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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, C Jackson, E Wheaton, G Griffith, JT Annema, C Dooms, KG Tournoy, E Deschepper, V Hughes, L Magee, M Buxton and RC Rintoul

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LD Sharples,[1]* C Jackson,[1] E Wheaton,[1] G Griffith,[2] JT Annema,[3] C Dooms,[4] KG Tournoy[5], E Deschepper,[5] V Hughes,[6] L Magee,[6] M Buxton[2] and RC Rintoul[6]

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Abstract

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

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Objective: To assess the clinical effectiveness and cost-effectiveness of endosonography (followed by surgical staging if endosonography was negative), compared with standard surgical staging alone, in patients with non-small cell lung cancer (NSCLC) who are otherwise candidates for surgery with curative intent.
Design: A prospective, international, open-label, randomised controlled study, with a trial-based economic analysis.
Setting: Four centres: Ghent University Hospital, Belgium; Leuven University Hospitals, Belgium; Leiden University Medical Centre, the Netherlands; and Papworth Hospital, UK.
Participants: Inclusion criteria: known/suspected NSCLC, with suspected mediastinal lymph node involvement; otherwise eligible for surgery with curative intent; clinically fit for endosonography and surgery; and no evidence of metastatic disease. Exclusion criteria: previous lung cancer treatment; concurrent malignancy; uncorrected coagulopathy; and not suitable for surgical staging.
Interventions: Study patients were randomised to either surgical staging alone ($n = 118$) or endosonography followed by surgical staging if endosonography was negative ($n = 123$). Endosonography diagnostic strategy used endoscopic ultrasound-guided fine-needle aspiration combined with endobronchial ultrasound-guided transbronchial needle aspiration, followed by surgical staging if these tests were negative. Patients with no evidence of mediastinal metastases or tumour invasion were referred for surgery with curative intent. If evidence of malignancy was found, patients were referred for chemoradiotherapy.
Main outcome measures: The main clinical outcomes were sensitivity (positive diagnostic test/nodal involvement during any diagnostic test or thoracotomy) and negative predictive value (NPV) of each diagnostic strategy for the detection of N2/N3 metastases, unnecessary thoracotomy and complication rates. The primary economic outcome was

cost–utility of the endosonography strategy compared with surgical staging alone, up to 6 months after randomisation, from a UK NHS perspective.

Results: Clinical and resource-use data were available for all 241 patients, and complete utilities were available for 144. Sensitivity for detecting N2/N3 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 ($p = 0.02$). Corresponding NPVs were 86% (66/77; 95% CI 76% to 92%) and 93% (57/61; 95% CI 84% to 97%; $p = 0.26$). There were 21/118 (18%) unnecessary thoracotomies in the surgical arm compared with 9/123 (7%) in the endosonography arm ($p = 0.02$). Complications occurred in 7/118 (6%) in the surgical arm and 6/123 (5%) in the endosonography arm ($p = 0.78$): one pneumothorax related to endosonography and 12 complications related to surgical staging. Patients in the endosonography arm had greater EQ-5D (European Quality of Life-5 Dimensions) utility at the end of staging (0.117; 95% CI 0.042 to 0.192; $p = 0.003$). There were no other significant differences in utility. The main difference in resource use was the number of thoracotomies: 66% patients in the surgical arm compared with 53% in the endosonography arm. Resource use was similar between the groups in all other items. The 6-month cost of the endosonography strategy was £9713 (95% CI £7209 to £13,307) per patient versus £10,459 (£7732 to £13,890) for the surgical arm, mean difference £746 (95% CI –£756 to £2494). The mean difference in quality-adjusted life-year was 0.015 (95% CI –0.023 to 0.052) in favour of endosonography, so this strategy was cheaper and more effective.

Conclusions: Endosonography (followed by surgical staging if negative) had higher sensitivity and NPVs, resulted in fewer unnecessary thoracotomies and better quality of life during staging, and was slightly more effective and less expensive than surgical staging alone. Future work could investigate the need for confirmatory mediastinoscopy following negative endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), the diagnostic accuracy of EUS-FNA or EBUS-TBNA separately and the delivery of both EUS-FNA or EBUS-TBNA by suitably trained chest physicians.

Trial registration: Current Controlled Trials 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.

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List of abbreviations

ASTER	Assessment of Surgical sTaging versus Endosonographic ultrasound in lung cancer: a Randomised clinical trial
AUC	area under the curve
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CrI	credible interval from a Bayesian posterior distribution
CONSORT	CONonsolidated Standards Of Reporting Trials
CT	computerised tomography
EBUS-TBNA	endobronchial ultrasound-guided transbronchial needle aspiration
EQ-5D	European Quality of Life-5 Dimensions
EUS-FNA	endoscopic ultrasound-guided fine-needle aspiration
FNA	fine-needle aspiration
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
ISRCTN	International Standard Randomised Controlled Trial Number
LUMC	Leiden University Medical Centre
MRC	Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NPV	negative predictive value
NSCLC	non-small cell lung cancer
PET	positron emission tomography
QALY	quality-adjusted life-year
R&D	research and development
RCT	randomised controlled trial
SCLC	small cell lung cancer
SD	standard deviation

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

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 (i.e. is cheaper and more effective). From the cost-effectiveness acceptability curve, at any cost-effectiveness threshold, about 80% of the posterior distribution lies in a region in which endosonography is cost-effective, i.e. has a positive expected net benefit.

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.

Chapter 1

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 78% of all cases, with an overall 5-year survival of approximately 8% in the UK.[1] As treatment of lung cancer is influenced by stage, accurate staging is important to optimise treatment.

At present, the mainstay of lung cancer staging involves imaging and biopsy of areas that are suspicious for metastatic spread. The incorporation of positron emission tomography (PET) into staging algorithms has considerably reduced the number of unnecessary thoracotomies performed by identifying locoregional and distant metastases. Positron emission tomography–computerised tomography (PET–CT) is more accurate than computerised tomography (CT) for assessing mediastinal lymph node involvement. Although the negative predictive value (NPV) of PET–CT for mediastinal disease is around 93%, a positive predictive value of 74–90% makes pathological verification of 18-fluorodeoxyglucose (18-FDG)-avid mediastinal nodes necessary in order to determine whether or not they are malignant.[2] Making the assumption that FDG-positive nodes are malignant will potentially deny many patients potentially curative surgery as it is recognised that non-malignant mediastinal nodes can take up FDG in other pathological states, such as infection and inflammation.

Historically, surgical staging of enlarged and/or PET–CT-positive mediastinal lymph nodes has relied on procedures such as mediastinoscopy, mediastinotomy or video-assisted thoracoscopic surgery. These are invasive procedures requiring general anaesthetic and hospitalisation and have low, but well-recognised, morbidity and mortality. The accuracy of these procedures is variable and ranges between 80% and 90%. Although specificity is near 100%, sensitivity ranges between 66% and 90% (see Detterbeck *et al.*[2] and associated references, Pinto Filho *et al.*,[3] Anraku *et al.*[4]). Thus, there is room for improvement in terms of the sensitivity of currently available surgical mediastinal staging investigations.

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. These techniques are normally performed in an outpatient setting under moderate sedation. EUS-FNA and EBUS-TBNA are complementary techniques. EUS permits access to mediastinal lymph node groups 2L, 4L, 7, 8L/R, 9L/R, whereas EBUS gives access to mediastinal lymph node stations 2R/L, 4R/L and 7. Using the techniques in combination it is possible to access the majority of mediastinal lymph nodes. EBUS-TBNA also allows access to hilar and intrapulmonary nodal stations 10R/L and 11R/L. In addition, in selected cases, endosonography offers the possibility to assess whether or not a tumour is invading mediastinal structures (T4).

A number of non-randomised prospective studies using EBUS-TBNA have reported sensitivity of around 90% for diagnosis of hilar and/or mediastinal lymph nodes.[5–8] In 2009, two meta-analyses reported pooled sensitivity for EBUS-TBNA of 0.88[9] [95% confidence interval (CI) 0.79 to 0.94] and 0.93[10] (95% CI 0.91 to 0.94). In a systematic review, Varela-Lema *et al.*[11] reported that sensitivity for the diagnosis of malignancy ranged from 85% to 100%. In all three of these reports the specificity quoted was 1.00, but this figure is artificial, as positive TBNA results were not

confirmed by surgical resection in any of these papers. In the case of EUS, reported sensitivity for mediastinal staging varies between 50% and 87%.[2,12–16] The lower figure may be a reflection of the fact that EUS is able to access only the left-sided mediastinal nodes along with the inferior posterior nodes.

To date, there have been three reports documenting a combined approach using both EBUS-TBNA and EUS-FNA for assessing the mediastinum.[17–19] In these series, sensitivity for detection of mediastinal disease ranged from 85% to 100%.

Taken together, it is clear that, although the reported sensitivity of EUS and EBUS for the detection of malignancy in mediastinal lymph nodes is similar to that of mediastinoscopy, 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, to date, no full economic evaluations investigating the cost-effectiveness of EBUS and EUS versus surgical staging have been published.

Therefore, in 2007, this group, led by clinical co-investigators in Ghent, Leiden, Leuven and Cambridge, undertook a prospective randomised controlled trial (RCT) comparing endosonography (combined EBUS-TBNA and EUS-FNA), followed by surgical staging if negative, with surgical staging alone for assessment of the mediastinum in (suspected) NSCLC. In addition to the clinical findings that were published in November 2010,[20] data on patient-reported quality of life and the incremental costs and benefits from the perspective of a health-care provider were collected. Here we report resource-use data collection and a cost-effectiveness analysis from a UK NHS perspective.

Chapter 2

Study design

Study objectives

The final protocol is provided in *Appendix 1*. This RCT was designed to assess whether or not EBUS-TBNA combined with EUS-FNA, followed by surgical staging if these tests were negative, is better than standard surgical staging techniques in the staging of lung cancer in terms of sensitivity, diagnostic accuracy and NPV. The null hypothesis is that there is no difference between the two diagnostic strategies in these outcomes. The health economic study was designed to compare European Quality of Life-5 Dimensions (EQ-5D) utility and cost-effectiveness of the two diagnostic strategies.

Specific study objectives were as follows:

- The primary research objective of the study was to determine whether or not EBUS-TBNA combined with EUS-FNA, followed by surgical staging if these tests were negative, is better than standard surgical staging techniques in terms of sensitivity for diagnosing and staging the mediastinum in lung cancer. The related NPV of the two diagnostic strategies was also calculated.
- Determination of the sensitivity and accuracy of EBUS and EUS, followed by surgical staging if these tests were negative, compared with surgical staging for determining mediastinal tumour invasion (T4).
- A comparative cost-effectiveness analysis of the diagnostic strategies of the two trial arms.
- Assessment of the complication rates in each arm.
- An estimation of the saving of surgical staging procedures that might be possible in the future if EBUS-TBNA/EUS-FNA, followed by surgical staging if these tests were negative, is shown to have greater sensitivity and diagnostic accuracy and becomes the new 'gold standard' staging approach.
- Estimation of how many futile thoracotomies can be avoided by performing EBUS-TBNA and EUS-FNA, followed by surgical staging if these tests were negative, rather than surgical staging alone.
- Assessment of interobserver variability of cytopathological evaluation of EBUS-TBNA and EUS-FNA samples.

Trial design

This was a prospective, international, multicentre, open-label randomised controlled study.

Trial centres

Four centres were involved in the trial: Ghent University Hospital, Belgium; Leuven University Hospitals, Belgium; Leiden University Medical Centre (LUMC), the Netherlands; and Papworth Hospital, UK. Details of the study, the main investigators, trial steering groups and data monitoring committees are provided in the *Acknowledgements*. In each centre there was

a core team comprising a lung cancer physician, a thoracic surgeon and a research nurse. Data collection was completed at each centre using paper-based clinical report forms. All centres followed the same protocol, with the exception of Leuven, where 'frozen-section' histopathological analysis was performed in some patients during surgical staging procedures and proceeding directly to thoracotomy was possible if there was no evidence of mediastinal nodal malignancy.

Ethics

The trial was approved by the Cambridge 1 Local Research Ethics Committee in the UK and by the ethical committees of the three participating European hospitals (LUMC in the Netherlands, the University Hospitals of Ghent and Leuven in Belgium). The trial was registered with International Standard Randomised Controlled Trial Number (ISRCTN 97311620) as ASTER (Assessment of Surgical sTaging versus Endosonographic ultrasound in lung cancer: a Randomised clinical trial).

Study population

All consecutive patients referred to the thoracic oncology clinics at the four participating hospitals for staging of lung cancer were considered for the study.

Inclusion criteria for the study were as follows:

- known or suspected NSCLC and suspected mediastinal lymph node involvement (either N2 or N3), based on available thoracic imaging (CT or CT–PET)
- pending the results of mediastinal staging, potentially suitable for surgical resection with an intention to cure
- clinically fit for bronchoscopy, endosonography and diagnostic surgical procedures
- no evidence of distant metastatic disease after routine clinical work-up
- able to give informed consent.

Exclusion criteria were as follows:

- previous treatment (chemotherapy, radiotherapy or surgery) for lung cancer
- any known clinical reason for not undergoing, or a contraindication to, endosonography or a surgical staging procedure, unsuitability for definitive surgical resection by thoracotomy
- based on available thoracic imaging, the likelihood that disease cannot be staged accurately by any surgical staging procedure (mediastinoscopy/-otomy, video-assisted thoracoscopic staging)
- a concurrent malignancy at another site
- an uncorrected coagulopathy
- inability to give informed consent.

Study design

Patients who were potentially eligible for participation in the study according to the inclusion and exclusion criteria listed above were identified at the weekly multidisciplinary lung oncology meetings held at each of the centres. The initial diagnostic assessment involved the recording of

medical history, a physical examination, full blood count, renal and liver function tests, CT of the chest and upper abdomen and whole-body PET–CT.

Patients were approached in the outpatient clinic by the local principal investigator and those who expressed interest in participating were given a copy of the patient information sheet. All patients were given at least 24 hours to consider participation, and those who indicated that they were willing to participate were consented and then 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).

Patients were randomly assigned in a 1:1 ratio to either surgical staging alone or endosonography followed by surgical staging. Group allocations were computer generated according to a simple randomisation strategy and were stratified for participating centre. A web-based program was developed, which, on registration of consented patients, provided the next, centre-specific group allocation.

The study design is shown in *Figures 1* and *2*.

Patients randomised to endosonography followed by surgical staging if negative

Patients underwent endosonography as detailed below (see *Investigation protocols*): if there was no evidence of mediastinal nodal metastases, surgical staging was performed as described. In the event of pathological evidence of mediastinal metastases (N2/N3) or mediastinal tumour invasion (T4), either after endosonography or after mediastinoscopy, patients were classified as having locally advanced disease (stage IIIA/B) and were referred for chemoradiotherapy. If after confirmatory surgical staging there was still no evidence of mediastinal nodal disease or direct tumour invasion, a thoracotomy with a systematic lymph node dissection was performed.

Patients randomised to surgical staging

Surgical staging was performed as described below (see *Investigation protocols*). In the event of pathological evidence of mediastinal metastases (N2/N3) or direct mediastinal tumour invasion (T4), patients were classified as having locally advanced disease (stage IIIA/B) and were referred for chemoradiotherapy. If there was no evidence of mediastinal metastases, a thoracotomy with a systematic lymph node dissection was performed.

Investigation protocols

Endosonography

Endosonography of the mediastinum was performed under moderate sedation. For reasons of convenience and patient comfort, EUS-FNA (Pentax 34UX/38UX, Pentax, Tokyo, Japan or Olympus GF-UCT140-AL5, Olympus, Tokyo, Japan) was performed prior to EBUS-TBNA (Olympus BF-UC160F-OL, Olympus, Tokyo, Japan). A systematic examination of at least left and right paratracheal, subcarinal and paraesophageal mediastinal nodes, as described above, was performed. Nodes that were suspicious on PET–CT or ultrasound imaging were sampled under real-time ultrasound guidance with 22-gauge needles and labelled according to the Mountain–Dresler lymph node classification.[21] When the primary lung tumour was visible

by endosonography, the presence or absence of direct mediastinal tumour invasion (T4) was recorded. The cytology preparations were analysed using either May–Grünwald–Giemsa or Papanicolaou stains, dependent on local practice, with additional preparation of cell blocks for histological analysis when appropriate. At completion of the study, all EUS and EBUS samples were re-evaluated by an independent reference pathologist (AGN) to assess interobserver agreement.

Surgical staging

Surgical staging was performed by a (video-) mediastinoscopy according to current guidelines.[2,22] 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 parasternal mediastinotomy or video-assisted thoracoscopy was performed to allow access to nodal stations 5 and 6 or 7–9, respectively. Combinations of the above procedures were permitted. The approach(es) taken were left entirely to the surgeon's discretion. Nodal samples were labelled and sent for pathological examination. Any evidence of direct mediastinal invasion by the primary tumour (T4) was noted.

Thoracotomy

Thoracotomy with nodal dissection was considered to be the reference in both study arms for patients without N2/N3 nor T4 involvement after mediastinal staging. Thoracotomy was performed when there was no mediastinal nodal metastasis or direct mediastinal tumour invasion following surgical staging in both groups and was carried out according to current guidelines.[23] At the time of lung resection a systematic lymph node dissection (at least three mediastinal stations, including the subcarinal station) was performed according to current guidelines. All hilar and intrapulmonary (N1) lymph nodes were counted as a single station. Histological examination of the resected nodes/resection specimen and pTpN classification were performed according to current guidelines.[24]

Histology

Cytology preparations were analysed using either May–Grünwald–Giemsa or Papanicolaou stains, dependent on local practice, with additional preparation of cell blocks for histological analysis where appropriate.

Sample size

The sample size calculation was based on demonstrating a 20% increase in sensitivity [the rate of detecting mediastinal nodal metastases (N2/N3)] from 70% with surgical staging alone to 90% with endosonography followed by surgical staging. Assuming 80% power and a two-tailed α-value of 5%, the required sample size was calculated to be 62 patients per group, total 124. It was further assumed that the prevalence of mediastinal nodal metastases would be 70% and the dropout rate 5%, giving a required sample size of 93 per group, or 186 in total. However, as interim monitoring revealed the prevalence of mediastinal nodal metastases to be 55% rather than 70%, the sample size was increased to 240 patients.

Outcome measures

The primary clinical outcome was the sensitivity of each diagnostic strategy for detection of mediastinal nodal (N2/N3) metastases. The denominator for the calculation of sensitivity was taken to be the number of patients in whom histological examination of nodal tissue biopsied during any procedure was positive for cancer (EUS/EBUS, mediastinoscopy, thoracotomy). The

numerator was the number of patients in whom histology was positive during the diagnostic phase (EUS/EBUS and/or mediastinoscopy, depending on group). Patients with tumour-positive nodal findings at EUS, EBUS or surgical staging were regarded as true-positives, as further validation of these findings was judged unethical. The final reference status of the patient was positive if *any* diagnostic test was positive or if nodal involvement was detected after thoracotomy. The related NPV was also calculated as the number of patients who were free of nodal involvement as a proportion of the number of patients with negative tests during the diagnostic phase. This is interpreted as the probability of a final diagnosis of no metastases given the diagnostic tests were all negative.

Other outcome measures were:

- determination of the sensitivity of EBUS and EUS (followed by surgical staging) compared with surgical staging alone for determining mediastinal tumour invasion (T4)
- EQ-5D items and associated utility at end of staging (before thoracotomy) and 2 and 6 months after randomisation
- cost–utility of the endosonography diagnostic strategy (including surgical staging if negative) relative to surgical staging alone up to 6 months after randomisation
- complication rates
- the rate of futile thoracotomies that could be avoided by performing EBUS-TBNA and EUS-FNA rather than surgical staging alone, defined as nodal metastases, tumour invasion, distant metastases, non-malignant disease or death within 30 days of procedure
- interobserver variability of cytopathological evaluation of EBUS-TBNA and EUS-FNA samples.

Statistical analysis

In the primary analysis, estimation of sensitivity and NPVs was performed on an intention-to-treat basis. Patients in whom diagnostic tests were negative and who did not undergo thoracotomy did not have a reference standard. For these patients, multiple imputation based on the binomial distribution was used for the missing reference standard. An additional worst-case scenario analysis assumed that patients who were staged node negative, but in whom surgical verification was missing, were considered to be false-negatives. A κ-value was calculated to assess the interobserver variability of EUS and EBUS cytology samples. In exploratory analysis, the groups were compared using Fisher's exact test for binary categorical variables, the chi-squared test for other categorical variables and the independent Student's *t*-tests for continuous normally distributed variables. EQ-5D utilities were compared using linear models that included the baseline value as well as the group allocation. Survival rates from randomisation to death or last known survival date were estimated using the Kaplan–Meier method, and compared using a log-rank test. Details of statistical methods used in the cost-effectiveness analysis are given below.

European Quality of Life-5 Dimensions analysis

The EQ-5D questionnaire consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each dimension, the patient indicates the level of problems experienced by one of three responses: no problems (score 1), some problems (score 2) or extreme problems (score 3).

