Outcomes and cost-effectiveness of alternative staging strategies for non-small-cell lung cancer

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

Health technology
The study examined three strategies for staging non-small cell lung cancer (NSCLC) patients. These were computed tomography (CT) of the chest alone, selective mediastinoscopy (med) (i.e. CT followed by med for those with a positive result), and routine med (i.e. med for all patients).

Type of intervention
Diagnosis.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients aged 60 years and over with 'pathologic evidence of NSCLC, a chest CT and a metastatic work-up that revealed no evidence of locally unresectable (T4) or metastatic (M1) disease.'

Setting
The setting was not explicitly stated, but could have been a secondary or tertiary care centre. The economic analysis was conducted at the Brigham and Women's Hospital, Boston, MA.

Dates to which data relate
The effectiveness data were collected from studies published between 1966 and 1998, although all but 2 were published between 1980 and 1998. The resource and cost data were collected from studies published between 1984 and 1999.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies.

Modelling
A decision tree and Markov model were used to estimate the costs and outcomes. The decision tree was used to model short-term treatment decisions, whilst the Markov model estimated long-term costs and outcomes to the point of death.

Outcomes assessed in the review
The variables assessed in the review were:

the sensitivity and specificity of CT and med;
the mortality of med, lung resection and neoadjuvant chemotherapy (NAC) with chemoradiation;
the morbidity of NAC and chemoradiation;
the probability of surgery after NAC;
the transition probabilities for moving to different cancer stages;
5-year survival probability;
the treatment effect of trimodality therapy for N2 disease and chemoradiation for N3 disease; and
health state utilities (postoperative, radiotherapy, chemotherapy and end-of-life).

Study designs and other criteria for inclusion in the review
The studies included were meta-analyses, prospective studies, case series and other trials. Expert opinion was also relied on to estimate some health state utilities. The authors did not state any inclusion or exclusion criteria for studies in the review.

Sources searched to identify primary studies
Not stated.

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

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

Number of primary studies included
Fifty-one primary studies were included.

Methods of combining primary studies
The primary studies were combined using a narrative method.

Investigation of differences between primary studies
Where there was wide variation in the published estimates, the authors chose an 'adverse' value as the base-case so as to bias against med.

Results of the review
All the following show the base-case estimate, followed by the range tested in the sensitivity analysis in brackets. Where there are no figures in brackets, the variables were not varied.

The sensitivity of CT was 0.79 (0.5 - 0.91) and the specificity was 0.89 (0.67 - 0.98).

The sensitivity of med was 0.92 (0.67 - 0.94) and the specificity was 1.00.

Mortality was 0.003 (0 - 0.05) for med and 0.04 (0 - 0.20) for lung resection.
For NAC with chemoradiation, mortality was 0.03 (0 - 0.1) and morbidity was 0.1 (0 - 0.18).

The probability of surgery after NAC was 0.75 (0.56 - 0.90).

The transition probabilities were 0.31 (0 - 1) to stage T1, 0.49 (0 - 1) to stage T2, and 0.2 (0 - 1) to stage T3.

Within stage T1, the transition probabilities were 0.66 to stage T1N0, 0.1 to stage T1N1, 0.09 to stage T1N2, and 0.15 to stage T1N3.

Within stage T2, the transition probabilities were 0.46 to stage T2NO, 0.24 to stage T2N1, 0.11 to stage T2N2, and 0.19 to stage T2N3.

Within stage T3, the transition probabilities were 0.17 to stage T3NO, 0.11 to stage T3N1, 0.27 to stage T3N2, and 0.45 to stage T3N3.

The estimated 5-year survival was 67% for T1N0 patients and 55% for T1N1 patients.

The estimated 5-year survival was 57% for T2N0 patients and 39% for T2N1 patients.

The estimated 5-year survival was 38% for T3N0 patients and 25% for T3N1 patients.

The estimated 5-year survival was 20% (0 - 23%) for TxN0 patients and 3% (0 - 6%) for TxN1 patients, where x is stage 1, 2 or 3.

The hazard ratio of treatment effects was 0.681 (0.413 - 1) for trimodality treatment therapy for N2 disease and 0.738 (0.596 - 1) for chemoradiation for N3 disease.

The health state utilities were 0.95 (0.75 - 1) for postoperative, 0.7 (0.65 - 0.8) for radiotherapy, 0.6 (0.5 - 0.7) for chemotherapy, and 0.2 (0.15 - 0.5) for end-of-life patients.

The health state utility for an inpatient stay was valued at 0, and remission after treatment at 1.

