TITLE: Endoscopic Ultrasound for the Diagnosis of Disease and Staging of Cancers in Adult Patients with Gastroenterological or Oncological Disease: A Review of the Clinical Effectiveness, Cost-effectiveness and Safety

DATE: 18 March 2014

CONTEXT AND POLICY ISSUES

Identification of cancers and gastroenterological diseases can be challenging, as clinicians must ensure the process for identification is accurate while minimizing complications and ensuring sustainability associated with procedures. In addition, for those with cancer, accurate staging is vital for guiding the most appropriate therapy.

There are a number of minimally invasive imaging strategies that may be used for identifying and staging different types of cancers, as well as identifying gastroentological disease. Examples of imaging strategies include computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS). Each strategy is associated with differing accuracy for different diseases, as well as when comparing diagnosis and staging of illness. In addition, each strategy is associated with other benefits and limitations. For example, EUS is often less expensive and more readily available relative to other imaging modalities like CT, PET and MRI, but CT, PET and MRI allow for visualization of a larger area compared with EUS. Also, the amount of radiation exposure, and need for contrast media, differs between each modality. Lastly, these imaging modalities may be complementary to one another, for example, using EUS to minimize exposure to the more invasive ERCP in people with acute biliary pancreatitis.

The purpose of this review was to evaluate the evidence for clinical effectiveness, safety, and cost effectiveness of EUS compared to other imaging modalities including CT, MRI, PET, or ERCP.

RESEARCH QUESTIONS

1. What is the evidence for the clinical effectiveness and safety of endoscopic ultrasound for the diagnosis of disease and staging of cancers in adult patients with gastroenterological or oncological disease?

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2. What is the evidence for the cost-effectiveness of endoscopic ultrasound for the diagnosis of disease and staging of cancers in adult patients with gastroenterological or oncological disease?

KEY FINDINGS

Evidence suggests that endoscopic ultrasound (EUS) has similar accuracy to endoscopic retrograde cholangiopancreatography (ERCP) for detecting choledocholithiasis, and was associated with a reduced risk for complications in patients with mild or moderate acute biliary pancreatitis and a reduction in ERCP exposure. Endobronchial ultrasound-guided transbronchial lung biopsy was as accurate for identifying lung cancer in patients with peripheral pulmonary lesions as CT-guided percutaneous needle biopsy, and was associated with a reduced risk for procedural complications. Results were inconsistent among the studies included evaluating EUS and CT in pancreatic cancer. One Australian economic analysis suggested that endobronchial ultrasound-guided lung biopsy was associated with similar costs compared with CT-guided needle biopsy, but was sensitive to complication costs.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and February 14, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications for relevancy, and evaluated the relevant full-text publications for the final article selection based on the criteria listed in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Questions 1 and 2: Adult patients with gastroenterological or oncological diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Questions 1 and 2: Endoscopic ultrasound</td>
</tr>
<tr>
<td>Comparator</td>
<td>Questions 1 and 2: Endoscopic Retrograde Cholangio-Pancreatography (ERCP); CT; PET; or MRI</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Question 1: Clinical effectiveness specific to the diagnosis of disease and staging of cancer; harms or safety</td>
</tr>
<tr>
<td></td>
<td>Question 2: Cost-effectiveness</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies</td>
</tr>
</tbody>
</table>
Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, if they were duplicate publications or included in a selected systematic review or meta-analysis, or were published prior to January 1, 2009.

Critical Appraisal of Individual Studies

Systematic reviews were critically appraised using the AMSTAR instrument. Randomized controlled trials were appraised using the Downs and Black checklist and economic analyses were appraised using Drummond’s Checklist. Numeric scores were not calculated, and instead, important methodological aspects of each study relating to validity of the study results were summarized.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search identified 624 citations, with an additional nine citations identified from the grey literature. After screening of the abstracts, 46 potentially relevant studies were identified for full-text review. A total of eight studies were included in this review, including three meta-analyses (MA), two systematic reviews (SR), two randomized controlled trials (RCT), and one economic analysis.

The PRISMA flowchart provides the details of the study selection process (Appendix 1).

Summary of Study Characteristics

Details on clinical and safety study characteristics, economic study characteristics, critical appraisal, and study findings are located in Appendices 2 through 5, respectively.

Study Design

There were three MAs, two SRs, two RCTs, and one economic analysis included in this review. The number of included studies in the MAs and SRs ranged from four to twelve, and the publication time frame of the included studies was 1991 to 2012.

Country of Origin

The countries of origin included Australia, India, Italy, Turkey, the United Kingdom, and the United States. One of the MAs involved authors from both New Zealand and the United States.

