Clinical effectiveness and cost-effectiveness of endobronchial and endoscopic ultrasound relative to surgical staging in potentially resectable lung cancer: results from the ASTER randomised controlled trial

LD Sharples,¹* C Jackson,¹ E Wheaton,¹ G Griffith,² JT Annema,³ C Dooms,⁴ KG Tournoy⁵, E Deschepper,⁵ V Hughes,⁶ L Magee,⁶ M Buxton² and RC Rintoul⁶

¹Medical Research Council (MRC), Biostatistics Unit, Cambridge, UK
²Health Economics Research Group, Brunel University, Uxbridge, Middlesex, UK
³Leiden University Medical Centre (LUMC), Leiden, the Netherlands
⁴University Hospitals Leuven, Leuven, Belgium
⁵Ghent University Hospitals, Ghent, Belgium
⁶Papworth Hospital NHS Foundation Trust, Cambridge, UK

*Corresponding author

Executive summary

Health Technology Assessment 2012; Vol. 16: No. 18
DOI: 10.3310/hta16180

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk
Executive summary

Background

Lung cancer is the second most common cancer in the UK and is the most common cause of cancer death. Non-small cell lung cancer (NSCLC) accounts for 85% of all cases, with an overall 5-year survival of approximately 8% in the UK. Optimal treatment depends on accurate staging. Historically, staging of mediastinal lymph nodes has relied on surgical methods, usually mediastinoscopy, which has a very high specificity but a sensitivity of around 78%. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and, more recently, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) are two relatively new, less invasive, diagnostic techniques that allow real-time controlled aspiration of mediastinal lymph nodes. With regard to the access to mediastinal nodes, these two approaches complement one another. Non-randomised trials in selected patient populations have suggested that the sensitivities of these techniques are in the same range as the surgical techniques and can obviate the need for surgical staging procedures in up to 70% of the cases. However, to date there are no reported prospective randomised studies comparing the accuracy of EBUS-TBNA, EUS-FNA and surgical staging for assessment of the mediastinum in lung cancer. Furthermore, no full economic evaluations investigating the cost-effectiveness of EBUS and EUS have been published.

Objective

To assess the clinical effectiveness and cost-effectiveness of the diagnostic staging strategy of EBUS-TBNA combined with EUS-FNA (followed by surgical staging if these tests were negative) compared with standard surgical staging techniques alone in patients with NSCLC who are otherwise candidates for curative surgery.

Methods

Design

A prospective, international, multicentre, open-label, randomised controlled study, with a trial-based economic analysis.

Setting

Four centres were involved in the trial: Ghent University Hospital, Belgium; Leuven University Hospitals, Belgium; Leiden University Medical Centre, the Netherlands; and Papworth Hospital, UK.

Participants

All patients referred to the thoracic oncology clinics at the four participating hospitals requiring mediastinal staging of lung cancer. Patients were eligible for inclusion if they (1) had known or suspected NSCLC and mediastinal lymph node involvement (either N2 or N3) was suspected; (2) were otherwise considered to be a candidate for surgical resection with an intention to cure; (3) were clinically fit for bronchoscopy, endosonography and diagnostic surgical procedures; or (4) had no evidence of distant metastatic disease after routine clinical work-up. Patients were excluded if they (1) had received previous treatment (chemotherapy, radiotherapy or surgery)
for lung cancer; (2) had a concurrent malignancy or uncorrected coagulopathy; and (3) were unlikely to be staged accurately by any surgical staging procedure.

