Cost effectiveness of endosonography versus surgical staging in potentially resectable lung cancer: a health economics analysis of the ASTER trial from a European perspective:

ONLINE SUPPLEMENT.

Robert C Rintoul FRCP PhD[1], Matthew J Glover MSc[2], Christopher Jackson PhD[3], Victoria Hughes PhD[1], Kurt G Tournoy MD PhD[4,5], Christophe Dooms MD[6], Jouke T Annema MD PhD[7,8], Linda D Sharples PhD[1,3]

1 Department of Thoracic Oncology, Papworth Hospital, Cambridge, UK

2 Health Economics Research Group, Brunel University, Middlesex, UK

3 MRC Biostatistics Unit, Institute of Public Health, Cambridge , UK

4 Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

5 Department of Respiratory Medicine, Onze-Lieve-Vrouwziekenhuis, Aalst, Belgium

6 Department of Respiratory Medicine, University of Leuven, Leuven, Belgium

7 Department of Pulmonology, Leiden University Medical Centre, Leiden, The Netherlands

8 Department of Pulmonology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

BACKGROUND

Accurate staging of the mediastinum in patients with lung cancer allows optimal identification of those best treated by surgical resection. Historically, mediastinal staging has been undertaken surgically by means of cervical mediastinoscopy, anterior mediastinotomy or video-assisted thoracoscopic surgery. In recent years a number of non-randomised prospective studies using endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) have reported sensitivity of around 90% for diagnosis of hilar and/or mediastinal lymph nodes. In 2009, two meta-analyses reported pooled sensitivity for EBUS-TBNA of 88% and 93% respectively.[1,2] Sensitivity of endoscopic ultrasound (EUS) for mediastinal staging varies between 50% and 87%.[3-6] In 2010 we reported a multi-centre randomised controlled study comparing surgical staging with combined endobronchial and endoscopic ultrasonography for staging of the mediastinum in lung cancer - the ASTER study.[7] Among patients with (suspected) non-small cell lung cancer (NSCLC), a staging strategy combining endosonography and surgical staging when compared with surgical staging alone resulted in greater sensitivity for mediastinal nodal metastases and fewer unnecessary thoracotomies. Data on patient reported quality of life and resource use were also collected. Preliminary cost-effectiveness results using economic methods predominant in the UK has been reported and showed that the endosonography strategy was cheaper and patients had better quality of life during staging.[8] However, health economic methodology varies substantially between different countries and the multi-national nature of the trials allows us to assess consistency of results in three European countries. Here we report survival, quality of life and resource use during the trial together with trial based, and country-specific cost effectiveness analyses.

METHODS

Methods for the ASTER clinical study have been published in full.[7,8] ASTER was a prospective, international, multi-centre randomised controlled trial carried out at Ghent University Hospital, Belgium; Leuven University Hospitals, Belgium; Leiden University Medical Centre, The Netherlands and Papworth Hospital, UK between February 2007 and April 2009. In brief, patients with confirmed or suspected NSCLC who required mediastinal staging based on CT and PET-CT were randomly assigned in a 1:1 ratio to either surgical staging alone or to combined endoscopic and endobronchial ultrasound followed by surgical staging (if no nodal metastases were found at endosonography). The primary endpoint was sensitivity, negative predictive value and accuracy of the endosonography strategy versus surgical staging alone for staging of the mediastinum. Secondary endpoints were the number of unnecessary thoracotomies and complications in each arm. The ASTER health economic study was designed to compare survival, quality of life and cost-effectiveness of the two diagnostic strategies over 6 months after randomisation.

Quality of Life

Quality of life was measured using the EuroQoL EQ-5D at baseline, end of staging (before thoracotomy) and at 2 and 6 months after randomisation.[9] The EQ-5D questionnaire consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D was completed for all patients recruited at Papworth and for patients recruited after April 2008 in the Dutch and Belgian centres, until the end of study follow up in October 2009. English, French, Dutch or Flemish language versions of the EuroQoL were used as appropriate.

The EQ-5D responses were transformed to utility values for each patient using standard methods [10]. Utilities were scaled so that full health = 1 and death = 0. For patients who died the EQ-5D utility was assigned a value of zero at the date of death and thereafter. In order to estimate EQ-5D utility values over time after randomisation of each patient, linear interpolation between the

recorded EQ-5D utility values was used. Quality-adjusted life-years (QALYs) were calculated as the area under the utility curve for each patient up to 6 months after randomisation.

Cost effectiveness analysis

Costs were estimated from a health care payer viewpoint using resource use from all patients in the study. The full breakdown of costs associated with each component of resource use is given in table A1 below. An NHS and personal social services perspective was adopted for the UK and a health service provider and patient co-payment perspective was used for the Netherlands and Belgium. For resource use a study specific data collection form was designed and this was completed prospectively after April 2008 and retrospectively from patient medical records for patients recruited before April 2008.

Individual patient resource use was collected during the trial for EBUS/EUS, surgical staging, thoracotomy, surgery other than planned thoracotomy, chemotherapy, radiotherapy, hospital and hospice stays. This information was multiplied by unit costs to estimate the total direct healthcare costs associated with the endosonography strategy and with surgical staging to derive mean costs per patient. Costing methods depended on nationally available cost data and locally recommended guidelines for costing in health technology assessments (HTAs).

United Kingdom

For standard treatments and procedures NHS Reference Costs (2008-09) [11] were used, as reported in the published cost effectiveness analysis of the ASTER results in a UK context [8] inflated to 2011 prices using Personal Social Services Research Unit indices.[12] An additional cost per excess bed day was applied to individual patient-level data (IPD) on length of stay to reflect particularly long hospital stays. Chemotherapy costs and radiotherapy costs were applied to IPD for treatment per cycle and per fraction respectively. Hospice admission costs were applied per day to IPD. For

combined EBUS-TBNA and EUS-FNA there were no available NHS reference costs so they were estimated by Papworth Hospital finance department.