Patient Population

The patient populations varied across the studies, and included patients with suspected choledocholithiasis, confirmed or suspected pancreatic cancer, suspected perianal fistulas, acute biliary pancreatitis, and individuals with peripheral pulmonary lesions.
**Interventions and Comparators**

The intervention in all studies was some form of endoscopic ultrasound, including endobronchial ultrasound\(^{15,16}\) and endoanal ultrasound (EAUS).\(^ {10}\) Comparisons included CT,\(^ {9,12,15,16}\) ERCP,\(^ {11,13}\) MRI,\(^ {10,12}\) and magnetic resonance cholangiopancreatography (MRCP).\(^ {14}\) Within the MAs and SRs, the MA evaluating EAUS reported the gold standard comparator for calculating sensitivity and specificity of EAUS and MRI as exam under anesthesia.\(^ {10}\)

**Clinical Outcomes**

Clinical outcomes also varied between studies, and included diagnosis, nodal staging, evaluation of vascular invasion, and evaluation of resectability in pancreatic cancer,\(^ {9,12}\) identification and evaluation of idiopathic and Crohn’s perianal fistulas,\(^ {10}\) avoidance of additional endoscopic procedures or ERCP in people with suspected choledocholithiasis or acute biliary pancreatitis,\(^ {11,13,14}\) and diagnostic performance and procedure-related complications associated with evaluating peripheral pulmonary lesions.\(^ {15}\)

The economic analysis used both cost-benefit and cost-effectiveness analysis to compare two modalities for assessing peripheral pulmonary lesions.\(^ {16}\) The perspective of the analysis was the health care system, and assumed that pathology costs were equal in each model arm, that regardless of how the diagnosis is made, downstream medical costs would be the same, and long-term outcomes would be equivalent.\(^ {16}\)

**Summary of Critical Appraisal**

A total of seven studies evaluated the clinical effectiveness and safety of EUS relative to other imaging modalities. Among these studies were three MAs,\(^ {9-11}\) two SRs without MAs,\(^ {12,13}\) and two RCTs.\(^ {14,15}\)

The quality of the included MAs and SRs varied considerably. All studies clearly specified the primary aim of the review, but none of the studies assessed the possibility of publication bias.\(^ {9-13}\) Two of the MAs measured heterogeneity between studies for pooled study results\(^ {10,11}\) and two studies did not evaluate quality of the studies included in the review.\(^ {12,13}\) Among the MAs that did evaluate study quality, the included studies varied and were limited by lack of blinding, and a lack of explanation regarding study withdrawals.\(^ {9-11}\) The included studies did appear to provide a representative sample of patients who would receive the evaluated tests in practice.\(^ {9-11}\) Searches were limited to two databases in two reviews,\(^ {9,13}\) and three studies did not report searching the grey literature for relevant evidence.\(^ {9,11,12}\) Lastly, four of the reviews did not report how studies were assessed for inclusion in the review in terms of how screening abstracts and manuscripts was conducted for full-text review.\(^ {9,10,12,13}\)

In terms of the two included RCTs, both clearly described both the aim of the study and the interventions evaluated.\(^ {14,15}\) One study reported how randomization was completed (using a computer-based random sequence generator),\(^ {15}\) and neither study was blinded due to the nature of the procedures.\(^ {14,15}\) A major limitation of each RCT was that neither calculated a sample size, so it is unclear whether each study was adequately powered to detect a difference between the intervention and comparison groups.\(^ {14,15}\) In spite of randomization, there were significant differences for some prognostic factors in one of the RCTs, and these differences were not adjusted for in the statistical analysis.\(^ {15}\)
One economic analysis comparing endobronchial ultrasound-guided transbronchial lung biopsy (EBUS-TBLB) to CT-guided peripheral needle biopsy (CT-PNB) for identification of lung cancer in patients with peripheral pulmonary lesions.\textsuperscript{16} The authors used a previously conducted RCT\textsuperscript{15} to derive costs associated with each procedure, and considered the health care system perspective.\textsuperscript{16} They included direct costs (physician, nursing, radiology and pathology costs) and indirect costs (equipment sterilization, repair costs, and non-clinician staff costs) in their calculations. However, the results may not be generalizable to all patients with peripheral pulmonary lesions given the small sample size of the RCT. Also, they did not specify the time horizon, although it appeared that time spanned to the point of diagnosis of the lesions.\textsuperscript{16} The study authors conducted sensitivity analyses, varying costs of potential complications, the sensitivity of each diagnostic method, and the prevalence of malignant disease to examine how costs may change with changing patient populations.\textsuperscript{16} In addition, the authors clearly defined the assumptions they used in the economic analysis, and used a disutility technique to account for the study question relating to diagnosis and screening, because utility techniques were designed for chronic diseases.\textsuperscript{16}

**Summary of Findings**

*What is the evidence for the clinical effectiveness and safety of endoscopic ultrasound for the diagnosis of disease and staging of cancers in adult patients with gastroenterological or oncological disease?*

