Cost-effectiveness analysis of computerized tomography in the routine follow-up of patients after primary treatment for 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
Three strategies for the diagnostic follow-up of patients after successful primary treatment for Hodgkin's disease (HD) were examined. The strategies were annual computed tomography (CT) for 10 years, annual CT for 5 years, and non-CT modalities only. Non-CT modalities included history and physical examination, routine blood work and chest X-ray. The CT modalities also included history and physical examination and routine blood work, but excluded chest X-ray. Routine CT examination involved the chest, abdomen and pelvis.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of asymptomatic patients (mean age 25 years) who had a complete response to primary treatment for HD. Two hypothetical cohorts of patients were considered and analysed separately. One cohort had Stage I-II HD and the other had Stage III-IV HD. Both cohorts were treated with doxorubicin, bleomycin, vinblastine and dacarbazine-based chemotherapy, with or without radiation therapy.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1992 and 2005. The dates to which the resource use referred were not reported. The price year was 2005.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and experts' opinions.

Modelling
A Markov decision analytic model was constructed to evaluate the costs and benefits of the alternative diagnostic strategies. The model had yearly cycles and a lifetime horizon. The health states considered were no evidence of disease, early-stage relapse, high-dose chemotherapy with autologous bone marrow transplant (ABMT) salvage, no evidence of disease after salvage, refractory disease and death. In each cycle, patients could die from HD, secondary malignancies, cardiac causes or natural causes.
Outcomes assessed in the review
The outcomes assessed from the literature were:

- the relapse rates for patients with Stage I-II HD and Stage III-IV HD;
- the proportion of patients with signs and symptoms with relapse;
- the sensitivity of history and physical examination plus non-CT modalities;
- the sensitivity and specificity of CT scan;
- the rate of death from high-dose chemotherapy with ABMT;
- the probability of death from conventional dose salvage and from high-dose chemotherapy with ABMT;
- the probability of high-dose chemotherapy after conventional salvage;
- the probability of complete response to high-dose chemotherapy;
- the probability of relapse after complete response to high-dose chemotherapy;
- the risk of progression after high-dose chemotherapy if advanced-stage at first relapse;
- death if persistent disease after salvage; and
- the utility values associated with specific conditions.

Study designs and other criteria for inclusion in the review
The authors did not report the methods and conduct of a systematic review of the literature. The primary studies appear to have been identified selectively. No information on the primary sources was provided.

Sources searched to identify primary studies
Not reported.

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

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

Number of primary studies included
Twenty-two studies provided the clinical data.

Methods of combining primary studies
A narrative approach appears to have been used to combine the primary estimates.

Investigation of differences between primary studies
Not reported.
Results of the review
The cumulative relapse rate by 10 years was 13% for Stage I-II HD and 30% for Stage III-IV.

The proportion of patients with signs and symptoms with relapse was 92%.

The sensitivity of history and physical examination plus non-CT modalities was 95%.

The sensitivity of CT scan was 80% (range: 71 to 88) and the specificity was 60% (range: 48 to 89).

The rate of death from high-dose chemotherapy with ABMT was 10% (range: 5 to 10).

The rate of death from conventional dose salvage was 3% (range: 3 to 5).

The probability of high-dose chemotherapy after conventional salvage was 50% (range: 24 to 50).

The probability of complete response to high-dose chemotherapy was 75% (range: 66 to 82).

Relapse after complete response to high-dose chemotherapy varied over time.

The risk of progression after high-dose chemotherapy if advanced-stage at first relapse was 1.66.

The annual probability of death if persistent disease after salvage was 66%.

Short-term disutility values were -0.01 for symptoms on follow-up, -0.02 for false-positive CT, -0.2 for high-dose chemotherapy, -0.15 for conventional dose salvage, and -0.3 for high-dose chemotherapy after failure of conventional salvage.

Long-term utility values were 1.0 for no evidence of disease, 0.9 for relapse, and 0.8 for persistent disease after high-dose chemotherapy.

Methods used to derive estimates of effectiveness
Some assumptions made by the authors or based on expert opinion were used to populate the decision model.

Estimates of effectiveness and key assumptions
The proportion of relapses that occurred in early stage was assumed to be 55%. The percentage of transformation from early to advanced-stage relapse if relapse was undetected within one cycle was 50%.

The rate of high-dose chemotherapy with ABMT was assumed to be 90% if early-stage relapse and 100% if advanced-stage relapse.

In the case of a false-positive CT result and biopsy, no patient experienced complications from the biopsy procedure (this assumption biased the analysis in favour of the CT strategies).

Measure of benefits used in the economic analysis
Two summary benefit measures were used in the economic analysis and were combined with the costs. These were survival and quality-adjusted life-years (QALYs). Both measures were derived using the modelling approach, and an annual discount rate of 3% was used. The QALYs were calculated by combining utility weights and survival, which were both derived from the literature.

Direct costs
The analysis of the costs included only the direct medical costs associated with history and physical examination, routine blood work, chest X-ray, CT (chest, abdomen and pelvis), work-up for positive CT (including both false- and
true-positives), early-stage relapse before salvage therapy, high-dose chemotherapy, conventional dose salvage therapy, advanced-stage relapse (biopsy and high-dose chemotherapy), and integrated care for last year of life in patients with progressive disease. Work-up for positive CT included per-procedural laboratory tests, CT for needle biopsy, fine-needle aspirate plus image, pathology processing, and cytology evaluation and report. Early-stage relapse before salvage therapy included office visit and laboratory tests, restaging scans, and biopsy to confirm relapse.