Belgium

Belgian unit costs for EBUS and EUS procedures were acquired from the finance department at Ghent University Hospital. For other items of resource use, tariff costs were acquired from the National Institute for Health and Disability Insurance (RIZIV).[13] Relevant procedure tariffs were acquired for surgical staging, thoracotomy and major thoracic surgery and these were provided as a total which excluded the cost of hospital stay. Therefore, when calculating the expected cost for each of these procedures, we added on the IPD length of stay from the ASTER trial multiplied by the *per diem* overnight tariff cost for an acute bed stay. The cost of associated consultations, drug resource use and diagnostic imaging were added to these procedure costs using lump sum tariffs as reimbursed by RIZIV. Radiotherapy costs were based on the RIZIV flat fee for a complex set of external beam therapy and chemotherapy costs were estimated per cycle, for a regimen of Gemcitabine and Cisplatin, as recommended by the European Medicines agency.[14] The cost of hospice admission was estimated from data published by KCE and inflated to 2011 prices.[15]

The Netherlands

Dutch unit costs for EUS and EBUS procedures were acquired from the finance department of Leiden University Medical Centre. Other surgical intervention tariff costs were acquired from the Dutch Healthcare Authority (NZa),[16] making use of DBC information on procedure costs.[17] Chemotherapy costs were taken from a published source investigating the costs of first line treatment of NSCLC in a Dutch context and applied to relevant ASTER trial IPD data per cycle.[18] Radiotherapy unit costs were acquired from NZa reimbursement data per fraction of treatment and applied to IPD. The cost of hospice care per day was taken from a Dutch publication of reference costs for economic evaluations and applied to IPD.[19]

Table A1 Unit costs compared between the Netherlands, Belgium and the UK in Euros (with UK costs adjusted to an average of the 2010 purchasing power parity in Netherlands and Belgium).

Resource	Netherlands (mean)	Belgium (mean)	UK (mean and quartiles)
EUS/EBUS procedure	1537	659	1647
Surgical staging procedure and associated hospital stay	3958	356 (add 400 per day in hospital)	4070 (3143, 4864) (add 438 (289, 565) for each day in hospital over 10 days)
Thoracotomy (lobectomy or pneumonectomy) with lymph node dissection	5515	1413 (add 400 per day in hospital)	8690 (7880, 9193) (add 423 (290, 610) for each day in hospital over 10 days)
Deliver simple Parenteral Chemotherapy	1233	550	362 (131, 312) for first attendance and 302 (161, 314) for subsequent cycles
Radical or palliative radiotherapy	376 for first fraction and 153 for	1938 for a course of radiothera	365 (164, 553) for first fraction and 149 (91, 182) for

	subsequent fractions	py	subsequent fractions
Hospital admission	4986 (add 484 per day in hospital after 32 days)	170 (add 400 per day in hospital)	2831 (2055, 3296) (add 298 (224, 341) per day in hospital after 32 days)
Hospice admission per day	252	447	531 (449, 541)
Other thoracic surgery	6306	659 (add 400 per day in hospital)	5487 (4258, 6229)
Laboratory costs following EUS/EBUS procedure	59	104	35 (9, 48)
Laboratory costs following Surgical Staging procedure or thoracotomy	59	142	23 (12, 29)

Statistical and economic analysis

Survival rates were estimated using the Kaplan-Meier product limit method and compared using the log-rank test. Mean utilities at each time point for patients with complete data were estimated from multivariate linear models including baseline measurement, country and treatment as independent variables. The proportion of patients who had each component of resource use in each country was compared using the Pearson's chi-squared test with continuity correction. Bayesian parametric modelling [20] was used to estimate expected costs and expected QALY over 6 months from randomisation under each diagnostic strategy using the software package WinBUGS.[21] This includes information from patients with partially-observed resource usage and QALY data, as well as patients with complete data. The methods are unbiased under the assumption that the missing data are 'missing at random'; in other words, whether 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' since only patients recruited at later time points had quality of life data collected. Since the number of patients with complete data was different for each resource use component, we fitted separate parametric models for each component adjusting for randomisation group, centre and stage.[22] The resulting posterior distributions of expected resource use were combined with the unit cost of each component to provide the overall posterior distribution of expected cost. In the models for QALY we adjusted for randomisation group, centre and baseline EQ5D. The distribution of costs for the UK was assumed to follow a Gamma distribution, the parameters of which were estimated from the mean and quartiles in table A1. Since there were only point estimates of the Belgian and Dutch unit cost and no interval estimates (i.e.no measure of how much between-centre variation there is within these countries), we assume Gamma distributions and that the coefficient of variation (standard deviation (SD)/ mean) is the same between countries. Technical details of the models have been published previously.[8]

RESULTS

Two hundred and forty one patients were randomised, 118 (49%) to surgical staging and 123 (51%) to endosonography. By country, 81 were recruited in The Netherlands (Leiden), 132 in Belgium (88 Ghent; 44 Leuven) and 28 from the UK (Cambridge). The mean age of patients was 64.5 years (SD 8.9).

Clinical results

Full clinical results have been published previously and are summarised here in brief.[7,8] In the intention to treat analysis, sensitivity for detecting mediastinal nodal metastases was 79% (41/52, 95% CI:66-88) for surgical staging alone and 94% (62/66, 95% CI:85-98) for the endosonography arm (p=0.02). The corresponding negative predictive values (NPV) were 86% (95% CI: 76-92) and 93% (95% CI: 84-97) respectively (p=0.26). There were 21/118 (18%) unnecessary thoracotomies in the surgical staging arm compared to 9/123 (7%) in the endosonography arm (p=0.02). The complication rate was 7/118 (6%) in the surgical arm versus 6/123 (5%) in the endosonography arm (p=0.78).

Survival

Patients were followed up for survival for 6 months after staging during which time there were 20 deaths, 9 in the endosonography group and 11 in the surgical staging group. Kaplan-Meier estimates show no difference in survival rates over the 6 month period (log-rank test p=0.57) [Figure A1].