Two studies, one MA and one SR, evaluated patients with pancreatic cancer or peri-ampullary adenocarcinomas.\textsuperscript{9,12} In the MA conducted by Nawaz et al., EUS was compared with CT for nodal staging, vascular invasion, and prediction of resectability,\textsuperscript{9} whereas in the SR, EUS was compared with CT or MRI for diagnosis, nodal staging, vascular involvement and resectability.\textsuperscript{12} There was overlap in terms of the studies included in the MA and SR.\textsuperscript{9,12} Sensitivity was found to be greater for EUS for both nodal staging (58%; 95% confidence interval [CI]: 44 to 70%) and assessment of vascular invasion (86%; 95% CI: 70 to 94%) relative to CT (24%; 95% CI 16 to 34% and 58%; 95% CI: 45 to 69%, respectively) in this study. No difference was found in terms of sensitivity or specificity for resectability, or specificity for nodal staging or vascular invasion for EUS compared with CT.\textsuperscript{9} In the second study, conducted by Shirkhande et al., the authors concluded that EUS was found to have a greater sensitivity for tumour detection relative to CT, and was found to be equivalent to MRI.\textsuperscript{12} In contrast to the MA, Shirkhande et al. concluded that CT was better for determining cancer resectability compared to EUS, but this was based on one study only, which could explain the differing results between the SR and MA.\textsuperscript{12} The sensitivity for nodal staging with EUS ranged from 21% to 61%.\textsuperscript{12} Lastly, sensitivity for assessment of vascular involvement ranged from 17% to 100% with EUS, and 45% to 67% with CT.\textsuperscript{12}

An MA and an SR were used to compare EUS to ERCP, and an RCT was used to compare EUS to MRCP for suspected choledocholithiasis or acute biliary pancreatitis.\textsuperscript{11,13,14} Among these studies, risk for procedure-related complications and acute pancreatitis was significantly less in the EUS group relative to the ERCP group,\textsuperscript{11,13} whereas there was no difference in risk of acute pancreatitis when comparing EUS and MRCP.\textsuperscript{14} ERCP was avoided in patients who received EUS in two studies\textsuperscript{13,14} and MRCP in one study.\textsuperscript{14} The avoidance of ERCP in people who were randomized to EUS (66.7%) was similar to those randomized to MRCP (61.7%). In addition, Di Lisi et al. found that ERCP could have been avoided in 35% to 74% of study participants, depending on the study population.\textsuperscript{13}
Siddiqui and colleagues completed an MA to compare endoanal ultrasound (EAUS) with MRI for detection of idiopathic and Crohn’s-related perianal fistulas, and found no difference in terms of sensitivity and specificity for each procedure. However, the authors noted that the overall specificity for identifying fistulas was poor (EAUS: 43%; 95% CI: 21 to 69%; MRI: 69%; 95% CI: 51 to 82%). Specificity was high for both EAUS and MRI for identifying sinuses. The results of this study are limited due to a high amount of heterogeneity among the included studies.

Lastly, Steinfort and colleagues conducted an RCT to compare EBUS-TBLB and CT-PNB for diagnosis of lung cancer in patients with peripheral pulmonary lesions. The authors found the diagnostic accuracy to be similar for EBUS-TBLB and CT-PNB, but individuals randomized to CT-PNB were significantly more likely to develop procedure-related complications compared to patients randomized to EBUS-TBLB.

What is the evidence for the cost-effectiveness of endoscopic ultrasound for the diagnosis of disease and staging of cancers in adult patients with gastroenterological or oncological disease?

One economic analysis was identified comparing EBUS-TBLB and CT-PNB for diagnosis of lung cancer in patients with peripheral pulmonary lesions, based on the perspective of the health care system. The same group who conducted the RCT evaluating EBUS-TBLB and CT-PNB conducted this study, and data from the RCT was used to identify costs for the economic analysis. In terms of the cost-benefit analysis, the authors found the cost of EBUS-TBLB to be $2,748 and the cost of CT-PNB to be $2,724 (costs in 2010/2011 Australian dollars). The study authors used a theoretical wait-trade-off for procedural complications of 20 days, and found CT-PNB to be more cost-effective ($2,778 per quality-adjusted life year [QALY]) relative to EBUS-TBLB ($2,816 per QALY). However, EBUS-TBLB was found to be more cost-effective in certain scenarios in the sensitivity analyses, including when the cost of complications exceeded $489, or if the complication rate associated with CT-PNB exceeded 40%.

LIMITATIONS

There are a number of limitations that must be noted when considering the information reported in this review. A number of pooled comparisons within the MAs were associated with significant heterogeneity, and therefore results must be interpreted with caution. In addition, none of the MAs or SRs assessed the possibility of publication bias, and as a result, studies may be missing from these reviews, which could impact the conclusions drawn in each review. Some studies within this review had conflicting conclusions. In addition, the RCTs included in this review had small sample sizes and did not include a sample size calculation in their methods, and as a result, it is unclear whether the results seen in these studies are correct, or if they are false negatives due to having inadequate power to detect a difference. Lastly, only one economic analysis was identified that included patients with peripheral pulmonary lesions, limiting the generalizability of the results to other patient populations. This economic analysis was conducted in Australia, so direct and indirect costs of EBUS-TBLB and CT-PNB may not be generalizable to a Canadian context.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One systematic review suggested that EUS has similar accuracy as ERCP for the detection of choledocholithiasis. It appears that EUS and MCRP are effective strategies for reducing
exposure to ERCP in patients with suspected choledocholithiasis or mild to moderate acute biliary pancreatitis, and EUS is associated with a reduced likelihood of procedure-related complications relative to ERCP. EBUS-TBLB and CT-PNB were both associated with high diagnostic accuracy for identifying lung cancer in patients with peripheral pulmonary lesions, but EBUS-TBLB was associated with a reduced risk for procedure-related complications relative to CT-PNB. Both EAUS and MRI had low diagnostic specificity for imaging of perianal fistulas, which could result in false positive results. Lastly, results were inconsistent among the studies included evaluating EUS and CT in pancreatic cancer.

