Endoscopic ultrasound-guided fine-needle aspiration in patients with non-small cell lung cancer and prior negative mediastinoscopy

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) for tissue evaluation of mediastinal lymphadenopathy in patients with non-small-cell lung cancer (NSCLC). EUS-FNA was performed under conscious sedation.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with NSCLC who underwent biopsy to confirm the need for surgical resection.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were gathered from July 2000 to July 2004. Other clinical estimates used in the cost analysis were derived from studies published between 1981 and 2004. No dates for the resource use data were reported. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a single study and a synthesis of published studies.

Link between effectiveness and cost data
The costing was carried out on a sample of patients different from that used in the effectiveness analysis.

Study sample
Power calculations were not reported. Of the 207 patients who were referred to EUS-FNA for invasive lymph node staging at the authors' institution, 113 had lung cancer and underwent EUS-FNA for invasive lymph node staging. Overall, 35 patients (53 lesions) with biopsy-proven lung cancer were included in the current study if they underwent mediastinoscopy prior to EUS, and had biopsy-proven benign lymphadenopathy in the anterior mediastinum. Data were also available on other diagnostic techniques, including PET (45 lesions) and CT (53 lesions). The mean age of the
sample of 35 patients was 64.5 (+/- 9.8) years (median 66; age range: 59 to 72), and there were 28 men (80%).

**Study design**
This was a prospective diagnostic study that was carried out at a single institution, the Department of Gastroenterology at the University of Alabama at Birmingham, USA. A single group of patients was considered and underwent the diagnostic approaches. The average length of follow-up was 219 days (Interquartile range: 131 to 287). No patient was lost to follow-up. The endosonographer was aware of the presence of suspicious lymph nodes but was masked to radiographs.

**Analysis of effectiveness**
All of the patients included in the initial study sample were considered in the analysis of effectiveness. The primary outcome measures were:

- the numbers of true positives, true negatives, false positives and false negatives;
- the sensitivity and specificity;
- positive predictive values and negative predictive values (PPVs and NPVs, respectively); and
- accuracy.

All these end points were assessed in the double comparison between CT and EUS-FNA on one side and between PET and EUS-FNA on the other.

**Effectiveness results**
With CT and EUS-FNA (53 lesions):

- there were 16 and 16 true positives, respectively, 6 and 36 true negatives, 30 and 0 false positives, and 1 and 1 false negatives;
- sensitivity was 94.1% (95% confidence interval, CI: 71.3 to 99.9) with CT and 94.1% (95% CI: 71.3 to 99.9) with EUS-FNA, while specificity was 16.7% (95% CI: 6.4 to 32.8) with CT and 100% (95% CI: 92 to 100) with EUS-FNA;
- the PPV was 34.8% (95% CI: 21.4 to 50.3) with CT and 100% (95% CI: 82.9 to 100) with EUS-FNA, while the NPVs were 85.7% (95% CI: 42.1 to 99.6) and 97.3% (95% CI: 85.8 to 99.9) respectively; and
- accuracy was 41.5% (95% CI: 28.1 to 55.9) with CT and 98.1% (95% CI: 89.9 to 100) with EUS-FNA.

Only the differences in specificity, PPVs and accuracy were statistically significant in favour of EUS-FNA, (p<0.001).

With PET and EUS-FNA (45 lesions):

- there were 11 and 10 true positives, respectively, 7 and 34 true negatives, 27 and 0 false positives, and 0 and 1 false negatives;
- sensitivity was 100% (95% CI: 76.2 to 100) with PET and 90.9% (95% CI: 58.7 to 99.8) with EUS-FNA, while specificity was 20.6% (95% CI: 8.7 to 37.9) with PET and 100% (95% CI: 91.6 to 100) with EUS-FNA;
- the PPV was 28.9% (95% CI: 15.4 to 45.9) with PET and 100% (95% CI: 74.1 to 100) with EUS-FNA, while the NPVs were 100% (95% CI: 65.2 to 100) and 97.1% (95% CI: 85.1 to 99.9), respectively; and
- accuracy was 40% (95% CI: 25.7 to 55.7) with PET and 97.8% (95% CI: 88.2 to 99.9) with EUS-FNA.

Again, only the differences in specificity, PPVs and accuracy were statistically significant in favour of EUS-FNA.
Clinical conclusions
The effectiveness analysis showed that EUS-FNA led to better accuracy, higher specificity, and higher PPVs than both CT and PET.

Modelling
A Monte Carlo analysis model was constructed to evaluate the expected costs and outcomes associated with the staging of NSCLC in a hypothetical cohort of patients presenting with enlarged anterior and posterior mediastinal lymph node. Two alternative strategies were compared. One was EUS-FNA as the initial biopsy technique, followed by mediastinoscopy if negative. The other was mediastinoscopy as the initial biopsy technique, followed by EUS-FNA if negative. Patients moved across health states until the following absorbing states: confirmation of mediastinal lymph node involvement by a biopsy method which precludes surgical resection; two negative biopsy modalities preceding surgical resection; death from complications. The model was run for a total of 10,000 simulations for each of the two strategies.

Outcomes assessed in the review
The outcomes estimated from the literature were the sensitivity, specificity, PPVs, NPVs, accuracy, complication rates, and mortality rates associated with both mediastinoscopy and EUS-FNA.

Study designs and other criteria for inclusion in the review
A review of the literature was undertaken to identify primary studies. However, details of the design of these studies were not reported.

Sources searched to identify primary studies
MEDLINE was searched from 1996 to July 2004. The keywords were .mediastinoscopy/ or .endosonography/, and .non-small cell lung carcinoma/.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Of the 103 articles initially identified, 21 relevant studies were finally considered.