**Interventions**

Study patients were randomised to either surgical staging alone or endosonography (combined EUS-FNA and EBUS-TBNA) followed by surgical staging (if no nodal metastases were found at endosonography). Endosonography of the mediastinum was performed under moderate sedation using EUS-FNA (Pentax 34UX/38UX, Pentax, Tokyo, Japan or Olympus GF-UCT140-AL5, Olympus, Tokyo, Japan) and EBUS-TBNA (Olympus BF-UC160F-OL, Olympus, Tokyo, Japan). A systematic examination of at least left and right paratracheal, subcarinal and para-esophageal mediastinal nodes was performed. Nodes that were suspicious on positron emission tomography (PET)–computerised tomography (CT) or ultrasound imaging were sampled under real-time ultrasound guidance with 22-gauge needles and labelled according to the Mountain–Dresler classification. Surgical staging was performed by (video-) mediastinoscopy, left anterior mediastinotomy or video-assisted thoracoscopy or combination. Using cervical mediastinoscopy, a systematic (five lymph node stations) assessment of left and right higher (2L and 2R) and lower paratracheal (4L and 4R) and subcarinal (7) nodes was performed. If necessary, a left anterior mediastinotomy or video-assisted thoracoscopy was performed to allow access to nodal stations 5 and 6 or 7, 8 and 9, respectively. For either technique, evidence of direct tumour involvement was noted (T4). In the event of pathological evidence of mediastinal metastases (N2/N3) or mediastinal tumour invasion (T4), either after endosonography or after surgical staging, patients were classified as having locally advanced disease (stage IIIA/B) and were referred for chemoradiotherapy. If after surgical staging there was no evidence of mediastinal nodal disease or direct tumour invasion, a thoracotomy with a systematic lymph node dissection was performed.

**Main outcome measures**

The primary clinical outcomes were the sensitivity, diagnostic accuracy and negative predictive value (NPV) of each diagnostic strategy for detection of mediastinal nodal (N2/N3) metastases. The final reference status of the patient was positive if any diagnostic test was positive or if nodal involvement was detected after thoracotomy. The primary economic outcome was cost–utility of the endosonography diagnostic strategy relative to surgical staging alone, up to 6 months after randomisation, from a UK NHS perspective. Bayesian parametric modelling was used to estimate final expected costs and quality-adjusted life-years (QALYs) while simultaneously estimating missing data based on randomisation group, centre and stage. The freely available software package WinBUGS Version 14 (MRC Biostatistics Unit, Cambridge, UK) was used to implement the analysis.

One potential alternative diagnostic strategy investigated the value of using endosonography as the only diagnostic modality to exclude nodal involvement by excluding the costs of the confirmatory surgical staging in this group, but adding in costs for additional futile thoracotomies that would have resulted from the lower sensitivity of these tests when used alone.

**Results**

**Clinical**

Between February 2007 and April 2009, 241 patients (88 from Ghent, 81 from Leiden, 44 from Leuven and 28 from Papworth) were randomised to surgical staging ($n = 118$) or to endosonography (followed by surgical staging if endosonography was negative for malignancy) ($n = 123$). Patients were followed up for survival for 6 months after staging, during which time there were 20 deaths: nine in the endosonography group and 11 in the surgical staging group.
Surgery alone detected mediastinal nodal (N2/N3) metastases in 41 out of 118 patients (35%), whereas endosonography and surgical staging combined detected metastases in 62 out of 123 patients (50%) \((p = 0.02)\). Sensitivity for detecting mediastinal nodal metastases was 79% [41/52; 95% confidence interval (CI) 66% to 88%] for the surgical arm compared with 94% (62/66; 95% CI 85% to 98%) for the endosonography strategy \((p = 0.02)\). The corresponding NPVs were 86% (66/77; 95% CI 76% to 92%) and 93% (57/61; 95% CI 84% to 97%) \((p = 0.18)\).

Thoracotomy was unnecessary in 21 out of 118 (18%) patients who were randomised to surgical staging compared with 9 out of 123 (7%) in those who were randomised to the endosonography strategy \((p = 0.02)\).

The overall complication rate was 7 out of 118 (6%) in the surgical staging arm compared with 6 out of 123 (5%) in the endosonography arm \((p = 0.78)\). There was one pneumothorax that was considered to be directly related to endosonography. The remaining 12 complications were all directly related to the surgical staging procedure.