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REFERENCES


APPENDIX 1: Selection of Included Studies

624 citations identified from electronic literature search and screened

587 citations excluded

37 potentially relevant articles retrieved for scrutiny (full text, if available)

9 potentially relevant reports retrieved from other sources (grey literature, hand search)

46 potentially relevant reports

38 reports excluded:
- irrelevant comparator (19)
- already included in at least one of the selected systematic reviews (1)
- not randomized (2)
- published in language other than English (1)
- other (review articles, editorials, cost to access the full text article was prohibitive) (15)

8 reports included in review
APPENDIX 2: Characteristics of the included meta-analyses, systematic reviews, and randomized controlled trials

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design, Length of Follow-up</th>
<th>Patient Characteristics, Sample Size (n)</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Clinical Outcomes</th>
</tr>
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<tbody>
<tr>
<td><strong>Meta-Analyses</strong></td>
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<tr>
<td>Nawaz, 2013, United States(^9)</td>
<td>Meta-analysis</td>
<td>Patients with pancreatic cancer</td>
<td>EUS</td>
<td>CT</td>
<td>Nodal staging</td>
</tr>
<tr>
<td></td>
<td>Years of included studies: 1992 to 2012</td>
<td>Total of 12 studies included: 8 studies for nodal staging, 12 studies for vascular invasion, and 6 studies for resectability</td>
<td>n = 281 for nodal staging</td>
<td>n = 272 for nodal staging</td>
<td>Vascular invasion</td>
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<td></td>
<td></td>
<td></td>
<td>n = 441 for vascular invasion</td>
<td>n = 431 for vascular invasion</td>
<td>Prediction of resectability</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>n = 250 for resectability</td>
<td>n = 280 for resectability</td>
<td></td>
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<tr>
<td>Siddiqui, 2012, United Kingdom(^10)</td>
<td>Systematic review</td>
<td>Studies comparing endoanal ultrasound to MRI for imaging of patients with a clinical suspicion of perianal fistulas</td>
<td>Endoanal ultrasound</td>
<td>MRI</td>
<td>Detection of idiopathic and Crohn’s perianal fistulas</td>
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<tr>
<td></td>
<td>Years of included studies: 1999 to 2004</td>
<td>4 studies included</td>
<td>n = 241</td>
<td>n = 240</td>
<td>Identification of the site of the fistula</td>
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<td>Sinuses identified</td>
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<td></td>
<td>Identification of the internal opening</td>
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<tr>
<td>Petrov, 2009, New Zealand and United States(^11)</td>
<td>Meta-analysis</td>
<td>Studies comparing EUS-guided ERCP versus ERCP alone in patients with suspected choledocholithiasis</td>
<td>EUS</td>
<td>ERCP</td>
<td>Avoidance of additional endoscopic procedures</td>
</tr>
<tr>
<td></td>
<td>Years of included studies: 2005 to 2009</td>
<td>n = 423</td>
<td>n = 213</td>
<td>n = 210</td>
<td>Complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 studies included</td>
<td></td>
<td></td>
<td>Acute pancreatitis</td>
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<tr>
<td><strong>Systematic Reviews</strong></td>
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<tr>
<td>Shirkhande, 2012, India(^12)</td>
<td>Systematic review</td>
<td>Studies comparing imaging modalities in patients with pancreatic and peri-ampullary adenocarcinomas</td>
<td>EUS</td>
<td>CT, MRI</td>
<td>Diagnosis</td>
</tr>
<tr>
<td></td>
<td>Years of included studies:</td>
<td></td>
<td>Number of patients not reported</td>
<td>Number of patients not reported</td>
<td>Resectability</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Nodal staging</td>
</tr>
<tr>
<td>First Author, Publication Year, Country</td>
<td>Study Design, Length of Follow-up</td>
<td>Patient Characteristics, Sample Size (n)</td>
<td>Intervention</td>
<td>Comparator(s)</td>
<td>Clinical Outcomes</td>
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<tr>
<td>De Lisi, 2011, Italy&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Systematic review Years of included studies: 1998 to 2008</td>
<td>Included studies comparing EUS with ERCP in patients with acute biliary pancreatitis n = 545 patients 7 studies included</td>
<td>EUS (n = 475)</td>
<td>ERCP (n = 367)</td>
<td>Vascular involvement Primary outcomes: Procedure success Detection of choledocholithiasis Secondary outcomes: Complications related to procedure Complications related to pancreatitis Length of hospital stay</td>
</tr>
</tbody>
</table>

**Randomized Controlled Trials**

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design, Length of Follow-up</th>
<th>Patient Characteristics, Sample Size (n)</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alper, 2012, Turkey&lt;sup&gt;14&lt;/sup&gt;</td>
<td>RCT, 1 year</td>
<td>Patients with mild-moderate acute biliary pancreatitis without an urgent need for ERCP (n = 95)</td>
<td>EUS (n = 48)</td>
<td>MRCP (n = 47)</td>
<td>Avoidance of ERCP Positive stone on ERCP Risk of recurrent pancreatitis</td>
</tr>
<tr>
<td>Steinfort, 2011, Australia&lt;sup&gt;15&lt;/sup&gt;</td>
<td>RCT, 1 year</td>
<td>Patients with peripheral pulmonary lesions (n = 51)</td>
<td>EBUS-TBLB (n = 32)</td>
<td>CT-PNB (n = 19)</td>
<td>Diagnostic performance Complications</td>
</tr>
</tbody>
</table>