**Measure of benefits used in the economic analysis**

The benefit measures were the life-years gained (LYGs) and the quality-adjusted life-years (QALYs) gained. The health states were valued by a combination of expert opinion and NSCLC patients' self-rating. The valuation tool used was not stated.

**Direct costs**

The quantities and the unit costs were reported separately. The costs included were relevant to a hospital or health-care payer. These were the cost of med, lung resection, radical radiotherapy, NAC for N2 disease, chemotherapy for N3 disease, continuing care with localised and loco-regional disease, end-of-life care for patients with localised and loco-regional disease, non-health care costs of the treatment week, and non-health care costs of the non-treatment week.

The cost data were sourced from a variety of publications, mostly other cost-effectiveness analyses. They were extrapolated to a longer time frame in the Markov model. All of the costs were converted to 1999 US dollars using the medical care component of the American Consumer Price Index. Where necessary, prices quoted in other currencies were converted to US dollars at the exchange rate for the year in question. Discounting was performed at 3%, as the model covered a period greater than one year. The study reported both the average and incremental costs.

The cost of CT was excluded from the analysis since all the patients underwent this procedure.

**Statistical analysis of costs**

The probabilities and costs were treated as point estimates.
**Indirect Costs**
To estimate the costs from a societal perspective, the income forgone by NSCLC patients and their carers was estimated. This was derived using the average hourly wage rate for individuals of 55 years of age taken from the US Census Bureau (1999). The quantities and the costs were stated separately, of which the quantities (hours) were assumed by the authors. As for the direct costs, the indirect costs were discounted in the analysis by 3%.

**Currency**
US dollars ($).

**Sensitivity analysis**
To investigate variability in the data, most probabilities and all costs were varied in one- and two-way sensitivity analyses. Where there was no obvious range through which to vary a parameter, the point estimate was halved and doubled to give an arbitrary range.

**Estimated benefits used in the economic analysis**
The following results were not discounted.

Patients with T1 stage cancer receiving CT alone lived, on average, 9.260 years after treatment. The corresponding values for med were 9.831 years (selective) and 9.853 (routine). Thus, the LYGs were 0.571 for selective med over CT, and 0.022 for routine med over selective med.

Patients with T2 stage cancer receiving CT alone lived, on average, 6.076 years after treatment. The corresponding values for med were 6.436 (selective) and 6.479 years (routine). Thus, the LYGs were 0.360 for selective med over CT, and 0.043 for routine med over selective med.

Patients with T3 stage cancer receiving CT alone lived, on average, 3.361 years after treatment. The corresponding values for med were 3.675 (selective) and 3.812 years (routine). Thus, the LYGs were 0.314 for selective med over CT, and 0.137 for routine med over selective med.

The average QALYs gained and discounted life-years were not shown individually.

**Cost results**
These results are not discounted. Note that the average costs exclude the cost of CT.

The cost of treating patients with T1 stage cancer until death was $54,700 with CT alone, $66,100 with selective med, and $67,700 with routine med. Thus, the incremental cost of selective med over CT was $11,400, and that of routine med over selective med, $1,600.

The cost of treating patients with T2 stage cancer until death was $45,700 with CT alone, $57,400 with selective med, and $59,000 with routine med. Thus, the incremental cost of selective med over CT was $11,700, and that of routine med over selective med, $1,600.

The cost of treating patients with T3 stage cancer until death was $31,500 with CT alone, $51,300 with selective med, and $52,500 with routine med. Thus, the incremental cost of selective med over CT was $19,800, and that of routine med over selective med, $1,200.

**Synthesis of costs and benefits**
The costs and benefits were combined in incremental cost-effectiveness ratios (ICERs) of both (incremental) cost per LYG and (incremental) cost per QALY gained. The ratios were presented both undiscounted (values in brackets) and with the costs and benefits discounted at 3%.
In T1 stage cancer patients the incremental cost per QALY, discounted at 3%, was $24,500 ($19,600) for selective med over CT alone, and $78,800 ($86,400) for routine med over selective med.

In T2 stage cancer patients the incremental cost per QALY, discounted at 3%, was $37,900 ($31,500) for selective med over CT alone, and $42,800 ($40,500) for routine med over selective med.

In T3 stage cancer patients the selective med strategy was eliminated by extended dominance. The incremental cost per QALY, discounted at 3%, was $53,400 ($47,300) for routine med over CT alone.

In T1 patients, the equivalent ratios of cost per LYG were $25,400 ($19,900) for selective med over CT alone and $65,800 ($70,700) for routine med over selective med.

