Costs and effectiveness of staging and treatment options in early-stage Hodgkin's disease
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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 health interventions examined in the study were six two-step strategies for staging and treatment of Hodgkin's disease (HD):

Strategy 1: laparotomy, followed by mantle and para-aortic (MPA) radiation therapy if pathological stage (PS) I-II, combined modality therapy (CMT) if PS III1A, or chemotherapy alone if PS III2-IVA;

Strategy 2: laparotomy, followed by MPA radiation therapy if PS I-II, or CMT if PS III-IV;

Strategy 3: laparotomy, followed by mantle radiation therapy alone if PS I-II, CMT if PS III1A, or chemotherapy alone if PS III12-IVA;

Strategy 4: laparotomy, followed by mantle radiation alone if PS I-II or CMT if PS III-IV;

Strategy 5: no laparotomy and treatment of all patients in clinical stage (CS) I-II with MPA radiation therapy; and

Strategy 6: no laparotomy and treatment of all patients in CS I-II with CMT.

Type of intervention
Diagnosis and treatment.

Economic study type
Cost-effectiveness analysis; Cost-utility analysis.

Study population
The study population comprised patients with early-stage Hodgkin's disease.

Setting
The setting was hospital. The economic study was carried out in the USA.

Dates to which data relate
Data on effectiveness were gathered from studies published between 1978 and 1997. Quantities of resources were gathered from 1998 to 1997. The price year was 1999.

Source of effectiveness data
Effectiveness data were derived from a review of the literature, augmented by authors' assumptions.

Modelling
A decision analytic model, based on Markov cycles of one year, was constructed to assess costs and benefits of the six strategies in a hypothetical cohort of 25-year old patients with HD. The health states included remission, refractory disease, relapse, secondary leukaemia, secondary solid tumour, and secondary non-Hodgkin's lymphoma. Annual transition probabilities were conditional upon the pathological stage and initial treatment. The risk of death from HD, secondary malignancies, cardiac causes, or natural causes depended on patient's health state. The decision model presented in the study was the modified version of a previous model used to assess costs and benefits of HD staging and treating, but modifications were required to more accurately represent prevailing clinical patterns.

**Outcomes assessed in the review**

The model inputs estimated in the analysis were:

- the probability of upstaging for CS I-II patients, the probability of PS III1A disease among PS III-IV, and the probability of perilaparotomy death;
- the relapse rate of PS I-II treated with MPA radiotherapy, the relapse rate of PS I-II treated with mantle radiotherapy, the relapse rate of PS I-II treated with chemotherapy, and the relapse rate of PS I-II treated with CMT;
- the relapse rate of PS III1A treated with MPA radiotherapy, the relapse rate of PS III1A treated with chemotherapy, the relapse rate of PS III1A treated with CMT, the relapse rate of PS III2A-IV treated with MPA radiotherapy, the relapse rate of PS III1A treated with chemotherapy, and the relapse rate of PS III1A treated with CMT;
- the absolute excess risk (AR) for secondary leukaemia after radiotherapy, the AR for secondary leukaemia after CMT, or the AR for secondary leukaemia after chemotherapy, the AR for solid tumour after radiotherapy, the AR for solid tumour after CMT, or the AR for solid tumour after chemotherapy, the AR for secondary non-Hodgkin's lymphoma; the relapse after radiotherapy salvaged with conventional dose therapy, the limited relapse after chemotherapy salvaged with conventional dose therapy, the diffuse relapse after chemotherapy/CMT rejected for transplant salvaged with chemotherapy alone, the diffuse relapse after chemotherapy/CMT salvaged with transplant;
- the survival after development of secondary leukaemia, the survival after development of secondary solid tumour, and the survival after development of secondary non-Hodgkin's lymphoma; and
- AR for cardiac mortality after radiotherapy, CMT, or chemotherapy.

