Mediastinoscopy in patients with presumptive stage I sarcoidosis: a risk/benefit, cost/benefit analysis
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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
Use of mediastinoscopy for causal diagnosis versus continued observation with presumed diagnosis of stage 1 sarcoidosis, in patients with asymptomatic bilateral hilar lymphadenopathy.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
Hypothetical patients with asymptomatic bilateral hilar lymphadenopathy and normal results on physical examination, aged between 20-40 years old.

Setting
Hospital and community. The economic study was carried out in Oregon, USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1952 and 1996. No information was given on the cost and resource use dates. The price year was unspecified, but is assumed to be 1996 (confirmed through correspondence with the author).

Source of effectiveness data
The effectiveness data were derived from previously published sources and expert opinion.

Modelling
A decision tree was used to model the costs and consequences associated with mediastinoscopy and continued observation for a cohort of hypothetical patients.

Outcomes assessed in the review
For each of the alternative diagnoses studied, namely tuberculosis, Hodgkin's disease and non-Hodgkin's lymphoma, the following parameters were assessed in the review: annual incidence of disease; percentage asymptomatic; percentage with isolated mediastinal disease; the percentage with isolated mediastinal involvement limited to bilateral hilar lymphadenopathy and complication rate for mediastinoscopy.
Study designs and other criteria for inclusion in the review
No specific design criteria were specified by the authors.

Sources searched to identify primary studies
MEDLINE was searched and studies cited in the articles identified by MEDLINE were also reviewed.

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
Approximately 30 studies were included.

Methods of combining primary studies
A meta-analysis for complication rates was carried out.

Investigation of differences between primary studies
Not stated.

Results of the review
The annual incidence (ages 20-40) of stage 1 sarcoidosis is 0.0037 %;
the annual incidence (ages 20-40) of tuberculosis is 0.0081%;
the annual incidence (ages 20-40) of Hodgkin's disease is 0.0037%;
the annual incidence (ages 20-40) of non-Hodgkin's lymphoma is 0.0021%.

The percentage with each alternative diagnosis who are asymptomatic is 18% for tuberculosis and 41% for Hodgkin's disease. The percentage with isolated mediastinal involvement is 0.26% for tuberculosis and 3% for Hodgkin's disease, and the percentage with mediastinal involvement limited to bilateral hilar lymphadenopathy is 0-24% (24% used in the calculation of the proportion of ABHL-TB) for tuberculosis. The complication rate for mediastinoscopy was 2%, half of whom required hospitalisation, 0.5% for minor complications and 0.5% for major complications, these values being retained from those in the literature and account for in relation to the lesser experience of surgeons in the community and the better general health of the patient group under investigation (assumed to offset one another). These data were then used as inputs to the decision model.

Methods used to derive estimates of effectiveness
Estimates of effectiveness were also based on the authors' assumptions.

Estimates of effectiveness and key assumptions
In patients with Hodgkin's disease, 0.27% with disease limited to the mediastinum and lacking anterior mediastinal adenopathy were assumed to have isolated BHL. The percentage of patients with asymptomatic non-Hodgkin's lymphoma was assumed to be 0.08 (a fifth of that for Hodgkin's disease); the percentage with isolated mediastinal
disease limited to bilateral hilar lymphadenopathy was assumed to be 0.000675 (a quarter of that for Hodgkin's disease). Medical outcome for those with tuberculosis was assumed not to be affected by the postponement of diagnosis. For those with Hodgkin's disease it was estimated that delayed diagnosis would lead to one additional death for every four patients, under the assumption that all cases progress to stage IV before diagnosis under observation. For those with non-Hodgkin's lymphoma it was estimated that delayed diagnosis would lead to one additional death for every 2.4 cases, under the assumption that all cases are aggressive and all progress to advanced stage before diagnosis under observation. The sensitivity and specificity of mediastinoscopy is assumed to be 100%. These data were used as inputs to the decision model.

Measure of benefits used in the economic analysis
The measure of benefits was cases of each alternative diagnosis identified and lives saved, derived using a decision tree.

Direct costs
Costs associated with the diagnostic procedures examined (mediastinoscopy and transbronchial biopsy) and hospitalisation costs associated with complications were included within the analysis. All costs were taken from fee schedules, although the year was not identified. The resource quantities were derived from the decision model. The quantity/cost boundary was that of the 3rd party payer. The costs were not discounted. The price year was 1996.

Statistical analysis of costs
Not stated.

Indirect Costs
Not included.

Currency
US dollars ($).

Sensitivity analysis
The authors tested the robustness of the results to variation in the incidence data, examining a best case scenario where incidence of alternative diagnoses were increased by 100%, and also through the determination of the threshold incidence of alternative diagnoses required to give mediastinoscopy a cost-effectiveness ratio in the range $10,000 - $20,000/alternative diagnosis. In addition, the threshold for procedural mortality rate required to offset the lives saved by the procedure was calculated.

