Modelling the cost-effectiveness of sentinel lymph node mapping and adjuvant interferon treatment for stage II melanoma
Wilson L S, Reyes C M, Lu C, Lu M, Yen C

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
Four strategies for managing patients with stage II melanoma were examined:

- treat all with low-dose interferon (IFN) after surgery;
- test and treat some, that is, test first with sentinel lymph node mapping (SLM) and treat those testing positive with high-dose adjuvant IFN while those testing negative get surgery alone;
- test and treat appropriately, that is, test first with SLM and treat those testing positive with high-dose IFN and those testing negative with low-dose IFN; and
- treat no one with adjuvant IFN, that is, treatment consists of surgery and observation only.

Type of intervention
Diagnosis and treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised hypothetical patients with stage II melanoma after surgical excision of their melanoma.

Setting
The setting was a hospital. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness and resource use data was came from studies published between 1994 and 2001. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from published studies.

Modelling
A modelling approach based on a decision tree was used to estimate the costs and benefits of the four strategies under examination. The time horizon of the model was 5 years. The model took recurrences and toxicity into consideration.
The decision tree was depicted graphically in the article.

**Outcomes assessed in the review**
The outcomes estimated from the published studies were:

- the probability of metastasis, and the sensitivity and specificity of the SLM test;
- the probability of toxicity or adverse events with low-dose IFN and high-dose IFN; and
- the probability of relapse-free survival (RFS) under a number of conditions. The conditions were:
  - no SLM, low-dose IFN plus surgery;
  - SLM, high-dose IFN plus surgery (for true-positive and false-positive results);
  - SLM, negative result, low-dose IFN (for true-negative and false-negative results);
  - SLM, negative result, surgery alone (for true-negative and false-negative results); and
  - no SLM, surgery alone.

The utility values associated with specific health states, which were considered in the decision model, were also derived from a published study. The literature was searched for evidence to support some assumptions made by the authors.

**Study designs and other criteria for inclusion in the review**
A formal review of the literature was not undertaken. Most of the studies used to derive the input probabilities were randomised trials, although the authors did not explicitly describe the design of the primary studies.

**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**
The effectiveness evidence was derived from approximately 9 studies.

**Methods of combining primary studies**
It appears that narrative methods have been used to combine the estimates derived from the primary studies.

**Investigation of differences between primary studies**
Not stated.
Results of the review

The probability of metastasis after the SLM test was 0.245.

The sensitivity of the SLM test was 0.99 and the specificity was 0.973.

The probability of toxicity or adverse events was 0.15 with low-dose IFN and 0.42 with high-dose IFN.

The probability of RFS was:

- 0.57 for no SLM, low-dose IFN plus surgery;
- 0.44 for SLM, high-dose IFN plus surgery for true-positive results and 0.49 for SLM, high-dose IFN plus surgery for false-positive results;
- 0.67 for SLM, negative result, low-dose IFN for true-negative results and 0.44 for SLM, negative result, low-dose IFN for false-negative results;
- 0.58 for SLM, negative result, surgery alone for true-negative results and 0.28 for SLM, negative result, surgery alone for false-negative results; and
- 0.49 for no SLM, surgery alone.

The low and high values for each probability were also reported.

The utility adjustment values were 0.9 for experiencing tolerable toxicity (no dose reduction), 0.835 for severe toxicity (requiring dose reductions), 0.62 for recurrence with prior IFN treatment, 0.61 for recurrence without prior IFN treatment, and 0.96 for disease-free state.

Based on data from the literature, the authors stated that SLM accurately detected micrometastasis to the sentinel lymph node, thus enabling the identification of eligible patients who could benefit from adjuvant IFN therapy. In addition, low-dose IFN led to an improvement in RFS in comparison with no treatment.

Measure of benefits used in the economic analysis

The summary health benefit used in the economic analysis was the quality-adjusted life-years (QALYs), considered as RFS after 5 years. This was obtained using the decision model. No discounting was performed. Patients who did not relapse or die after 5 years had an expected RFS of 5 years. For patients who relapsed, the mean time to relapse was calculated as the area under the RFS curve only for those patients who experienced a negative event (relapse or death). The utility weights were obtained from a published study (see Other Publications of Related Interest).

Direct costs

A 3% annual discount rate was applied to the costs that were incurred during the 5-year timeframe. The unit costs were reported separately from the quantities of resources used. The health services included in the economic evaluation considered six phases of the diagnostic and treatment approaches. These were diagnosis (visits and tests), surgery (surgical procedures, hospitalisations, laboratory tests, and visits), drug treatment and tests (visits, drugs, and diagnostic and laboratory tests), toxicity (treatment of side effects), relapse-free period (visits and tests), and recurrence costs (hospitalisations). The cost/resource boundary adopted in the study appears to have been that of the health care payer.

