Cost-effectiveness of screening for hepatocellular carcinoma in patients with cirrhosis due to chronic hepatitis C

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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
Screening for hepatocellular carcinoma (HCC) in patients with chronic hepatitis C and compensated cirrhosis was assessed. The strategies used combined abdominal ultrasonography (US) or computerised tomography (CT) with serum alpha-foetoprotein (AFP) at 6 to 12 month intervals.

Type of intervention
Screening.

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

Study population
The target population was a hypothetical cohort of 40-year-old patients with chronic hepatitis C and compensated cirrhosis (Child's class A) and no other risk factors for HCC apart from hepatitis C virus-related cirrhosis. This age group was selected so that screening started 15 to 20 years before the mean age of HCC occurrence.

Setting
Although not explicitly reported, the setting was likely to have been secondary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness evidence was derived from literature published from 1976 to 2003. The dates to which the resource use data related were not reported. Some costs were derived from literature published from 1984 to 1998. Prices relating to year 2003 were used.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies.

Modelling
A Markov model was used to estimate the costs and benefits of the screening strategies assessed. The Markov cycle length was 1 month. Screening was stopped at the age of 70 years. The model ran until all the patients died. During each month every patient faced the possibility of dying, remaining in the same state, progressing to the decompensated cirrhosis state (Child's class B or C), or entering other states. These other states represented various other scenarios with diagnosed or undiagnosed, and resectable or unresectable HCC.

Confirmatory diagnostic tests were performed on patients with positive screening results, symptoms suggestive of HCC,
or incidental laboratory or radiologic findings. Confirmatory tests included triphasic abdominal CT or magnetic resonance imaging, as well as US-guided fine-needle biopsy in selected patients. Patients diagnosed with HCC were treated with tumour resection for resectable lesions, or palliative treatment for unresectable lesions. Palliative treatment comprised transarterial chemoembolisation (TACE), percutaneous ethanol injection (PEI), or thermoablation. Liver transplantation was not modelled in the primary analysis, as donor organ shortages would not allow such an option. However, in a secondary analysis, liver transplantation was considered as a possible therapy for all eligible patients with or without HCC.

Outcomes assessed in the review
The outcomes assessed were:

excess annual mortality rates of different states of cirrhosis and HCC,

procedure-related mortality rates,

age-adjusted mortality rates,

progression rates of cirrhosis and HCC,

the incidence of HCC (new cases or recurrences after resection), and

the characteristics of screening and confirmatory tests.

Study designs and other criteria for inclusion in the review
Not stated.

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
At least 34 primary studies were included in the review.

Methods of combining primary studies
Although the authors appear to have combined the results of individual primary studies, the method used was not explicitly described.

Investigation of differences between primary studies
Differences between the primary studies were not discussed.

Results of the review
The excess annual mortality rate was:
0.02 for Child's class A cirrhosis and 0.21 for Child's class B/C cirrhosis;
0.96 for unresectable HCC;
0.05 for resectable untreated HCC (Child's class A);
0.04 (Child's class A) and 0.22 (Child's class B/C) for resected HCC;
0.11 (Child's class A) and 0.30 (Child's class B/C) for TACE- or PEI-treated HCC;
0.1 (first year) and 0.04 (subsequent years) for postliver transplant for HCC.
The perioperative HCC resection mortality rate was 0.04.
The perioperative mortality rate of liver transplant was 0.06
The laparotomy mortality rate was 0.01.
The TACE OR PEI procedure-related complication rate was 0.03.
Age-adjusted mortality rates were not reported.
The progression rate WAS 0.06 from Child's class A to Child's class B/C cirrhosis, 0.3 from resectable to unresectable HCC (untreated), and 0.2 from resectable to unresectable HCC (TACE treated).
The incidence of new HCC was 0.02 to 0.1 depending on the duration of cirrhosis.
The AFP-US combination had a sensitivity of 0.85 and a specificity of 0.8.
AFP alone had a sensitivity of 0.54 and a specificity of 0.93.
Confirmatory tests had a sensitivity of 0.95 and a specificity of 0.99.

**Methods used to derive estimates of effectiveness**
The authors made some few assumptions that were consistent with the literature.

**Estimates of effectiveness and key assumptions**
Treatment compliance was assumed to be 100% in the primary analysis and 70 to 99% in the secondary analysis. In addition, it was assumed that TACE or PEI entailed a "toll" of one day, which was apparently subtracted from the final life-year (LY) benefit.