CT: computed tomography; CT-PNB: computed tomography-guided percutaneous needle biopsy; EBUS-TBLB: endobronchial ultrasound-guided transbronchial lung biopsy; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; MRCP: magnetic resonance cholangiopancreatography; MRI: magnetic resonance imaging; RCT: randomized controlled trial
### APPENDIX 3: Characteristics of the included economic analysis

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Type of Economic Evaluation, Study Perspective</th>
<th>Patient Population</th>
<th>Intervention (n)</th>
<th>Comparator(s) (n)</th>
<th>Assumptions</th>
</tr>
</thead>
</table>
| Steinfort, 2013, Australia\(^{16}\)    | CBA, CEA; Health care system perspective     | Patients with peripheral pulmonary lesions | EBUS-TBLB (n = 12) | CT-PNB (n = 12) | • The outcome of diagnosis of peripheral pulmonary lesions was made for each arm of the decision model;  
• Long-term outcomes were equivalent in each model arm;  
• Once a diagnosis is made, regardless of method of diagnosis, downstream medical care costs were the same;  
• Thoracotomy/thoracoscopy had a diagnostic accuracy of 100% for evaluation of peripheral pulmonary lesions;  
• Regardless of how tissue samples were obtained, pathology costs were equal in each model arm. |

CBA: cost-benefit analysis; CEA: cost effectiveness analysis; CT-PNB: computed tomography-guided percutaneous needle biopsy; EBUS-TBLB: endobronchial ultrasound-guided transbronchial lung biopsy
### APPENDIX 4: Critical appraisal of all included studies

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td><strong>Meta-Analyses</strong></td>
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<tr>
<td>Nawaz, 2013 9</td>
<td>• Primary aim of the meta-analysis is clearly specified.</td>
<td>• Search was limited to MEDLINE and Embase only.</td>
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<tr>
<td></td>
<td>• Data extraction was duplicated by two individuals.</td>
<td>• No mention of searching the grey literature.</td>
</tr>
<tr>
<td></td>
<td>• Method of assessing study quality clearly described.</td>
<td>• Unclear how studies were selected for inclusion in the review.</td>
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<tr>
<td></td>
<td></td>
<td>• Description of the included studies was limited.</td>
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<tr>
<td></td>
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<td>• Authors did not measure heterogeneity for pooled results.</td>
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<tr>
<td></td>
<td></td>
<td>• Publication bias was not assessed.</td>
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<tr>
<td></td>
<td></td>
<td>• Gold standard for calculating sensitivity, specificity, PPV and NPV was not reported.</td>
</tr>
<tr>
<td>Siddiqui, 2012 10</td>
<td>• Primary aim of the meta-analysis is clearly specified.</td>
<td>• Unclear how studies were selected for inclusion in the review.</td>
</tr>
<tr>
<td></td>
<td>• The authors used a comprehensive search strategy to identify literature.</td>
<td>• Publication bias was not assessed.</td>
</tr>
<tr>
<td></td>
<td>• Method of assessing study quality clearly described.</td>
<td></td>
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<tr>
<td></td>
<td>• Data extraction was duplicated by two individuals, and checked by a third individual.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Authors measured heterogeneity for pooled results.</td>
<td></td>
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<td></td>
<td>• Detailed description of the included studies was provided.</td>
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<td></td>
<td>• Reported that examination under anesthetic as the gold standard for calculating sensitivity and specificity.</td>
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</tr>
<tr>
<td>Petrov, 2009 11</td>
<td>• Primary aim of the meta-analysis is clearly specified.</td>
<td>• No mention of searching the grey literature.</td>
</tr>
<tr>
<td></td>
<td>• Method of assessing study quality clearly described.</td>
<td>• Unclear how many people performed data extraction.</td>
</tr>
<tr>
<td></td>
<td>• Authors measured heterogeneity for pooled results.</td>
<td>• Publication bias was not assessed.</td>
</tr>
<tr>
<td></td>
<td>• Authors assessed and reported scientific quality of the included studies.</td>
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<td><strong>Systematic Reviews</strong></td>
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<td>Shirkhande, 2012 12</td>
<td>• Primary aim of the systematic review was clearly specified.</td>
<td>• No mention of searching the grey literature.</td>
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<td>• Study inclusion and exclusion criteria were clearly specified.</td>
<td>• Unclear how studies were selected for inclusion in the review.</td>
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<tr>
<td></td>
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<td>• No assessment of study quality performed.</td>
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<tr>
<td>First Author, Publication Year</td>
<td>Strengths</td>
<td>Limitations</td>
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</table>
| De Lisi, 2011<sup>13</sup> | Primary aim of the systematic review was clearly specified.  
Study inclusion and exclusion criteria were clearly specified.  
Searched reference lists of review articles, primary studies, and abstracts from major gastroenterology meetings to supplement database search.  
Two individuals duplicated data extraction.  
Detailed description of the included studies was provided. | Search was limited to MEDLINE and Cochrane Controlled Trials Register.  
Unclear how studies were assessed for inclusion in the systematic review.  
No assessment of study quality.  
Publication bias was not assessed.  
Gold standard for studies calculating sensitivity and specificity was not reported. |