The EQ-5D questionnaire was completed using standard pro forma at baseline, at the end of staging (after surgical staging but before thoracotomy) and after 2 months and 6 months for

all patients recruited at Papworth Hospital.[25] This information was collected for patients in the continental European centres who were recruited after April 2008. For these patients the established Dutch- or Flemish-language versions of the EQ-SD were used. Between February 2007 and April 2008 EQ-5D, data were not available from the continental European centres. As this represented a block of time for which no patient completed the EQ-5D, this information was reasonably assumed to be missing at random.

The social tariff for the EQ-5D, as estimated by Dolan *et al.*,[26] was applied to each patient's self-reported classification in order to calculate utility values for each patient.[26] Although European tariffs exist for the EQ-5D, this report is from a UK perspective so the UK tariff was applied to all responses. Utilities were scaled so that full health = 1 and death = 0. In the case of patients in whom between one and four dimensions (out of five) of the EQ-5D were missing, a single imputation using an ordinal logistic regression model was used to impute the missing values.

Initially, utilities were summarised according to the nominal times of completion (baseline, end of staging, 2 months, 6 months) of the questionnaires. In order to estimate EQ-5D values at the same times after randomisation for each patient, the exact dates that the questionnaires were completed were used and linear interpolation between the recorded EQ-5D values on these dates gave an estimate at specific days post-randomisation. This allowed estimation of utilities at times 0, 7, 61 and 183 for all patients, and these were summarised. If EQ-5D questionnaire dates were not available, end of staging, 2- and 6-month questionnaires were assumed to have been completed at 7, 61 and 183 days after randomisation, respectively.

In the case of patients who died within 183 days of randomisation (four EUS/EBUS and seven surgical patients), EQ-5D was assumed to be '0' at the date of death and thereafter. Interpolation between the last recorded EQ-5D and an EQ-5D of '0' at the date of death was carried out to obtain EQ-5Ds for each time point (0, 7, 61 and 183 days).

For patients who died after 183 days but did not have EQ-5Ds recorded for all dates up to day 183, interpolation was again performed between the last known EQ-5D and an EQ-5D of '0' at the date of death (two EUS/EBUS and two surgical patients).

For patients who had monotonic missing EQ-5D values (i.e. had an EQ-5D value up to a certain time point, but all subsequent EQ-5D values missing) and did not die within or after the study, the last recorded EQ-5D value was carried forward. One patient (randomised to the endosonography strategy) had the baseline EQ-5D value carried forward to 6 months. Two patients (one EUS/EBUS and one surgical staging) had the end of staging EQ-5D carried forward. Four patients (one EUS/EBUS and three surgical staging) had the 2-month value carried forward to 6 months. The analysis was repeated using a subset of data that excluded these patients from the quality-adjusted life-year (QALY) calculations and the results were very similar.

For the patients who had an EQ-5D recorded at each time point and did not die within or after the study but the 6-month EQ-5D was earlier than 183 days after randomisation, the last EQ-5D was carried forward. Twelve people from the EUS/EBUS group and 13 from the surgical staging group were included in this group. All had last dates recorded that were within 10 days of the end of the study, except one patient who had the final follow-up at 155 days. This was considered to be a reasonable method to use, as the EQ-5D for these patients would have been unlikely to change dramatically without the investigators knowledge in such a short time period.

Exploratory cost-effectiveness analysis

The 6-month QALY was estimated for each patient using the area under the curve (AUC) method. The maximum QALY achievable was therefore 0.5 years. As the groups were randomised, adjustment for baseline utility was unnecessary in the exploratory analysis.

Costs were estimated from a health-service provider viewpoint using resource use from all of the patients in the trial and, in the base case, costs from a UK NHS perspective. For resource use, a study-specific data collection form was designed (see *Appendix 2*). Data were recorded prospectively after April 2008 and retrospectively for patients recruited before April 2008. Forms were returned to the Papworth Hospital research and development (R&D) unit for data processing and analysis.

Figure 1 shows the flow diagram of resource use for the ASTER trial.

The following resource-use components were recorded: EBUS/EUS, surgical staging, thoracotomy, surgery other than planned thoracotomy, chemotherapy, radiotherapy, hospital stays and hospice stays.

The final costs assigned to each component of resource use are summarised in *Table 1*. For standard treatments and procedures the *NHS Reference Costs 2008–09*[27] was used, with specific procedures as shown in *Table 1*. For EBUS-TBNA and EUS-FNA there were no NHS reference costs, so they were estimated by Papworth Hospital finance department. The costs included staff time, bed occupancy, and hospital costs and equipment, which were assumed to have a 5-year lifetime. Full details of the costing of the endosonography procedures are given in *Table 2*. Similar unit costs for staging using EBUS/EUS were elicited by the finance departments at the centres in Ghent (€671.8) and Leiden (€1506).

The total expected costs from randomisation to 6 months were estimated by summing the resource use multiplied by its unit cost and taking the sample average for each group. The incremental cost-effectiveness ratio (difference in costs divided by difference in effects) was calculated using the sample differences.

A first analysis was restricted to 'completers', i.e. individuals for whom both complete cost and QALY information was available. All patients completed a resource-use questionnaire and data surrounding the initial diagnostic strategy was complete. However, because subsequent treatment was often administered in a patient's local oncology centre (distant from the tertiary diagnostic referral centre), some resource-use information was missing. The number of missing data for each category was:

1. EBUS/EUS (0 missing)
2. surgical staging (0 missing)
3. thoracotomy (0 missing)
4. surgery other than planned thoracotomy (28 missing)
5. chemotherapy (35 missing for 0–2 months, 30 missing for 2–6 months)
6. radiotherapy (22 missing for 0–2 months, 26 missing for 2–6 months)
7. hospital stays (34 missing for 0–2 months, 28 missing for 2–6 months)
8. hospice stays (26 missing for 0–2 months, 29 missing for 2–6 months).

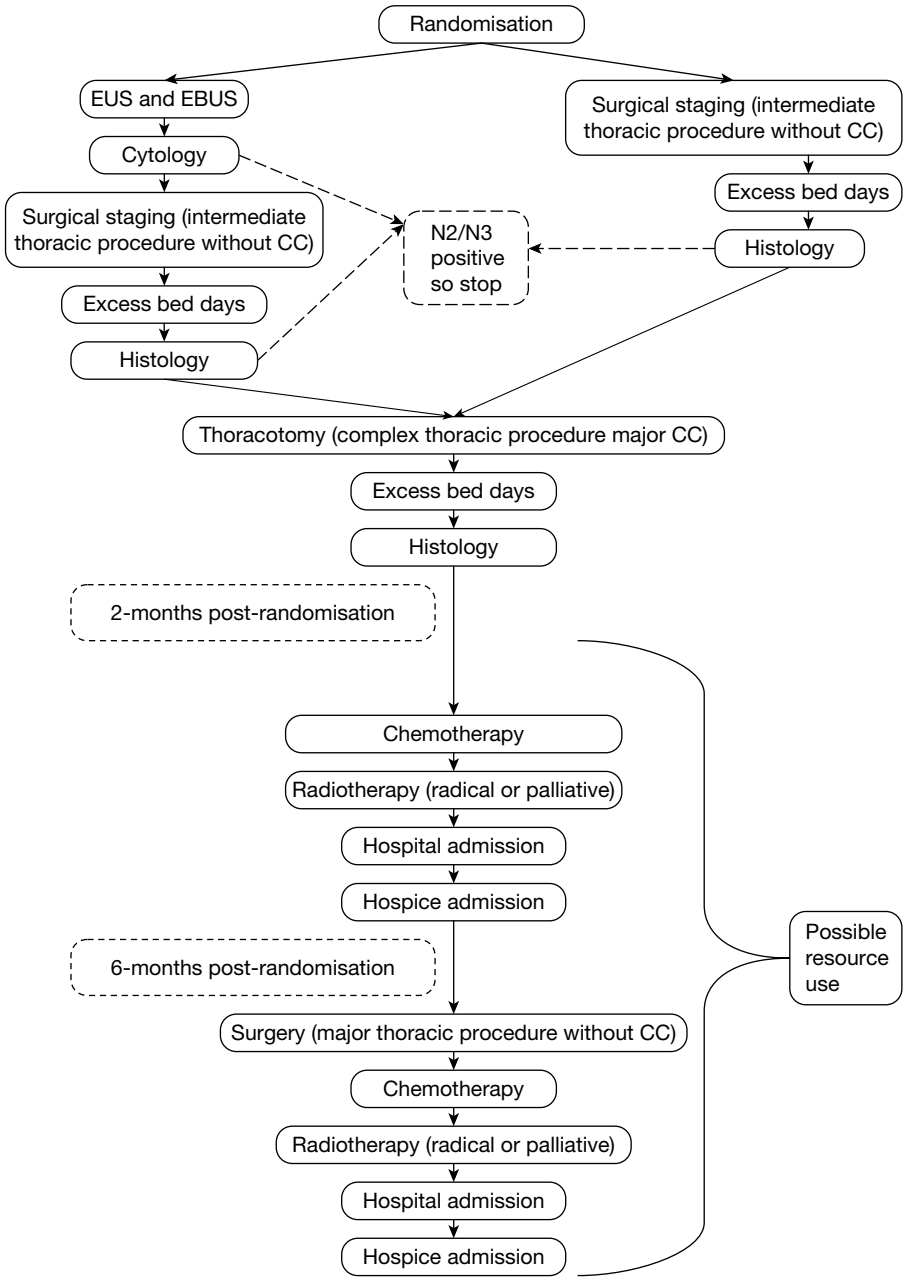


FIGURE 1 Potential resource use in the first 6 months. CC, complication and comorbidity.

Values were imputed for these missing resource-use items. In this exploratory analysis, a single imputation was performed as follows. Patients were divided by centre, randomisation group and stage (N2-/N3-positive or N2-/N3-negative, as determined at the end of the surgical staging procedure in both groups – i.e. for the EUS/EBUS group, this was the number of people who were found to be N2/N3 positive after endosonography added to the number found to be N2/N3 positive after endosonography followed by surgical staging). Within each of these subgroups, the mean cost for each item was calculated from cases with available information and imputed for those with missing values.

To estimate the standard errors and CIs for the mean cost and QALY, bootstrap samples were generated and the results plotted on the cost-effectiveness plane and as a cost-effectiveness acceptability curve (CEAC).

TABLE 1 Unit costs and quartiles and the source of the information

NHS resource	Mean unit cost (quartiles) (£)	Source
Hospital/hospice costs		
EUS/EBUS procedure	1237	Papworth NHS finance department estimates
Surgical staging procedure	3056 (2360 to 3652)	Code DZ04B[27]
Surgical staging procedure cost from day 10	329 (217 to 424)	Code DZ04B[27]
Thoracotomy (lobectomy or pneumonectomy) with lymph node dissection	6525 (5917 to 6903)	DZ02B[27]
Thoracotomy cost from day 44	318 (218 to 458)	Code DZ02B[27]
Deliver simple parenteral chemotherapy at first attendance[1]	272 (98 to 234)	Code SB12Z[27]
Deliver subsequent elements of a chemotherapy cycle[a]	227 (121 to 236)	Code SB15Z[27]
Radical radiotherapy (very first fraction)	274 (123 to 415)	Code SC02Z[27]
Subsequent radical radiotherapy fractions	112 (68 to 137)	Code SC22Z[27]
Palliative radiotherapy (very first fraction)	274 (123 to 415)	Code SC02Z[27]
Subsequent palliative radiotherapy fractions	112 (68 to 137)	Code SC22Z[27]
Hospital admission	2126 (1543 to 2475)	Code DZ17B[27]
Cost of hospital admission per day from day 32	224 (168 to 256)	Code DZ17B[27]
Hospice admission per day	399 (337 to 406)	Code SD01A[27]
Surgery	4120 (3197 to 4677)	Code DZ03B[27]
Laboratory costs		
Following EUS/EBUS procedure	17 (9 to 22)	Code DAP838[27]
Following surgical staging procedure	26 (7 to 36)	Code DAP824[27]
Following thoracotomy (lobectomy or pneumonectomy) with lymph node dissection	26 (7 to 36)	Code DAP 824[27]

The chemotherapy cost per cycle is the sum of the cost for delivering the simple parenteral chemotherapy at first attendance and the cost for delivering subsequent elements of a chemotherapy cycle. Therefore, the chemotherapy cost per cycle is £499. Note that the mean cost is greater than the upper quartile, indicating that there are some hospitals for which these costs are very high. Source: *NHS Reference Costs 2008–09*.[27]

TABLE 2 Details of costing of endosonography estimated by Papworth Hospital finance department

Component	Total cost including VAT (£)	Equipment life (years)	Activity	Unit cost (£)	Notes
EBUS scope	61,000	5	150	81	Assumes 5-year life
EUS scope	92,500	5	100	185	Assumes 5-year life
Ultrasound processor	58,300	5	150	78	Assumes 5-year life
Two consultants	300,000		3404	88	Assumes 1-hour procedure
Two Band 6 nurses	60,510		3404	18	Assumes 1-hour procedure
One health-care assistant	15,500		1702	9	Assumes 1-hour procedure
Aspiration needle	155		2	310	As per consumables schedule
Balloon	15		1	15	As per consumables schedule
Single-use suction valve	3		1	3	As per consumables schedule
Sterilisation of scopes	16		2	32	
Maintenance contract	19,000		150	127	Assumes maintenance for above equipment only
Day ward bed-day	150		1	150	
Hospital overheads, including capital charges – 15%	945	15%		142	Trust overhead included in annual trust costing exercise
Total				1237	

Full data cost-effectiveness analysis

Bayesian parametric modelling[28] was used to estimate expected costs and QALYs. This allowed the estimation of cost-effectiveness to include information from all of the patients rather than just patients for whom complete cost and QALY data were available. The methods are unbiased under the assumption that the missing data were 'missing at random'; in other words, whether or not an observation is missing depends on other variables for which we adjust, but not on the missing value itself. The QALY can be assumed to be missing 'completely at random', as quality-of-life data collected were collected only for patients recruited at later time points.

Overall, QALYs over 6 months were missing for 97 out of 241 patients. The model used for imputation of the missing QALYs was a truncated normal distribution (see *Table 3*). The mean before truncation was modelled in terms of predictors (randomisation group, centre and baseline EQ-5D) and the resulting posterior distribution for the expected QALY over 6 months was used in the cost-effectiveness estimate.

As described in the exploratory analysis, some resource-use costs were missing As these costs arise as counts of events (multiplied by a fixed unit cost), a model was defined for each of these event counts. Different parametric models were used to represent the distribution of the event counts for each component.

Although there were no missing data for EUS/EBUS, it was modelled as a binary outcome in order to include it in the model for total mean cost. Surgery other than the planned thoracotomy was modelled as a binary outcome. For the remaining events, owing to the high number of zero counts, a hurdle count-data model was used.[29] In this methodology, a proportion of the patients did not have the event and so were given a value of zero, whereas the remaining patients did have the event and were given a value greater than zero to reflect, for example, the number of days in hospital or the number of fractions of radiotherapy. The non-zero count was assumed to come from a standard count model such as the binomial or Poisson distribution truncated below to be greater than zero. Overdispersed equivalents of these models were used where the counts had a high variance. Binomial or beta-binomial distributions were used for count data with theoretical maximum values. In this case, the number of days spent in hospital over 6 months has a theoretical maximum of 183 days. The beta-binomial is an overdispersed version of the binomial, whereby the outcome probability is allowed to vary according to a beta prior. Poisson distributions were used for theoretically unbounded count data, with a gamma prior assigned

TABLE 3 Models used for imputation of missing data

Parameter	Imputation model
Observed QALYs between randomisation and 6 months	Truncated normal, truncated between the theoretical minimum (–0.297) and maximum (0.5)
Day in hospital for EBUS/EUS (0 or 1)	Bernoulli
Days in hospital for surgical staging	Beta-binomial
Days in hospital for thoracotomy	Beta-binomial
Surgery other than planned thoracotomy (0 or 1)	Binomial
Chemotherapy cycles	Poisson
Radiotherapy fractions	Poisson-gamma
Days in hospital	Beta-binomial
Days in hospice	Binomial

to the rate parameter when necessary to allow for overdispersed counts. Specific models for the resource-use components are summarised in *Table 3*.

Several individuals had a particular cost component observed for 0–2 months, but missing for 2–6 months, and vice versa. For these cases, this component was modelled as right censored at the observed cost value.

The probability of a non-zero cost was modelled in terms of covariates using logistic regression. For hospice admission, the only covariate used in this part of the model was randomisation group. For all other events, randomisation group, centre and stage were included as covariates. Where appropriate, the mean of the Poisson(-gamma) or (beta-)binomial non-zero component is also modelled in terms of randomisation group, centre and stage, except for radiotherapy, for which there was insufficient information to be able to model any covariates. For the Poisson distribution, log-linear regression on the rate was assumed, and, for the beta-binomial distribution, adjustment was based on logistic models.

The total expected cost was calculated as the sum of the component-specific expected costs for each randomisation group, while averaging over the other patient characteristics.

As a Bayesian model was used, uncertainty about the unit costs could be acknowledged. The UK mean unit cost estimates and upper and lower quartiles were available for each resource (see *Table 3*). These were used to define gamma prior distributions for each unit cost.[30] The point estimates of the unit cost in *Table 2* were assigned to the mean, and the variance was estimated as the variance of the normal distribution with the same mean and interquartile range (IQR), so that IQR = 1.35 standard deviation (SD).

The freely available software package WinBUGS[31] (MRC Biostatistics Unit, Cambridge, UK) was used to estimate the joint posterior distribution of all unknown parameters involved in the cost and QALY models, hence the posterior distributions of expected total cost and QALY. The 'WBDev' add-on to WinBUGS was used to calculate the lower tail probabilities and conditional tail expectations of the binomial distribution, which was required because of the time-dependent change in costs for certain components, for example after 32 days in hospital.

Deterministic sensitivity analysis

One potential alternative diagnostic strategy was identified a priori for investigation. The value of using endosonography as the only diagnostic modality to exclude nodal involvement was assessed 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. The QALYs were not adjusted, as the difference between groups was very small and the proportion of patients for whom utilities would change is also small.

Chapter 3

Clinical outcomes

Trial progress

Between February 2007 and April 2009, 357 consecutive patients with potentially resectable (confirmed or suspected) NSCLC were assessed for eligibility. Of these, 98 patients did not meet the inclusion criteria owing to previous therapy for lung cancer ($n = 54$), concurrent cancer at another site ($n = 17$), improbability of being staged correctly by surgery ($n = 20$) or inability to give informed consent ($n = 7$). Eighteen patients were eligible but not included because the patient refused consent ($n = 6$), referring doctors were unwilling to include the patient ($n = 7$), the patient was too deaf to complete study requirements ($n = 1$), urgent thoracotomy was required ($n = 1$), the patient was known to be non-compliant ($n = 1$), the patient had no health insurance (one continental European patient) or there were logistic problems ($n = 1$). The remaining 241 patients were randomised, 118 (49%) to surgical staging and 123 (51%) to endosonography followed by surgery if negative [*Figure 2*, the CONSORT (CONonsolidated Standards Of Reporting Trials) diagram]. Of the 241 patients recruited, 88 were from Ghent, 81 from Leiden, 44 from Leuven and 28 from Papworth.

Baseline characteristics

The average age of patients was 64.5 years [standard deviation (SD) 8.9 years] and men were in the majority in both groups (74% men in the surgical staging arm and 80% men in the endosonography arm). Further clinical characteristics can be found in *Table 4*.

Surgical staging alone

Surgical staging was performed in 117 out of the 118 randomised patients. A distant metastasis was found in one patient after randomisation but before the surgical staging procedure could be performed. Cervical mediastinoscopy was performed in 116 of the 117 (99%) which was combined with parasternal mediastinoscopy in three and a thoracoscopy in two. Only one patient underwent a thoracoscopy. Of the 117 who underwent mediastinoscopy, data on mediastinal nodal status were incomplete in seven patients for the following reasons:

- In one patient, mediastinal invasion (T4) was found during mediastinoscopy without verification of the nodal status.
- Three patients in whom surgical mediastinoscopy staging was negative, declined verification by thoracotomy.
- In one patient in whom surgical mediastinoscopy staging was negative, thoracotomy was not possible because of rapid clinical deterioration.
- One patient underwent an open–close thoracotomy without nodal verification because of haemodynamic instability.
- In one patient, direct mediastinal invasion was observed at thoracotomy and the surgeon decided to close the thorax without taking nodal biopsies.