When discounted at 3%, selective med was eliminated by extended dominance for T2 patients (ICER, of $32,300 when not discounted). The discounted incremental cost per LYG of routine med over CT alone was $39,300. The undiscounted ICER of routine med over selective med was $35,500.

In T3 patients, selective med was eliminated by extended dominance. The incremental cost per LYG from routine med over CT alone was $52,800 ($46,400).

The results did not substantially change in response to changes in the parameters, except for one extreme scenario with very low baseline survival of N2 patients. The mortality of med needed to exceed 0.6% before selective med became more effective than routine med. The ICER of routine med compared with selective med became "less favourable" as the cost of med approached $4,500 (base-case value is $2,100).

**Authors' conclusions**
Routine mediastinoscopy (med) in patients with known non-small-cell lung cancer (NSCLC) and T2 or T3 stage tumours resulted in the greatest health benefit, at an incremental cost-effectiveness (compared with selective med) that was comparable with other accepted medical technologies. In patients with T1 tumours, the incremental cost-effectiveness ratio (ICER) of routine versus selective med was fairly high. Thus, selective med may be preferable in these patients.

**CRD COMMENTARY - Selection of comparators**
The comparators chosen for the analysis seem appropriate for the study. You should decide if they are appropriate to your setting.

**Validity of estimate of measure of effectiveness**
The authors did not state that a systematic review of the literature had been undertaken. In addition, the effectiveness estimates were combined using a narrative method. The transparency of the study would have been enhanced had the methods for searching for and extracting the data been more clearly represented. For example, it is unclear whether the authors took into account factors such as sample size and type of study to weight the combined results from several studies. The literature search does, however, appear to have been very comprehensive, with the use of meta-analyses and prospective trials where possible. Further, the authors investigated differences between published parameter estimates in a sensitivity analysis.

**Validity of estimate of measure of benefit**
The estimation of health benefit (LYGs and QALYs gained) was obtained directly from the model. The initial valuation of the (quality-adjusted) health states in the Markov model appeared somewhat arbitrary, although the sensitivity analysis confirmed that the "model was insensitive to the utility values used to quality-adjust life expectancy". Thus the valuations appeared justified. The transparency and understanding of the model would have been enhanced with a diagram of the Markov model. It was unclear how the transition probabilities in Table 1 related to patient pathways.
Validity of estimate of costs
All the relevant categories of cost for the perspective chosen were included. The authors stated that they excluded the cost of CT because this was common to patients in all three groups. This implies that those in the routine med group have a CT scan, then, whatever the result, they undergo a med. This may be the protocol followed in the authors' setting. However, this is not how it was illustrated in the decision tree. It was also unnecessary to undergo a diagnostic test when it was known it would have no bearing on the patient’s subsequent care pathway.

The costs and the quantities were reported separately. The quantities appear to have been based on protocols in the authors' setting. A sensitivity analysis of quantities was not performed. Prices were taken from a mixture of the authors' setting and published sources. There was no statistical analysis of the costs, although a sensitivity analysis of all cost inputs was performed. Where estimates from the literature were not available, the authors arbitrarily halved and doubled the estimates to give a wide range to test. All the costs were converted to 1999 US dollars using the medical care component of the consumer price index, and overseas currencies were converted at the prevailing rate for the appropriate year.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. The issue of generalisability to other settings was addressed by limiting the analysis to "widely available, commonly used staging strategies", and the use of (relatively) less specialist equipment. The authors did not present their results selectively, and the conclusions fully reflected the scope of the analysis.

The authors reported a number of potential limitations to their study. First, the analysis was limited to those with known NSCLC, and excluded those with unresectable or metastatic disease. The authors felt this was not a drawback, as patients reaching the staging process would already have had NSCLC confirmed. A further drawback was the use of small trials to estimate some of the parameters. These trials had also been criticised over their entry criteria and poor survival in the control arms. Finally, the authors pointed out that the use of some Canadian cost data may have affected the results, due to the differences in health systems: the ICER of routine med against selective med was sensitive to the cost of radiotherapy, which was estimated from a Canadian source.

In summary, this was, on the whole, a very clear and transparent model of alternative staging strategies for NSCLC, which should be of good use to decision-makers.

Implications of the study
Routine med in patients with T2 or T3 tumours maximises health benefit at an acceptable ICER. In patients with T1 tumours, routine med would also maximise health benefit, but at a less favourable ICER. Selective med may be economically more attractive for T1 patients.

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