Resource use was estimated using probability data from the literature and the authors' assumptions. The follow-up protocol for stage II patients prior to recurrence was obtained from the Melanoma Clinic at the University of California, San Francisco. The unit costs were estimated from Medicare data and published studies (see Other Publications of Related Interest). The drug costs were based on average wholesale prices. Costs rather than charges were used and, when only charges were available (such as for physician fees), a Medicare cost-to-charge ratio of 0.45 was applied. All of the costs were inflated to 2001 values using the Consumer Price Index for each type of medical service.
item.

Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
One-way sensitivity analyses were conducted on all input probabilities to address the issue of variability in the data. The ranges of values used in the sensitivity analyses were derived from the literature. The costs of relapse and utility values were also varied. All model inputs were then varied simultaneously in a Monte Carlo sensitivity analysis to determine the distribution of the incremental cost-effectiveness ratio for 1,000 trials.

Estimated benefits used in the economic analysis
The estimated QA-RFS was 3.06 with surgery alone, 3.37 with test and treat some, 3.48 with treat all with low-dose IFN, and 3.68 with test and treat appropriately.

Cost results
The total costs per patient were $18,400 with surgery alone, $24,200 with test and treat some, $30,500 with treat all with low-dose IFN, and $33,800 with test and treat appropriately.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio was used to combine the costs and benefits of the four strategies.

The incremental cost per QALY was $18,700 with test and treat some over surgery alone, and $31,100 with test and treat appropriately over test and treat some.

The option of treat all with low-dose IFN was excluded by extended dominance in comparison with the test and treat some option.

The variables that had the greatest impact on the estimated cost per QALY were the relapse costs, probability of testing positive, and 5-year RFS probability for true negatives. Variations in the utility weights used to calculate the QALYs also had a modest impact.

The results of the Monte Carlo analysis showed that the 25th and 75th percentile values fell within reasonable cost-effectiveness ratios.

Authors' conclusions
The combination of more accurate staging with interferon (IFN) treatment (either high-dose therapy of those patients testing positive with sentinel lymph node mapping, or appropriate adjuvant IFN dosing) was a cost-effective approach for managing patients with stage II melanoma. However, the study aimed to clarify the economic consequences of the four treatment strategies, rather than suggest a treatment strategy, due to the uncertainty surrounding the IFN therapy.
CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was discussed. The authors considered surgery alone as the reference comparator because it represented the most conservative approach for treating patients with stage II melanoma. The remaining strategies represented more innovative approaches whose clinical evaluation is still underway. The use of SLM and IFN is currently under evaluation in ongoing trials. You should decide whether they represent valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence used in the decision model came from published studies. However, a formal review of the literature was not undertaken and the authors used the primary studies selectively. The study design was reported in some articles (clinical trials), whereas details of the study sample and other characteristics of the patients involved in the trials were not provided. Thus, the validity of the evidence used to derive the probability values was unclear. However, the authors conducted multivariate sensitivity analyses to deal with the issue of uncertainty surrounding the estimates.

Validity of estimate of measure of benefit
QALYs were used as the summary benefit measure in the economic analysis. The choice of QALYs appears to have been appropriate to estimate the impact of the four health interventions on the quality and quantity aspects of patient survival. The use of QALYs also permits the benefits of the interventions studied to be compared with those of other health technologies. However, it is worth noting that RFS was used rather than overall survival (a more commonly used measure for calculating QALYs) due to the lack of data on survival stratified by micrometastasis, while RFS data for a node-positive sub-group of patients were available. The method used to calculate RFS was described in detail in an appendix to the original paper.

Validity of estimate of costs
The authors stated that a societal perspective was adopted in the economic analysis. However, only the direct costs relevant to the health care system were included in the analysis. Thus, the perspective would have been more appropriately described as a payer perspective. A detailed breakdown of the costs was provided and the unit costs and price year were reported. This facilitates reflation exercises in other settings. It seems that all the relevant categories of costs have been included in the analysis, although the inclusion of the indirect and non-medical costs would have been interesting. The source of the cost data was reported for all cost items. The cost estimates were often derived from the literature. The costs were treated deterministically, but sensitivity analyses were conducted on the main cost driver (recurrence cost).

Other issues
The authors compared their findings with those obtained in three economic evaluations, carried out on the basis of data coming from a single trial on IFN. The conclusions were similar to those observed in the present study. The authors did not address the issue of the generalisability of the study results to other settings, although several sensitivity analyses were conducted. The fact that the cost and probability data were presented in detail simplifies the replication of the study and enhances the external validity of the analysis. The authors carried out an incremental analysis to combine the costs and benefits. This was appropriate as the more effective strategies were also more expensive. The authors discussed some limitations of their analysis, such as the use of data that had no yet been confirmed in the literature and the limited time horizon of the analysis.

Implications of the study
The study results suggested that the combination of SLM and IFN treatment represents a cost-effective approach for the management of patients with stage II melanoma. The authors noted that further clinical research should be conducted to evaluate the additional benefits of SLM.
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Other publications of related interest


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