Investigating extrathoracic metastatic disease in patients with apparently operable lung cancer


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 comparison of limited versus full investigation of extrathoracic metastatic disease in patients with apparently operable lung cancer. Limited investigation consisted of a chest computed tomography (CT) scan and a mediastinoscopy. Full investigation meant the addition of bone scintigraphy and liver, adrenal gland and head CT scans.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with apparently operable non-small cell lung cancer.

Setting
The settings were tertiary and secondary care hospitals. The economic study was carried out at various sites across Canada.

Dates to which data relate
The effectiveness and resource use data were collected between January 1992 and August 1997. The price year was 1998.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The resource use data were collected prospectively on the same patient sample as that used in the effectiveness study.

Study sample
The investigators reviewed patients referred to the participating surgeons, who had no findings on history, physical examination, laboratory testing, or imaging that suggested extrathoracic metastases. In all, 2,222 patients were reviewed. Of these, 1,588 (71.5%) were ineligible because they met one or more of the 13 exclusion criteria. The study included 634 patients. There were 318 in the full investigation group and 316 in the limited investigation group. The authors reported that the two groups were similar across a range of characteristics and provided the supporting data. The
authors state that the study sample is appropriate when surgeons use conservative criteria for determining the possible presence of metastatic disease. No sample size calculations were reported.

**Study design**

This was a randomised controlled trial involving 11 clinical centres in 7 different cities. Randomisation was stratified by centre and by whether the patient had lost 10% of their body weight over the last 6 months. Within these strata, the patients were randomised in blocks of 4 using a computer-generated random number table. Randomisation was concealed as it was centralised at a single methods centre, which clinical centres contacted by telephone. The patients were followed-up for 2 years. There was no loss to follow-up. The investigators and analysts were blinded to the patient groups until the primary analyses were complete.

**Analysis of effectiveness**

Since there was no loss to follow-up, the data were analysed on an intention to treat basis. The primary health outcome was the number of thoracotomies without cure. There were defined as exploratory thoracotomies (open and close), incomplete resections and thoracotomies with subsequent recurrence. The authors also defined an end point called "unnecessary thoracotomies". This included thoracotomies without cure, and thoracotomies during which the disease is discovered to be benign.

**Effectiveness results**

There were 58 thoracotomies without a cure in the full investigation group and 73 in the limited investigation group. The relative risk (RR; full versus limited) of 0.80 (95% confidence interval, CI: 0.56 - 1.13; p=0.20). These included 43 (full) and 61 (limited) patients, respectively, who had recurrent disease after the thoracotomy (RR 0.70, 95% CI: 0.47 - 1.03; p=0.07). Patients who received a full investigation were significantly more likely to have avoided thoracotomy because of evidence of extrathoracic metastases (RR 2.19, 95% CI: 1.04 - 4.59; p=0.04). There were 77 unnecessary thoracotomies in the full investigation group and 95 in the limited investigation group (RR 0.81, 95% CI: 0.60 - 1.10; p=0.17).

There were 6 negative invasive tests in the full investigation group and one in the limited investigation group (RR 6.1, 95% CI: 0.72 - 51.0; p=0.10). The total number of invasive tests was 11 (full) and 6 (limited) in the two groups, respectively (RR 1.84, 95% CI: 0.68 - 4.98; p=0.23).

**Clinical conclusions**

The authors conclude that this study provides limited evidence that the full investigation reduced the number of unnecessary thoracotomies and does not appear to cause harm.

**Modelling**

A published model (unspecified in this article) was used to determine the per patient costs.

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

This was a cost-consequences study and there was no summary measure of benefit.

**Direct costs**

The hospital costs included in the analysis were for the bed days (hospital, thoracic ward, intensive care and a step-down unit), professional fees, and all major procedures including imaging. The unit costs were derived using a model of the full allocation of costs, and was based on one hospital. The quantities were not reported separately from the costs. Discounting was not carried out since it was irrelevant. The resource use data were collected between 1992 and 1997. The costs were reported in 1998 Canadian dollars.
Statistical analysis of costs
Since the distribution of the costs was skewed, the authors used a non-parametric bootstrapping method to calculate the CIs for the difference between the mean hospital costs, patient costs and total costs in the two groups.

Indirect Costs
The indirect costs were not included in this analysis.

Currency
Canadian dollars (Can$).

Sensitivity analysis
No sensitivity analysis is reported.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
In the full investigation group, per patient hospital costs of Can$9,459 and professional fees of Can$1,876 were incurred for a total cost of Can$11,335. In the limited investigation group, the corresponding figures were Can$10,508 (hospital costs), Can$1,645 (professional fees) and Can$12,154 (total costs). Thus, the average difference in the total costs was Can$819 in favour of full investigation (95% CI: -2,482 - 725). These figures include the costs of "unnecessary thoracotomies" and negative invasive tests.

Synthesis of costs and benefits
Not applicable.

Authors’ conclusions
The findings were not statistically significant. However, a full investigation approach may reduce the number of thoracotomies without cure, and may cost less than a limited investigation approach that leads to more surgery being performed.

CRD COMMENTARY - Selection of comparators
Neither investigation approach was explicitly chosen as the comparator. The authors explained the rationale for choosing these two alternatives. There is professional uncertainty about how extensively to look for extrathoracic metastases when initial examinations suggest there are none.

Validity of estimate of measure of effectiveness
This was a well-designed randomised controlled trial, which was appropriate for the study question. Appropriate statistical analyses of the data were carried out. However, no sample size calculations were reported. The findings were inconclusive and, as the authors acknowledged, this may have been due to an insufficient sample size.

Validity of estimate of measure of benefit
No summary benefit measure was used.
Validity of estimate of costs
This study excluded primary care costs, although these were likely to be small in comparison to the hospital costs. The generalisability of the cost data is limited by the fact that the resource use quantities were not reported.

Although the authors report using unit prices, these are likely to represent the costs to the public health care system. The unit costs were based on one of the participating hospitals and may not apply to hospitals of different sizes or with different characteristics (for example, teaching versus non-teaching). The overall cost data were subjected to a statistical analysis that suggested that the full investigation group was cheaper. However, this finding did not reach conventional statistical significance.

Other issues
The authors discussed the relevance of the threshold they used to exclude patients from the trial on the basis of signs of metastatic disease. The investigators used a low threshold, that is, erring on the side of excluding the patients. It was suggested that these results may not be generalisable to situations in which surgeons are less likely to consider borderline symptoms suggestive of metastatic disease. However, in other respects this was a pragmatic trial designed to reflect real-world practice, which may enhance the generalisability of the effectiveness findings to other settings where the practice is similar.

On the subject of the costs, the authors point out that the generalisability to other settings will depend on the similarity of the relative costs of professional services to hospital costs, to those used in this study.

The article made little comparison with other studies. An invited commentary following the article was more helpful in this respect. The authors' conclusions are tempered to reflect the fact that statistical significance was not attained, and are therefore justifiable given the high-quality study design.

Implications of the study
The authors conclude that a full investigation approach may be helpful in avoiding unnecessary thoracotomies. However, they also mentioned that it is likely to be more beneficial, the higher the threshold for considering symptoms to be suggestive of metastatic disease, in other words, when surgeons are less likely to look for distant metastases in a patient with borderline symptoms.

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