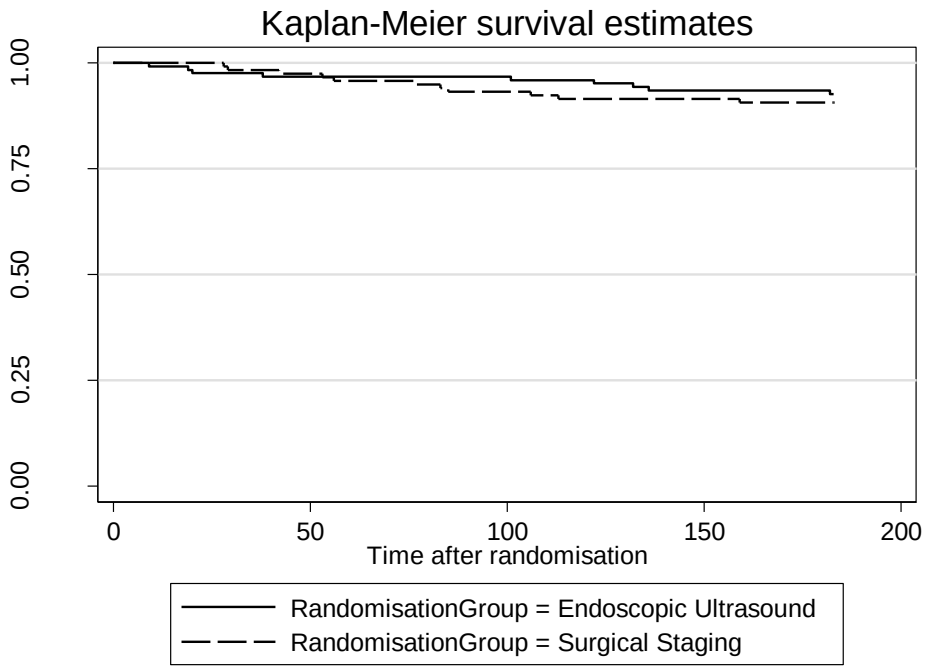

Figure A1 Kaplan-Meier survival estimates for time (in days) to death.

EuroQoL EQ-5D

Of the 241 patients, the 144 (60%) who were randomised after April 2008 completed the EQ-5D questionnaire at baseline. At the end of staging and at 2 months and 6 months, 139 (97%), 132 (92%) and 124 (86%) patients completed the questionnaires. Of 539 (144+139+132+124) completed questionnaires, only 6 (1.1%) had one or more of the EQ-5D dimension missing. When the 5 dimensions of the EQ-5D were converted to the quality of life utility scale (recall 0 for death and 1 for maximum health status) the mean difference between the groups in EQ-5D utility (95% confidence intervals) at each stage was summarised in figure A2 for patients with complete data.

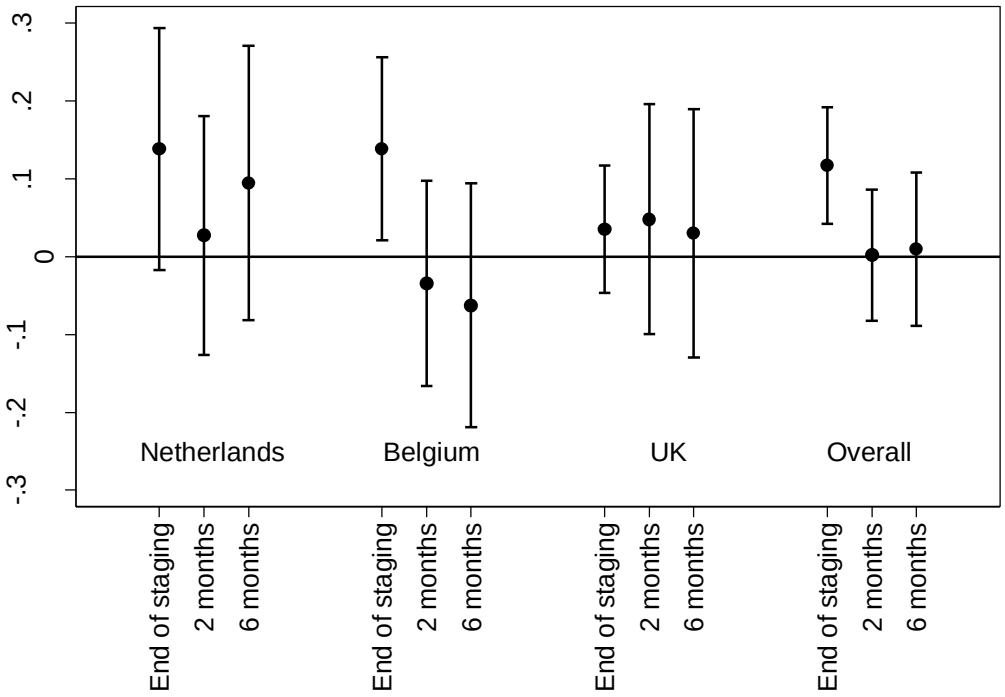

Figure A2 Difference in mean EQ-5D utility (95%CI) between endosonography strategy and surgical staging groups, by country, adjusted for baseline. Values above zero favour the endosonography strategy.

Throughout the 6 months the endosonography strategy and surgical staging groups had very similar EQ-5D utility, with the mean difference lying close to the zero line, and the confidence interval crossing the zero line. For patients in the Netherlands and the UK there was little difference between the groups at any time point, whilst in Belgium the endosonography strategy resulted in slightly higher utility during staging and slightly lower utility during follow up. When these utilities are combined with survival the overall mean (95%CI) increase in quality adjusted survival due to endosonography staging for the three countries was very similar, being 0.014 QALYs (-0.018, 0.046) in the Netherlands, 0.016 (-0.020, 0.054) in Belgium, and 0.016 (-0.021, 0.056) in the UK. This resulted in overall increase in QALYS for endosonography compared with surgical staging alone of 0.015 QALYs (-0.023, 0.052) over 6 months.

Resource use

The full breakdown of resources used during the study, based on patients who had complete resource use data, is provided in table A2 below. The main cost drivers were staging procedures and thoracotomy. Length of stay in hospital following thoracotomy was longer in Belgium (median 13 days, interquartile range 9-13 days) and shorter in the Netherlands (median 8 days, IQR 7-11 days) than in the UK (median 10 days, IQR 8-15 days), p=0.001. All bar one patient (surgical staging arm) received the staging strategy to which they were assigned.