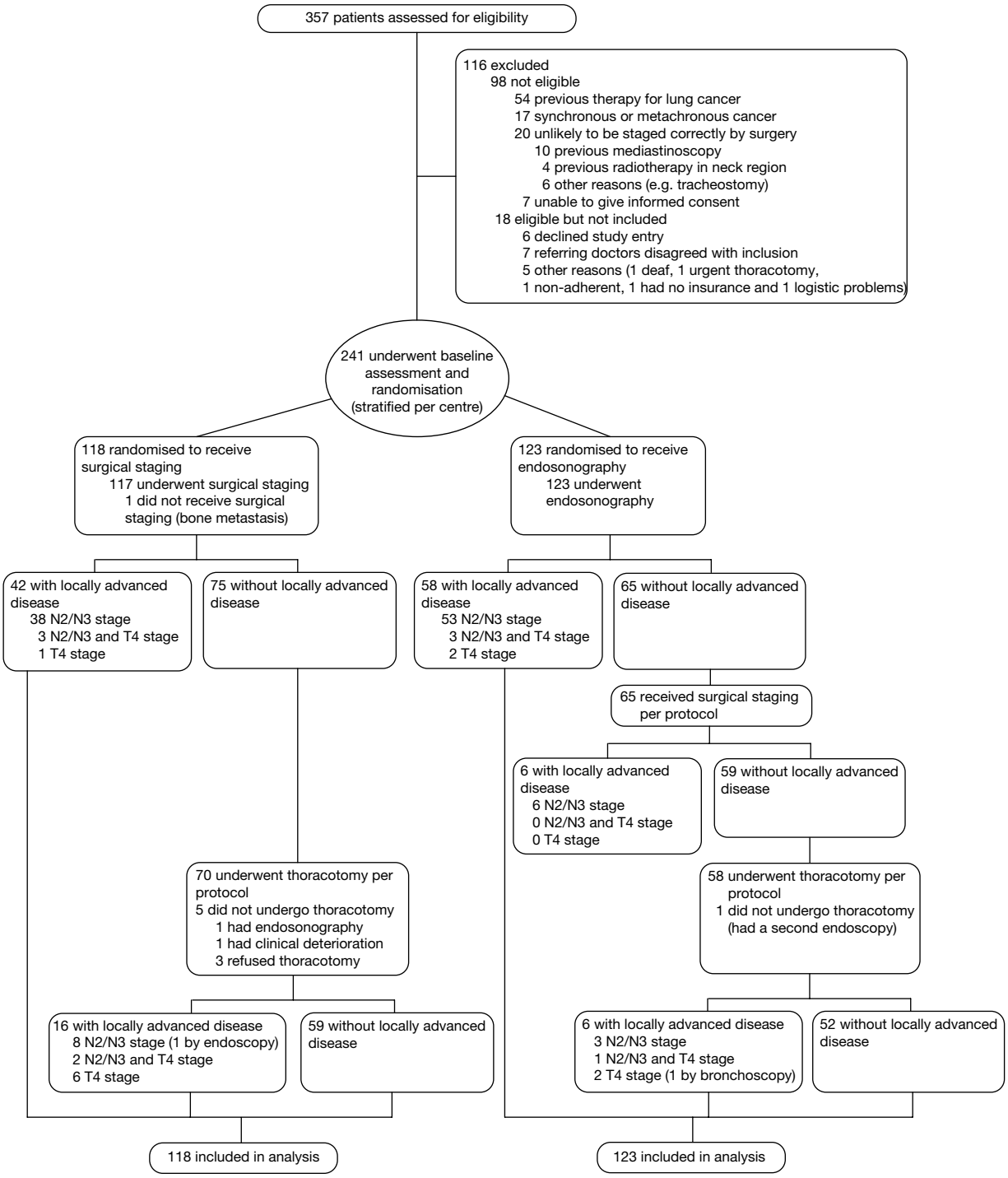


FIGURE 2 Enrolment and randomisation of study patients.

In the 110 patients in whom staging was complete, a median of four (range 1–5) mediastinal nodal stations were sampled at surgical staging.

Overall, during staging, mediastinal metastases (N2/N3) were found in 41 out of 118 (35%) patients. In four patients, one without nodal metastases, direct mediastinal invasion of the lung tumour in the mediastinum (T4) was found. Thus, 42 patients had either mediastinal metastases (N2/N3) or mediastinal invasion (T4), or both. Thoracotomy was performed in 70 patients, and

TABLE 4 Baseline characteristics by group

Baseline variable	Surgical staging alone (*n* = 118)	Endosonography and surgical staging (*n* = 123)
Mean (SD) age, years	64.5 (9.1)	64.6 (8.7)
No. (%) men	87 (74)	99 (80)
Centre, no. (%)		
LUMC	39 (33)	42 (34)
Ghent	43 (36)	45 (37)
Papworth	14 (12)	14 (11)
Leuven	22 (19)	22 (18)
Indication for staging, no. (%)		
Quamous cell carcinoma	44 (37)	46 (37)
Adenocarcinoma	21 (18)	28 (23)
Adenosquamous	2 (2)	3 (2)
Large cell carcinoma	3 (3)	6 (5)
Bronchoalveolar cell carcinoma	1 (1)	0 (0)
Carcinoma not specified	18 (15)	16 (13)
Suspected NSCLC	29 (25)	24 (20)
Tumour location, no. (%)		
Left lower lobe	17 (14)	27 (22)
Left upper lobe	18 (15)	25 (20)
Right upper lobe	30 (25)	28 (23)
Middle lobe	9 (8)	10 (8)
Right lower lobe	44 (37)	33 (27)
Tumour stage on PET/CT, no. (%)		
T1	26 (22)	22 (18)
T2	66 (56)	80 (65)
T3	11 (9)	11 (9)
T4	15 (13)	10 (8)
Nodal status on PET/CT, no. (%)		
N0	15 (13)	9 (7)
N1	17 (14)	20 (16)
N2	66 (56)	78 (63)
N3	20 (17)	16 (13)
Mean (SD) short axis of largest lymph node (mm)	12.3 (5.1)	13.2 (4.2)
ACCP class, no. (%)		
Massive enlargement (A)	0 (0)	0 (0)
Discrete enlargement (B)	73 (62)	76 (62)
Central tumour or hilar node (C)	35 (30)	33 (27)
Nodes < 10 mm (D)	10 (8)	14 (11)
Final histopathology grade, no. (%)		
Squamous cell carcinoma	47 (40)	51 (41)
Adenocarcinoma	40 (34)	40 (33)
Adenosquamous	5 (4)	6 (5)
Large cell carcinoma	6 (5)	2 (2)
Bronchoalveolar carcinoma	0 (0)	1 (1)
Carcinoma not specified	12 (10)	19 (15)
Small cell carcinoma	1 (1)	4 (3)
Benign lesion	5 (4)	0 (0)
Unknown	2 (2)	0 (0)

ACCP, American College of Chest Physicians.

two patients underwent further diagnostic tests or had clinical evidence of metastatic disease. Of these patients, 10 had nodal metastases (of whom two also had mediastinal tumour invasion) and a further six had mediastinal invasion alone . Three patients who did not have evidence of mediastinal node involvement after surgical staging refused thoracotomy, so that their final nodal status was not confirmed.

Endosonography followed by surgical staging

Endosonography was performed in 123 patients and detected mediastinal nodal metastases in 56 out of 123 (46%). In five patients it was obvious on endosonographic imaging that the primary lung tumour invaded the mediastinum (T4); two of the five did not have nodal verification. Thus, surgical staging was avoided due to endosonography findings in 47% of patients (58/123). Sixty-five patients without evidence of mediastinal nodal metastases or mediastinal tumour invasion underwent surgical staging showing nodal metastases in six additional patients. These missed mediastinal metastases were located in stations 4R ($n=3$), 5 ($n=1$), 6 ($n=1$) and 7 ($n=1$), with those in stations 5 and 6 being out of reach for endosonography.

Fifty-eight (out of 59) patients in whom endosonography or surgical staging revealed no evidence of nodal metastases underwent thoracotomy with nodal dissection. One patient was found to have undeniable mediastinal invasion based on a second endosonography, but did not have nodal verification. In the 58 patients who underwent thoracotomy, nodal metastases were found in four, one of whom also had mediastinal tumour invasion; two others were found to have mediastinal tumour invasion without confirmation of nodal metastases. At endosonography and surgical staging a median of three (range 1–7) different mediastinal nodal stations were sampled. For 121 patients in the endosonography group, the interobserver agreement in relation to cytological diagnosis of samples was assessed by an independent pathologist (*Table 5*) with $\kappa=0.97$ (95% CI 0.92 to 1.00).

Final diagnosis and false-negative findings

Of the 241 patients, 229 (95%) were diagnosed with NSCLC, five (2%) with small cell lung cancer (SCLC) and five (2%) with other diagnoses, such as sarcoidosis; in two patients (1%), the diagnosis could not be ascertained during the study. Overall, the prevalence of mediastinal nodal metastases (N2/N3) was 49% (117/241). At thoracotomy, a median of five (range 0 to 10) lymph node stations were obtained in both study arms. At pre-operative staging, nodal metastases were missed in 10 patients in the surgical staging arm (stations 4L, 4R, 5 and 7) and in four patients in the endosonography arm (stations 3A, 4L, 4R, 5, 8L and 8R). In eight patients (7%) in the surgical staging arm, negative lymph node findings at staging were not verified by surgery. One of these eight patients had bone metastases before staging and in one surgical staging

TABLE 5 Interobserver agreement for cytological diagnosis of samples obtained using endosonography

	Reference observer's result		
Local result	**Benign**	**Malignant**	**Total**
Benign	63	2	65
Malignant	0	56	56
Total	**63**	**58**	**121**

revealed clear T4 disease and so nodes were not sampled; in a further four of the eight patients, mediastinoscopy was negative and they received no further treatment (three refused thoracotomy and one deteriorated clinically) and in two patients who underwent thoracotomy lymph node confirmation of stage was not performed. There were three patients (2%) in the endosonography arm in whom negative lymph node findings at staging were not verified by surgery: in two of these endosonography clearly demonstrated T4 disease and in one T4 disease was diagnosed by bronchoscopy.

Diagnostic accuracy

Mediastinal nodal (N2/N3) metastases were found in 41 out of 118 patients (35%) by surgery alone compared with 62 out of 123 patients (50%) by endosonography followed by surgical staging if negative ($p = 0.02$). In the intention-to treat analysis, sensitivity for detecting mediastinal nodal metastases by each of the staging strategies was 79% (41/52, 95% CI 66% to 88%) versus 94% (62/66, 95% CI 85% to 98%) ($p = 0.02$; *Table 6*). The corresponding NPVs were 86% (66/77, 95% CI 76% to 92%) and 93% (57/61, 95% CI 84% to 97%) ($p = 0.18$; *Table 6*). In the worst-case scenario of treating cases with no surgical verification of negative staging as false-negatives, the sensitivity of surgical staging alone was 68% (41/60, 95% CI 57% to 80%) compared with 90% (62/69, 95% CI 81% to 95%) for endosonography with surgical staging if negative, respectively ($p = 0.006$), with corresponding NPVs of 75% (58/77, 95% CI 66% to 85%) and 87% (53/61, 95% CI 78% to 94%), respectively ($p = 0.08$).

Detection of locally advanced disease

In addition to the patients with N2/N3 involvement identified above, the tumour was observed to have invaded the lymph nodes (T4) in one patient in the surgical staging group and in two patients in the endosonography strategy group. Tumour invasion alone was detected by thoracotomy in a further six patients in the surgical staging group and two in the endosonography strategy group. One further patient in the endosonography strategy group was referred for thoracotomy but underwent a second endosonography before planned surgery, which showed clear tumour invasion. Thus, 42 patients (36%) in the surgical staging arm were found to have locally advanced diseases (nodal metastases and/or unforeseen direct mediastinal invasion) during staging, compared with 65 patients (53%) in the endosonography arm ($p = 0.009$). When the one patient in the endosonography arm who had a second endosonography was removed, the difference remained significant ($p = 0.01$).

TABLE 6 Summary of diagnostic accuracy results

Nodal invasion (N2/N3)	Surgical staging ($n = 118$)	Endosonography and surgical staging ($n = 123$)	*p*-value
No. (%) positive on endosonography	–	56/123 (46%)	–
No. (%) positive on surgical staging	41/117 (35%)	6/65 (9%)	–
No. (%) positive on thoracotomy	10/70 (14%)	4/58 (7%)	
Sensitivity of initial strategy	41/52[a] (79%)	62/66 (94%)	0.02
NPV of initial strategy	66/77 (86%)	57/61 (93%)	0.18

a Denominator includes one patient who had metastases but did not undergo staging.

Unnecessary thoracotomies and complications

There were 21 unnecessary thoracotomies among the 118 patients randomised to surgical staging (18%), compared with nine unnecessary thoracotomies in 123 patients randomised to endosonography followed by surgical staging if negative (7%; $p = 0.02$) (*Table 7*).

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 ($p = 0.78$; *Table 8*). There was one pneumothorax that was considered to be directly related to endosonography. This occurred during a EUS-FNA procedure, during which the primary tumour was biopsied. With pleural drainage, full lung expansion was achieved.

The remaining 12 complications were all directly related to the surgical staging procedure. The most common adverse event was persistent hoarseness as a result of recurrent nerve palsy, which was considered to be a severe complication if it lasted at least 6 months and was attributable to the mediastinoscopy. One patient presented with fever 24 hours after mediastinoscopy and mediastinitis was diagnosed; treatment with antibiotics resulted in full recovery.

TABLE 7 Unnecessary thoracotomies

Reason	Surgical staging ($n = 118$)	Endosonography and surgical staging ($n = 123$)
N2/N3[a]	5	2
N2/N3/death within 30 days	1	1
N2/N3/M1	1	0
N2/N3/T4	2	0
N2/N3/T4/death within 30 days	0	1
T4	6	1[b]
M1	0	2
SCLC	0	1
Benign lesions	2	0
Exploratory thoracotomy	2	0
Death within 30 days	2	1
Total	**21**	**9**

a In 10 patients within the surgical staging group, mediastinoscopy was negative and these patients were referred for thoracotomy. Of these, nine underwent the procedure; nodal invasion was identified by endosonography in the other patient.
b There were three patients in the endosonography arm who were referred for thoracotomy and who turned out to have T4 disease. Of these, only one patient actually underwent the procedure; one was identified by bronchoscopy and one by a second endosonography.

TABLE 8 Complications during the staging process

Complication	Surgical staging ($n = 118$)	Endosonography and surgical staging ($n = 123$)
Persistent hoarseness	2	4
Pneumothorax	1	1
Mediastinitis	0	1
Major bleeding	3	0
Conversion to thoracotomy	1	0
Total	**7**	**6**

Endosonography alone versus surgical staging

It is possible to estimate the diagnostic accuracy of endosonography alone using the first part of the endosonography arm strategy (i.e. without additional surgical staging). Of the 66 patients identified with mediastinal nodal involvement, this was observed during endosonography in 56 cases. The sensitivity estimates for surgical staging alone and endosonography alone were 79% (41/52; 95% CI 68% to 89%) and 85% (56/66; 95% CI 74% to 92%), respectively ($p = 0.62$). The corresponding NPVs were 86% (66/77; 95% CI 75% to 92%) and 85% (57/67; 95% CI 74% to 92%) ($p = 1.00$), respectively. Complications occurred in 7 out of 118 patients (6%) after surgical staging and in 1 out of 123 patients (1%) following endosonography alone ($p = 0.03$). Endosonography alone would have resulted in an additional six cases of unnecessary thoracotomy.

Summary

The clinical component of this RCT showed that a strategy of using combined EUS–FNA and EBUS-TBNA (followed by surgical staging only if these tests were negative) had higher sensitivity (94% vs 79%) and negative predicted probability (93% vs 86%) than surgical staging alone, and resulted in a lower rate of unnecessary thoracotomy (7% vs 18%). Other benefits of endosonography include less invasive testing, with no requirement for general anaesthesia or open surgery, and the small number of minor complications (1%).

Chapter 4

Survival and health-related quality of life

Patients were followed up for survival for 6 months after staging, during which period there were 20 deaths: nine in the endosonography strategy group and 11 in the surgical staging group. Kaplan–Meier estimates in *Figure 3* show no difference in survival rates over the 6-month period (log-rank test, $p = 0.57$).

Compliance

Of the 241 patients randomised into the study, 144 (60%) randomised after April 2008 were asked to complete the EQ-5D questionnaire at baseline, at the end of staging and 2 months and 6 months post-randomisation. All 144 patients completed the questionnaire at baseline. At end of staging and 2 months and 6 months post-randomisation, 139 (97%), 132 (92%) and 124 (86%) patients, respectively, completed the questionnaires. This gave a total of 539 completed questionnaires.

European Quality of Life-5 Dimensions

Of the 539 completed questionnaires, one or more of the dimensions of the EQ-5D was missing in six (1.1%). The missing values were imputed using a single imputation based on an ordinal logistic regression model, including the five dimensions of the EQ-5D.

Figure 4 shows the percentage of patients reporting a problem in each dimension (i.e. those patients indicating some/moderate or extreme problems – score 2 or 3). At baseline, anxiety/depression was the most common problem in both groups, and the surgical group had approximately 15% more patients experiencing these symptoms. In all other dimensions, there was a < 10% difference between the groups. At the end of staging (for the endosonography group after surgical staging if the EBUS/EUS was negative or after the EBUS/EUS if it was positive), the surgical group reported more problems in every dimension than the endoscopic group. This was

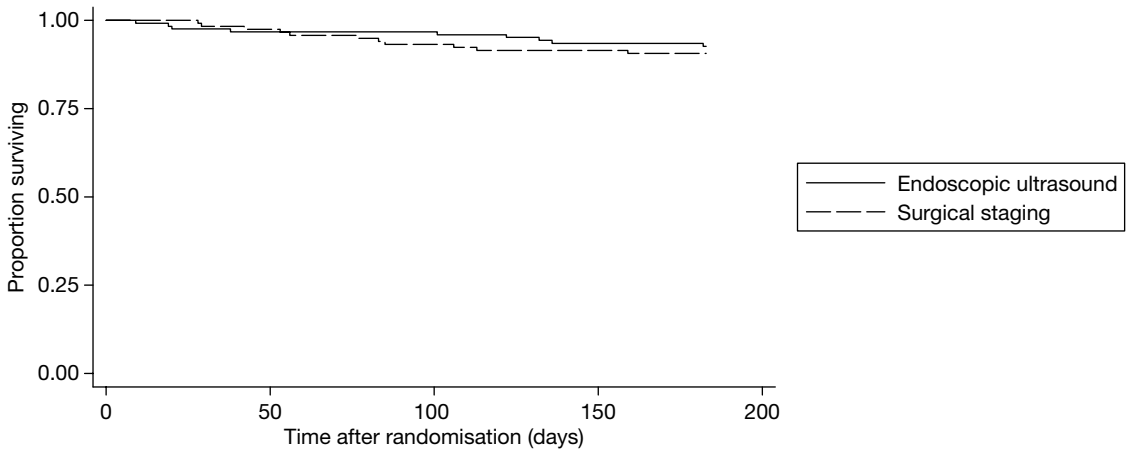
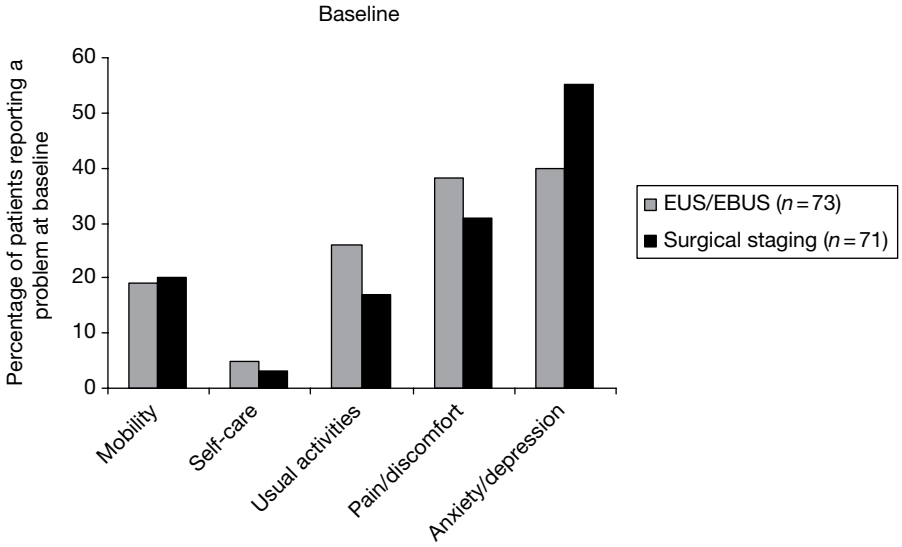


FIGURE 3 Kaplan–Meier survival estimates for time (in days) to death.