The unit costs were reported but quantities of resources used were not. The costs were derived from Medicare reimbursement rates and published studies. The sources of resource use were not reported. Discounting was relevant, as long-term costs were assessed, and an annual rate of 3% was used. The price year was 2005.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
A univariate sensitivity analysis was carried out to assess the robustness of the results to variations in all model inputs, including probability estimates, costs and utility values. The source of the alternative values was not reported.

Estimated benefits used in the economic analysis
In patients with Stage I-II HD, the expected survival was 21.24 years with non-CT follow-up and 21.25 years with both CT strategies.

The expected QALYs were 21.19 with non-CT follow-up, 21.17 with CT for 5 years, and 21.14 with CT for 10 years.

In patients with Stage III-IV HD, the expected survival was 19.33 years with non-CT follow-up and 19.36 years with both CT strategies.

The expected QALYs were 19.23 years with non-CT follow-up and with CT for 5 years, and 19.20 years with CT for 10 years.

Cost results
In patients with Stage I-II HD, the expected costs per patient were $14,000 with non-CT follow-up, $19,000 with CT for 5 years, and $24,000 with CT for 10 years.

In patients with Stage III-IV HD, the expected costs per patient were $23,000 with non-CT follow-up, $27,800 with CT for 5 years, and $32,100 with CT for 10 years.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios (i.e. the cost per life-year gained) and cost-utility ratios (i.e. the cost per QALY gained) were calculated to combine the costs and benefits of the alternative strategies.

In relation to the cost-utility ratios, the incremental analysis revealed that non-CT follow-up was the dominant strategy (both more effective and less expensive) than both CT-based strategies in patients with Stage I-II HD. In this cohort of patients, the incremental cost per life-year gained was $291,500 with CT for 5 years and $14,447,300 with CT for 10 years.
years (compared with non-CT follow-up).

In the cohort of patients with Stage III-IV HD, the incremental cost was $9,042,300 per QALY with CT for 5 years and $149,900 per life-year gained (compared with non-CT follow-up).

CT for 10 years was dominated within the cost-utility framework, while the incremental cost per life-year gained was $9,507,000.

The sensitivity analysis showed that, in most scenarios, CT strategies remained dominated by non-CT diagnostic work-up or had high cost-effectiveness or cost-utility ratios even in favourable scenarios. For example, in the cohort of early-stage patients, the sensitivity of CT could be as high as 100% but CT remained dominated.

Authors’ conclusions
The use of routine computed tomography (CT) in the follow-up of asymptomatic patients with complete response after primary treatment for Hodgkin's disease (HD) was not cost-effective in comparison with non-CT diagnostic strategies in both early- and advanced-disease in the USA.

CRD COMMENTARY - Selection of comparators
The choice of the comparators was appropriate and the authors justified their choice. Two different durations for CT-based strategies were considered. The authors stated that positron emission tomography was not considered to be a relevant comparator given the limited information available and the small number of patients involved in published studies. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were mainly derived from published studies. However, the authors did not report the methods and conduct of a systematic review of the literature. Thus, it appears that the primary studies might have been identified selectively. The authors did not report any information about the primary studies, thus it was not possible to assess the validity of the primary sources of data. Similarly, the issue of heterogeneity was not addressed and it was unclear whether procedures and patients were similar amongst the studies. Some assumptions were also made in order to bias the analysis in favour of CT strategies. Due to the uncertainty surrounding some clinical inputs, an extensive sensitivity analysis was run.

Validity of estimate of measure of benefit
Both benefit measures were appropriate and valid because they capture the impact of the intervention on (quality-adjusted) survival, which represents the most important dimension of health for patients with HD. The benefits were discounted according to US guidelines. Limited information on the utility weights used to calculate QALYs was provided, as these weights were derived from published studies.

Validity of estimate of costs
The analysis of the costs was restricted to the direct medical costs. A list of costs together with unit costs was presented, although some costs were reported as macro-categories and a detailed breakdown of cost items was not given. This was because of the use of costs derived from Medicare and other published studies. Details of resource consumption were not reported, which limits the possibility of replicating the analysis in other settings. The costs were treated deterministically, but the cost estimates were varied in the sensitivity analysis to account for variability in charges. The price year was reported, thus facilitating reflation exercises in other time periods.

Other issues
The authors reported the results in terms of the diagnostic accuracy of other studies, both in the pre- and post-CT era, and stated that these findings were similar to those observed in the current analysis. However, they stated that this was
the first cost-effectiveness analysis of routine CT follow-up of asymptomatic patients after complete response to HD therapy. The issue of the generalisability of the study results to other settings was not explicitly addressed, although the extensive use of sensitivity analysis should have enhanced the external validity of the study. The results of the base-case and sensitivity analyses were extensively presented.

**Implications of the study**

The study results do not support the use of CT strategies for surveillance of asymptomatic HD patients with complete response after primary treatment, despite the fact that US boards have recommended CT follow-up. The authors pointed out that "CT in follow-up of HD patients should be limited to investigation of symptoms or signs and avoided as a routine surveillance modality'.

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**Other publications of related interest**


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