**Study designs and other criteria for inclusion in the review**

No inclusion criteria for studies in the review were reported. Although the authors stated that most of the evidence was derived from retrospective or prospective single arm 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**

Forty-four studies were used as source of the effectiveness outcomes.
**Methods of combining primary studies**

The effectiveness outcomes were combined using narrative methods.

**Investigation of differences between primary studies**

Not reported.

**Results of the review**

The results of the review were as follows:

The probability values were:

- 0.25 for upstaging for CS I-II patients, 0.86 for PS IIIA disease among PS III-IV, 0.05 for perilaparotomy death;

- 18.5% for relapse rate of PS I-II treated with MPA radiotherapy, 25.7% with mantle radiotherapy, 20% with chemotherapy, and 8.45% CMT;

- 18.5% for relapse rate of PS III1A treated with MPA radiotherapy, 20% with chemotherapy, and 8.45% CMT;

- 85% for relapse rate of PS III2A treated with MPA radiotherapy, 22% with chemotherapy, and 10.6% with CMT;

- 3/10,000 person years (pys) for AR for secondary leukaemia after radiotherapy, 34/10,000 pys after CMT, and 21/10,000 pys after chemotherapy;

- 73/10,000 pys for AR for solid tumour after radiotherapy, 96/10,000 pys after CMT, and 69/10,000 pys after chemotherapy;

- 16/10,000 pys for AR for secondary non-Hodgkin's lymphoma; 79.8% for relapse after radiotherapy salvaged with conventional dose therapy, 66.3% for limited relapse after chemotherapy salvaged with conventional dose, 45% for diffuse relapse after chemotherapy/CMT rejected for transplant salvaged with chemotherapy alone, and 63.8% for diffuse relapse after chemotherapy/CMT salvaged with transplant;

- 5% for survival after development of secondary leukaemia, 45% after development of secondary solid tumour, and 55% after development of secondary non-Hodgkin's lymphoma; and

- 19.7/10,000 pys for AR for cardiac mortality after radiotherapy or after CMT, and 0 for AR for cardiac mortality after chemotherapy.

**Methods used to derive estimates of effectiveness**

The authors made some assumptions on the utility weights used in the analysis.

**Estimates of effectiveness and key assumptions**

The utility values used for short-term quality of life adjustments were 0.7 for 6 months for chemotherapy, 0.5 for 8.4 months for CMT, 0.9 for 1.2 months for mantle radiotherapy, 0.7 for 2.4 months for MPA radiotherapy, 0 for 2 days for laparotomy, and 0 for 1.2 months for transplant.

The utility values used for long-term quality of life weights were 1 for remission state, 0.99 for both post-laparotomy state and relapse state, and 0.98 for both refractory disease state and secondary malignancy state.

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

The main benefit measure used in the economic analysis was quality-adjusted life-years (QALYs). Life-years (LYs) were also reported. A 3% discount rate was used for future benefits. Utility weights used to calculate QALYs were
derived from assumptions made by the authors.

**Direct costs**
A 3% discount rate was used as lifetime costs were calculated in the analysis. Unit costs and quantities of resources were reported separately for almost all cost items considered in the economic evaluation. The health service costs reported in the study were laparotomy, MPA radiation therapy, mantle radiation, chemotherapy, and CMT. The cost/resource boundary adopted in the analysis appears to have been that of the reimbursement system. Costs were based on actual data and were estimated from bills for three different samples of patients hospitalised at the Brigham and Women's Hospital. A charge to cost ratio was then applied to convert charges into costs. Professional costs were estimated using Medicare and commercial insurance reimbursement rates. Costs were inflated to 1999 (the price year) using the medical component of the US Consumer Price Index.

**Statistical analysis of costs**
Costs were treated deterministically in the base case.

**Indirect Costs**
Indirect costs were not included in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
One-way sensitivity analyses were conducted to assess the robustness of the decision model and to investigate the impact of data variability on the results of the analysis. Discount rate, utility values, cost estimates, and transition probabilities were all varied within the ranges reported in the published studies used as the source of the effectiveness evidence.

