patient compared to conventional TBNA for staging or diagnosis. Calculations that were based on the Canadian population suggest that the use of EBUS-TBNA instead of conventional TBNA could provide an annual cost savings of between C$839,000 and C$1,286,400.

## Conclusions and Implications for Decision- or Policy-Making

Based on the existing evidence, EBUS is an accurate and safe tool for use in lung cancer diagnosis and staging. The cost-effectiveness of EBUS has not been formally evaluated, but findings from cost-analyses showed that compared to TBNA, EBUS-TBNA reduced the per patient staging cost by 24%. There are minimal data comparing EBUS to its current comparator, mediastinoscopy.

**Title:** Endobronchial Ultrasound for Lung Cancer Diagnosis and Staging: A Review of the Clinical- and Cost-Effectiveness

**Date:** August 2009

# 1 CONTEXT AND POLICY ISSUES

Despite advances in treatment, lung cancer is the leading cause of death from malignancies in Canada and worldwide.[1] Accurate diagnosis and staging of lung cancer are needed not only to start early treatment and determine the prognosis, but also to decide the most suitable treatment plan.[2,3] The presence or absence of metastatic disease in the mediastinal lymph nodes is determined during staging.[2-4] Mediastinal staging includes non-invasive staging (imaging) and invasive staging (sampling). Computed tomography (CT), positron emission tomography (PET), and PET-CT are used for non-invasive staging.[5,6] Invasive staging, which provides a definitive tissue diagnosis, involves the use of surgical biopsy (mediastinoscopy); or needle biopsy, such as transesophageal ultrasound (EUS), endobroncheal ultrasound (EBUS), conventional transbronchial needle aspiration (TBNA), CT fluoroscopy-guided TBNA, EUS-guided fine needle aspiration (EUS-FNA), CT-guided transthoracic needle aspiration (CT-TTNA), electromagnetic guidance bronchoscopy-TBNA, and EBUS-guided TBNA (EBUS-TBNA).[5,6]

EBUS is a new technology that involves the introduction of an ultrasound probe into the thoracic region via the bronchial airway while patients are under conscious sedation or general anesthesia.[7] The probe is used to generate images of pulmonary and mediastinal structures. Its use allows minimally invasive sampling of peripheral pulmonary lesions, and mediastinal and hilar lesions.[8,9] The development of the built-in linear probe, as opposed to a radial probe, enables real time guidance during EBUS-TBNA.[10,11]

Because of its recent introduction and its increased use in clinical practice, a review of the clinical-effectiveness and cost-effectiveness of EBUS for the diagnosis and staging of lung cancer is needed.

# 2 RESEARCH QUESTIONS

1. What is the clinical-effectiveness of endobronchial ultrasound (EBUS) for the diagnosis and staging of lung cancer?
2. What is the cost-effectiveness of EBUS for the diagnosis and staging of lung cancer?

# 3 METHODS

The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and EMBASE. Parallel searches were run in PubMed and The Cochrane Library (Issue 1, 2009). The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. No filters were applied to limit the retrieval by study type. See Appendix 1 for the detailed search strategies.

The search was restricted to English language articles that were published between 2004 and April 2009. Regular alerts were established on EMBASE and MEDLINE, and information that was retrieved via alerts was current to May 2009.

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment (HTA) and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional information. These searches were supplemented by hand-searching the bibliographies and abstracts of key papers, and through contacts with appropriate experts and agencies.

Studies that were published in languages other than English or French, and that satisfied the inclusion criteria, were translated only if the abstract indicated that the outcomes were likely to have an impact on the findings in the report. Duplicate publications of the same trial were excluded.

The quality of the HTA and meta-analysis were assessed using the Oxman and Guyatt criteria for the quality of systematic reviews.[12] Economic study quality was assessed using Drummond's quality checklist.[13]

# 4 SUMMARY OF FINDINGS

One health technology assessment, one meta-analysis, two cost analyses, and three observational studies were identified regarding the use of EBUS for lung cancer diagnosis and staging. The flow chart documenting the process for selection of the included reports appears in Appendix 2.