Estimated benefits used in the economic analysis
In a cohort of 33,000 patients (aged 20-40) with asymptomatic bilateral hilar lymphadenopathy and normal results on physical examination, 8 cases of tuberculosis (identified through a policy of vigilant observation and whose outcome would not be adversely affected by therapeutic postponement), 9 cases of Hodgkin's disease and 1 case of non-Hodgkin's lymphoma will be identified; 32,982 patients will be confirmed as having stage 1 sarcoidosis. In addition, 407 patients will require hospitalisation as a result of the procedure, with 204 involving major complications. The 32,982 patients confirmed as stage 1 sarcoidosis and the 8 patients with tuberculosis will gain no additional benefit from the diagnosis. 2 patients with Hodgkin's disease and less than 1 patient (approximately 0.4) with non-Hodgkin's lymphoma will survive as a result of the early diagnosis. Thus approximately 2.4 lives will be saved as a result of mediastinoscopy applied to this cohort.

Cost results
The cost of using mediastinoscopy for diagnosis in the cohort was between $101 million and $211 million, whilst using
a test for angiotensin I-converting enzyme prior to mediastinoscopy would reduce the cost to between $50 million and $100 million for this cohort. The costs of complications and hospitalisations were included within the analysis. Costs were not discounted.

**Synthesis of costs and benefits**
The incremental cost per life saved from the use of mediastinoscopy versus continuous observation was reported as $37 million ($5 - $11 million per alternative diagnosis identified). A procedural mortality rate of just 0.01% would offset the gain in life years. In order for the cost per case identified to fall in the range $10,000 - $20,000 the incidence of alternative diagnoses would need to be 1,000 times higher than those used within the analysis.

**Authors’ conclusions**
Routine mediastinoscopy of patients with asymptomatic bilateral hilar lymphadenopathy and normal results on physical examination is neither beneficial to patients nor cost-effective. The preferred policy within this patient group should be continued and vigilant observation.

**CRD COMMENTARY - Selection of comparators**
The policy of presumptive diagnosis and continued observation was used as the comparator to mediastinoscopy because stage 1 sarcoidosis is the most frequent cause of asymptomatic bilateral hilar lymphadenopathy and continued observation should enable the identification of alternative diagnoses in time. As a result several authors have advocated the use of this policy. The authors also considered other alternatives (for example transbronchial biopsy, favoured by 6 out of 8 responders to the questionnaire who recommended histologic confirmation) but these were shown to be less sensitive, less specific and not cost-effective. You, as a user of this database, should consider whether these health technologies apply to your setting.

**Validity of estimate of measure of effectiveness**
The authors conducted a systematic review of the literature in determining input parameters for the model. However, the studies were not homogenous and as such a selective approach was necessary (for example median, median and highest in the range were used for percentage asymptomatic, percentage with isolated mediastinal involvement and percentage with isolated mediastinal involvement with BHL, respectively). The authors do point out, on the other hand, that the analysis was deliberately weighted in favour of mediastinoscopy in that it overestimated both the likelihood of alternative diagnoses and the likely benefit of earlier diagnosis, underestimated the likelihood the prior probability of SIS in the African-Americans and assumed 100% sensitivity and specificity for mediastinoscopy. In spite of these assumptions, the result was overwhelmingly in favour of observation.

**Validity of estimate of costs**
Prices were derived from 3rd party payer fee schedules in the USA, which, whilst internally valid, are not generalisable to the UK. Costs of medications, tests, respiratory procedures and professional charges were omitted as were physician costs associated with the policy of continued observation. However, the authors point out that these would be unaffected by mediastinoscopy as the same follow-up would be necessary.

**Other issues**
The authors relied upon published data, which has inherent biases. The data are often from specialised medical settings and may not be externally valid, although the authors attempted to adjust for this through the use of assumptions. A single table of parameters used in the decision tree, and their sources, would have helped in understanding the modelling process adopted. The assumption that mediastinoscopy is perfectly sensitive and specific for all alternative diagnoses could bias the results in favour of the procedure (justified above). The authors assumed no effect upon prior probability of stage 1 sarcoidosis due to ethnicity, which could also bias in favour of mediastinoscopy. However, the threshold analysis undertaken suggests that the authors’ conclusions are justified. The issue of generalisability to other settings and countries has not been addressed. Appropriate comparisons with other studies were made. The authors specified the analysis as cost-benefit whereas the health outcomes were expressed in terms of natural units and therefore the study was actually a cost-effectiveness analysis.
Implications of the study
(Note by CRD Research Fellow: the authors argue that in the USA, among patients with ABHL (or with symptoms typical of sarcoidosis), 5 people in 10,000, at most, will have an alternative diagnosis ascertained by means of mediastinoscopy; and that, in these 5, less than half are likely to benefit as a consequence of early diagnosis).

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