Table A2: Resource Use by country (for patients who had complete information for all resource items; EBUS/EUS n=85; Surgical staging n=87)

	Number of people using each resource item (%)							
	Netherlands		Belgium		UK		Total	
Resource Item	EUS/ EBUS n=30	SS n=29	EUS/ EBUS n=44	SS n=48	EUS/ EBUS n=11	SS n=10	EUS/ EBUS n=85	SS n=87
EUS/EBUS procedure	30 (100%)	0 (0%)	45* (101%)	1** (2%)	11 (100%)	0 (0%)	86 (101%)	1 (1%)
Surgical staging procedure	19 (63%)	28*** (97%)	23 (52%)	48 (100%)	5 (45%)	10 (100%)	47 (55%)	86 (99%)
Thoracotomy (lobectomy or pneumonectomy) with LN dissection	17 (57%)	18 (62%)	22 (50%)	32 (67%)	6 (55%)	7 (70%)	45 (53%)	57 (66%)
Chemotherapy in the first 2 months	13 (43%)	9 (31%)	26 (59%)	25 (52%)	4 (36%)	5 (50%)	43 (51%)	39 (45%)
Radiotherapy in the first 2 months	5 (17%)	4 (14%)	5 (11%)	5 (10%)	0 (0%)	0 (0%)	10 (12%)	9 (10%)
Hospital admission in the first 2 months	2	2	14	15	2	2	18	19

	(7%)	(7%)	(32%)	(31%)	(18%)	(20%)	(21%)	(22%)
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%)	2 (5%)	5 (10%)	1 (9%)	1 (10%)	7 (8%)	9 (10%)
Chemotherapy between months 2 and 6	10 (33%)	9 (31%)	24 (55%)	28 (58%)	6 (55%)	6 (60%)	40 (47%)	43 (49%)
Radiotherapy between months 2 and 6	6 (20%)	10 (34%)	20 (45%)	14 (29%)	6 (55%)	3 (30%)	32 (38%)	27 (31%)
Hospital admission between months 2 and 6	5 (17%)	6 (21%)	18 (41%)	17 (35%)	5 (45%)	2 (20%)	28 (33%)	25 (29%)
Hospice admission between months 2 and 6	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (9%)	0 (0%)	1 (1%)	0 (0%)

* One patient had a second endosonography rather than the protocol thoracotomy

** One had endosonography in addition to surgical staging

*** One patient did not undergo their assigned surgical staging

Figure A3 shows the proportion of patients in each randomisation group and country who used each component of resource.

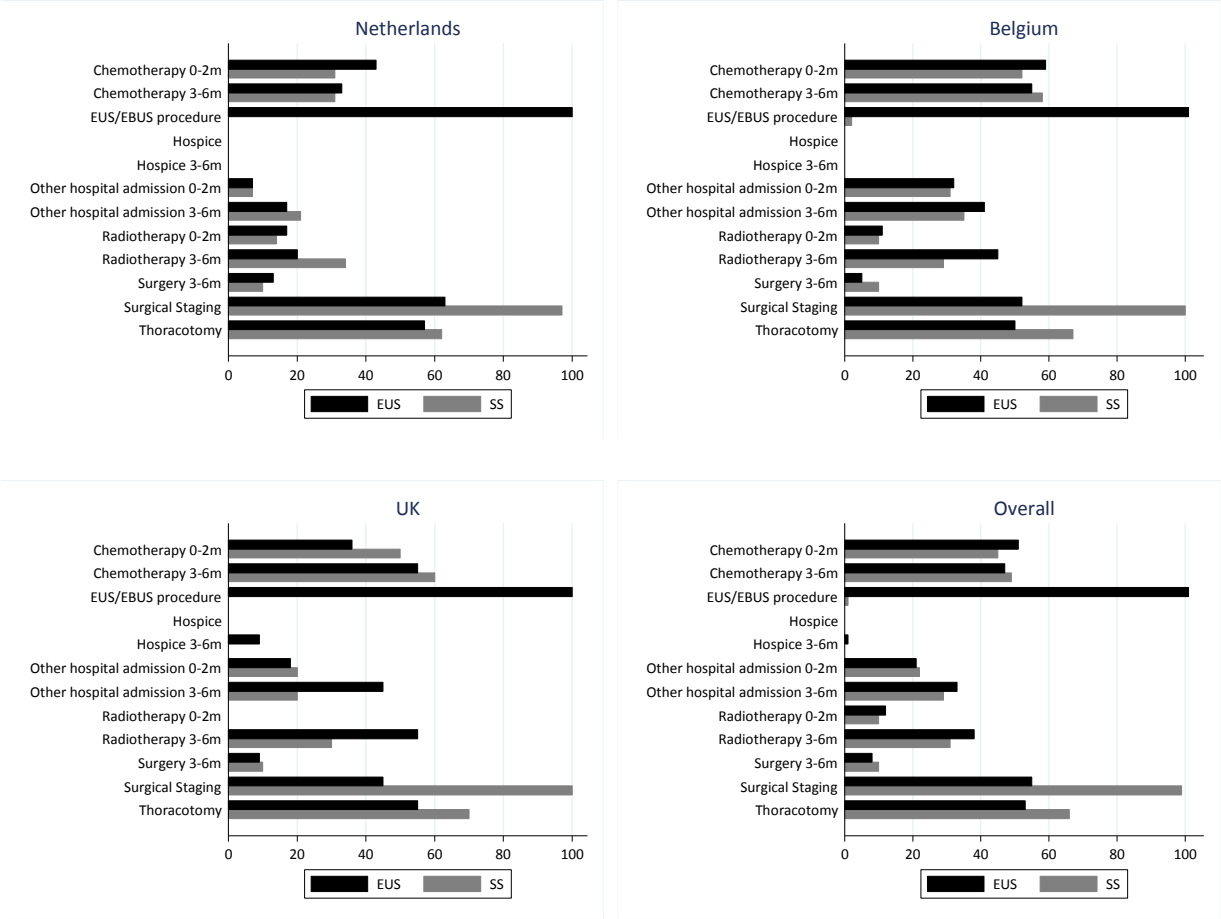

Figure A3 Percentage of patients using each resource item overall and by country and randomisation group (for patients who had complete information for all resource items; EBUS/EUS n=85; Surgical staging n=87. Note: one patient had a second endosonography rather than the protocol thoracotomy, one had endosonography in addition to surgical staging, and one patient did not undergo their assigned surgical staging)

There was some variation between countries in the proportion of patients who had each additional treatment. For example, Belgian patients were more likely to have chemotherapy in the first 2

months (p=0.054) and Dutch patients were less likely to have chemotherapy after 2 months (p=0.0097). Compared with Belgian and UK patients, Dutch patients were also less likely to be admitted to hospital in the first 2 months (p=0.0014) and after the first 2 months (p=0.04). However, these therapies had less influence on the overall costs and their average costs were similar between diagnostic strategy groups.

Table A3 shows the mean differences between the endosonography and surgical staging groups in costs attributed to the diagnostic and patient management components of resource use for patients who had complete resource use data.