## 4.1 Clinical-effectiveness of EBUS

A 2009 meta-analysis assessed the overall diagnostic accuracy of EBUS-TBNA in detecting metastatic mediastinal lymph nodes in lung cancer.[14] The meta-analysis included 11 prospective studies that enrolled a total of 1,299 patients, ranging in age from 58 years old to 69 years old (median 61 years old), who were suspected of having lung cancer. Eight studies enrolled patients who were selected on the basis of positive CT or PET results, and the remaining three studies enrolled patients regardless of CT or PET results. Among the patients who had positive CT or PET results of suspected lymph node metastasis, the sensitivity of EBUS-TBNA was higher (0.94, 95% CI, 0.93 to 0.96) compared to those who did not have positive CT or PET results (0.76, 95% CI, 0.65 to 0.85). EBUS-TBNA had a pooled sensitivity of 0.93 (95% CI, 0.91 to 0.94) and a pooled specificity of 1.00 (95% CI, 0.99 to 1.00) for lung cancer detection and staging. Complications occurred in two patients (0.15%). One patient experienced a major pneumothorax and required chest tube drainage after the EBUS-TBNA procedure, and one patient experienced minor hypoxemia during the procedure (this complication is not EBUS-specific). The meta-analysis received a high-quality score when it was assessed, based on Oxman and Guyatt's criteria for scientific quality.[12]

Two of the studies that were included in the meta-analysis compared EBUS-TBNA to conventional TBNA[15] and to mediastinoscopy.[16] EBUS-TBNA was found to be more sensitive than conventional TBNA. It detected 69% compared with 36% of malignant lymph nodes ($P = 0.003$) in 138 patients who had lung or mediastinal abnormality on CT. In another population of 66 patients who were clinically suspected of having non-small cell lung cancer (NSCLC), EBUS-TBNA detected 91% of malignancies compared to 78% with mediastinoscopy ($P = 0.007$). Three prospective trials looked at the diagnostic accuracy of EBUS-TBNA in a total of 500 patients who were suspected of having lung cancer.[17-19] The findings from these prospective studies agree with the conclusion of the meta-analysis. The sensitivities of mediastinal lymph node staging range from 85% to 90%, with specificities of 100%.

A 2008 HTA focussed on the effectiveness and safety of EBUS in the detection and staging of lung cancer in patients with established or suspected lung cancer.[20] This HTA did not include a meta-analysis, and the conclusions of the report were based on an assessment of the findings from the individual trials. The HTA found that EBUS-TBNA statistically significantly increased the diagnostic yield for mediastinal lymph nodes compared to conventional TBNA (80% versus 71%, $P < 0.05$), particularly for locations other than subcarinal lymph nodes (84% versus 58%, $P < 0.001$). Based on Oxman and Guyatt's assessment tool for scientific quality,[12] this HTA was not considered to be of high quality. There were no methods to combine the findings of the relevant studies, and the conclusions were partially supported by the data.

## 4.2 Cost-effectiveness of EBUS

A cost-effectiveness analysis published in 2008 examined whether or not the introduction of EBUS-guided procedures for the investigation of NSCLC, mediastinal and hilar masses, endobronchial cancer, and peripheral lung lesions represented value for money in the Australian health care system.[21] The cost analysis indicated that the cost of EBUS-TBNA was A$1,120 per procedure (C$996), which translated to a savings of A$347 per patient (C$308) compared with conventional TBNA for NSCLC staging or diagnosis of mediastinal and hilar masses. This reflects the economic benefits that are associated with the improved yield resulting from the use of EBUS-guided procedures. This cost analysis was considered to be rigourous, based on Drummond's quality checklist for economic studies.[13] A cost study also found that a combined approach of TBNA, EBUS-TBNA, and mediastinoscopy is the most cost-effective for mediastinal lymph node staging in NSCLC, compared to TBNA alone, EBUS-TBNA, or mediastinoscopy.[22]

According to the Australian cost analysis, the estimated number of patients who are eligible per year to undergo pathological assessment for NSCLC staging and diagnosis of mediastinal masses ranges from 1,456 to 2,262 (15% to 23%) among a total of 9,611 patients with lung cancer. Based on Canadian Cancer Statistics,[1] the number of new cases of lung cancer in Canada in 2009 is estimated to be 23,400.

Assuming that the figures in Australia apply to Canada and that the procedural costs in the two countries are similar, between 3,510 and 5,382 Canadian patients could undergo EBUS-TBNA per year, with total costs ranging from an estimated C$3,496,000 to an estimated C$5,360,000 per year. The use of EBUS-TBNA instead of conventional TBNA would provide an annual cost-savings of C$839,000 to C$1,286,400.