(a)



(b)

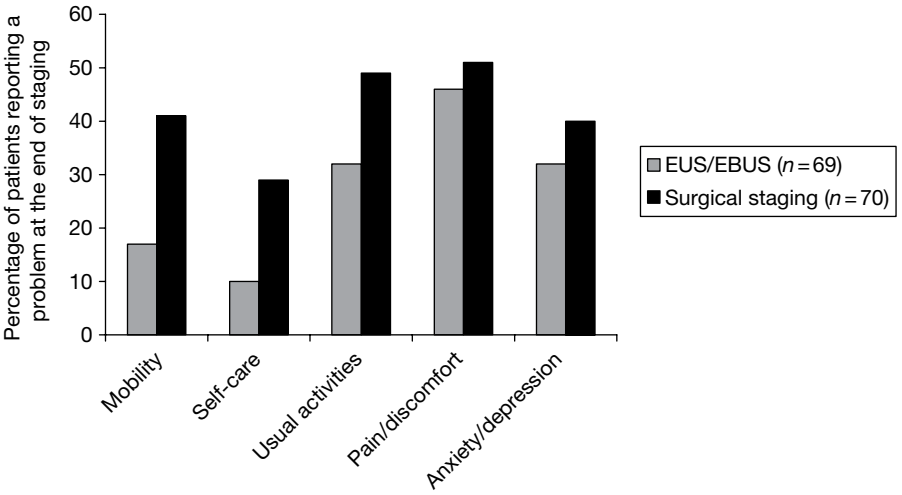


FIGURE 4 Percentage of patients reporting at least some problems on the EQ-5D dimensions. a, Baseline; b, end of staging; c, 2 months; d, 6 months. (*continued*)

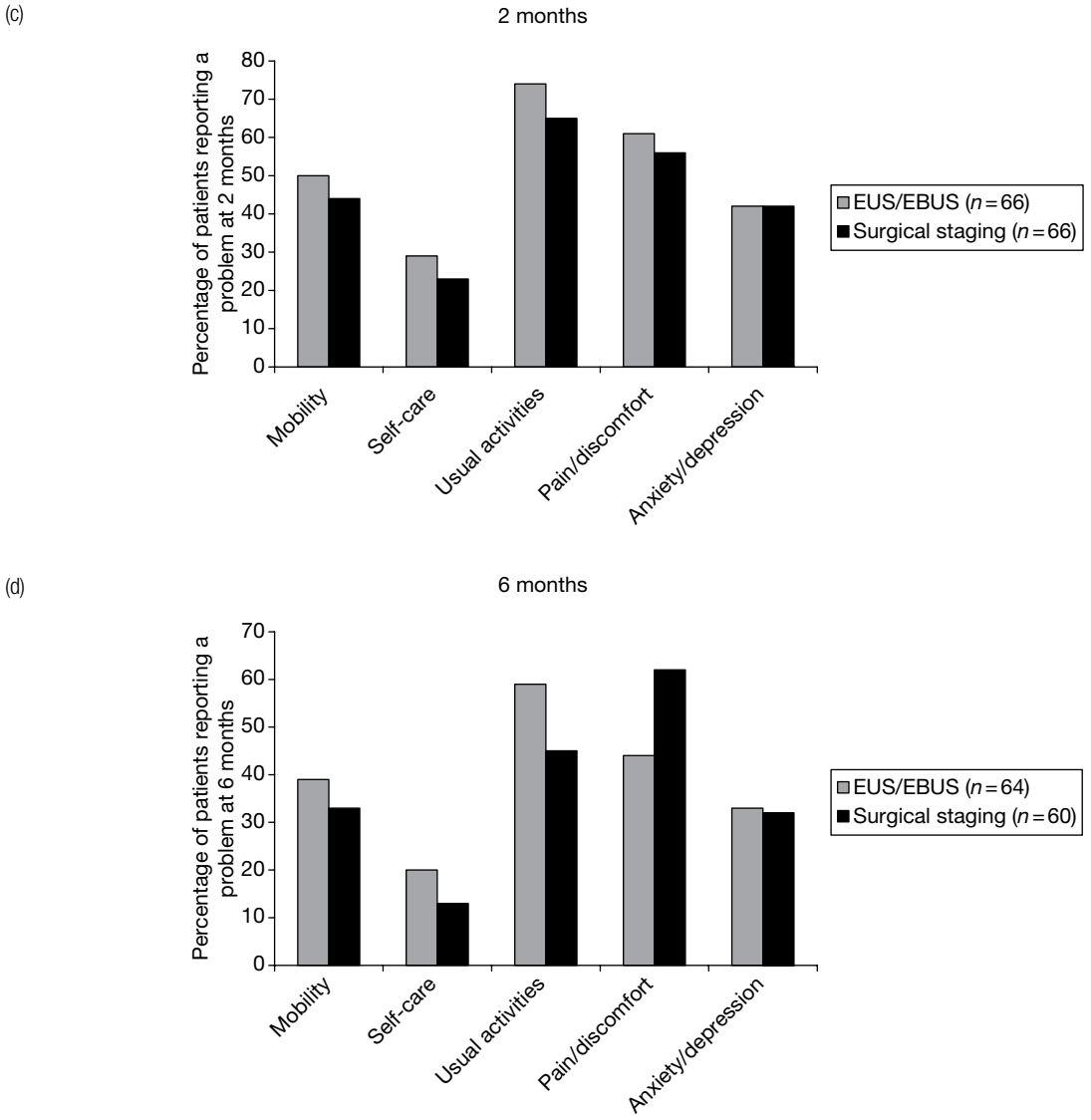


FIGURE 4 Percentage of patients reporting at least some problems on the EQ-5D dimensions. a, Baseline; b, end of staging; c, 2 months; d, 6 months.

particularly noticeable in the mobility dimension, for which > 20% more patients in the surgical group reported problems. By 2 months the situation was reversed, with those in the endoscopic group faring worse in each dimension, although the differences were < 10%. At 6 months, the endoscopic group reported slightly more problems with usual activities, whereas the surgical group reported more problems with pain/discomfort. The other dimensions were similar between the groups.

European Quality of Life-5 Dimensions utility

The mean (SD) of the EQ-5D utility, by group, at each stage is summarised in *Table 9*. The values shown are for the nominal time points of baseline, end of staging, and 2 months and 6 months post-randomisation, not the actual dates that the questionnaires were collected. Therefore, there may be some inaccuracies in these estimates if, for example, the surgical staging group completed the end of staging questionnaire at a different time to the EUS/EBUS strategy group. Furthermore, this analysis includes only patients for whom questionnaires were completed. It does not make any attempt to impute missing EQ-5D information. The average age of patients was 65 years (SD 9 years) in both arms, and both groups had a majority of men (74% for the surgical staging arm vs 80% for endosonography and surgical staging). For a population with similar age and sex characteristics to patients in this study, the average EQ-5D score was 0.78.[32]

At baseline, the groups were very similar with values slightly above the population average. However, by the end of staging, the average value for the surgical staging group had decreased by 0.20 compared with only 0.04 for the EUS/EBUS group. By 6 months, both groups were again similar but now slightly lower than the population average values.

European Quality of Life-5 Dimensions index at specified time points

Table 10 and *Figure 5* show the estimated mean (SD) EQ-5D utility at days 0, 7, 61 and 183 after randomisation for all patients. This allows for a more accurate comparison between groups. There are 73 and 71 patients in the endosonography (followed by surgical staging if negative) group and surgical staging groups, respectively. All patients who completed a questionnaire at baseline had an EQ-5D calculated at each subsequent time point, with zero utility representing death. When compared with *Table 9*, the average value for the surgical staging group at the end of staging decreased from baseline to a similar extent. By 6 months, the average value had decreased from baseline by 0.13 and 0.16 for the EUS/EBUS and surgical staging groups, respectively.

Table 11 shows the difference in EQ-5D between surgical staging and EUS/EBUS groups, both unadjusted and adjusted for baseline. In both analyses, there was a statistically significant

TABLE 9 Mean (SD) EQ-5D utility using nominal time points

Time point	EUS/EBUS	Surgical staging
Baseline ($n=73$, $n=71$)	0.81 (0.18)	0.83 (0.14)
End of staging ($n=69$, $n=70$)	0.77 (0.26)	0.63 (0.34)
2 months ($n=66$, $n=66$)	0.65 (0.26)	0.70 (0.24)
6 months ($n=64$, $n=60$)	0.74 (0.26)	0.75 (0.22)

difference between the groups at the end of staging, with those patients randomised to EUS/EBUS having a higher utility than those in the surgical staging group. However, at the other time points, there was little difference between the groups (*Figure 6*).

Figure 7 shows the mean difference (95% CI) in EQ-5D values between surgical staging and EUS/EBUS groups adjusted for baseline. This highlights the statistically significant difference between the groups at the end of staging ($p = 0.003$) when surgical staging patients had a worse quality of life than EUS/EBUS patients.

TABLE 10 Mean (SD) EQ-5D utility estimated at specific times post-randomisation

Time point	EUS/EBUS ($n = 73$)	Surgical staging ($n = 71$)
Baseline (day 0)	0.81 (0.18)	0.83 (0.14)
End of staging (day 7)	0.78 (0.23)	0.67 (0.29)
2 months (day 61)	0.64 (0.27)	0.65 (0.26)
6 months (day 183)	0.68 (0.30)	0.67 (0.31)

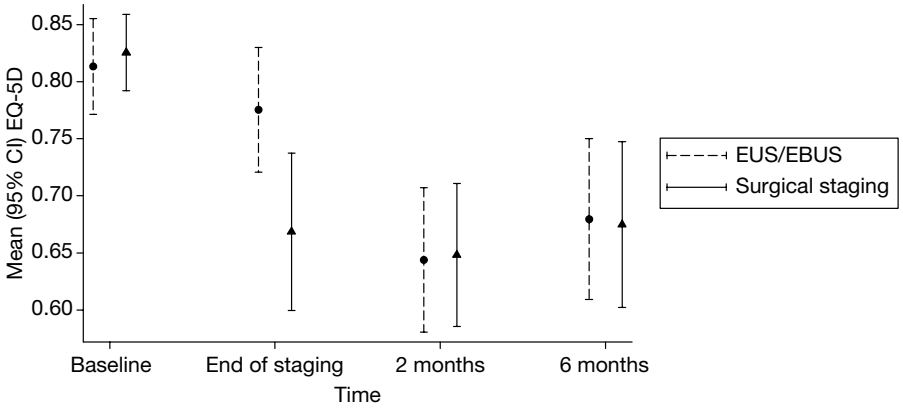


FIGURE 5 Mean (95% CI) EQ-5D utility at each time point in each group.

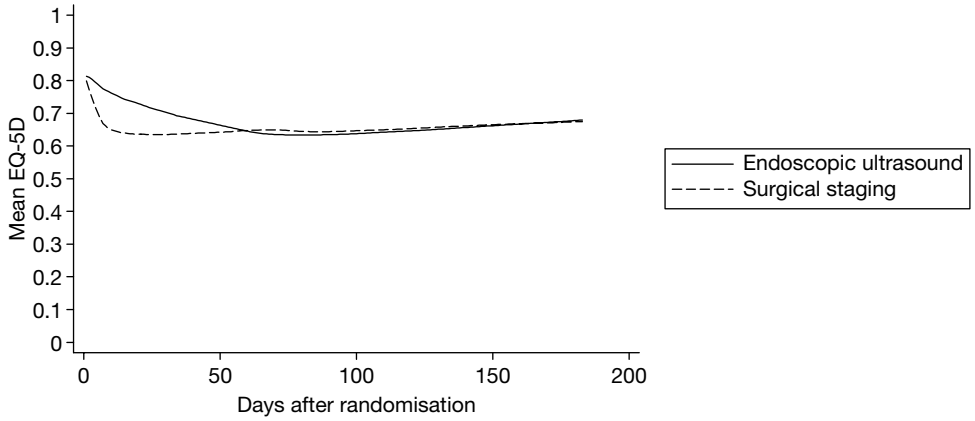


FIGURE 6 Mean EQ-5D utility by day after randomisation.

TABLE 11 Mean difference (95% CI) between endosonography (followed by surgical staging if negative) and surgical staging groups in EQ-5D[a]

Time point	Difference between EUS/EBUS and surgical staging (95% CI)	*p*-value
Unadjusted		
End of staging	0.107 (0.020 to 0.194)	0.02
2 months	–0.004 (–0.092 to 0.084)	0.92
6 months	0.005 (–0.096 to 0.105)	0.92
Adjusted for baseline		
End of staging	0.117 (0.042 to 0.192)	0.003
2 months	0.002 (–0.082 to 0.086)	0.96
6 months	0.010 (–0.089 to 0.108)	0.84

a Values > 0 favour the EUS/EBUS group.

Quality-adjusted life-year results by randomisation group

Table 12 shows that the mean (SD) 6-month QALY gain was very similar in the two randomisation groups. Once adjusted for baseline EQ-5D utility, the surgical staging group had a mean QALY gain that was 0.011 less than that of the EUS/EBUS group. The difference was not clinically or statistically significant ($p = 0.55$; *Table 13*).

Comparison of European Quality of Life-5 Dimensions and quality-adjusted life-year between centres

There were some differences in the EQ-5D scores between the centres (see *Appendix 3*). In all centres except Ghent, EQ-5D values at the end of staging were lower in patients undergoing surgical staging than in those who had been allocated to EUS/EBUS. This was particularly apparent at Leuven, where the difference in average values was almost 0.30. By 6 months, EUS/EBUS patients from LUMC and Papworth were doing slightly better, on average, than the surgical patients, whereas the opposite was the case in Ghent and Leuven. However, this was an unadjusted analysis and simply reflects the fact that, at LUMC and Papworth, baseline EQ-5D scores were slightly higher in EUS/EBUS patients than in surgical patients, whereas in Ghent and Leuven baseline EQ-5D scores were slightly better in the surgical staging group than the EUS/EBUS group. The number of patients in each randomisation group, in each centre, was small so that these differences were consistent with between-centre variation. There were no significant differences in QALY gains between the surgical staging and the EUS/EBUS staging strategy in any of the centres. Details for each centre are given in *Appendix 3*.

Summary

The survival and quality-of-life components of this RCT show that a strategy of using combined EUS–FNA and EBUS-TBNA (followed by surgical staging only if these tests are negative) has no significant impact on survival to 6 months after randomisation and is only slightly more effective, with an increase in QALYs (over 6 months) of 0.011 (95% CI –0.026 to 0.048). However, we

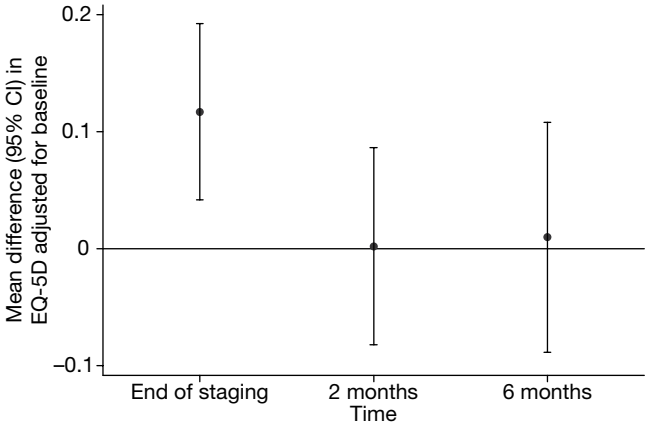


FIGURE 7 Difference in mean EQ-5D (95% CI) between EUS/EBUS (followed by surgical staging if negative) and surgical staging alone, adjusted for baseline. Values >0 favour the EUS/EBUS group.

TABLE 12 Mean (SD) 6-month QALY in each group; the maximum possible is 0.5

Measurement	EUS/EBUS (*n* = 73)	Surgical staging (*n* = 71)
6-month QALY	0.34 (0.12)	0.33 (0.12)

TABLE 13 Mean difference (95% CI) between the surgical staging and endosonography (followed by surgical staging if negative groups) in 6-month QALY

Analysis	Mean (95% CI) difference in QALY between surgical staging and EUS	*p*-value
Unadjusted	0.008 (–0.032 to 0.047)	0.70
Adjusted for baseline EQ-5D	0.011 (–0.026 to 0.048)	0.55

found that patients undergoing the endosonography staging strategy (including surgical staging if negative EUS/EBUS) had better quality of life at the end of staging than those who underwent surgical staging alone (mean difference 0.117; 95% CI 0.042 to 0.192). At all other time points, quality of life was similar in the two groups.

Chapter 5

Economic evaluation

A cost–utility analysis of surgical staging alone compared with EUS/EBUS and surgical staging (if the former was negative) from a health service perspective was undertaken. The time horizon was 6 months post-randomisation and all costs were reported in 2008–9 prices (£).

In terms of resource use, all patients followed the protocol for their group with the following exceptions:

- One patient randomised to surgical staging did not have the procedure because of bone metastases.
- Three patients randomised to surgical staging had a negative surgical mediastinoscopy staging, but refused thoracotomy.
- In one patient randomised to surgical staging mediastinoscopy was negative, but because of rapid clinical deterioration the patient did not undergo thoracotomy.
- One patient randomised to surgical staging who had a negative mediastinoscopy underwent endosonography rather than having a thoracotomy.
- One patient in the EUS/EBUS group who had negative surgical staging underwent a second endosonography instead of having a thoracotomy.
- Two patients in the EUS/EBUS group underwent additional surgical staging off protocol.

In addition, where both thoracotomy and surgical resection were recorded within 2 months of randomisation, this was assumed to be the same procedure unless there was evidence to the contrary.

Cost breakdowns for patients who had complete information on each resource item

The number and percentage of patients in each group using each resource item is shown in *Table 14*. Aside from the initial procedure (EUS/EBUS followed by surgical staging if negative, or surgical staging alone), the main difference in resource use was in the number of thoracotomies, 57 out of 87 (66%) patients in the surgical staging group compared with 45 out of 85 (53%) in the endosonography strategy group. Resource use was similar between the groups in all other items.

The total mean costs for each resource item are presented in *Table 15* for those patients who had complete information on all resource items. This includes 85 out of 123 (69%) in the endosonography arm and 87 out of 118 (74%) in the surgical staging arm.

Total trial costs for patients who had complete information on each resource item

The total mean (SD) and median (IQR) trial costs are presented in *Table 16* and *Figure 8* for those patients who had complete information on all resource items.

TABLE 14 Resource use for patients who had complete information on all resource items

Resource item	No. of patients using each resource item (%)	
	EUS/EBUS ($n=85$)	Surgical staging ($n=87$)
EUS/EBUS procedure	85 (100)	1 (1)
Surgical staging procedure	47 (55)	86 (99)
Thoracotomy (lobectomy or pneumonectomy) with lymph node dissection	45 (53)	57 (66)
Chemotherapy in the first 2 months	43 (51)	39 (45)
Radiotherapy in the first 2 months	10 (12)	9 (10)
Hospital admission in the first 2 months	18 (21)	19 (22)
Hospice admission in the first 2 months	0 (0)	0 (0)
Surgery between months 2 and 6	7 (8)	9 (10)
Chemotherapy between months 2 and 6	40 (47)	43 (49)
Radiotherapy between months 2 and 6	32 (38)	27 (31)
Hospital admission between months 2 and 6	28 (33)	25 (29)
Hospice admission between months 2 and 6	1 (1)	0 (0)

TABLE 15 Mean cost per patient for each resource item for patients who had complete information on all resource items

Resource item	Mean cost per patient (£)		
	EUS/EBUS ($n=85$)	Surgical staging ($n=87$)[a]	Difference (95% CI)
EUS/EBUS procedure[b]	1254	14	1240 (1211 to 1268)
Surgical staging procedure[c]	1712	3058	–1346 (–1682 to –1010)
Thoracotomy (lobectomy or pneumonectomy) with lymph node dissection[d]	3543	4292	–749 (–1737 to 239)
Total chemotherapy cost in the first 2 months	528	401	127 (–35 to 288)
Total radiotherapy cost in the first 2 months	225	292	–68 (–318 to 183)
Total hospital admission costs in the first 2 months	450	464	–14 (–279 to 250)
Hospice admission in the first 2 months	0	0	0 (0 to 0)
Surgery between months 2 and 6	339	426	–87 (–449 to 275)
Total chemotherapy cost between months 2 and 6	493	574	–80 (–289 to 128)
Total radiotherapy cost between months 2 and 6	1082	884	198 (–249 to 645)
Total hospital admission costs between months 2 and 6	766	747	19 (–436 to 473)
Hospice admission between months 2 and 6	9[7]	0	9 (–9 to 28)

a One patient did not have surgical staging, but did have endosonography.
b Including laboratory costs.
c Including laboratory costs and additional costs from day 10.
d Including laboratory costs and additional costs from day 44.

TABLE 16 Total trial costs for patients who had complete information on all resource items

Randomisation group	Mean (SD) total cost (£)	Median (quartiles) total cost (£)
EUS/EBUS ($n=85$)	10,402 (3639)	10,887 (7279 to 12,384)
Surgical staging ($n=87$)	11,154 (3567)	11,130 (9633 to 12,801)

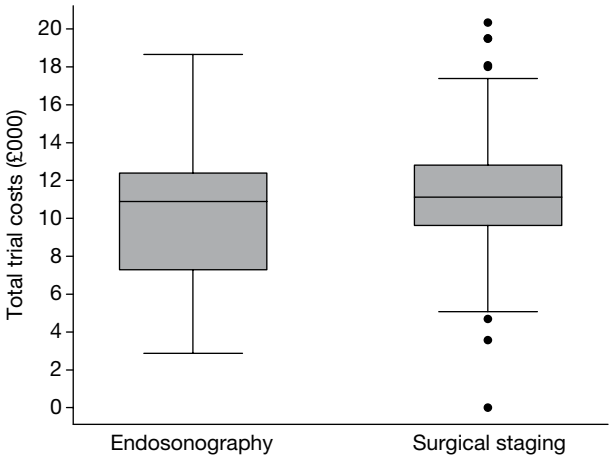


FIGURE 8 Box plot of total trial costs for patients who had complete information on all resource items: endosonography, $n = 85$; surgical staging, $n = 87$.

Cost–utility for completers (patients who have both complete costs and a quality-adjusted life-year estimate)

Both complete cost and QALY information was available for 58 out of 123 (47%) patients in the endosonography (followed by surgical staging if negative) group and 56 out of 118 (47%) in the surgical staging group.