Table A3. Incremental mean costs for patients who had complete information for all resource items; EBUS/EUS n=85; Surgical staging n=87). Presented for Dutch, Belgian and UK costs in euros. UK Pounds converted to euros using purchasing power parity rate (average of Dutch and Belgian).

Resource Item	Netherlands mean cost difference (n=59)	Belgian mean cost difference (n=92)	UK mean cost difference (n=21)
EUS/EBUS procedure**	1519	651	1651
Surgical staging procedure**	-1724	-478	-1793
Thoracotomy with lymph node dissection	-694	-373	-997
Total chemotherapy cost in the first 2 months	313	140	169
Total radiotherapy cost in the first 2 months	-92	28	-89
Total hospital admission costs in the first 2 months	-33	-117	-19
Hospice admission in the first 2 months	0	0	0
Surgery between months 2 and 6	-133	-51	-116
Total chemotherapy cost between months 2 and 6	-185	-82	-108

Total radiotherapy cost between months 2 and 6	270	128	264
Total hospital admission costs between months 2 and 6	115	108	25
Hospice admission between months 2 and 6	3	5	12

Although there were differences in the way in which different countries cost resource use there were some consistent patterns. For example, all countries estimated a lower cost due to surgical staging and thoracotomy in the endosonography arm (i.e. negative mean difference) and the sum of these savings outweighed the additional costs of endosonography. The cost of chemotherapy was greater in the endosonography group in the first 2 months, but greater in the surgical staging arm after 2 months. In general, the reverse is true for radiotherapy and hospital admissions, which cost more for the surgery arm in the first 2 months and more for the endosonography group after 2 months.

Cost effectiveness

Table A4 gives *bottom-line* total costs over the first 6 months for the three countries involved in the study, and the mean difference in costs between the two arms. All three countries reported a mean cost saving for the endosonography strategy, which was greatest in the UK. The cost-effectiveness acceptability curve is plotted in figure A4, which shows the probability that the endosonography strategy is cost-effective (i.e. represents value in terms of delivering health outcomes, given the cost) against the amount a decision maker is prepared to pay for one additional QALY (the cost effectiveness threshold).

Table A4 Expected costs and cost comparisons (posterior mean and 95% credible intervals; CI) using a Bayesian model to combine all patients including those with incomplete QALY or resource use data. Costs in Euros, adjusted to average of Belgian and Dutch 2010 purchasing power parity, compared between three countries.

	Netherlands		Belgium		UK	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
Expected costs (€)						
Endosonography +/- surgical staging	13374	(9571, 19198)	10345	(6023, 18769)	12944	(9573, 17654)
Surgical staging	13511	(9664, 18864)	10625	(6035, 19381)	13953	(10349, 18468)
Expected cost comparisons (€)						
Endosonography strategy – Surgical staging	-138	(-2331 to 1943	-280	(-2437, 1537)	-1010	(-3381, 992)

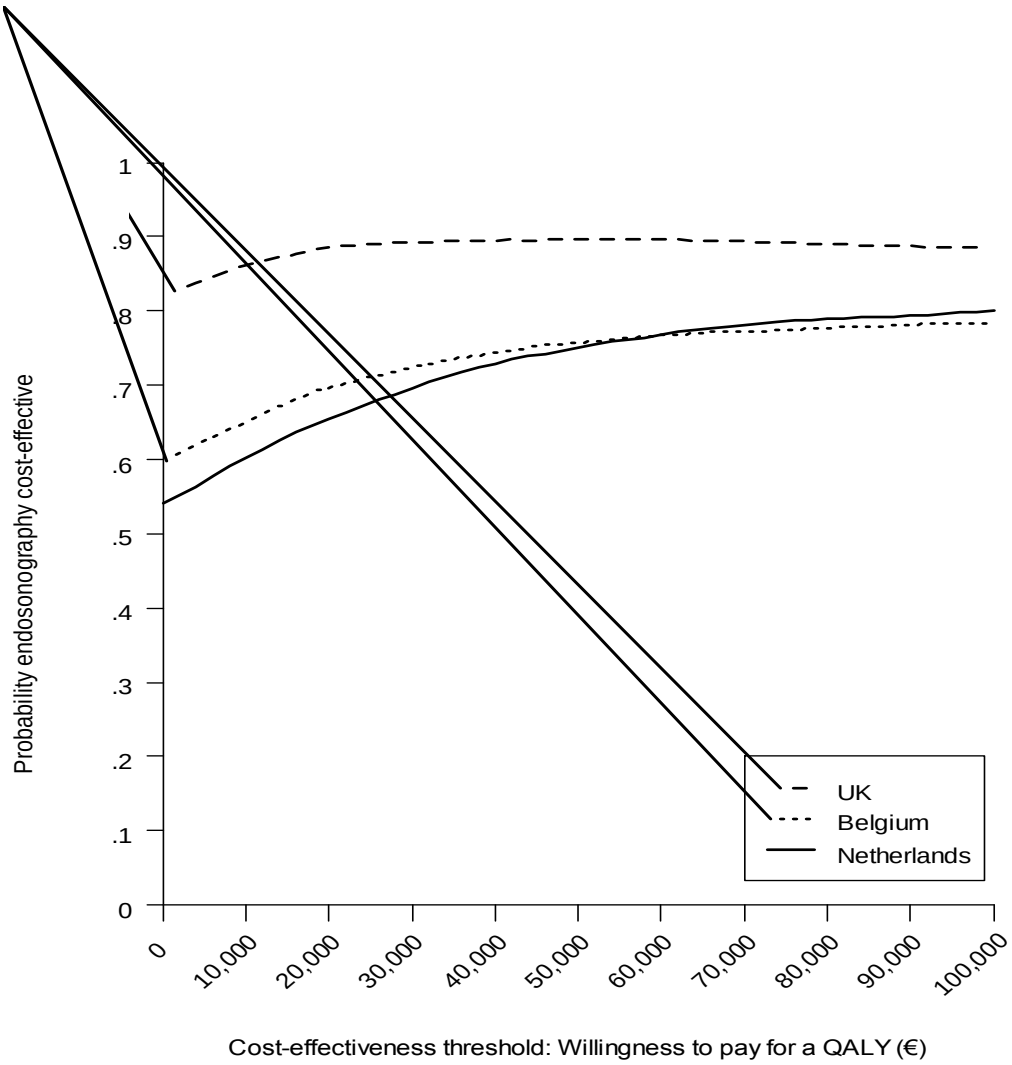

Figure A4 Cost-effectiveness acceptability curve under base-case full Bayesian model: costs compared between three countries.