### Randomized Controlled Trials

| Alper, 2012, Turkey<sup>14</sup> | Aim of the study was clearly described.  
Interventions were clearly described.  
Individuals were randomized to the intervention groups.  
Prognostic factors were evenly distributed between groups.  
No reported losses to follow up. | Blinding was not possible given the nature of the procedures.  
A sample size calculation was not reported, so it is unclear whether the study was adequately powered to detect a difference between groups.  
It is unclear how many people were screened for inclusion in the study.  
Generalizability is limited to those with mild to moderate acute biliary pancreatitis, as those who needed urgent ERCP were excluded from the study.  
Unclear whether consecutive patients were included.  
| |

| Steinfort, 2011, Australia<sup>15</sup> | Aim of the study was clearly described.  
Interventions were clearly described.  
Individuals were randomized to the intervention groups.  
Randomization conducted using a computer-based random sequence generator. | Blinding was not possible given the nature of the procedures.  
A sample size calculation was not reported, so it is unclear whether the study was adequately powered to detect a difference between groups.  
3 people randomized to CT-PTB did not undergo CT-PTB  
Some prognostic factors were not evenly distributed between groups, including lesion size and distance of lesion from pleura.  
Comparisons were not adjusted for |
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<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
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<td>differences in prognostic factors between groups.</td>
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**Economic Analysis**

Steinfort, 2013, Australia\(^{16}\)

- Aim of the economic analysis was clearly described.
- Evidence of non-inferiority of EBUS-TBLB and CT-PNB was previously established in a small RCT.
- Costs derived from patient data from the author’s hospital.
- Included direct costs (physician, nursing, radiology, and pathology costs) and indirect costs (equipment sterilization, repair costs, non-clinician staff costs).
- Sensitivity analyses performed varying the measured sensitivity of each diagnostic method, for both benign and malignant peripheral pulmonary lesions, as well as the CT-PNB complication rate, the prevalence of malignancy, and the mean cost of complications.
- Costs were updated to 2010/2011 prices in Australian dollars.
- Authors used disutility based on the wait-trade-off technique in place of time-trade-off and utility measures because utility measures were designed for chronic disease states, whereas wait-trade-off and disutility was designed for use in states related to diagnosis and screening.
- Clearly defined assumptions, and the assumptions were appropriate.

- Study considered the health system perspective only.
- Cost data based on a small sample size (n = 24 patients).
- Unclear how clinician costs were measured.
- Results may not be generalizable to the entire population with peripheral pulmonary lesions given the small sample size.
- Time horizon was no specified.

CT-PTB: computed tomography-guided percutaneous needle biopsy; EBUS-TBLB: endobronchial ultrasound-guided transbronchial lung biopsy; NPV: negative predictive value; PPV: positive predictive value
## APPENDIX 5: Main study findings and authors’ conclusions

<table>
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<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
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<tr>
<td><strong>Meta-Analyses</strong></td>
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| Nawaz, 2013<sup>9</sup>       | Sensitivity for nodal staging:  
  EUS: 58% (95% CI: 44 – 70%)  
  CT: 24% (95% CI: 16 – 34%)  
  Specificity for nodal staging:  
  EUS: 85% (95% CI: 73 – 92%)  
  CT: 88% (95% CI: 77 – 94%)  
  PPV for nodal staging:  
  EUS: 81% (95% CI: 68 – 89%)  
  CT: 67% (95% CI: 52 – 79%)  
  NPV for nodal staging:  
  EUS: 64% (95% CI: 56 – 71%)  
  CT: 51% (95% CI: 43 – 59%)  
  Sensitivity for vascular invasion:  
  EUS: 86% (95% CI: 70 – 94%)  
  CT: 58% (95% CI: 45 – 69%)  
  Specificity for vascular invasion:  
  EUS: 93% (95% CI: 88 – 96%)  
  CT: 95% (95% CI: 89 – 98%)  
  PPV for vascular invasion:  
  EUS: 88% (95% CI: 82 – 92%)  
  CT: 90% (95% CI: 78 – 95%)  
  NPV for vascular invasion:  
  EUS: 90% (95% CI: 82 – 94%)  
  CT: 75% (95% CI: 69 – 81%)  
  Sensitivity for resectability:  
  EUS: 87% (95% CI: 63 – 96%)  
  CT: 90% (95% CI: 77 – 96%)  
  Specificity for resectability:  
  EUS: 89% (95% CI: 63 – 97%)  
  CT: 69% (95% CI: 41 – 87%)  
  PPV for resectability:  
  EUS: 86% (95% CI: 63 – 95%)  
  CT: 72% (95% CI: 53 – 85%)  
  NPV for resectability:  
  EUS: 88% (95% CI: 75 – 95%)  
  CT: 87% (95% CI: 78 – 93%)  | EUS was more sensitive than CT for assessing nodal staging and vascular invasion for patients with pancreatic cancer. No significant difference was found in terms of sensitivity of resectability, or specificity of nodal staging, vascular invasion, or resectability of pancreatic cancer between EUS and CT. |
| Siddiqui, 2012<sup>10</sup>    | Detection of idiopathic and Crohn’s perianal fistulas  
  • Combined sensitivity of EAUS: 0.87; 95% CI: 0.70 – 0.95  
  • Combined sensitivity of MRI: 0.87; 95% CI: 0.60 – 0.95 | The authors concluded that the limited amount of data and high degree of heterogeneity among included studies limited the conclusions that could be drawn. |
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| Petrov, 2009¹¹ | Avoidance of additional endoscopic procedures in those who underwent EUS-guided ERCP compared to ERCP alone:  
- RR: 2.46; 95% CI: 1.34 – 4.52; I² = 60%  
Complications in those undergoing EUS-guided ERCP compared to ERCP alone:  
- RR: 0.35; 95% CI: 0.20 – 0.62; I² = 0% | from the evidence. The authors also noted that the specificity of both MRI and EAUS for identifying fistulas was diagnostically poor. |