**Quality of life**

At randomisation, the groups had similar mean (standard deviation, SD) European Quality of Life-5 Dimensions (EQ-5D) utility: 0.81 (0.18) in the endosonography arm and 0.83 (0.14) in the surgical staging group. At the end of staging, utility in the surgical arm had decreased by 0.16, compared with a decrease of 0.03 in the endosonography group. Thereafter, utility in both groups decreased further, with mean utility at 6 months of 0.68 (0.30) in the endosonography strategy arm and 0.67 (0.31) in the surgical staging arm. Adjusting for baseline, the difference between the arms at the end of staging was 0.117 (95% CI 0.042 to 0.192; \(p = 0.003\)). There were no other significant differences in utility.

**Resource-use results**

Of those for whom complete EQ-5D and resource-use data were available, all 85 patients randomised to the endosonography strategy underwent EUS/EBUS (100%), compared with one (1%) in the surgical arm. Conversely, 55% of those randomised to the endosonography strategy underwent subsequent surgical staging, compared with 99% in the surgical arm. Apart from the initial procedure (EUS/EBUS or surgical staging), the main difference in resource use was in the number of thoracotomies: thoracotomy was performed in 57 out of 87 (66%) patients in the surgical staging group compared with 45 out of 85 (53%) patients in the endosonography group. Resource use was similar between the groups in all other items. The mean difference (95% CI) in costs (endosonography strategy arm – surgical arm) for these three items was £1240 (£1211 to £1268), –£1346 (£–1682 to £–1010) and –£749 (£–1737 to £239) per patient for endosonography, surgical staging and thoracotomy, respectively.

**Cost-effectiveness analysis**

In the full Bayesian analysis of all 241 patients, the total mean cost [95% credible interval (CrI)] for the strategy of initial endosonography followed by surgical staging if negative was £9713 (£7209 to £13,307) per patient over 6 months. Surgical staging cost a mean of £10,459 (95% CrI £7732 to £13,890). There was no significant difference in expected cost between the two strategies: the posterior mean expected cost under the endosonography strategy was –£746 less than under surgical staging, but the 95% CrI for the difference spanned zero (–£2494 to £756). The expected QALY gain over 6 months was 0.344 (95% CrI 0.292 to 0.383) for the endosonography strategy and 0.329 (95% CrI 0.274 to 0.371) for surgical staging. The mean difference in QALYs was 0.015 (−0.023 to 0.052) in favour of the endosonography arm (with surgical staging if negative). Thus, based on the point estimates of incremental cost and QALYs, the strategy of initial endosonography followed by surgical staging if negative dominates.
Deterministic sensitivity analyses

The Bayesian model was adapted to assume that patients randomised to endosonography do not receive confirmatory surgical staging, and that their chance of receiving a futile thoracotomy is slightly increased (by 6/123). The expected cost under the endosonography strategy is reduced from £9713 to £8335, significantly less than under surgical staging, for which the cost is unchanged (mean saving of £2124, 95% CrI £167 to £4560). The QALY gain for either strategy was assumed to remain the same. Under this simple alternative scenario, the distribution of cost-effectiveness is shifted in favour of endosonography, so that the probability that endosonography alone is cost-effective is approximately 90%.

Conclusions

In this randomised controlled trial (RCT), a strategy of using combined state-of-the-art, non-invasive endosonography (EUS–FNA and EBUS-TBNA) followed by surgical staging (only if these tests were negative) had higher sensitivity and negative predicted probability, resulted in a lower rate of unnecessary thoracotomy and better quality of life during staging, and was slightly more effective and less expensive than the current practice of lung cancer staging using surgical staging alone. Although the endosonography strategy dominated in this study (was cheaper and more effective), CrIs for both the difference in costs and the difference in QALY included zero. Further benefits of endosonography include less invasive testing with no requirement for general anaesthesia or open surgery, and the small number of minor complications in this study.

Implications for health care

Taking the clinical, quality-of-life and health-resource data together, evidence from this study suggests that lung cancer staging could commence with a combined EUS/EBUS examination, followed by surgical staging if these tests are negative. If there is no evidence for mediastinal nodal disease in either test, then patients could proceed directly to thoracotomy with lymph node dissection. The number of centres in the UK where both EBUS and EUS can be performed in a single session is very limited. A structured training programme in EBUS and EUS could support chest physicians and thoracic surgeons involved in lung cancer staging in the UK.