Sensitivity of results to country-specific valuations of the EQ-5D

We assessed the sensitivity of the cost-effectiveness analyses to the assumption that preferences for states of health-related quality of life were the same between the three countries. In this analysis, instead of deriving utilities from EQ-5D responses using valuations obtained from a UK population, we used country-specific valuations for each patient in ASTER. [23,24] The resulting QALYs accumulated over six months were an average of 0.03 less among patients in Belgium (SD 0.03) when changing to country-specific preferences, but only 0.005 less (SD 0.02) among patients in the

Netherlands. Under the full Bayesian model, this led to a reduced incremental QALY over 6 months (EUS/EBUS - surgical staging) of 0.005 (-0.03, 0.04), compared to 0.015 (-0.02. 0.053) when using UK preferences for patients in all countries. However even with this adjustment the probability that the endosonography strategy is cost-effective does not change substantially (52% in the Netherlands to 83% in the UK if the decision maker is not willing to pay any amount for one QALY – Figure A5).

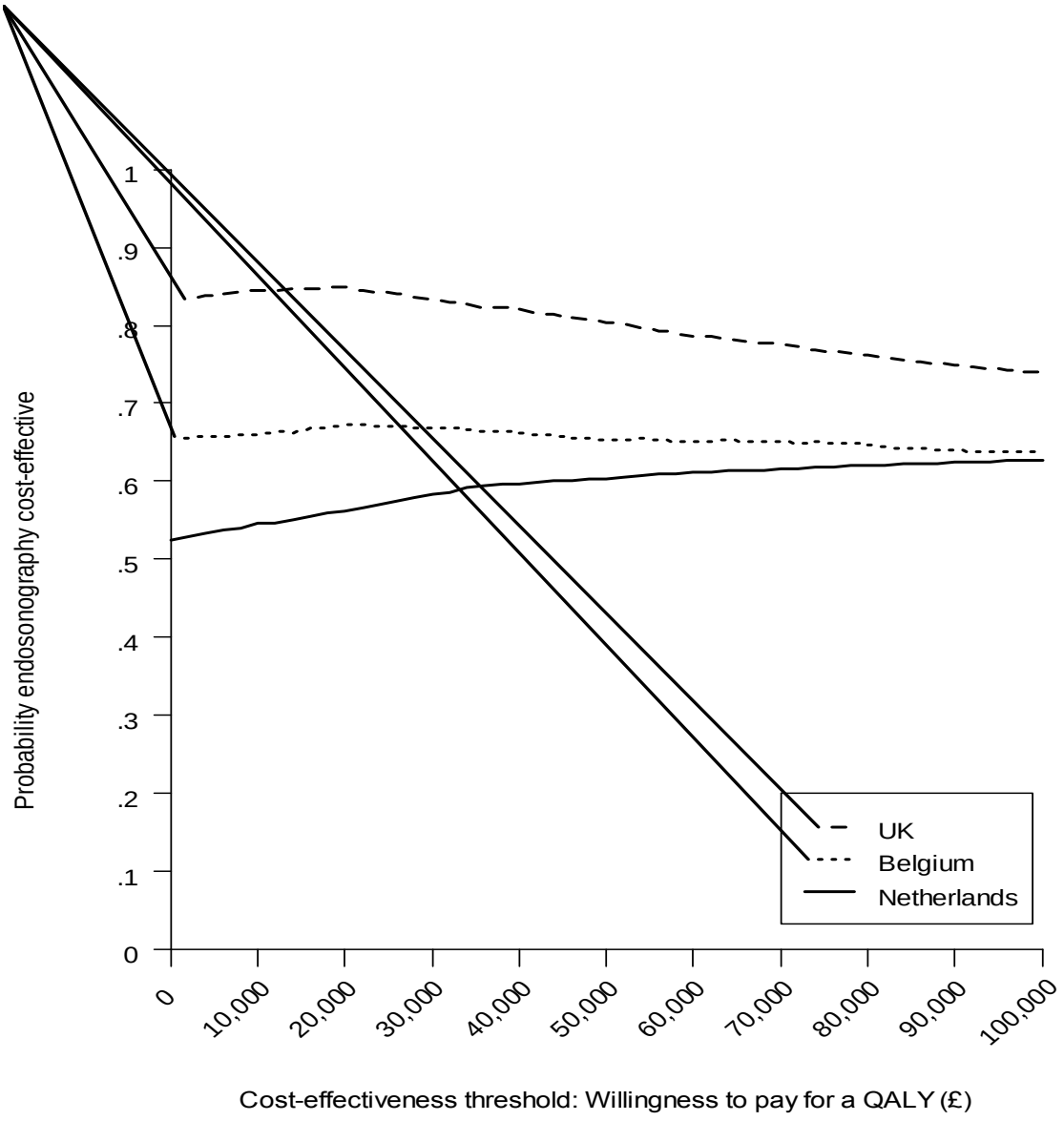

Figure A5: Cost-effectiveness acceptability curve under base-case full Bayesian model: costs compared between three countries. Sensitivity analysis using country-specific valuations of EQ-5D.

DISCUSSION

This study has examined the cost effectiveness of mediastinal staging using endosonography compared with surgical staging, for patients with non small cell lung cancer who are otherwise suitable for thoracotomy, in the three countries that took part in the ASTER trial.[7] In all three countries the endosonography arm had lower mean cost and greater mean QALY estimates, which means that this strategy is *dominant* in an economic sense. Although there were substantial differences in subsequent patient management, and in the way that resource use components were costed, estimates of the mean difference in overall 6 month costs for all three countries were lower in the endosonography strategy. Due to the small sample size within each country and the variation in management of individual patients the intervals around these estimates were wide. This uncertainty has been characterised by the cost-effectiveness acceptability curve in figure A4, which shows the probability that the endosonography strategy is cost-effective against the amount a decision maker is prepared to pay for one additional QALY. If a decision maker is not prepared to pay any additional Euros then the probability that the new endosonography strategy is cost-effective compared with surgical staging varies from 55% in the Netherlands to 82% in the UK. This suggests it is likely that endosonography delivers greater health outcomes at lower or equal cost, or cost savings with equal health outcomes. European decision makers do, however, often display a degree of willingness to pay for additional QALYs, although the threshold is not always well defined. This would lead to the likelihood of cost effectiveness increasing. In the UK, the National Institute for Health and Clinical Excellence (NICE) uses £20,000-£30,000 (approximately €25,800 – €38,600) as a guide to whether the NHS should adopt new treatments [25] and in the Netherlands the Council for Public Health and Health Care notes that an absolute maximum threshold might be considered €80,000 for the most serious of conditions.[26] In Belgium however, the KCE does not readily define any possible range [27] from which to make inferences about cost effectiveness. Even so, the curves remain above 50% (i.e. more likely than not to be cost-effective) irrespective of the amount we are willing to pay for additional benefit, suggesting that endosonography is more likely than not to be

cost-effective although there does remain some uncertainty in the decision regarding the most cost-effective strategy.