- 95% CI: 0.63 – 0.96  
- Combined specificity of EAUS: 0.43; 95% CI: 0.21 – 0.69  
- Combined specificity of MRI: 0.69; 95% CI: 0.51 – 0.82  
- Heterogeneity was high (I² > 90%) for sensitivity examinations, but < 50% for specificity measurements

Identification of the site of the fistula  
- Sensitivity and specificity of EAUS and MRI varied based on location of the fistula, including extra/suprasphincteric fistulas, transsphincteric fistulas, and intersphincteric fistulas.

Sinuses identified  
- Two studies reported on sinus identification, and the sensitivity for EAUS was 0% and 40%, and specificity was 97% and 100%. Sensitivity for MRI was 0% and 60%, and specificity was 100% in both studies.

Identification of the internal opening  
- Three studies reported identification of the internal opening. Sensitivity was 88% to 91%, and specificity was 43% to 100% for EAUS. Sensitivity was 19%, 31%, and 97%, and specificity was 71 to 100% for MRI.
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|                                | Acute pancreatitis in those undergoing EUS-guided ERCP compared to ERCP alone:  
  • RR: 0.21; 95% CI: 0.06 – 0.83; I² = 0% | reduced risk for complications and acute pancreatitis relative to ERCP alone.  
  The authors suggest reserving the ERCP-only strategy for patients with a high probability of common bile duct stones, and using EUS for patients with a low or intermediate probability of having common bile duct stones. |

**Systematic Reviews**

**Shirkhande, 2012**

**Diagnosis**

- Five studies evaluated diagnosis of pancreatic and periampullary cancers in those with EUS versus CT or MRI. Among these, four compared EUS to CT and one compared EUS, CT and MRI. Results consistently demonstrated that EUS was better for tumour detection relative to CT (sensitivity of EUS ranged from 75% to 100%; sensitivity of CT ranged from 63% to 82%). EUS was found to be equivalent for tumour detection when compared to MRI in one study (accuracy of EUS was 98%; accuracy of MRI was 81%).

**Resectability**

- One study compared EUS to CT for resectability. CT was found to be better for determining tumour resectability relative to EUS (data not provided).

**Nodal staging**

- Six studies examined measurement of nodal staging; among these, three compared EUS to CT, and three compared EUS, CT and MRI. Sensitivity of EUS ranged from 21% to 61%, sensitivity of CT ranged from 33% to 42%, and sensitivity of MRI was...
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| De Lisi, 2011\(^1\)          | found to be 15% in one study. Specificity of EUS ranged from 80% to 100%, 73% to 92% for CT, and 100% for MRI. Accuracy ranged from 65% to 84% for EUS, 44% to 68% for CT, and 61% to 77% for MRI. Vascular involvement  
• Four studies examined measurement of vascular involvement. Three of these studies compared EUS to CT, and one compared EUS, CT and MRI. The sensitivity of EUS ranged from 17% to 100%, 45% to 67% for CT, and 59% for MRI. Specificity of EUS ranged from 67% to 100% for EUS, 87% to 100% for CT, and 85% for MRI.  

Procedure success  
• EUS was successful for imaging the bile duct in all but 6 patients  
• ERCP was successful in all but 17 patients, where cannulation of the common bile duct was unsuccessful  

Detection of choledocholithiasis  
• Sensitivity of EUS ranged from 86 – 100%  
• Specificity of EUS ranged from 85 – 100%  
• PPV of EUS ranged from 92 – 100%  
• NPV of EUS ranged from 92 – 100%  
• Sensitivity of ERCP ranged from 92 – 100%  
• Specificity of ERCP ranged from 87 – 100%  
• PPV of ERCP ranged from 65 – 100%  
• NPV of ERCP ranged from 92 – | EUS was associated with less complications related to the procedure, and had similar sensitivity and specificity for detecting choledocholithiasis. The authors found that ERCP was or could have been avoided in 35% - 74% of study participants, depending on the study population. The authors conclude that early EUS in patients with acute biliary pancreatitis can exclude choledocholithiasis without increasing procedure-related complications. |
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<tr>
<td></td>
<td>100%</td>
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<tr>
<td></td>
<td>• ERCP was or could have been avoided in 31.5% to 74% of study participants</td>
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<tr>
<td>Complications related to procedure:</td>
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<tr>
<td>• No complications occurred in patients who underwent EUS</td>
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<td>• Complications in those who underwent ERCP included post sphincterotomy hemorrhage (10 patients) and fever (2 patients)</td>
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<tr>
<td>Complications related to pancreatitis</td>
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<tr>
<td>• No statistical difference found between EUS and ERCP for complications related to pancreatitis</td>
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<tr>
<td>Length of hospital stay</td>
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<td>• Was reported in one study, and was median 6 days in the EUS group and 6.5 days in the ERCP group</td>
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**Randomized Controlled Trials**