# 5 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

Given the existing evidence, EBUS is an accurate and safe tool in lung cancer diagnosis and staging. The cost-effectiveness of EBUS has not been evaluated, but cost-analyses show that EBUS-TBNA reduced the staging cost by 24% per patient. Using Australian cost-analysis data, and assuming that the costs are similar in Canada, the use of EBUS-TBNA compared to the use of conventional TBNA in Canada for NSCLC staging and the diagnosis of mediastinal masses could lead to estimated savings of C$0.8 million to C$1.3 million per year in the Canadian health care system. The limitation of this cost analysis is that conventional TBNA is not the standard of care for mediastinal staging. There are minimal data on the comparison of EBUS to mediastinoscopy.

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# APPENDIX 1: Literature Search Strategy

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | EMBASE <1996 to 2009 Week 26><br>Ovid Medline In-Process & Other Non-Indexed Citations <1950 to present><br>**Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | April 20, 2009 |
| Alerts: | Monthly search updates began April 20, 2009 and ran until May 30, 2009. |
| Study Types: | All study types |
| Limits: | Publication years 2004-May 2009<br>Humans<br>English |

| SYNTAX GUIDE | |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| .sh | At the end of a phrase, searches the phrase as a subject heading |
| MeSH | Medical Subject Heading |
| fs | Floating subheading |
| exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| # | Truncation symbol for one character |
| ADJ | Requires words are adjacent to each other (in any order) |
| ADJ# | Adjacency within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |

**MULTI-DATABASE STRATEGY**

| Line # | Search Strategy | Results |
|---|---|---|
| 1 | EBUS.ti,ab. or bronchi/us | 331 |
| 2 | Bronchi/ or Bronchoscopy/ or Bronchoscopes/ | 57113 |
| 3 | (Endobronchial or bronchial or bronchi or bronchoscope*or esophageal).ti,ab | 89896 |
| 4 | 1 or 3 or 2 | 124023 |
| 5 | Endosonography/ or Ultrasonography/ | 135211 |
| 6 | (ultrasound* or ultrasonography or endosonograph* or endoscop* or ultrasonic).ti,ab. | 415364 |
| 7 | 6 or 5 | 477712 |
| 8 | 3 or 2 | 124007 |
| 9 | 8 and 7 | 5255 |

| MULTI-DATABASE STRATEGY | | |
|---|---|---|
| 10 | Lung neoplasms/ or NSCLC.ti,ab. | 138244 |
| 11 | ((lung or pulmonary) adj3 (neoplasm* or cancer* or carcinoma* or biopsy or biopsies)).ti,ab. | 138985 |
| 12 | 11 or 10 | 203424 |
| 13 | 1 or 9 | 5281 |
| 14 | 13 and 12 | 1266 |
| 15 | limit 14 to yr="2004 -Current" | 535 |
| 16 | exp Endobronchial ultrasonography/ | 117 |
| 17 | (EBUS or endobronchial echograph* or endobronchial ultrasound* or echo-endoscop* or esophageal ultrasound* or bronchial ultrasound* or endobronchial ultrasonograph* or bronchial ultrasonograph* or bronchial echography or esophageal ultrasonograph* or esophageal echograph*).ti,ab. | 709 |
| 18 | 16 or 17 | 744 |
| 19 | Lung cancer/ | 152594 |
| 20 | Lung cancer/ or nsclc.ti,ab. | 161332 |
| 21 | ((lung or pulmonary) adj3 (neoplasm* or cancer* or carcinoma* or biopsy or biopsies)).ti,ab. | 138985 |
| 22 | 21 or 19 or 20 | 210637 |
| 23 | 22 and 18 | 358 |
| 24 | 23 or 14 | 1308 |
| 25 | limit 24 to english language | 843 |
| 26 | limit 25 to yr="2004 - 2009" | 437 |
| 27 | 26 use prmz | 208 |
| 28 | 26 use emef | 229 |

| OTHER DATABASES | |
|---|---|
| PubMed | Same MeSH, keywords, limits, and study types used as per Medline search, with appropriate syntax used. |
| Cochrane Library Issue 1, 2009 | Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases. |

## Grey Literature

| | |
|---|---|
| Dates for Search: | January 2004 – April 2009 |
| Keywords: | EBUS, endobronchial ultrasound, lung cancer |
| Limits: | Publication years 2004 – April 2009 |

The following sections of the CADTH grey literature checklist, *Grey Matters: A Practical Search Tool for Evidence-Based Medicine* (http://www.cadth.ca/index.php/en/cadth/products) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Clinical Trials (ongoing)
- Databases (free)
- Internet Search
- Open-Access Journals.

## Organizations

Canadian Cancer Society (http://www.cancer.ca/Canada-wide.aspx?sc_lang=en).

# APPENDIX 2: Selected Reports for Clinical and Economic Review