**Estimated benefits used in the economic analysis**
QALYs and LYS were reported only for the strategies not dominated. The estimated benefits were 19.60 QALYs and 19.83 LYS for strategy 5, 19.94 QALYs and 20.36 LYS for strategy 3, and 19.97 QALYs and 20.43 LYS for strategy 6.

**Cost results**
Only the costs of the strategies not dominated were reported. Overall costs were $26,900 for strategy 5, $35,000 for strategy 3, and $37,200 for strategy 6.

**Synthesis of costs and benefits**
Incremental cost-effectiveness and cost-utility analyses were performed to combine the costs and benefits of the six strategies. Strategies 1, 2, and 4 were dominated, meaning that there was at least one alternative more effective and less costly. As regards the remaining strategies, the incremental cost per QALY (and per LYS) was $24,100 (and $15,300) for strategy 3 over strategy 5, and $61,700 (and $32,800) for strategy 6 over strategy 3. Sensitivity analyses showed that these results were quite sensitive to minor variations in a number of model inputs, mainly due to the very small differences in effectiveness between some of the strategies. The analysis was particularly sensitive to variations in the discount rate and the utility value of the post-laparotomy health state.

**Authors' conclusions**
The authors concluded that strategy 6 (no laparotomy and CMT) represented the most effective strategy, but its cost per
QALY was $61,700 in comparison with strategy 3, which presented a cost per QALY of $24,100 over strategy 5. The authors acknowledged that these conclusions were highly sensitive to variations in several baseline assumptions.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear, as the authors included all possible strategies for staging and treatment of HD. However, the authors noted that some of the strategies may not have reflected actual clinical management options for patients with HD. You, as a user of this database, should decide whether they are widely used interventions in your own setting.

Validity of estimate of measure of effectiveness
The analysis of the effectiveness was mainly based on data derived from published studies, but no formal review of the literature was undertaken. Primary studies were combined using narrative methods and it was not stated whether potential differences between primary studies were considered when estimating effectiveness. However, the authors stated that, although baseline estimates may have been prone to bias, the model was validated, thus the potential biases were negligible. The utility values were estimated on the basis of a consensus of the senior authors of the study and the authors recognised that this process may have been arbitrary. Due to the uncertainty around these data, extensive sensitivity analyses were conducted to test the robustness of the study conclusions.

Validity of estimate of measure of benefit
LYs and QALYs were used as benefit measures in the economic analysis. The use of both QALYs and LYs enhanced the comparability of the benefit of the interventions assessed in the present study with those funded in the health care system. The decision model used to derive QALYs was validated using actual observed long-term data. Discounting was performed.

Validity of estimate of costs
The analysis of costs appears to have been conducted from the perspective of the reimbursement system and all relevant categories of costs were included in the analysis. Unit costs were reported separately from quantities of resources. Costs were treated deterministically in the base case, but several sensitivity analyses were conducted. The source of cost data was reported and the authors commented that the use of data derived from a single hospital may not have reflected national average costs. However, sensitivity analyses demonstrated that the estimated cost-effectiveness ratios were robust to variations in baseline costs. The price year was reported, thus simplifying reflation exercises to other settings, and appropriate discounting was performed. A charge to cost ratio was applied to convert charges into costs.

Other issues
The authors did not compare their findings with those from other studies. The issue of the generalisability of the study results to other settings was partially addressed as the authors stated that cost data may not have reflected national costs. However, extensive sensitivity analyses were conducted and the variables with the greatest affect on the results of the study were identified. The analysis referred to patients with HD and this was reflected in the conclusions of the analysis. The authors commented on some of the potential limitations of the study.

Implications of the study
The main implication of the study, as the authors noted, is that patient preferences should be taken into account when choosing the more appropriate strategy, as the cost-effectiveness of the strategies was driven by differences in effectiveness and utility. The fact that costs played a minor role in the analysis should be reassuring from the physician's perspective.

Source of funding
None given.