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<tr>
<th>Alper, 2012, Turkey</th>
<th>Avoidance of ERCP</th>
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<tr>
<td></td>
<td>ERCP was avoided in 32 people (66.7%) randomized to EUS and 29 people (61.7%) randomized to MRCP</td>
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<tr>
<td>Positive stone on ERCP</td>
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<tr>
<td>• Among those with positive findings at EUS (16), 14 (87%) were found to have a bile duct stone on ERCP</td>
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<tr>
<td>• Among those with positive findings at MRCP (18), 16 (88%) were found to have a bile duct stone on ERCP</td>
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<td>Risk of recurrent pancreatitis</td>
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<tr>
<td>• No significant difference was found for recurrent pancreatitis within 1 year for those who received MRCP (2, 4.2%) or EUS (3, 6.3%)</td>
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<tr>
<td>No statistical difference was found in terms of avoidance of ERCP, identification of a positive stone on ERCP, or risk of recurrent pancreatitis. The authors concluded that EUS was not more effective than MRCP for evaluating the need for therapeutic ERCP in a patient with acute biliary pancreatitis.</td>
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<tr>
<td>First Author, Publication Year</td>
<td>Main Study Findings</td>
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| Steinfort, 2011, Australia¹⁶ | **Diagnostic performance**  
- Diagnostic accuracy was similar for EBUS-TBLB (87.5%; 95% CI: 71 – 96%) and CT-PNB (93.3%; 95% CI: 68 – 99%) p = 1.0  
- Sensitivity for identifying lung cancer was 86% (95% CI: 68 – 95) with EBUS-TBLB and 92% (95% CI: 62 – 99) with CT-PNB, p = 1.0. | The authors concluded that both procedures had high diagnostic accuracy, and EBUS-TBLB was non-inferior to CT-PNB for diagnosis of peripheral pulmonary lesions.  
The authors found that the proportion of patients developing complications was significantly lower in the EBUS-TBLB group compared to the CT-PNB group, and as a result, since EBUS-TBLB was found to be non-inferior to CT-PNB, EBUS-TBLB might be the preferred method for evaluating peripheral pulmonary lesions for possibility of cancer. |
|                            | **Risk of recurrent pancreatitis**  
- No significant difference was found for recurrent pancreatitis within 1 year for those who received MRCP (2, 4.2%) or EUS (3, 6.3%) | |
|                            | **Complications**  
- Four individuals (27%) experienced complications due to CT-PNB, including 3 developing pneumothorax and one person requiring hospital admission, compared to one individual (3%) developing pneumothorax due to EBUS-TBLB, p = 0.03. | |

**Economic Analysis**

| Steinfort, 2013, Australia¹⁶ | Cost-benefit analysis:  
- Cost of EBUS-TBLB: $2,748  
- Cost of CT-PNB: $2,724  
- Sensitivity analyses demonstrated that if the cost of managing complications exceeded $501 per episode, EBUS-TBLB became more cost-beneficial | The authors concluded that the difference between EBUS-TBLB and CT-PNB was negligible, but costs varied by clinical acumen because diagnostic accuracy and likelihood of complications varies based on clinical factors.  
The authors also stated that further research is needed to evaluate patient preference and how this impacts cost-effectiveness. |
|                            | Cost-effectiveness analysis:  
- With a theoretical wait-trade-off for a non-diagnostic procedure of 20 days, CT-PNB remained more cost-effective relative to EBUS-TBLB. If costs of complications exceeded $560, if sensitivity of EBUS-TBLB for benign disease exceeded 71% or if sensitivity of |
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|                               | CT-PNB for malignant disease was less than 89%, EBUS-TBLB became the more cost effective alternative  
• With a theoretical wait-trade-off for procedural complications of 20 days, CT-PNB was more cost effective ($2,778 per QALY) compared to EBUS-TBLB ($2,816 per QALY). If costs of complications exceeded $489, if the complication rate for CT-PNB exceeded 40% or if sensitivity of EBUS-TBLB for benign disease exceeded 65%, EBUS-TBLB became the more cost effective alternative |                                                                                                                                                                          |

CI: confidence interval; CT: computed tomography; CT-PNB: computed tomography-guided percutaneous needle biopsy; EAUS: endoanal ultrasound; EBUS-TBLB: endobronchial ultrasound-guided transbronchial lung biopsy; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; MRCP: magnetic resonance cholangiopancreatography; RR: relative risk; QALY: quality-adjusted life year