Table 17 and *Figure 9* show summaries of total costs for these patients. *Figure 10* shows a box plot for the 6-month QALYs by group.

Endosonography (followed by surgical staging if negative) was cheaper overall than surgical staging (*Table 18*). However, the CI for the mean difference goes from it being cheaper by £2246 to being £394 more expensive. The difference in QALY between the groups is very close to zero. This would make any estimation of the incremental cost-effectiveness ratio (ICER) extremely unreliable.

Figure 11 shows 5000 bootstrapped estimates of the cost and QALY differences: 2917 out of 5000 (58%) points show that endosonography, followed by mediastinoscopy if negative, is dominant, i.e. less costly and more effective (bottom right-hand quadrant); 1687 out of 5000 (34%) points show that the endosonography strategy is less costly and less effective (bottom left-hand quadrant); 253 out of 5000 (5%) points show that the endosonography strategy is more costly and more effective (top right-hand quadrant); and 143 out of 5000 (3%) points show that the endosonography strategy is dominated, i.e. more costly and less effective (top left-hand quadrant).

The CEAC for endosonography followed by surgery if negative (*Figure 12*) crosses the *y*-axis at 0.92, meaning that 92% of the density involves cost savings. It is a decreasing function of the willingness to pay because not all of the joint density involves health gains, hence the CEAC asymptotes to a value of < 1. At a willingness to pay of £30,000, there is a 91% chance that endosonography strategy compared with surgical staging strategy is cost-effective. The corresponding probability of cost-effectiveness for a willingness to pay of £20,000 is 92%.

TABLE 17 Total trial costs for patients who had complete cost information and a QALY estimate

Randomisation group	Mean (SD) total trial cost (£)	Median (IQR) total trial cost (£)
EUS/EBUS ($n=58$)	10,808 (3787)	10,887 (7778 to 13,013)
Surgical staging ($n=56$)	11,735 (3477)	11,629 (9633 to 13,755)

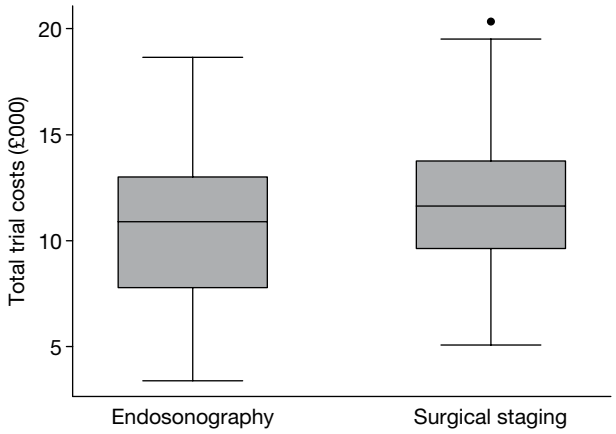


FIGURE 9 Total trial costs for patients who had both complete cost and QALY information: endosonography, $n=58$; surgical staging, $n=56$.

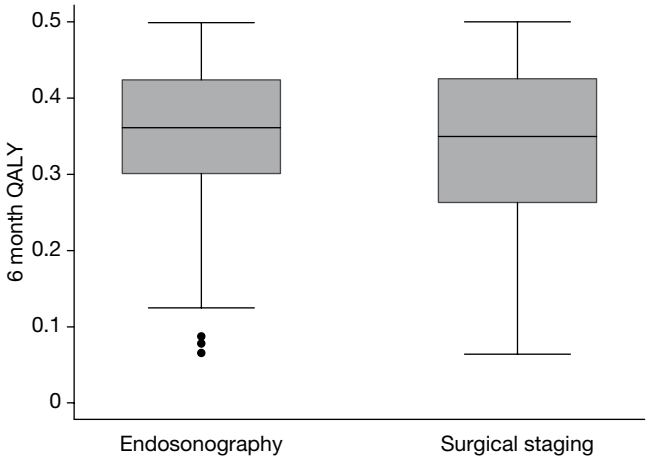


FIGURE 10 Six-month QALY for patients who had both complete cost and QALY information: endosonography, $n=58$; surgical staging, $n=56$.

Deterministic sensitivity analysis

The only a priori defined scenario analysis was used to compare surgical staging with endosonography alone, hence assuming that patients randomised to EUS/EBUS did not incur any surgical staging costs, but would be more likely to have a futile thoracotomy. In the case of patients who underwent EUS/EBUS and surgical staging but not thoracotomy, the mean thoracotomy cost was added to the total trial cost to reflect the fact that EUS/EBUS was negative in these patients and they would have then gone on to receive thoracotomy. The total mean (SD) and median (IQR) trial costs, assuming that the EUS/EBUS patients did not undergo surgical staging, are shown in *Table 19* and *Figure 13*.

TABLE 18 Cost-effectiveness summaries for patients for whom complete information on trial costs and QALYs is available (endosonography, $n = 58$; surgical staging, $n = 56$)

Parameter	Mean	Median	SD	95% CI for mean
Costs (£)				
Endosonography and surgical staging	10,808	10,887	3787	9843 to 11,764
Surgical staging	11,735	11,629	3477	10,843 to 12,674
Cost comparisons (£)				
Endosonography – surgical staging	–927		5141	–2246 to 394
QALY				
Endosonography and surgical staging	0.348	0.361	0.103	0.321 to 0.373
Surgical staging	0.342	0.350	0.100	0.316 to 0.367
QALY comparisons				
Endosonography – surgical staging	0.00652		0.143	–0.0298 to 0.0418
Cost per QALY gained				
Endosonography – surgical staging (from sample)	Dominance			
Bootstrapped mean ICER	Dominance			

a Bootstrapped estimates.

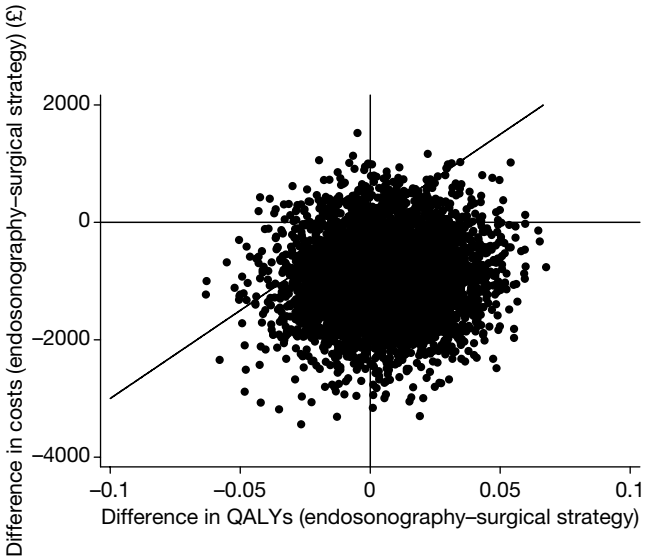


FIGURE 11 Five thousand bootstrapped samples from the joint distribution of the difference in costs (endosonography strategy – surgical staging) and the difference in QALYs. Positive values indicate that endosonography (followed by surgery if negative) costs more and has greater QALYs. The line shows an ICER of £30,000 per QALY.

The corresponding cost-effectiveness results (*Table 20*) show that in this scenario endosonography is £2413 cheaper than surgical staging, and there remains very little difference in mean QALY. Because of the very small QALY difference, the ICER cannot be estimated reliably and the analysis reduces to a cost comparison.

Figure 14 shows the bootstrapped estimates plotted on the cost-effectiveness plane and *Figure 15* shows the corresponding CEAC. In the cost-effectiveness plane (see *Figure 14*), 3170 out of 5000

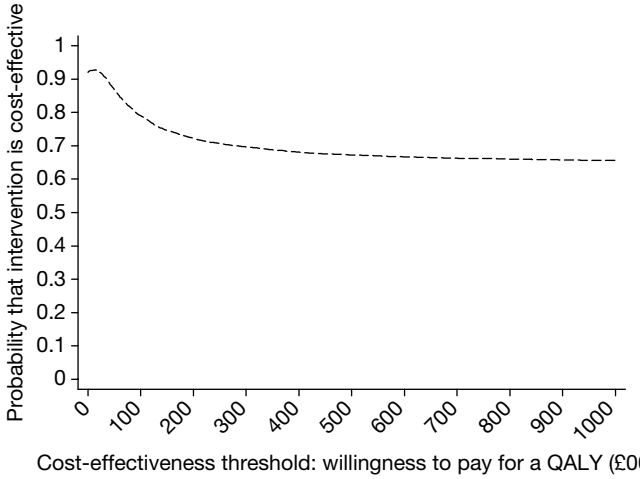


FIGURE 12 Cost-effectiveness acceptability curve for endosonography (with surgical staging if negative) relative to surgical staging alone, based on completers only (endosonography strategy, $n = 58$; surgical staging, $n = 56$).

TABLE 19 Total costs for the complete case analysis, ignoring the cost of surgical staging and increasing the futile thoracotomy rate for the EUS/EBUS group

Randomisation group	Mean (SD) total cost (£)	Median (IQR) total cost (£)
EUS/EBUS ($n = 85$)	8922 (2785)	7805 (7279 to 11,123)
Surgical staging ($n = 87$)	11,154 (3567)	11,130 (9633 to 12,801)

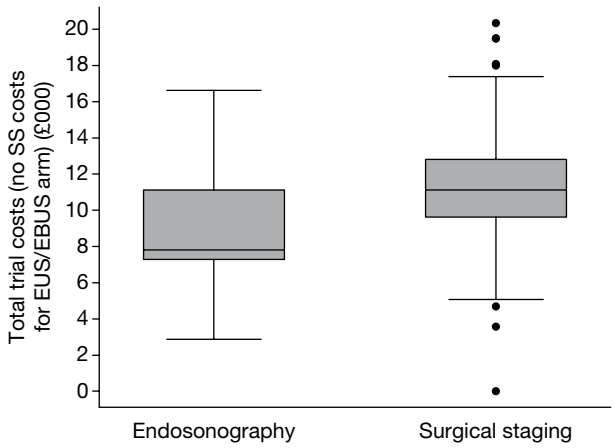


FIGURE 13 Total costs complete case analysis ignoring the costs of surgical staging and increasing the futile thoracotomy rate for the EUS/EBUS group.

(63%) of the bootstrapped samples show that endosonography alone is less costly and more effective than surgical staging (bottom right-hand quadrant); 1830 out of 5000 (37%) points show that endosonography is less costly and less effective (bottom left-hand quadrant); and 4999 out of 5000 (99.98%) points are below the £30,000 ICER line.

The CEAC (see *Figure 15*) crosses the *y*-axis at 1 with a willingness to pay per QALY of £0.00 showing that EUS/EBUS as the sole staging modality will result in cost savings with probability close to 100%.

TABLE 20 Cost-effectiveness summaries for people who have complete information on trial costs and QALY (endosonography, $n = 58$; surgical staging, $n = 56$), assuming that there are no surgical staging costs but increased futile thoracotomy rate for EUS/EBUS patients

Parameter	Mean	Median	SD	95% CI for mean
Costs (£)				
Endosonography alone ($n = 58$)	9322	7822	2958	8551 to 10,079
Surgical staging ($n = 56$)	11,735	11,629	3477	10,843 to 12,674
Cost comparisons (£)				
Endosonography – surgical staging	–2413		4565	–3605 to –1271
QALY				
Endosonography alone	0.348	0.361	0.103	0.321 to 0.373
Surgical staging	0.342	0.350	0.100	0.316 to 0.367
QALY comparisons				
Endosonography – surgical staging	0.00652		0.143	–0.0298 to 0.0418
Cost per QALY gained (£)				
Endosonography – surgical staging	Dominant			
Mean ICER from bootstrapping	50,688			

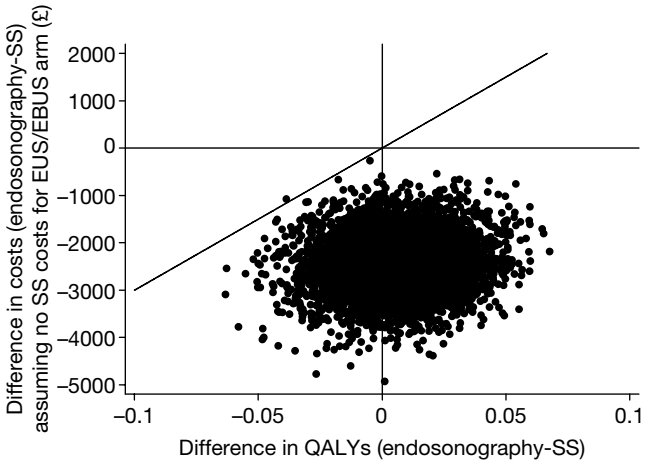


FIGURE 14 Five thousand bootstrapped samples from the joint distribution of the difference in costs and the difference in QALY, assuming no surgical staging costs but increased thoracotomy rate for EUS/EBUS patients. Positive values indicate that endosonography costs more and has greater QALYs. The line shows an ICER of £30,000 per QALY.

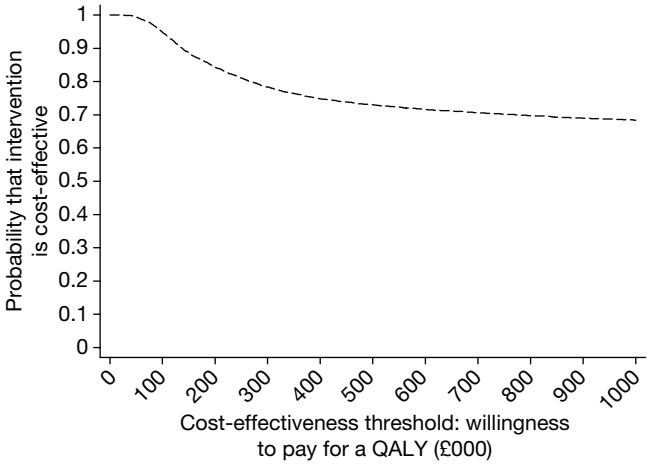


FIGURE 15 Cost-effectiveness acceptability curve for complete cases (endosonography, $n = 58$; surgical staging, $n = 56$) assuming no surgical staging costs, but increased futile thoracotomy rate for the EUS/EBUS group.

Comparison of resource use and cost-effectiveness between centres for patients with complete data

There were some differences between the centres in resource use (see *Appendix 3*). The two Belgian centres were the most different, in that Leuven had the highest percentage (77%) of EUS/EBUS randomised patients going on to have surgical staging, whereas Ghent had the lowest (42%). Leuven also had the highest percentage of EUS/EBUS patients (77%) undergoing thoracotomy compared with Ghent, which had the lowest (39%). The percentage of patients in the surgical staging group undergoing thoracotomy was similar in all centres. Radiotherapy in the first 2 months was used more often in LUMC and Ghent – no patients from Papworth, and only one patient from Leuven, underwent this treatment in the first 2 months. The percentage of patients who required hospital admission was much higher in Leuven (62% in EUS/EBUS and 60% in surgical staging) than in the other centres, where the rate was ≤ 20%. LUMC showed consistently lower rates of chemotherapy, both in the first 2 months and between 2 and 6 months, compared with the other centres. These differences represent the diversity of practice in tertiary centres and the number of patients in each randomisation group, in each centre, was too small to reliably estimate centre-specific results.

Full Bayesian economic analysis

Base-case analysis

Table 21 presents cost-effectiveness of the two strategies using the fully Bayesian model that combines information from all 241 patients, including those with complete data alongside those for whom some or all resource usage or health-related quality of life data were missing. The expected 6-month costs under both strategies were around £1000 less than those that were calculated using the 114 patients with complete data only. Again there was no significant difference in expected cost between the two strategies – the posterior mean expected cost under endosonography (followed by surgical staging if negative) was £746 less than under surgical staging alone, but the 95% credible interval (CrI) for the difference spanned zero. Similarly, expected QALYs were substantively the same between the two strategies, with only a very small increase for the endosonography arm, therefore an ICER for endosonography (followed by surgical staging if positive) would not be meaningful.

Figure 16 represents the uncertainty about the expected costs and effects as a posterior distribution on the cost-effectiveness plane. The associated CEAC for endosonography (followed by surgical staging if positive) is given in *Figure 17*. At any cost-effectiveness threshold, about 80% of the posterior distribution lies in a region where endosonography (followed by surgical staging if positive) is cost-effective, i.e. has a positive expected net benefit.

Results by centre are summarised in *Appendix 4* and are similar to those for the completers analysis.

Deterministic sensitivity analyses

The Bayesian model was adapted to assume that patients randomised to endosonography do not undergo surgical staging after negative tests, and that their chance of receiving a futile thoracotomy is slightly increased [by 6/123, i.e. in 6 out of the 123 patients randomised to endosonography (followed by surgical staging if positive) tests were negative but subsequent surgical staging revealed locally advanced disease]. The expected cost for endosonography alone is reduced from £9713 to £8335 (*Table 22*), significantly less than under surgical staging, for which the cost is unchanged. The QALY for either strategy is unchanged. The distribution of cost-effectiveness (*Figure 18*) under this assumption is shifted in favour of endosonography, so that the probability that endosonography is cost-effective (*Figure 19*) is about 90%.

Alternative Bayesian models were explored in further sensitivity analyses. Different sets of predictors (age, sex and cancer stage, as well as randomisation group and study centre) were used to infer the missing resource usage components from those with partially observed data. Under none of these alternatives did expected costs and QALYs differ significantly between randomisation groups or differ substantially from the base-case model.

Summary

In the exploratory analysis of resource use, the strategy of EUS–FNA and EBUS-TBNA (followed by surgical staging only if these tests were negative) resulted in fewer staging mediastinoscopies

TABLE 21 Cost-effectiveness summaries using a Bayesian model to combine all patients including those with incomplete QALYs or resource-use data (endosonography, $n = 123$; surgical staging, $n = 118$)

Parameter	Posterior mean	Posterior 95% CrI
Expected costs (£)		
Endosonography and surgical staging	9713	7209 to 13,307
Surgical staging	10,459	7732 to 13,890
Expected cost comparisons (£)		
Endosonography – surgical staging	–746	–2494 to 756
Expected QALY		
Endosonography and surgical staging	0.344	0.292 to 0.383
Surgical staging	0.329	0.274 to 0.371
Expected QALY comparisons		
Endosonography – surgical staging	0.015	–0.023 to 0.052

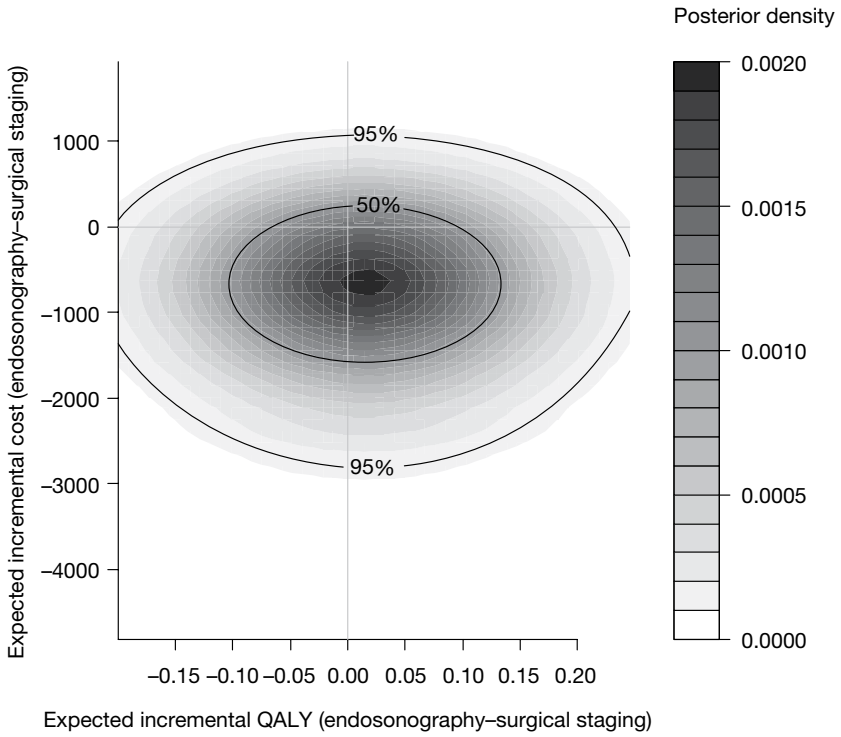


FIGURE 16 Posterior distribution of incremental cost and QALY under base-case full Bayesian model.

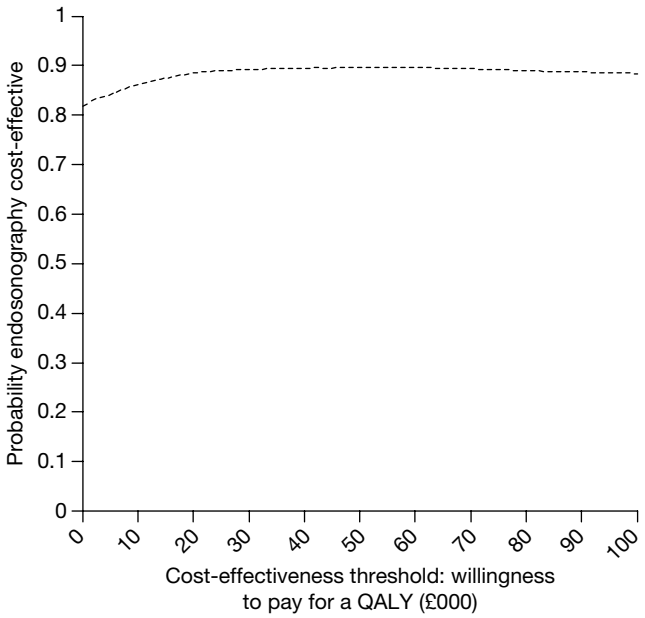


FIGURE 17 Cost-effectiveness acceptability curve under base-case full Bayesian model.