Methods of combining primary studies
A narrative approach appears to have been used to combine the primary estimates. Lower and upper values found in the different studies were reported.

Investigation of differences between primary studies
Not reported.
Results of the review
For mediastinoscopy:

the sensitivity ranged from 63 to 93% and the specificity from 100 to 100%;

the PPV ranged from 100 to 100% and the NPV from 80 to 100%;

accuracy ranged from 90 to 96%;

the complication rate ranged from 2 to 4%; and

the mortality rate range from 0 to 0.08%.

For EUS-FNA:

the sensitivity ranged from 79 to 93% and the specificity from 99 to 100%;

the PPV ranged from 99 to 100% and the NPV from 62 to 94%;

accuracy ranged from 84 to 98%;

the complication rate ranged from 0 to 2%; and

the mortality rate ranged from 0 to 0%.

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used in the economic evaluation. In effect, a cost-consequences analysis was carried out.

Direct costs
The analysis of the costs appears to have been carried out from the perspective of the third-party payer. The categories of costs included were EUS-FNA, pathology processing, cytopathology interpretation and report, EUS-FNA complications, death from EUS-FNA, mediastinoscopy, anaesthesia, pathology processing, cytopathology interpretation and report, perioperative hospital stay, surgical complications, and death from mediastinoscopy. The unit costs were not presented separately from the quantities of resources for all items, and some costs were given as macro-categories. Some information on resource use was based on data derived from the literature. However, the sources of data for the number of tests, other procedures, and length of hospital stay were not reported. The costs came from Medicare reimbursement rates, diagnosis-related groups, published studies, and the University of Alabama at Birmingham Hospital. Discounting was not relevant since the costs were incurred during less than 2 years because of the poor survival of NSCLC patients. The price year was 2004.

Statistical analysis of costs
The costs were presented as mean values with standard deviations.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).
Sensitivity analysis
Sensitivity analyses were not carried out. However, the Monte Carlo simulation model provided results over a large range of parameter values.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The costs per patient were $1,867 (+/- 4,308) with EUS-FNA and $12,900 (+/- 4,164.4) with mediastinoscopy. Thus, the initial use of EUS-FNA in place of mediastinoscopy would result in an average cost-saving of $11,033 per patient.

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant as a cost-consequences analysis was carried out.

Authors' conclusions
In patients with non-small-cell lung cancer (NSCLC) and combined anterior and posterior lymphadenopathy, the initial use of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) would reduce the use of mediastinoscopy in about one third of the patients, and also result in cost-savings from the perspective of the third-party payer.

CRD COMMENTARY - Selection of comparators
Two different comparisons were made. Specifically, EUS-FNA versus either PET or CT and EUS-FNA versus mediastinoscopy. Both comparators were appropriate for the respective objectives of the analysis and were described in detail. Other diagnostic techniques, such as transthoracic or transbronchial fine-needle aspiration, were not considered. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a diagnostic study, which was appropriate for the study question. The diagnostic study has the advantage of applying both the comparator and the new intervention to the same sample of patients. Thus, a control group was not required, which reduces the potential impact of selection bias and confounding factors. The sequence of the diagnostic interventions was reported, and patients underwent EUS-FNA after either PET or CT. However, the endoradiographer was blinded to the results of the previous imaging approach. The evidence came from a single institution, and it was unclear whether the study sample was representative of the patient population. No justification for the size of the sample was provided. The small number of patients included in the analysis should be considered when evaluating the robustness of the effectiveness results. A review of the literature was undertaken to identify clinical parameters used in the cost model. Few details of the review were reported, and it is not possible to judge the internal validity of the studies used to estimated model parameters. However, the Monte Carlo simulation was applied over a large range of values for the parameters.

Validity of estimate of measure of benefit
No summary benefit measure was used because a cost-consequences analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
The analysis of the costs was consistent with the stated perspective. Likewise, the sources used to derive the costs reflected the cost/resource boundary of the third-party payer. Some costs were presented as macro-categories and a detailed breakdown of items was not provided, which limits the possibility of replicating the analysis in other settings. The costs were estimated using a modelling approach, which was extensively described. The cost estimates were
specific to the study setting and the impact of altering the costs was not investigated. The source of much of the resource use data was unclear and might have involved authors' opinions. The price year was reported, which will facilitate reflation exercises in other time periods.

Other issues
The authors reported some results from other studies but explicit comparisons with the current findings were not made. The issue of the generalisability of the study results to other settings was not explicitly addressed, although some model parameters appear to have been varied in the Monte Carlo simulation. All procedures were performed by a single experienced endosonographer, which might reduce the transferability of the results to private practice settings where EUS-FNA is not widely disseminated. The authors noted that their findings are generalisable to all patients with enlarged combined anterior and posterior lymph nodes detected by imaging modalities such as CT and PET scans.

Implications of the study
The authors suggested that patients with either combined anterior and posterior lymphadenopathy alone or left adrenal enlargement should undergo EUS-FNA first, while patients with anterior lymphadenopathy could be best served by mediastinoscopy.

Source of funding
None stated.

Bibliographic details

PubMedID
16181845

DOI
10.1016/j.athoracsur.2005.04.001

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Biopsy, Fine-Needle /economics /methods; Carcinoma, Non-Small-Cell Lung /complications /pathology /surgery /ultrasonography; Cost-Benefit Analysis; False Negative Reactions; Female; Humans; Lung Neoplasms /complications /pathology /surgery /ultrasonography; Lymphatic Diseases /etiology /pathology /surgery /ultrasonography; Male; Mediastinoscopy /economics /methods; Middle Aged; Monte Carlo Method; Neoplasm Staging /economics /methods; Sensitivity and Specificity; Thoracoscopy /economics /methods; Treatment Outcome