**Measure of benefits used in the economic analysis**
The benefits were expressed as the LYs and quality-adjusted life-years (QALYs) gained. The health-state utilities for different stages of liver disease and HCC were derived from quality of life studies using standard gamble and time trade-off techniques. The QALYs were discounted at an annual rate of 3%. This might also have been the case for the LYs, but it was not explicitly stated.

**Direct costs**
The direct costs of the hospital were included. These comprised costs associated with laboratory tests, radiologic tests, intervention procedures, surgical procedures, outpatient care and terminal care. The laboratory tests were AFP screening and preoperative tests. The radiologic tests were US screening, triphasic abdominal CT, and hepatic angiography or portography. The intervention procedures comprised US-guided biopsy, TACE and PEI. The surgical
procedures included partial hepatectomy, laparotomy and liver transplantation. Outpatient care covered cirrhosis-related and post-transplant care. Terminal care covered cirrhosis or HCC-related terminal care and death from surgery.

The unit costs were reported. The quantities were an output of the model. All costs, with the exception of terminal care costs, were derived using micro-costing techniques based on a hospital cost accounting system. Such costs therefore reflected true costs rather than charges. The year to which the quantities and unit costs referred was not reported. The costs of terminal care costs were derived from literature published between 1984 and 1998. The total costs were derived using modelling. Year 2003 prices were used. The costs were appropriately discounted at an annual rate of 3%, as they were incurred over a patient's lifetime.

**Statistical analysis of costs**
The costs were treated deterministically. No statistical analysis of the costs was undertaken.

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

**Currency**
US dollars ($).

**Sensitivity analysis**
A sensitivity analysis was carried out to test the robustness of the results to a range of parameter values. A one-way sensitivity analysis was undertaken for all probability and utility values. Plausible ranges, based on the lowest and highest numbers reported in the studies in the review, were used. A sensitivity analysis of the costs was performed using 50% to 150% to 200% of the base-case value, if plausible. In addition, two- and three-way sensitivity analyses were conducted.

**Estimated benefits used in the economic analysis**
The total benefits of screening ranged from 8.634 to 9.093 LYs and from 6.269 to 6.661 QALYs per patient for all strategies evaluated (including the no screening option). The incremental benefits per patient for each strategy versus the next most efficacious strategy are listed here from the least to the most efficacious, so the incremental benefits refer to each strategy versus the previous strategy reported.

In the analysis that included only AFP-US strategies, the incremental benefits were:

- no screening, 0;
- annual AFP-US, 0.331 LYs and 0.300 QALYs;
- biannual AFP-annual US, 0.056 LYs and 0.048 QALYs;
- biannual AFP-US, 0.036 LYs and 0.033 QALYs.

In the analysis including both the AFP-US and AFP-CT strategies, the incremental benefits were:

- no screening, 0;
- annual AFP-US, 0.331 LYs and 0.300 QALYs;
- annual AFP-CT, 0.018 LYs and 0.014 QALYs;
- biannual AFP-annual US, 0.038 LYs and 0.034 QALYs;
biannual AFP-annual CT, 0.010 Lys and 0.008 QALYs;
biannual AFP-US, 0.026 Lys and 0.025 QALYs;
biannual AFP-CT, 0.013 Lys and 0.011 QALYs.

The benefits were incurred over a patient's lifetime. The QALYs were discounted at an annual rate of 3% (this might have been the case for the Lys, but it was not reported in the paper).

Cost results
The total costs of screening ranged from $46,232 to $58,232 per patient for all strategies evaluated (including the no screening option). The incremental costs per patient for each strategy versus the next most costly strategy are ranked here from the least to the most costly, so the incremental costs refer to each strategy versus the previous strategy reported.

In the analysis that included only AFP-US strategies, the incremental costs were:

no screening, 0;
annual AFP-US, $6,913;
biannual AFP-annual US, $1,588;
biannual AFP-US, 2,435.

In the analysis including both the AFP-US and AFP-CT strategies, the incremental costs were:

no screening, 0;
annual AFP-US, $6,913;
annual AFP-CT, $510;
biannual AFP-annual US, $1,078;
biannual AFP-annual CT, $414;
biannual AFP-US, $2,021;
biannual AFP-CT, $1,064.

The costs were incurred over a patient's lifetime and were discounted at an annual rate of 3%.

Synthesis of costs and benefits
The costs and benefits were combined in the form of incremental cost-effectiveness Ratios (ICERs). The ICERs were calculated for every screening strategy versus the next most efficacious strategy (in terms of QALYs). The least efficacious screening strategy was compared with no screening. The ICERs are listed here for the least to the most efficacious strategy, so comparisons are made between each strategy and the previous strategy reported.