TABLE 22 Cost-effectiveness summaries under Bayesian model: sensitivity analysis assuming no surgical staging after negative endosonography

Parameter	Posterior mean	Posterior 95% CrI
Expected costs (£)		
Endosonography alone	8335	6270 to 11,343
Surgical staging	10,459	7732 to 13,890
Expected cost comparisons (£)		
Endosonography – surgical staging	–2124	–4560 to –167
Expected QALY		
Endosonography alone	0.344	0.292 to 0.383
Surgical staging	0.329	0.274 to 0.371
Expected QALY comparisons		
Endosonography – surgical staging	0.015	–0.023 to 0.052

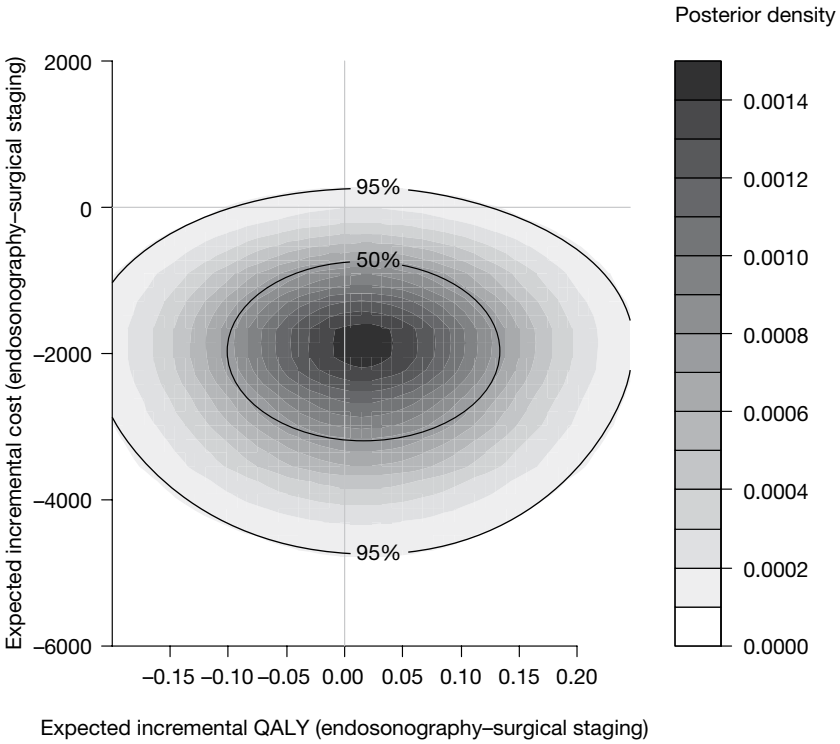


FIGURE 18 Posterior distribution of incremental cost and QALY under Bayesian model: sensitivity analysis assuming no surgical staging after negative endosonography.

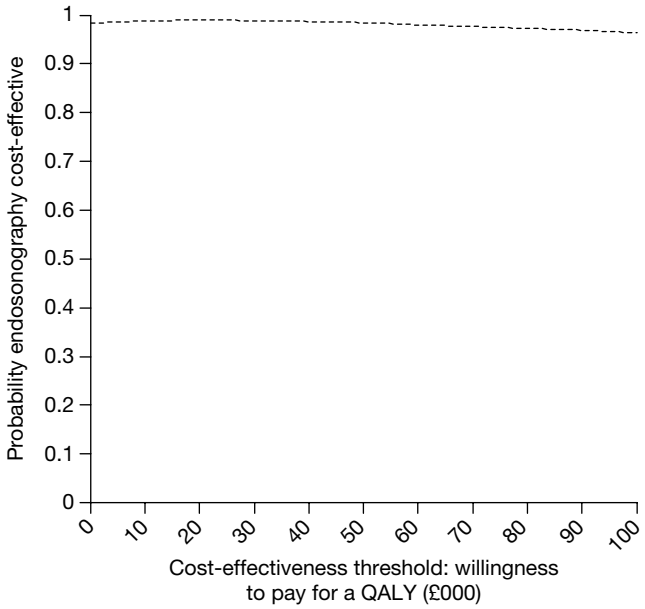


FIGURE 19 Cost-effectiveness acceptability curve under Bayesian model: sensitivity analysis assuming no surgical staging after negative endosonography.

(55% vs 99%) and fewer thoracotomies (53% vs 66%) than surgical staging alone, which must be weighed up against the number of EUS–FNA and EBUS-TBNA investigations required (100% vs 1%). In the full Bayesian analysis, which simultaneously estimates cost-effectiveness outcomes and missing data, the strategy of EUS–FNA and EBUS-TBNA (followed by surgical staging only if these tests were negative) cost £746 (95% CrI –£756 to £2494) less than surgical staging alone, with the diagnostic work-up and thoracotomy accounting for the majority of the difference. There was a small but non-significant gain in QALYs for endosonography followed by surgical staging if positive (0.015, 95% CrI –0.023 to 0.052). Thus, the endosonographic strategy is said to dominate (is cheaper and more effective), although there remains some uncertainty in the decision (CrIs cross zero and the probability that endosonography, followed by surgical staging if positive, is cost-effective of approximately 80%). A simple sensitivity analysis suggested that omitting the confirmatory surgical staging in the event of a negative EUS–FNA and EBUS-TBNA investigation might result in greater cost-effectiveness, but this is based on a number of uncertain assumptions.

Chapter 6

Discussion and recommendations

In this RCT, a strategy of using combined non-invasive endosonography (EUS–FNA and EBUS-TBNA), followed by surgical staging if these tests were negative, had higher sensitivity (94% vs 79%) and NPV (93% vs 86%), resulted in a lower rate of unnecessary thoracotomy (7% vs 18%) and better quality of life during staging (difference in utility 0.117), and was slightly more effective (difference in QALY 0.015) and less expensive (difference in costs £746) than the current practice of lung cancer staging using surgical methods 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 QALYs included zero. The CEACs, both for completers and in the full Bayesian analysis, suggested that endosonography (followed by surgical staging if positive) has a probability of at least 65% of being cost-effective, but there remains considerable uncertainty about the cost-effectiveness decision. 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.

Based on this study, initial endosonographic staging, followed by surgical staging in the event that endosonography is negative for malignancy, provides an accurate strategy for mediastinal staging. The estimate of sensitivity of 94% for the combined EUS–FNA and EBUS-TBNA procedure was higher than in many studies that used either test alone, with reported sensitivity ranging from 50% to 84% for EUS-FNA alone and from 46% to 94% for EBUS-TBNA, when used in practice.[33] Although we did not formally assess specificity in this study, the rate of unnecessary thoracotomy gives an indication of the false-negative rate and at 93% the false-negative rate was similar to specificities reported in the literature.[33] Similarly, the diagnostic accuracy of surgical staging observed in this study is consistent with published reports[2] giving support for the generalisability of our results.

Accurate staging of the lymph nodes is important, as subsequent patient management will depend on whether or not there has been metastatic spread of the disease. The most useful measurements of diagnostic accuracy are the sensitivity (true-positive rate) and the related NPV (disease-free rate in those with negative tests). In this study of staging strategies, as in other diagnostic studies in this area, not all patients underwent the gold standard assessment of nodal involvement, as it was considered unethical for patients to undergo thoracotomy if there was already evidence of metastatic disease. Thus, our results rely on the assumption that histology of cells from sampling of lymph nodes during these tests has a false-positive rate of zero. That is, we assume that if we see cancerous cells in the lymph nodes then metastasis has occurred. We consider this to be a realistic assumption in this context, as the diagnosis was made on the basis of histology and our validation study suggested that the staging from these samples was robust. The rate of N2/N3 involvement was higher in the endosonography group (54% vs 44%) but the difference was not significant ($p = 0.137$) and the randomised trial design suggests that any difference in the rate could have arisen by chance.

Although RCTs provide robust estimates of treatment effects, they are limited in the number of possible treatment pathways that can be included. In this study we chose to concentrate on the (pre-trial) current standard practice in our centres (mediastinal surgical staging) and a likely alternative pathway of combined EUS-FNA/EBUS-TBNA followed by surgical staging if endosonography was negative for malignancy. In addition to a cost-effectiveness analysis, this

design also allowed us to assess sensitivity of endosonography against a composite gold standard of surgical staging and thoracotomy. A potential alternative pathway that was analysed in the clinical study was to exclude the confirmatory surgical staging step following a negative-for-malignancy endosonography, and to proceed straight to thoracotomy. Using the trial data, we re-estimated the difference in costs in a deterministic sensitivity analysis based on this proposed pathway and found that EUS-FNA/EBUS-TBNA alone was significantly cheaper than surgical staging alone, although the effect on QALYs was difficult to assess without making further assumptions about utilities in patients who were treated by thoracotomy inappropriately. Based on the assumption that QALYs would not change relative to the trial strategies, endosonography alone was judged to be cost-effective with high probability. However, this analysis is speculative, based on untestable assumptions, and should be interpreted cautiously.

This is the first RCT of surgical staging versus endosonography (followed by surgical staging if positive) to be reported.[20] The recently published 2011 National Institute for Health and Clinical Excellence (NICE) guideline[33] for lung cancer diagnosis and treatment includes an economic model for a number of potential diagnostic pathways, with patients split into three groups according to the findings on CT imaging. However, the model was limited by the lack of empirical evidence on endosonography, as well as other competing modalities, and was largely based on expert judgement. Probabilistic sensitivity analysis was also not possible, with only point estimates presented. Despite this, the differences in costs and QALY between the surgical staging and endosonography strategies were consistent with this study, strengthening the external validity of our trial. The cost of endosonography used in the NICE guideline[33] was provided by the University Hospital in Leicester, and at £1365 for EBUS alone was slightly higher than our unit cost of £1237.

The diagnosis and staging of lung cancer is complicated, and there are other modalities that can provide information on diagnosis and stage. The 2011 NICE guideline[33] also provided cost-effectiveness estimates for PET–CT, non-ultrasound-guided TBNA and ultrasound of the neck, together with combination strategies and varying time order of the different tests.[33] The analysis found that PET–CT alone was the best strategy for patients with no enlarged nodes (short axis < 10 mm) on CT. PET–CT followed by conventional non-ultrasound-guided TBNA was most cost-effective for patients with more than one small-volume (short axis 10–20 mm) node(s) on CT, and for patients with any node of short axis > 20 mm the preferred strategy was neck ultrasound followed by non-ultrasound-guided TBNA, followed by PET–CT. It should be noted that these results were based on expert judgement and some strong methodological assumptions, without any probabilistic sensitivity analysis, so interpretation should be cautious. This is reflected in the fact that a degree of flexibility was incorporated into the management algorithms. For example, in the intermediate category (node short axis 10–20 mm) ultrasound-guided or non-ultrasound-guided TBNA was recommended to reflect the fact that ultrasound-guided tests have greater accuracy, yet are still well below the cost threshold.

In line with the findings of this study, the updated NICE lung cancer guidelines[33] state that mediastinal staging can begin with combined endobronchial and endoscopic ultrasound in place of surgical staging. However, in the event of a negative endosonographic examination, surgical staging is recommended if clinical suspicion of malignancy remains high.

This multicentre study was adequately powered for the clinical outcomes and carried out in a well-defined population, with few exclusions, and was based on intention-to-treat analysis, so that results should be generalisable to other lung cancer centres. However, it is noted that all the centres involved in this trial were able to perform combined EUS-FNA and EBUS-TBNA, and

all EUS and EBUS operators were highly experienced practitioners. Although EUS and EBUS are now available at many centres in the UK, there is only a handful of groups that can currently offer both techniques combined in the same session. For the most part, EBUS is performed by respiratory physicians in the UK and few are trained in EUS. In practice, this means that a combined EBUS and EUS may require two operators, a chest physician for EBUS and a gastroenterologist or radiologist for EUS. However, Annema *et al.*[14] have recently reported on an EUS implementation study in which respiratory physicians in several centres in the Netherlands underwent a structured training programme in EUS and were shown to achieve similar levels of diagnostic sensitivity and accuracy to the expert centre after 50 cases. A similar implementation strategy could be used in the UK. Recently, two groups have reported their initial experience of using the linear endobronchial ultrasound bronchoscope to perform EBUS and EUS in a single session.[34,35] Although this approach was not addressed in the current study, it offers a potential future strategy for the complete assessment of the mediastinum. Such an approach would potentially be less costly, as only an endobronchial ultrasound bronchoscope would be required and both procedures could be performed by a single operator. The estimated cost saving for endosonography would be of the order of £355 per case (no separate EUS, single operator, single needle and lower sterilisation costs), so that the cost difference between surgical staging and endosonography (followed by surgical staging if negative) would be £1101 per case (95% CrI –£401 to £2849). Further research is required to establish the diagnostic accuracy of this single-operator approach.

The multicentre, multinational nature of this trial did introduce some difficulties. Varying times of entry into the cost-effectiveness component of the study for the different centres meant that the EQ-5D questionnaire was not administered in the first half of the trial. Resource-use data collection was simple and covered only 6 months after randomisation, and the majority of the data could be retrieved retrospectively, but EQ-5D scores could not. Although the full Bayesian analysis allowed simultaneous estimation of missing data and cost-effectiveness outcomes, the results were estimated with less precision than expected. Nevertheless, the analysis based on patients for whom data were complete and the full Bayesian analysis gave similar point estimates.

Although there were only 20 deaths during the 6-month follow-up period, 144 patients contributed an EQ-5D utility curve from which to estimate mean QALYs. This number of patients, coupled with the measurement properties of the EQ-5D (continuous coverage over the measurement space, bounded, sensitivity to within- and between-patient changes), suggests that effectiveness results were robust and measured reasonably precisely. A further limitation of the EQ-5D is that it is a generic quality-of-life measure that is unlikely to illustrate changes in quality of life that are specific to the disease course. The addition of detailed quality-of-life studies would have been useful in understanding the impact that the diagnostic process and subsequent management had on patients, but was not considered feasible in the current multinational study. Furthermore, the EQ-5D utility was able to pick up small changes in quality of life occurring during the initial staging and management.

The cost-effectiveness study was trial based and restricted to the first 6 months after randomisation. Beyond this time we expect costs and effects to be determined by the course of the lung cancer and the success of the initial treatments, and these should not be affected to a large extent by the initial diagnostic strategy taken. This is supported by the utility curves in *Figure 6*, which are very similar beyond the initial period in which staging and thoracotomy is undertaken. Thus, we believe that a long-term economic model is not necessary, as it is unlikely to change the cost-effectiveness decision and it may require a complicated model, involving many assumptions.

Implications for practice

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. All the centres involved in this trial were able to perform combined EUS-FNA and EBUS-TBNA, and all EUS and EBUS operators were experienced practitioners. The number of centres in the UK where both EBUS and EUS can be performed in a single session is very low (probably 5–10). A structured training programme in EBUS and EUS could support chest physicians and thoracic surgeons who are involved in lung cancer staging in the UK.

Recommendations for 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. 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 the following:

1. Is mediastinoscopy following negative EBUS/EUS really needed? Further work is required before we can confidently recommend omitting confirmatory surgical staging in the event of negative endosonographic examination.
2. Can chest physicians 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. Does combined EBUS/EUS using a single EBUS scope provide 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.

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Contribution of authors

Linda D Sharples conceived and designed the cost-effectiveness study, contributed to trial monitoring in the UK, supervised the cost-effectiveness analysis and, jointly with RCR, produced the final report.

Chris Jackson designed and implemented the final Bayesian cost-effectiveness model, and drafted the sections of the report relating to this analysis.

Ella Wheaton conducted the initial exploratory analysis of the resource-use and quality-of-life data, and drafted the sections of the report relating to this analysis.

Gethin Griffith designed the resource-use data collection, provided appropriate unit costs and drafted the sections of the report relating to this analysis.

Jouke T Annema conceived and designed the clinical part of the study, took responsibility for trial conduct in Leiden, and analysed and reported on the clinical results.

Christophe Dooms took responsibility for trial conduct in Leuven, and analysed and reported on the clinical results.

Kurt G Tournoy conceived and designed the clinical part of the study, took responsibility for trial conduct in Ghent, and analysed and reported on the clinical results.

Ellen Deschepper conducted the statistical analysis, and contributed to the reporting of the clinical results.

Vikki Hughes contributed to the design of the cost-effectiveness study and managed the UK arm of the trial.

Lavinia Magee contributed to the design of the cost-effectiveness data collection and was responsible for data collection in the UK.

Martin Buxton conceived and designed the cost-effectiveness study, and supervised the costing study.

Robert C Rintoul contributed to the design of the cost-effectiveness study, took responsibility for trial conduct in Papworth, analysed and reported on the clinical results, contributed to the cost-effectiveness analysis and, jointly with LDS, produced the final report.

All authors contributed to the production and editing of the final report. Linda Sharples and Robert Rintoul contributed equally to the report.

Publication

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Appendix 1

Final protocol

Assessment of Surgical sTaging versus Endoscopic ultrasound in lung cancer: a Randomised controlled trial (ASTER)

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- Dr Linda Sharples: — Papworth Hospital, Cambridge, UK
- Date of Registration: — 8/2/2007 (http://clinicaltrials.gov/)
- Registration Nr: NCT00432640
- Protocol version 3.0 Dated 27th March 2008

1. Summary

Background:

Lung cancer is the second most common cause of cancer in the UK and has a very high mortality rate. Both treatment and prognosis depend upon stage at presentation. Mediastinal staging is a field that is rapidly developing. Staging by FDG-PET has dramatically reduced the rate of futile thoracotomies. EUS-FNA and EBUS-TBNA are two complementary ultrasound-guided biopsy techniques which together allow access to almost all mediastinal lymph nodes (LN): for EUS-FNA: 4L, 7, 8L/R, 9L/R and for EBUS-TBNA: 2R/L, 4R/L, 7. This means that the combination of both techniques allows a comprehensive (bilateral N2 and N3) mediastinal examination (with the exception of the para-aortic stations 5 and 6). Non-randomised case series have indicated the potential of EUS-FNA and EBUS-TBNA for mediastinal staging. However, these techniques have not been validated against the current 'gold standard' of care which is surgical staging in a prospective randomised controlled fashion.

Hypothesis:

The null hypothesis is that there is no difference between sensitivity, diagnostic accuracy and negative predictive value of endobronchial with endoscopic ultrasound-guided biopsy of lymph nodes and surgical staging.

Patients:

Patients with (suspected) NSCLC who are judged to be candidates for surgical resection but in whom malignant N2/N3 lymph node involvement is suspected based on clinical staging (including chest X-ray, CT thorax, FDG-PET or integrated FDG-PET/CT) are eligible for this study. A cytological or histological diagnosis of lung cancer is not required at the time of randomisation. Patients with proven distant metastases (M1) are excluded from this study.

Study design:

A prospective randomised controlled multi-centre double arm diagnostic phase III trial in which patients are randomly assigned to either surgical staging (arm B) or echo-endoscopic staging with both EUS-FNA and EBUS-TBNA (arm A). EUS-FNA and EBUS-TBNA are performed

in one session. Surgical staging is defined as cervical mediastinoscopy, anterior (parasternal) mediastinotomy, thoracoscopic mediastinal exploration or any combination.

EUS-FNA/EBUS-TBNA will be considered positive if one or both of the diagnostic procedures yield tissue proof of mediastinal metastases (N2/N3).

In arm A (study arm), if no N2 or N3 lymph node metastases are found by either EUS-FNA or EBUS-TBNA patients will subsequently be offered a confirmatory surgical staging procedure prior to proceeding to a thoracotomy with systematic lymph node dissection.

Objectives:

- Primary objective:
  - The primary research objective of the study is to determine whether EBUS-TBNA combined with EUS-FNA is better than standard surgical staging techniques in terms of sensitivity, diagnostic accuracy and negative predictive value for diagnosing and staging the mediastinum in lung cancer.
- Secondary objectives are:
  - Determination of the sensitivity and accuracy of EBUS and EUS compared with surgical staging for determining mediastinal tumour invasion (T4).
  - A comparative cost analysis of the diagnostic strategies of the two trial arms.
  - Assessment of the complication rates in each arm
  - An estimation of the saving of surgical staging procedures that might be possible in the future if EBUS-TBNA/EUS-FNA is shown to have greater sensitivity and diagnostic accuracy and becomes the new 'gold standard' staging procedure.
  - Estimation of how many futile thoracotomies can be avoided by performing EBUS-TBNA and EUS-FNA rather than surgical staging procedures.
  - Assessment of inter-observer variability of cytopathological evaluation of EBUS-TBNA and EUS-FNA samples.