Although endosonography is being increasingly recognised as the initial test of choice for mediastinal staging [28,29], there have been few studies examining the cost-effectiveness of endosonography and surgical staging in this setting. We believe that this is the first report examining cost-effectiveness linked to a randomised trial. Previous work has been based on retrospective data and has used decision analysis approaches to produce models of possible outcomes and applied cost-minimization analysis in order to determine the most economical health care strategy among various alternatives.[30,31] Invariably, construction of such a model requires many assumptions and while endosonography strategies dominate one must be cautious in interpretation. The recently published 2011 NICE guideline for lung cancer diagnosis and treatment includes an economic model for a number of potential diagnostic pathways.[32] 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 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.

Looking forward, the increasing use of the endobronchial ultrasound bronchoscope within the oesophagus to perform EUS, so called EUS-B, means that costs for endosonography may further reduce as a standard EUS scope may not be required. Recent work has shown that EUS-B has similar diagnostic accuracy to standard EUS.[33] If further work supports this approach, endosonography may become even more cost-effective for mediastinal staging.

Limitations

Our results were derived from a rigorously conducted randomised controlled trial in three countries. All diagnostic procedures were carried out by experts in specialist thoracic oncology units, so that results will only be generalisable to practitioners and centres that can, after appropriate training, achieve similar sensitivity and NPV to those achieved in the ASTER study.

The number of centres and cases in each country was small, limiting generalisability, and cost estimates for individual patients varied widely, so that cost-effectiveness was measured imprecisely. In addition, the methods for assigning costs to clinical events and tests varied between countries, dependent on the best information available, so that we could not combine them in a meaningful way. For example, for the Netherlands costing we were able to assign a single cost for thoracotomy, whereas for Belgium we assigned a cost for the surgery plus a *per diem* cost for hospital stay and for UK costing assigned a fixed cost for a thoracotomy with up to 10 days stay in hospital plus a *per diem* cost for each day in hospital after the 10^{th} day. The consistency of estimates of cost and QALY differences in the three countries is reassuring but further confirmatory studies of cost-effectiveness in larger cohorts are required.

This study is trial based and so does not extend beyond the 6-month follow up period of the trial. However the majority of the differences between the groups results from the diagnostic tests and the thoracotomies, both of which occur early after randomisation. Thereafter, survival, quality of life and resource use are expected to be determined by the course of lung cancer, so that costs and effects are unlikely to diverge further beyond this point. Thus there is likely to be little additional benefit in developing a lifetime cost-effectiveness model.

A further limitation of the analysis arose due to the later start of the cost-effectiveness component of the study, resulting in some missing EQ-5D questionnaires, and to a lesser extent some resource use components. Although we used modern, sophisticated statistical methods (Bayesian parametric modelling with multiple imputation for incomplete data) in an attempt to minimise any bias this may have introduced, we cannot be sure that this was completely eradicated.

Conclusions

Based on data from the ASTER trial, a strategy of endosonography-guided mediastinal lymph node staging sampling, followed by surgical staging if endosonography shows no malignancy, appears cost effective compared with surgical staging alone. Despite differences in patient management and costing methodology between different countries the endosonography strategy cost less on average and had slightly higher mean QALY in all three countries.

ACKNOWLEDGEMENTS

We are grateful to the ASTER trial steering committee members who oversaw the running of the trial and met regularly to discuss study progress. The international group comprised Jouke Annema, Kurt Tournoy, Christophe Dooms, Robert Rintoul, Klaus Rabe, Ellen Deschepper and Olaf Dekkers. The Papworth ASTER management group comprised Robert Rintoul, Linda Sharples, Robert Buttery, Martin Buxton, Alistair Grant, Gethin Griffith, Victoria Hughes, Nicholas Carroll and Lavinia Magee. We are also grateful for the advice of the independent data monitoring committee members: Mick Peake (Chairman), Edwin Chilvers, John Edwards and Sarah Barry (independent statistician). We also thank all of the staff at the participating centres, the referring chest physicians and the patients for their participation. We thank Clazien Bouwmans-Frijters of the Institute for Medical Technology Assessment, Erasmus University, Rotterdam, The Netherlands and Ann Tanghe and Jorgen Bauwens of Hict, Bruges, Belgium for providing unit costs for The Netherlands and Belgium respectively.

REFERENCES

1. Adams K, Shah PL, Edmonds L et al. Test performance of endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: systematic review and meta-analysis. *Thorax* 2009;64:757-762.
2. Gu P, Zhao YZ, Jiang LY et al. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: A systematic review and meta-analysis. *European Journal of Cancer* 2009;45:1389-1396.
3. Micames CG, McCrory DC, Pavey DA et al. Endoscopic ultrasound-guided fine-needle aspiration for non-small cell lung cancer staging: A systematic review and metaanalysis. *Chest* 2007;131:539-548.
4. Sawhney MS, Kratzke RA, Lederle FA et al. EUS-guided FNA for the diagnosis of advanced lung cancer. *Gastrointestinal Endoscopy* 2006;63:959-965.
5. Annema JT, Bohoslavsky R, Burgers S et al. Implementation of endoscopic ultrasound for lung cancer staging. *Gastrointestinal Endoscopy* 2010;71:64-70.
6. Szlubowski A, Zielinski M, Soja J et al. A combined approach of endobronchial and endoscopic ultrasound-guided needle aspiration in the radiologically normal mediastinum in non-small-cell lung cancer staging - a prospective trial. *European Journal of Cardio-Thoracic Surgery* 2010;37:1175-1179
7. Annema JT, van Meerbeeck JP, Rintoul RC et al. Mediastinoscopy versus endosonography for mediastinal lymph node staging of lung cancer: a randomised trial. *JAMA* 2010;304:2245-2252
8. Sharples LD, Jackson C, Wheaton E et al. 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. *Health Technol Assess* 2012;16(18)