In the analysis that included only AFP-US strategies, the ICERs were:

annual AFP-US (versus no screening), $20,885/LY and $23,043/QALY gained;
biannual AFP-annual US, $28,357/LY and $33,083/QALY gained;
biannual AFP-US, $67,639/LY and $73,789/QALY gained.

In the analysis including both the AFP-US and AFP-CT strategies, the ICERs were:

- annual AFP-US (versus no screening), $20,885/LY and $23,043/QALY gained;
- annual AFP-CT, $28,333/LY and $36,429/QALY gained;
- biannual AFP-annual US, $28,368/LY and $31,706/QALY gained;
- biannual AFP-annual CT, $41,400/LY and $51,750/QALY gained;
- biannual AFP-US, $77,731/LY and $80,840/QALY gained;
- biannual AFP-CT, $81,846/LY and $96,727/QALY gained.

The results were not substantially different in the secondary analysis, where compliance rates were assumed to be 70 to 99%. The ICERs were higher when the liver transplant option was modelled. In this situation, screening resulted in ICERs of $44,883/QALY (annual AFP-US), $38,684/QALY (biannual AFP-annual US) and $95,913/QALY (biannual AFP-US), compared with the next most efficacious screening strategy.

One-way sensitivity analysis did not change the rank order of the evaluated strategies. The ICERs ranged from $15,000 to $42,000/QALY for annual AFP-US, from $14,000 to $89,000/QALY for biannual AFP-annual US, and from $16,000 to $201,000/QALY for biannual AFP-US screening. The most influential parameter was the postresection mortality of HCC patients. Two- and three-way sensitivity analyses focusing on combinations of clinically related variables had no substantial impact on the results.

**Authors' conclusions**

Screening for hepatocellular carcinoma (HCC) in patients with chronic hepatitis C and compensated cirrhosis was as cost-effective as other accepted screening protocols. Of the strategies evaluated, biannual alpha-foetoprotein (AFP) combined with annual ultrasonography (US) gave the highest gain in quality-adjusted life-years (QALYs), while still maintaining a cost-effectiveness ratio of less than $50,000/QALY. Screening in patients awaiting liver transplant was also cost-effective. Biannual AFP combined with annual computed tomography (CT) might also be cost-effective.

**CRD COMMENTARY - Selection of comparators**

Several screening strategies for HCC in cirrhotic patients with chronic hepatitis C were evaluated. Screening for HCC is a widely used practice in the USA and other countries. One of the strategies evaluated was characterised as the most commonly used by gastroenterologists in the USA. You should decide whether any of these screening strategies reflect routine practice in your own setting.

**Validity of estimate of measure of effectiveness**

The authors did not state that a systematic review of the literature had been undertaken for any of the clinical parameters. The effectiveness estimates from the primary studies were apparently combined, but the method used was not reported.

**Validity of estimate of measure of benefit**

The estimation of QALYs and LYs was modelled. The utility weights were derived from the literature, but the methods used were not specified.

**Validity of estimate of costs**

Although the authors stated that the costs were estimated from a societal perspective, they excluded productivity losses.
All the relevant categories of direct medical costs were included in the analysis. Micro-costing techniques were used to estimate all the costs, which should therefore be accurate. The use of true costs that reflected resource use, instead of charges, was a strong point of the analysis. The authors noted that the estimated costs referred to an academic medical centre and community hospital costs might be somewhat lower. Discounting was appropriately undertaken since the costs were incurred over a patient's lifetime. The unit costs were reported. A sensitivity analysis of the costs was conducted, using plausible ranges. The date to which the prices referred was reported. All these latter points improve the generalisability of the results.

Other issues
The authors compared their findings with those from other studies and found them to be consistent. The issue of generalisability to other settings was not discussed (with the exception of academic medical centre care versus community hospital care costing issues), but an extensive sensitivity analysis was conducted. The authors considered some of the key assumptions in their model structure as limitations. For example, the kind of treatment following resectable HCC and the exclusion of interferon and ribavirin as treatment options. Nevertheless, some of their assumptions were examined in the secondary or the sensitivity analysis. The results of the study were reported in full. The authors' conclusions reflect the scope of the analysis.

Implications of the study
It can be inferred from the study conclusions that screening for HCC in a well-defined patient population should become (or remain) routine practice under an economic perspective. The authors did not recommend any specific screening protocol, but felt that annual US with biannual AFP was a reasonable strategy to follow, based on the study results. They suggested that further studies on the cost-effectiveness of screening with CT instead of US should be conducted.

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