Statistical analysis:

In the sample size calculation the following assumptions were made:

- The prevalence of mediastinal nodal disease in patients with lung cancer is 70%. The sensitivity of mediastinoscopy to detect mediastinal nodal involvement is 70%. The sensitivity of EUS-FNA and EBUS-TBNA for detection of mediastinal nodal involvement is 90%.
- Using standard calculation techniques, the sample size required is (2×71 in each arm) with a power of $1\text{-}\beta = 0.8$, type 1 error $\alpha = 0.05$ and two sided testing. Assuming 5% incomplete CRFs and assuming that only 70% of patients will have mediastinal disease the total sample size becomes 214 patients.

2. Introduction

2.1 Background

Lung cancer is the second most common cancer in England and Wales and is the most common cause of cancer death. Non small cell lung cancer (NSCLC) accounts for 80% of all cases. The overall five-year survival is approximately 10%[1]. Treatment of lung cancer is influenced by stage. Accurate staging is therefore important in order to optimise treatment regimens. The incorporation of positron emission tomography (PET) into staging algorithms has considerably reduced the number of futile thoracotomies[2]. PET/CT is more accurate than computerised tomography (CT) in detecting mediastinal lymph node metastases, with a negative predictive value of 93–95%. However, a positive predictive value of 74–90% makes pathological

verification of mediastinal hotspots necessary in order to avoid patients being denied possible curative surgery[3–5].

The current standard of care requires surgical staging of enlarged and/or FDG-PET/CT avid mediastinal lymph nodes by a surgical staging procedure such as mediastinoscopy, mediastinotomy or thoracoscopic mediastinal exploration[6]. However, these techniques are invasive and require general anaesthesia and hospitalisation. In addition, the accuracy of these procedures is variable and ranges between 80–90%[6;7]. Although the specificity is 100%, the sensitivity is lower and ranges between 66%[8] and 75–90%[6]. The accuracy of mediastinoscopy to stage lung cancer is therefore mainly determined by the high specificity while there is room to improve the sensitivity and the negative predictive value.

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and more recently endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) are two minimally invasive diagnostic techniques that allow real-time controlled punctures of mediastinal lymph nodes[8–16]. These techniques are performed in an outpatient setting under conscious sedation. Non-randomised trials in selected patient populations have suggested that these techniques can obviate the need for surgical staging procedures in up to 70% of the cases[9;17]. EUS-FNA and EBUS-TBNA are complementary techniques with EUS allowing access to mediastinal lymph node groups 4L, 7, 8L/R, 9L/R and EBUS giving access to mediastinal lymph node stations 2R/L, 4R/L, 7,[18;13]. This means that the combination of both techniques enables a complete (bilateral) mediastinal examination. With EBUS-TBNA hilar and intrapulmonary nodal stations 10R/L, 11R/L can also be assessed. In addition, in selected cases echoendoscopy offers the possibility to assess whether a tumour is invading the mediastinum (T4)[8]. In previous studies we have reported the value of adding EUS-FNA to mediastinoscopy regarding mediastinal staging[8] and the impact of EUS-FNA on the prevention of surgical staging[9;12].

Data regarding combined echo-endoscopic staging (EUS-FNA combined with EBUS-TBNA) compared with surgical staging for evaluation of mediastinal lymph nodes are currently not available.

2.2 Rationale for this study

Current international guidelines for the staging of NSCLC advocate staging by mediastinoscopy when locally advanced disease is suspected[6;19;7;20]. Locally advanced disease is defined as either N2 or N3 or T4. Mediastinoscopy has limitations in its diagnostic reach to access some mediastinal nodes, is expensive and requires an in-patient stay. Recent reports suggest that complete accurate loco-regional staging can be assessed by the combination of EUS-FNA and EBUS-TBNA in an ambulatory setting. (Villman ref 18, Wallace, World EUS/DDW 2006). If this holds true, improved, less invasive and more cost-effective care can be provided for this large group of patients.

3. Study Objectives

3.1 Primary objectives

The primary research objective of the study is to determine whether EBUS-TBNA combined with EUS-FNA is better than standard surgical staging techniques in terms of sensitivity, diagnostic accuracy and negative predictive value for diagnosing and staging the mediastinum in lung cancer.

The null hypothesis is that there is no difference between sensitivity, diagnostic accuracy and negative predictive value of EBUS-TBNA combined with EUS-FNA and surgical staging.

3.2 Secondary objectives

- Determination of the sensitivity and accuracy of EBUS and EUS compared with surgical staging for determining mediastinal tumour invasion (T4).
- A comparative cost analysis of the diagnostic strategies of the two trial arms.
- Assessment of the complication rates in each arm.
- An estimation of the saving of surgical staging procedures that might be possible in the future if EBUS-TBNA/EUS-FNA is shown to have greater sensitivity and diagnostic accuracy and becomes the new 'gold standard' staging procedure.
- Estimation of how many futile thoracotomies can be avoided by performing EBUS-TBNA and EUS-FNA rather than surgical staging procedures.
- Assessment of inter-observer variability of cytopathological evaluation of EBUS-TBNA and EUS-FNA samples.

4. Study Plan and Procedures

4.1 Overall study design

This is a prospective international multi-centre open randomised controlled phase III study.

4.2 Clinical work-up (CWU)

Patients are evaluated by history, physical examination, full blood count, renal and liver function tests, chest X-ray, bronchoscopy, CT of the chest and upper abdomen and whole body FDG-PET or integrated whole body FDG-PET/CT. If clinical suspicion exists, a brain scan (CT or MRI) or a bone scan can be performed.

4.3 Randomisation

Recruitment and randomisation will occur when clinical work-up identifies a patient with (suspected) lung cancer in whom further loco-regional staging is indicated. Randomisation will be performed in a 1:1 ratio. Randomisation will occur using a web based program and will be stratified for each participating institution.

4.4 Detailed study design: flow chart

4.5 Inclusion criteria

Consecutive patients with known or suspected NSCLC and in whom mediastinal lymph node involvement (either N2 or N3) is suspected based on the available thoracic imaging (CT or CT-PET).

Pending the results of mediastinal staging the patient must be considered to be a candidate for surgical resection with an intention to cure.

The patient is clinically fit for bronchoscopy, endoscopy and diagnostic surgical procedures.

There is no evidence of distant metastatic disease after routine clinical work up.

The patient is able to give informed consent.

4.6 Exclusion criteria

- Previous treatment (chemotherapy or radiotherapy or surgery) for lung cancer
- Any clinical reason why it is thought that the patient is unable to undergo or has a contra-indication to a bronchoscopy, endoscopy, a surgical staging procedure or who is not suitable for definitive surgical resection by thoracotomy.
- Patients who, based on available thoracic imaging, are unlikely to be staged accurately by any surgical staging procedure (mediastinoscopy/-otomy, VATS).
- A Concurrent malignancy.

- An uncorrected coagulopathy.
- Inability to give informed consent.
- Patients who are eligible for this study but who are not included (no informed consent obtained, logistical reasons) will be recorded with the reason why study participation did not occur.

4.7 EUS-FNA and EBUS-TBNA (Arm A)

Systematic evaluation of all mediastinal lymph node stations will be undertaken by either EUS-FNA or EBUS-TBNA. Aspirates will be taken of nodes suspected for malignant involvement. It is not in the scope of this study to compare EUS-FNA and EBUS-TBNA, and thus, it is not necessary to double evaluate those lymph node stations that can be reached by either endoscope (for example LN 7). It is also not in the scope of this study to evaluate the additional value of EBUS-TBNA after EUS-FNA precluding split-echoendoscopy sessions. For reasons of convenience and patient-comfort EUS-FNA will be performed before EBUS-TBNA.

EUS-FNA is performed in a fasting patient as described[21]. Pharyngeal anaesthesia and intravenous conscious sedation will be administered according to local practice. If necessary, prophylaxis for endocarditis will be given according to local institutional practice. If the patient takes oral anticoagulation (warfarin and derivatives or clopidogrel), then this medication should be stopped before the procedure, and proof of normalisation of coagulation tests should be available pre-procedure. It is not necessary to stop aspirin or NSAID before this procedure, unless the investigator feels that this is necessary. During the procedure monitoring of pulse rate and oxygen saturation will be performed. EUS will be performed with a linear scanning ultrasound endoscope with Doppler flow imaging for the detection of blood vessels. The EUS endoscope will be introduced into the distal oesophagus, and the investigator will evaluate the mediastinal lymph nodes by scanning 360° transaxially at 1- to 2-cm intervals upwards up to level 2 lymph nodes.

Lymph nodes will be assessed using ultrasonographic criteria for malignancy (short axis diameter, echo-texture, shape, margins, vascular pattern) and suspicious nodes will be biopsied using a 22-guage needle (Echotip®, Wilson-Cook Medical Inc.; Hancke–Vilmann, Winston-Salem, NC or EUS needle, Olympus). Lymph node selection is at the discretion of the operator – it is not within the scope of this study to puncture all lymph nodes. In each patient, lymph nodes suspected of harbouring N3 disease will be sampled first. The presence or absence of direct mediastinal tumour invasion (T4) will also be recorded. If rapid on-site cytopathological evaluation is available it will be utilised although it is not essential within the study. If ROSE is not available suspicious lymph nodes will be sampled a minimum of four times. The number of biopsies per node will be recorded. If necessary, several lymph nodes can be sampled. Samples will be categorised as positive (tumour cells present), negative (lymphocytes present but no tumour cells), or inconclusive (poor cellularity, or unable to perform adequate biopsy).

EBUS will be performed immediately following EUS. EBUS will be performed with a linear scanning ultrasound bronchoscope (BF-UC160F-OL8, Olympus Ltd) connected to a processor unit (Olympus EU C2000) with Doppler flow imaging for the detection of blood vessels. The bronchoscope will be introduced via the mouth with the patient lying supine and the operator standing behind the patient. Blood vessels will be confirmed using the Doppler mode. Lymph nodes will be evaluated by scanning transaxially at 1- to 2-cm intervals from the peripheral regions of interest (lymph node stations 10–11) upwards to station 2. Lymph nodes will be assessed using ultrasonographic criteria for malignancy (short axis diameter, echo-texture, shape, margins, vascular pattern) and suspicious nodes will be biopsied using a 22-guage needle (EBUS needle NA-201SX-4022, Olympus, Ltd) with a 10-mL syringe for suction. The presence or absence of mediastinal invasion of the primary tumours (T4 or not) will be assessed.

In the event of a patient who is randomised to the test arm being unable to tolerate EBUS/EUS then they will be offered a surgical staging procedure under general anaesthesia. This is in keeping with standard clinical practice. Data will be interpreted on an 'intention to treat' basis for those patients who are randomised.

The mediastinal lymph node map of the American Joint Committee on Cancer will be used to localise abnormalities at CT, FDG-PET or integrated FDG-PET/CT, EUS-FNA, EBUS-TBNA and for mediastinal dissection[22].

4.8 Surgical intervention procedures (Arm B)

These include cervical mediastinoscopy, left anterior mediastinotomy or thoracoscopic mediastinal exploration. Surgeons will perform these procedures according to their local institutional practice. However, for cervical mediastinoscopy, the standard of practice requires a systematic sampling of the following lymph node stations: 2R/L, 4R/L and 7[6].

In the event of mediastinal lymph node evaluation in the EBUS-TBNA/EUS-FNA arm being negative, the patient will proceed to a confirmatory surgical staging procedure prior to a thoracotomy with surgical resection.

At thoracotomy with intra-operative staging, the IASLC guidelines will be followed[23]. This means that a 'systematic lymph node dissection' will be performed for each patient who progresses to a thoracotomy (lobectomy or pneumonectomy). Systematic lymph node dissection is the technique of choice for accurate intraoperative mediastinal staging[24]. It is not mandatory that all mediastinal tissue is removed during intra-operative staging[23].

The following LN stations should be considered:

- Right upper lobe: 2R, 4R and 7
- Right middle lobe: 2R, 4R and 7
- Right lower lobe: 4R, 7, 8 and 9
- Left upper lobe: 4, 5, 6 and 7
- Left lower lobe: 7, 8 and 9.

4.9 Assessment of lymph node cytology

Lymph node biopsies will be collected and processed by the pathology department according to local protocols. Papanicolau and Giemsa stains will be performed. If sufficient cellular material is available a cell block will be made aiming to complete the cytological analysis of the tumour cells by immunocytochemistry (IHC). The outcome of the cytological analysis will be the presence or absence of malignant cells. The presence of lymphocytes will be regarded as proof of a representative lymph node puncture. A sample of fine needle aspirates obtained by EUS-FNA and EBUS-TBNA will be evaluated by an independent reference cytopathologist in order to assess inter-observer variability. However, the findings of the initial cytopathologist will be used for patient management and the primary analysis. In the event of any dubiety on the part of the pathologist reporting a lymph node biopsy specimen a confirmatory surgical staging procedure or thoracotomy will be undertaken to ensure that the patient is not in any way disadvantaged by a possible false positive result.

4.10 Safety measures and variables

Continuous clinical monitoring and oxygen saturation monitoring during EUS-FNA and EBUS-TBNA procedures will be performed. For all other procedures, routine safety precautions according to local institutional practice will be followed. Any complications of either the EUS-FNA and EBUS-TBNA procedures as well as the surgical procedures will be recorded.

5. Data Collection and Management

Data collection will be performed in all participating centres. Electronic patient record forms (CRF forms) will be provided in ACCESS. Patient demographics will be recorded. Further recording includes randomisation arm (0 = ARM A and 1 = ARM B) and randomisation date. All imaging techniques will be recorded (X-ray chest, CT-scan Thorax, CT-scan abdomen, bone scan, FDG-PET/CT scan, brain scan; 0 = not done, 1 = performed). Following intrathoracic lymph node staging either by EUS-FNA/EBUS-TBNA or surgical staging or both, a cTNM will be noted. Of highest importance, a pTNM will be recorded following each thoracotomy.

Specific EUS/EBUS variables will be recorded. For each lymph node station the presence (1) or absence (0) of enlarged lymph nodes and whether the LN was punctured (0 = no, 1 = yes), the ultrasonographic characteristics of each LN, the presence of complications (0 = no, 1 = yes).

Data collection and analysis will be monitored according to good clinical practice. Clinical monitoring will be organised in a cross-over fashion where CRF files will undergo a quality check. Members of each centre will assess some of the files of each other centre. An independent data monitoring and ethics committee and a trial steering group will meet regularly to review the progress of the study and to evaluate the implications of any adverse clinical incidents.

6. Health Economics

A cost-utility analysis from a health service perspective will be undertaken up to 6 months post-randomisation. Resource use and cost data to be collected prospectively during the study will include resource use associated with the staging and surgical procedures; inpatient length of stay; any adverse events requiring hospital re-admission; and any concomitant oncology treatment (radiotherapy/chemotherapy) that the patients may receive. The outcome measure of interest in the economic evaluation is quality-adjusted survival, measured by QALYs (Quality-adjusted life-years). In order to calculate QALYs, patient utilities will be derived from the EQ-5D questionnaire and combined with patient-specific survival. The EQ-5D questionnaire will be administered to patients at the following points: a) baseline (at time of randomisation); b) immediately post-staging (EUS/EBUS for group A or surgical staging for group B); c) 2 months post-randomisation; and d) 6-months post-randomisation. The 6-month total mean costs and QALYs will be combined in order to calculate the ICER (incremental cost-effectiveness ratio).

7. Statistical Methods

7.1 Sample size and outcomes

In the sample size calculation the following assumptions were made:

- The prevalence of mediastinal nodal disease in patients with lung cancer is 70%. The sensitivity of mediastinoscopy to detect mediastinal nodal involvement is 70%. The sensitivity of EUS and EBUS for detection of mediastinal nodal involvement is 90%.
- Therefore, using standard calculation techniques, the sample size required is (2 x 71 in each arm) with a power of $1-\beta = 0.8$, type 1 error $\alpha = 0.05$ and two sided testing. Assuming 5% incomplete CRFs and assuming that only 70% of patients will have mediastinal disease the total sample size becomes 214 patients.
- For the purposes of statistical analysis, a case of mediastinal disease is defined as a patient with tumour in lymph nodes detected by any of the following: EBUS, EUS, surgical staging techniques or histology following thoracotomy. Thus the 'gold standard' definition is based on a series of tests. Since this definition does not allow for false positive test results, both the specificity and the positive predictive value are necessarily one. Therefore, analysis will focus on the estimation of sensitivity (probability of a positive test in those who have mediastinal disease) and the negative predictive value (probability of no mediastinal disease in those with a negative test). The negative predictive value does depend upon the prevalence of

mediastinal disease and as discussed above the *a priori* rate of 70% has been assumed for the study population. Formal comparison of the sensitivities will be performed using Fisher's Exact test.

8. Publication and Authorship

Investigators who significantly contribute to the conduct, analysis and publication of the study will be eligible to be a co-author. The study will be registered in the international RCT trial registry.

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Appendix 2

Resource-use collection pro forma

ASTER

Case report form (CRF) – Health Economics

PART 1: IDENTIFIERS (so that this CRF data can be tied up with main CRF)

1. Patient initials __ (first letter first name) __ __ (first two letters surname)

2. Date of birth (DD–MM–YYYY)

3. Sex: ❍ M ❍ F

4. Study centre:
   - ❍ LUMC
   - ❍ Ghent
   - ❍ Papworth
   - ❍ Leuven
5. Study number (e.g. LUMC 001, etc.)

6. Randomisation group:
   i. ❍ A (endoscopic ultrasound)
   ii. ❍ B (surgical staging)

PART 2: ADMISSION/DISCHARGE DATES (please complete relevant sections)

What date was the patient admitted for the EUS/EBUS procedure?
(DD–MM–YYYY)

What date was patient discharged following EUS/EBUS procedure?
(DD–MM–YYYY)

Date of admission for surgical staging procedure
(DD–MM–YYYY)

Date of discharge following surgical staging procedure
(DD–MM–YYYY)

Date of admission for thoracotomy?
(DD–MM–YYYY)

Date of discharge following thoracotomy
(DD–MM–YYYY)

PART 3: HEALTH RESOURCE DATA

1. Did the patient complete the EQ-5D questionnaire at baseline?
   ❍ yes, ❍ no

2. If yes, date of completion
   (DD–MM–YYYY)

3. Did the patient complete the EQ-5D questionnaire after:
   EBUS/EUS procedure for patients in arm A
   Surgical staging procedure for patients in arm B
   ❍ yes, ❍ no

4. If yes, date of completion
   (DD–MM–YYYY)

5. Did the patient complete the EQ-5D questionnaire at 2 months post-randomisation?
   ❍ yes, ❍ no

6. If yes, date of completion
   (DD–MM–YYYY)

7. Did the patient complete the EQ-5D questionnaire at 6 months post-randomisation?
   ❍ yes, ❍ no

8. If yes, date of completion
   (DD–MM–YYYY)

PART 4: 2 MONTHS POST RANDOMISATION (AT CLINIC OR VIA TELEPHONE/POST)

1. Has the patient undergone surgical resection in the last 2 months?
   ❍ yes, ❍ no

2. Has the patient undergone chemotherapy treatment in the last 2 months?
   ❍ yes, ❍ no

3. If yes, how many cycles? (circle) 1 2 3 4

4. Has the patient undergone any radiotherapy treatment in the last 2 months?
   ❍ yes, ❍ no

5. If yes, was it:
   ❍ radical
   ❍ palliative

6. If yes, how many fractions did the patient receive? ____

7. Has the patient been admitted to hospital in the last 2 months for any reason OTHER than for a trial procedure?
   ❍ yes, ❍ no

8. If yes, what was their length of stay in hospital? ___ days

9. Has the patient been admitted to a hospice in the last 2 months?
   ❍ yes, ❍ no

10. If yes, what was their length of stay in the hospice? ___ days

PART 5: 6 MONTHS POST RANDOMISATION (AT CLINIC OR VIA TELEPHONE/POST)

1. Has the patient undergone surgery in the last 4 months (i.e. since last questionnaire)?
   ❍ yes, ❍ no

2. Has the patient undergone chemotherapy treatment in the last 4 months (ie since last questionnaire)?
   ❍ yes, ❍ no

3. If yes, how many cycles? (circle) 1 2 3 4

4. Has the patient undergone any radiotherapy treatment in the last 4 months (since last questionnaire)?
   ❍ yes, ❍ no

5. If yes, was it:
   ❍ radical
   ❍ palliative

6. If yes, how many fractions did the patient receive? ___

7. Has the patient been admitted to hospital in the last 4 months OTHER than for a trial procedure?
   ❍ yes, ❍ no

8. If yes, what was their length of stay in hospital? ___ days

9. Has the patient been admitted to a hospice in the last 4 months?
   ❍ yes, ❍ no

10. If yes, what was their length of stay in the hospice? ___ days

PART 6

DATE OF DEATH (IF APPLICABLE) DD–MM–YYYY

Appendix 3

Quality of life and resource use by centre

European Quality of Life-5 Dimensions analysis by centre

Table 23 shows the mean (SD) EQ-5D utility by centre and *Figure 20* shows the mean (95% CI) EQ-5D utility by centre.

