Results from the ASTER randomised controlled trial

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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Executive summary

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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.

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Publication

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