Recommendations for future research

This RCT considered standard surgical staging and a single alternative for patients with lung cancer who were potential candidates for surgery and in whom mediastinal nodal involvement had to be ruled out. Other possibilities for staging include PET–CT, non-ultrasound-guided TBNA and ultrasound of the neck, together with combination strategies, and these alternative methods should be subject to the same rigorous evaluation used in ASTER (Assessment of Surgical sTaging versus Endosonographic ultrasound in lung cancer: a Randomised clinical trial). The cost–utility analysis was trial based and did not model the long-term effects of the diagnostic strategies. Given the short-lived effect on utility observed in ASTER, we do not consider development of a long-term model to be a useful extension of this work.
Further research could consider whether or not:

1. mediastinoscopy following negative EBUS/EUS is really needed – additional work is required before we can confidently recommend omitting confirmatory surgical staging in the event of negative endosonographic examination
2. chest physicians can be trained to perform both EBUS and EUS effectively – in the ASTER trial EBUS was performed by a chest physician and EUS by a gastrointestinal endoscopist
3. combined EBUS/EUS using a single EBUS scope provides equivalent diagnostic accuracy to using separate EBUS and EUS scopes – in the ASTER study we used separate EBUS and EUS scopes, but recently a licence has been given for the EBUS scope to be used in the oesophagus.

**Trial registration**

The trial was registered as ASTER (Assessment of Surgical sTaging versus Endosonographic ultrasound in lung cancer: a Randomised clinical trial), ISRCTN 97311620.

**Funding**

This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 16, No. 18. See the HTA programme website for further project information.

**Publication**

How to obtain copies of this and other HTA programme reports

An electronic version of this title, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable DVD is also available (see below).

Printed copies of HTA journal series issues cost £20 each (post and packing free in the UK) to both public and private sector purchasers from our despatch agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per issue and for the rest of the world £3 per issue.

How to order:
– fax (with credit card details)
– post (with credit card details or cheque)
– phone during office hours (credit card only).

Additionally the HTA website allows you to either print out your order or download a blank order form.

Contact details are as follows:
Synergie UK (HTA Department) Email: orders@hta.ac.uk
Digital House, The Loddon Centre Tel: 0845 812 4000 – ask for ‘HTA Payment Services’
Wade Road (out-of-hours answer-phone service)
Basingstoke
Hants RG24 8QW Fax: 0845 812 4001 – put ‘HTA Order’ on the fax header

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in pounds sterling, made payable to University of Southampton and drawn on a bank with a UK address.

Paying by credit card
You can order using your credit card by phone, fax or post.

Subscriptions

NHS libraries can subscribe free of charge. Public libraries can subscribe at a reduced cost of £100 for each volume (normally comprising 40–50 titles). The commercial subscription rate is £400 per volume (addresses within the UK) and £600 per volume (addresses outside the UK). Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

How do I get a copy of HTA on DVD?

Please use the form on the HTA website (www.hta.ac.uk/htacd/index.shtml). HTA on DVD is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.
The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

### Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 06/302/216. The contractual start date was in December 2007. The draft report began editorial review in June 2011 and was accepted for publication in December 2011. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

**Editor-in-Chief:** Professor Tom Walley CBE  
**Series Editors:** Dr Martin Ashton-Key, Professor Aileen Clarke, Dr Tom Marshall, Professor John Powell, Dr Rob Riemsma and Professor Ken Stein  
**Associate Editor:** Dr Peter Davidson  
**Editorial Contact:** edit@southampton.ac.uk

**ISSN** 1366-5278 (Print)  
**ISSN** 2046-4924 (Online)  
**ISSN** 2046-4932 (DVD)

© Queen's Printer and Controller of HMSO 2012. This work was produced by Sharples et al. under the terms of a commissioning contract issued by the Secretary of State for Health.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (http://www.publicationethics.org/).

This journal may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NETSCC, Health Technology Assessment, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA. Printed on acid-free paper in the UK by Charlesworth Press.