Table 24 shows the differences between the endosonography (followed by surgical staging if positive) and surgical staging groups, by centre, both unadjusted and adjusted for baseline. *Figure 21* shows adjusted differences. At the end of staging, only Leuven showed a statistically significant difference between the groups, favouring the endosonography strategy ($p = 0.009$) in the unadjusted and adjusted analyses. Ghent showed a borderline statistically significant difference in the unadjusted analyses, favouring surgical staging, but when adjusted for baseline this was no longer true. LUMC showed a borderline statistically significant difference between the groups at end of staging, favouring EUS/EBUS. At no other stages in either analysis were statistically significant differences seen.

TABLE 23 Mean (SD) EQ-5D by centre

Centre, time point	EUS/EBUS	Surgical staging
LUMC (n = 22 and n = 19)		
Baseline	0.83 (0.13)	0.82 (0.15)
End of staging	0.80 (0.26)	0.65 (0.32)
2 months	0.73 (0.25)	0.69 (0.27)
6 months	0.77 (0.27)	0.66 (0.30)
Ghent (n = 21 and n = 17)		
Baseline	0.80 (0.21)	0.90 (0.09)
End of staging	0.74 (0.26)	0.87 (0.10)
2 months	0.60 (0.32)	0.72 (0.25)
6 months	0.62 (0.35)	0.75 (0.34)
Papworth (n = 14 and n = 14)		
Baseline	0.83 (0.11)	0.78 (0.12)
End of staging	0.77 (0.09)	0.71 (0.14)
2 months	0.68 (0.14)	0.61 (0.22)
6 months	0.66 (0.14)	0.58 (0.27)
Leuven (n = 16 and n = 21)		
Baseline	0.78 (0.24)	0.80 (0.16)
End of staging	0.78 (0.26)	0.49 (0.35)
2 months	0.56 (0.30)	0.57 (0.29)
6 months	0.66 (0.37)	0.69 (0.31)

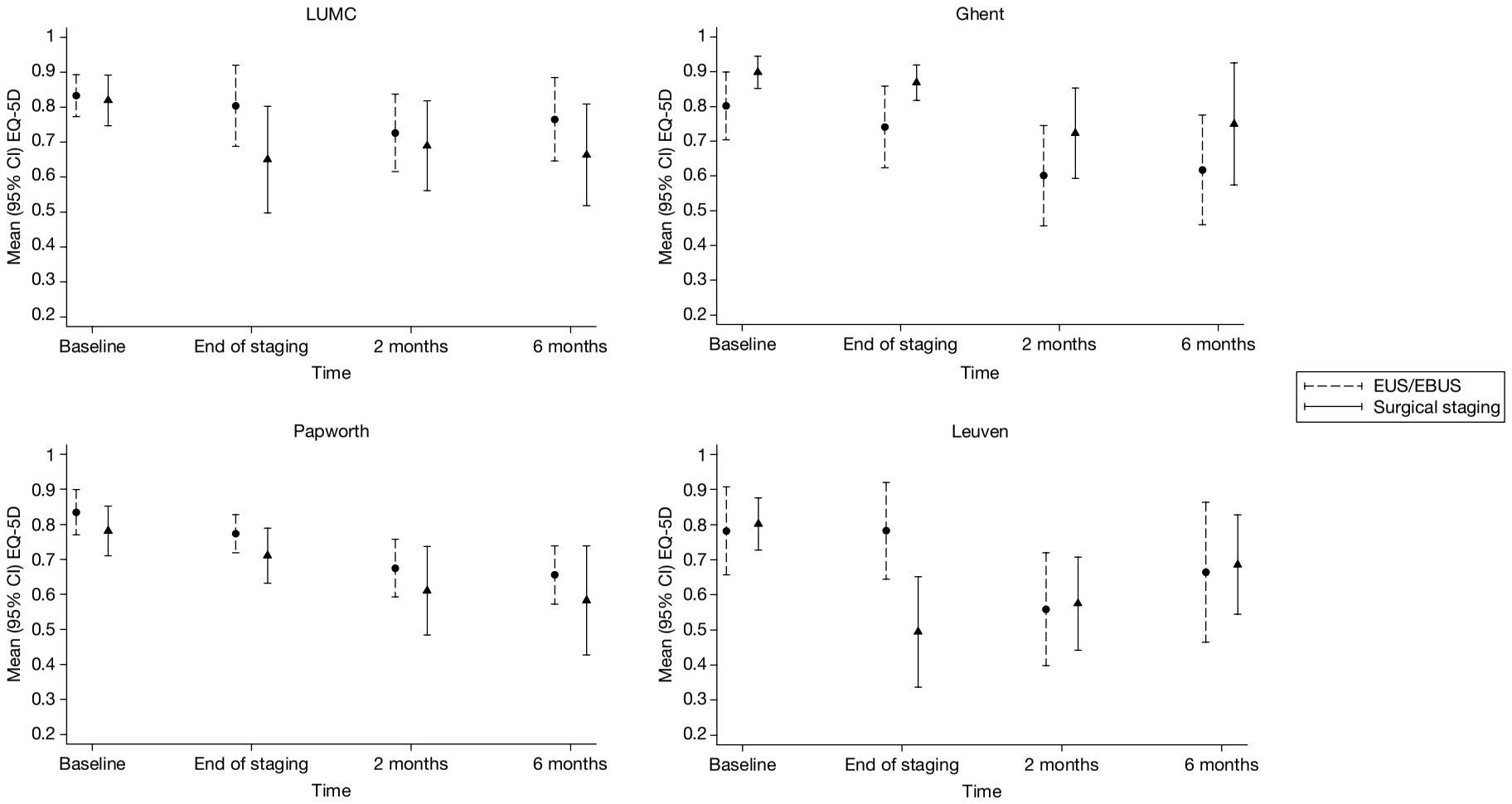

FIGURE 20 Mean (95% CI) EQ-5D by centre.

TABLE 24 Mean difference (95% CI) between endosonography (followed by surgical staging if positive) and surgical staging groups in EQ-5D by centre

	LUMC		Ghent		Papworth		Leuven	
Analysis, time point	**Difference (95% CI)**	***p*-value**	**Difference (95% CI)**	***p*-value**	**Difference (95% CI)**	***p*-value**	**Difference (95% CI)**	***p*-value**
Unadjusted								
End of staging	0.154 (–0.029 to 0.336)	0.10	–0.128 (–0.262 to 0.007)	0.06	0.063 (–0.028 to 0.154)	0.17	0.288 (0.078 to 0.498)	0.009
2 months	0.037 (–0.127 to 0.200)	0.65	–0.122 (–0.314 to 0.070)	0.21	0.065 (–0.079 to 0.208)	0.36	–0.016 (–0.216 to 0.184)	0.87
6 months	0.102 (–0.078 to 0.282)	0.26	–0.132 (–0.360 to 0.096)	0.25	0.072 (–0.096 to 0.241)	0.38	–0.022 (–0.250 to 0.207)	0.85
Adjusted for baseline								
End of staging	0.138 (–0.017 to 0.294)	0.08	–0.043 (–0.140 to 0.053)	0.37	0.035 (–0.047 to 0.117)	0.39	0.299 (0.099 to 0.499)	0.005
2 months	0.027 (–0.126 to 0.181)	0.72	–0.053 (–0.237 to 0.131)	0.56	0.048 (–0.010 to 0.196)	0.51	–0.012 (–0.214 to 0.189)	0.90
6 months	0.095 (–0.082 to 0.271)	0.28	–0.076 (–0.307 to 0.155)	0.51	0.030 (–0.130 to 0.190)	0.70	–0.021 (–0.254 to 0.211)	0.85

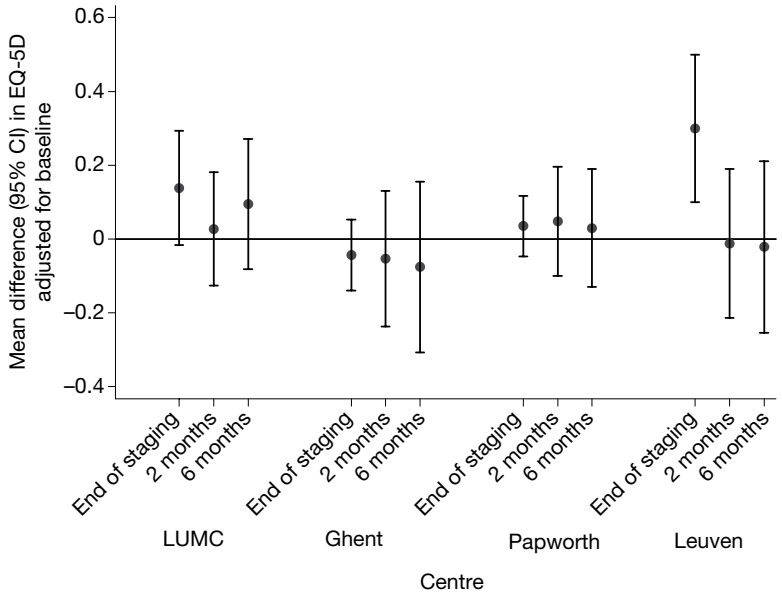

FIGURE 21 Difference in mean EQ-5D (95% CI) between endosonography (followed by surgical staging if negative) and surgical staging groups, by centre, adjusted for baseline. Values >0 favour the endosonography strategy.

Quality-adjusted life-year results by centre

Table 25 and *Figure 22* show the average 6-month QALYs by centre. The biggest difference between groups was seen in Ghent, where the average QALY value was 0.07 higher in the surgical staging group than in the EUS/EBUS group. However, once adjusted for baseline this difference reduced to 0.03. *Table 25* also shows the mean (95% CI) difference in QALYs adjusted for baseline. There were small differences between the groups; no difference was statistically significant.

TABLE 25 Six-month QALY by centre

Centre	EUS/EBUS	Surgical staging	Difference adjusting for baseline EQ-5D (EUS/EBUS – surgical staging)
LUMC ($n=22$, $n=19$)	0.38 (0.12)	0.34 (0.12)	0.034 (–0.036 to 0.10)
Ghent ($n=21$, $n=17$)	0.31 (0.13)	0.38 (0.11)	–0.030 (–0.10 to 0.043)
Papworth ($n=14$, $n=14$)	0.34 (0.06)	0.30 (0.10)	0.021 (–0.043 to 0.085)
Leuven ($n=16$, $n=21$)	0.31 (0.14)	0.29 (0.13)	0.015 (–0.076 to 0.11)

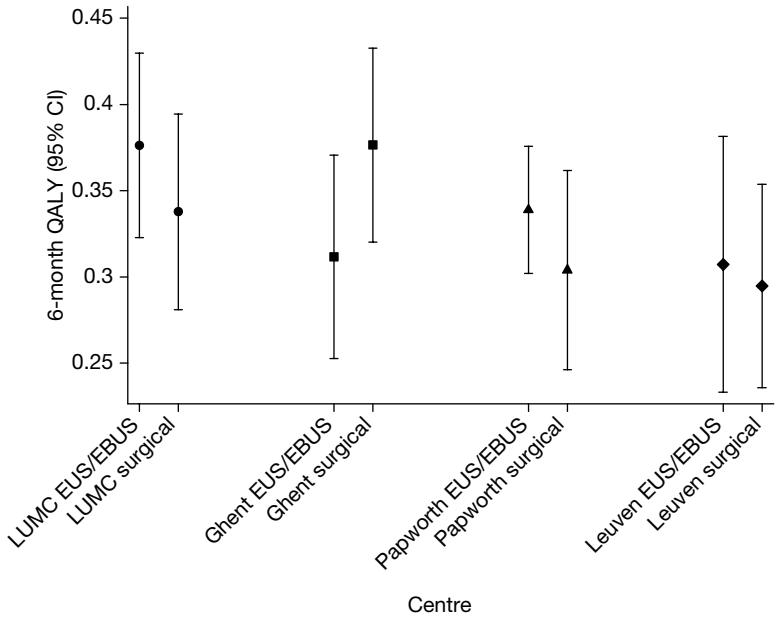

FIGURE 22 Six-month QALY by centre (unadjusted for baseline utility).

Resource-use analysis by centre for patients who had complete information on each resource item

Table 26 shows resource use by centre.

TABLE 26 Resource use by centre (for patients who had complete information on all resource items: $n = 85$, $n = 87$

	No. of people using each resource item (%)							
	LUMC		Ghent		Papworth		Leuven	
Resource item	EUS/EBUS ($n = 30$)	Surgical staging ($n = 29$)	EUS/EBUS ($n = 31$)	Surgical staging ($n = 28$)	EUS/EBUS ($n = 11$)	Surgical staging ($n = 10$)	EUS/EBUS ($n = 13$)	Surgical staging ($n = 20$)
EUS/EBUS procedure	30 (100)	0 (0)	32 (101)	1 (4)	11 (100)	0 (0)	13 (100)	0 (0)
Surgical staging procedure	19 (63)	28 (97)	13 (42)	28 (100)	5 (45)	10 (100)	10 (77)	20 (100)
Thoracotomy (lobectomy or pneumonectomy) with lymph node dissection	17 (57)	18 (62)	12 (39)	17 (61)	6 (55)	7 (70)	10 (77)	15 (75)
Chemotherapy in the first 2 months	13 (43)	9 (31)	19 (61)	14 (50)	4 (36)	5 (50)	7 (54)	11 (55)
Radiotherapy in the first 2 months	5 (17)	4 (14)	5 (16)	4 (14)	0 (0)	0 (0)	0 (0)	1 (5)
Hospital admission in the first 2 months	2 (7)	2 (7)	6 (19)	3 (11)	2 (18)	2 (20)	8 (62)	12 (60)
Hospice admission in the first 2 months	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Surgery between months 2 and 6	4 (13)	3 (10)	4 (13)	3 (10)	1 (9)	1 (10)	2 (15)	2 (10)
Chemotherapy between months 2 and 6	10 (33)	9 (31)	17 (55)	16 (57)	6 (55)	6 (60)	7 (54)	12 (60)
Radiotherapy between months 2 and 6	6 (20)	10 (34)	18 (58)	12 (43)	6 (55)	3 (30)	2 (15)	2 (10)
Hospital admission between months 2 and 6	5 (17)	6 (21)	9 (29)	4 (14)	5 (45)	2 (20)	9 (69)	13 (65)
Hospice admission between months 2 and 6	0 (0)	0 (0)	0 (0)	0 (0)	1 (9)	0 (0)	0 (0)	0 (0)

Total trial costs by centre, for patients who had complete information on each resource item

The total mean (SD) and median (IQR) trial costs by centre are presented in *Table 27* and *Figure 23*.

TABLE 27 Total trial costs by centre for people who had complete information on all resource items

	EUS/EBUS ($n=85$)			Surgical staging ($n=87$)		
Centre	***n***	**Mean (SD) cost (£)**	**Median (IQR) total cost (£)**	***n***	**Mean (SD) cost (£)**	**Median (IQR) total cost (£)**
LUMC	30	9762 (3488)	10,887 (7279 to 10,887)	29	10,213 (3422)	9882 (9633 to 12,322)
Ghent	31	9609 (2931)	8897 (6833 to 10,887)	28	11,064 (3609)	10,427 (8661 to 12,758)
Papworth	11	10,461 (4498)	12,011 (5652 to 15,009)	10	10,848 (3388)	11,380 (7480 to 12,035)
Leuven	13	13,723 (3217)	11,123 (10,887 to 17,135)	20	12,797 (3484)	12,291 (9633 to 15,632)

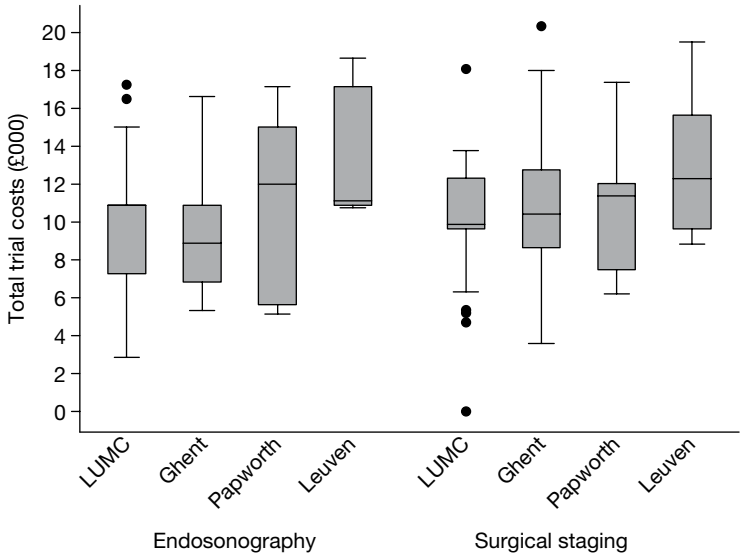

FIGURE 23 Box plots by centre of the total trial costs for patients who had complete information on all resource items.

Total trial costs by centre for patients who had complete information on each resource item, assuming that there are no surgical staging costs for the EUS/EBUS group

Table 28 and *Figure 24* show the total mean (SD) and median (IQR) trial costs by centre for completers, ignoring the cost of surgical staging for the EUS/EBUS group.

TABLE 28 Total trial costs by centre for completers, ignoring the cost of surgical staging and increasing the futile thoracotomy rate for the EUS/EBUS group

	EUS/EBUS			Surgical staging		
Centre	*n*	Mean (SD) cost (£)	Median (IQR) total cost (£)	*n*	Mean (SD) cost (£)	Median (IQR) total cost (£)
LUMC	30	8247 (2673)	7805 (7279 to 9423)	29	10,213 (3422)	9882 (9633 to 12,322)
Ghent	31	8527 (2277)	7805 (6833 to 9302)	28	11,064 (3609)	10,427 (8661 to 12,758)
Papworth	11	9060 (3184)	9647 (5652 to 11,927)	10	10,848 (3388)	11,380 (7480 to 12,035)
Leuven	13	11,301 (2817)	11,123 (7805 to 14,053)	20	12,797 (3484)	12,291 (9633 to 15,632)

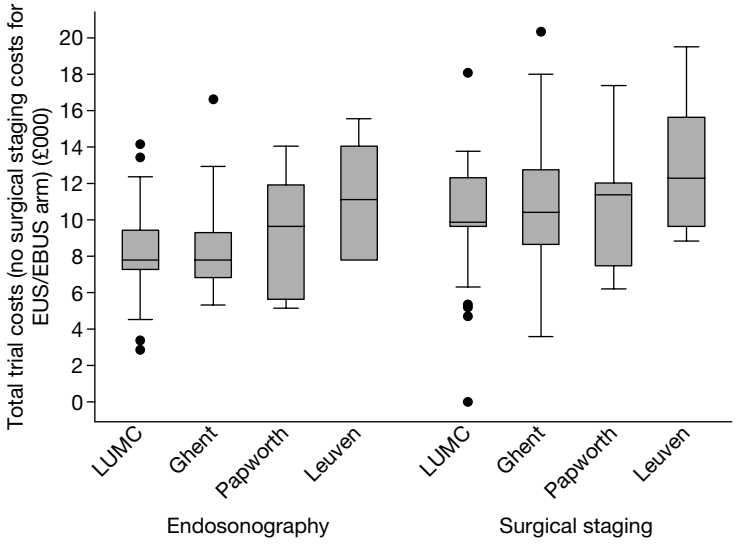

FIGURE 24 Box plots by centre of the total trial costs for completers, ignoring the costs of surgical staging and increasing the futile thoracotomy rate for the EUS/EBUS group.

Appendix 4

Full Bayesian analysis by centre

The Bayesian model was also used to estimate expected costs and QALYs by centre (*Table 29*). Expected 6-month costs under either strategy are estimated to be around £2000–3000 higher in Leuven (the highest) than in Ghent (the lowest). In Ghent, the endosonography strategy is expected to be about £1100 cheaper than surgical staging alone, whereas in Leuven it is around £200 cheaper than surgical staging. Expected QALYs over 6 months (which are adjusted for baseline EQ-5D) differ between centres by about 0.03. All CrIs for the difference between the two diagnostic strategies span zero reflecting the lack of precision when considering each centre individually.

TABLE 29 Cost-effectiveness summaries using base-case full Bayesian model, by centre

	Endosonography and surgical staging		Surgical staging		Incremental (endosonography – surgical staging)	
Centre	Posterior mean	Posterior 95% CrI	Posterior mean	Posterior 95% CrI	Posterior mean	Posterior 95% CrI
Expected costs (£)						
LUMC	9401	7494 to 11,652	10,023	7711 to 12,737	–621	–2136 to 740
Ghent	8694	6845 to 10,872	9818	7455 to 12,590	–1125	–2884 to 365
Papworth	10,651	8268 to 13,334	11,368	8674 to 14,387	–718	–2506 to 759
Leuven	11,748	9433 to 14,424	11,983	9433 to 14,937	–235	–1679 to 995
Expected QALYs						
LUMC	0.357	0.32 to 0.387	0.344	0.304 to 0.375	0.013	–0.02 to 0.046
Ghent	0.346	0.306 to 0.381	0.331	0.282 to 0.371	0.015	–0.022 to 0.052
Papworth	0.333	0.284 to 0.375	0.317	0.263 to 0.362	0.016	–0.024 to 0.056
Leuven	0.322	0.274 to 0.365	0.305	0.257 to 0.347	0.017	–0.027 to 0.058

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We look forward to hearing from you.

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