9. Kind P. The EuroQoL instrument: an index of health-related quality of life. In: Spilker B, ed. Quality of Life and Pharmacoeconomics in Clinical Trials, Second Edition. Philadelphia, PA: Lippincott-Raven Publishers, 1996:191-201
10. Dolan P, Gudex C, Kind P et al. A social tariff for EuroQoL: results from a UK general population. A discussion paper 138. York:University of York; 1995. http://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20138.pdf (Accessed December 2012)
11. Department of Health (DoH). NHS Reference Costs 2008-09. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591 (accessed January 2010)
12. Curtis L. Unit Costs of Health and Social Care. Canterbury: Personal Social Services Research Unit, 2011.
13. Rijksinstituut voor Ziekte- en Invaliditeitsverzekering. Honoraires, prix et remboursements. http://www.riziv.be/insurer/nl/rate/history/history2011.htm (accessed October 2012).
14. Europeans Medicines Agency. Gemzar Article 30 referral: Annex I, II,III http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Gemzar/human_referral_000031.jsp&mid=WC0b01ac0580024e9a **(**accessed October2012).
15. Keirse E, Beguin C, Desmedt M et al. Organisation of palliative care in Belgium: Health Services Research (HSR) KCE reports 115C. Brussels: Belgian Health Care Knowledge Centre (KCE); 2009 (D/2009/10.273/42)Organisation for Economic Co-operation and Development. GDP deflator indices http://stats.oecd.org/Index.aspx?QueryId=14744# (accessed October 2012)

16. Dutch Health Care Authority (NZa). DBC-tariefapplicatie tot en met 2011 http://www.nza.nl/zorgonderwerpen/dossiers/dbc-dossier/ (accessed October 2012)
17. Oostenbrink JB and Rutten FF. Cost assessment and price setting of inpatient care in the Netherlands. The DBC case-mix system. *Health Care Manag Sci* 2006;9:287-294.
18. Pompen M, Gok M, Novak A et al. Direct costs associated with the disease management of patients with unresectable advanced non-small-cell lung cancer in the Netherlands. *Lung Cancer* 2009; 64:110-116L.
19. Hakkaart-van Roijen L, Tan SS, Bouwmans C. Handleiding voor kostenonderzoek: Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. (In Dutch). Amstelveen: College voor zorgverzekeringen (CVZ); 2010
20. Nixon RM, Thompson SG. Parametric modelling of cost data in medical studies. *Stat Med* 2004;23:1311-1331
21. Lunn D, Best N, Spiegelhalter D. WinBUGS: a Bayesian modelling framework: concepts, structure and extensibility. *Stat Comput* 2000;10:325-337
22. Lambert PC, Billingham LJ, Cooper NJ et al. Estimating the cost-effectiveness of an intervention in a clinical trial when partial cost information is available: a Bayesian approach. *Health Economics* 2008;17:67-86
23. Lamers LM, McDonnell J, Stalmeier PF et al. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Economics* 2006;15:1121–1132
24. Cleemput I. A social preference valuations set for EQ-5D health state in Flanders, Belgium. *Eur J Health Econ* 2010;11:205–213)
25. National Institute of Health and Clinical Excellence (NICE). Social Value Judgements: Principles for the development of NICE guidance. London:NICE;2009.
26. Raad vor de Volksgezondheid & Zorg (RVZ). Sensible and sustainable care: Recommendations produced by the Council for Public Health and Health Care to the Minister of Health, Welfare and Sport. Zoetermeer: RVZ;2006

27. Cleemput I, Neyt M, Thiry N et al. Threshold values for cost-effectiveness in health care: Health Technology Assessment (HTA) KCE reports 100C. Brussels: Belgian Health Care Knowledge Centre (KCE); 2008. (D/2008/10.273/96)
28. Vansteenkiste J, De Ruysscher D, Eberhardt WE et al. Early and locally advanced non small cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Ann Oncol 2013 Jul 16 [Epub ahead of print].
29. Silvestri GA, Gonzalez AV, Jantz MA et al. Methods for staging non small cell lung cancer: Diagnosis and management of lung cancer, 3rd Ed: American College of Chest Physicians evidence based clinical practice guidelines. Chest 2013; 143:e211S-50S.
30. Steinfort DP, Liew D, Conron M et al. Cost benefit of minimally invasive staging of non small cell lung cancer: a decision tree sensitivity analysis. *J Thorac Oncol* 2010;5:1564-1570
31. Harewood GC, Pascual J, Raimondo M et al. Economic analysis of combined endoscopic and endobronchial ultrasound in the evaluation of patients with suspected non-small cell lung cancer. *Lung Cancer* 2010;67:366-371
32. National Institute of Health and Clinical Excellence (NICE). The diagnosis and treatment of lung cancer. Clinical Guideline 121. London:NICE;2011.
33. Hwangbo B, Lee GK, Lee HS et al. Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. Chest 2010;138:795-802.

CONTRIBUTORS

RCR and LDS conceived and designed the cost-effectiveness study, contributed to data collection and trial monitoring in the UK, supervised the cost-effectiveness analysis and wrote the first draft of the paper. MJG obtained resource use costs from each centre, performed resource use modelling and drafted the sections of the report relating to this analysis. CJ designed and implemented the final Bayesian cost-effectiveness model and drafted the sections of the report relating to this analysis. VH contributed to the design of the cost-effectiveness study and managed the UK arm of the trial. KGT, CD and JTA took responsibility for the conduct of the trial in their respective centres and supervised local clinical and health economic data collection. All authors reviewed and approved the final draft of the manuscript.

FUNDING

The study was funded by a grant from the UK National Health Service R&D Health Technology Assessment programme (project no. 06/302/216). LDS and CJ were funded by the Medical Research Council programme number U015232027. RCR was supported, in part, by the NIHR Cambridge Biomedical Research Centre and Cambridge Experimental Cancer Medicine Centre. Local support for data collection at Ghent University Hospital was provided by the Zorg-programma Oncologie Ghent (ZOG). The trial was registered as ISRCTN 97311620 and with ClinicalTrials.gov as NCT00432640.

COMPETING INTERESTS

Papworth Hospital acts as a reference centre for Olympus UK. Olympus UK provide a non-entailed educational grant towards the Papworth EBUS course for which RCR is the director.