Cost-effectiveness of hepatocellular carcinoma surveillance in patients with hepatitis C virus-related cirrhosis

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 model assessed the following strategies for surveillance for hepatocellular carcinoma (HCC).

Surveillance/resection: surveillance followed by resection of small or medium HCC in patients with compensated cirrhosis.

Surveillance/cadaveric liver transplantation (CLT): surveillance followed by CLT listing for small or medium HCC and compensated or decompensated cirrhosis, as well as decompensated cirrhosis without HCC.

Surveillance/living donor liver transplantation (LDLT): surveillance followed by LDLT for small or medium HCC and compensated or decompensated cirrhosis, as well as decompensated cirrhosis without HCC.

No surveillance programme: this represented the natural history of the disease.

Surveillance in this study consisted of surveillance with serum alpha-fetoprotein (AFP) and abdominal ultrasonography (US) every 6 months until age 70 years. Helical triple-phase computed tomography (CT) was performed after any positive screening test (AFP greater than 20 microg/L or mass on US).

Type of intervention
Screening and treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 45 year-old patients with HCV-related compensated cirrhosis.

Setting
The study setting was secondary care. The economic study was undertaken in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1980 and 2003. The resource use data were derived from Medicare schedules and studies published between 1996 and 2003. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies.
Modelling
A state-transition Markov model was created to simulate the natural history of HCV-related cirrhosis including the risk of decompensation, HCC, and death from liver disease or other causes. The principal health states were compensated or decompensated cirrhosis, without or with small ($\leq 2$ cm), medium (3 - 5 cm), or large (>5 cm or multifocal) HCC. Large HCC represented an untreated tumour. Patients with untreatable HCC received palliative care. The three surveillance strategies were then superimposed on the natural history model. Patients were followed until age 80 years or death. The transition cycles were every 6 months.

The model assumed that all patients were listed for CLT as soon as decompensation of cirrhosis was noted or HCC was confirmed by CT.

Outcomes assessed in the review
The outcomes assessed in the review were:

- the annual mortality rate from compensated and decompensated cirrhosis;
- the annual rate of cirrhosis decompensation; the annual HCC incidence;
- the probability of HCC growth;
- the annual mortality from untreatable HCC;
- the perioperative mortality from HCC resection;
- the annual mortality after HCC resection;
- the probability of CLT after listing;
- the perioperative mortality from CLT;
- the annual mortality after CLT;
- the perioperative mortality from LDLT;
- the annual mortality after LDLT;
- the sensitivity and specificity of AFP plus US; and
- the follow-up CT sensitivity.

Utilities were assessed for the compensated cirrhosis, decompensated cirrhosis, untreatable HCC, post-resection, post-CLT and post-LDLT health states.

Study designs and other criteria for inclusion in the review
Only English-language reports that provided data on HCV-infection, cirrhosis, HCC, screening, hepatic resection, CLT and LDLT were included in the review.

Sources searched to identify primary studies
MEDLINE was searched from 1980 to 2003 for primary studies.

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
Approximately 46 primary studies were included in the review.

Methods of combining primary studies
Some effectiveness parameters derived from the primary studies were combined using a narrative method.

Investigation of differences between primary studies
The authors did not report whether differences between the primary studies were investigated.

Results of the review
The annual mortality rate was 2% from compensated cirrhosis and 23% from decompensated cirrhosis.
The annual rate of cirrhosis decompensation was 4%.
The annual HCC incidence was 2%.
The probability of HCC growth, per 6-month cycle, was 45%.
The annual mortality from untreatable HCC was 70%.
The perioperative mortality from HCC resection was 5%.
The annual mortality after HCC resection was 20%.
The probability of CLT after listing ranged from 43% in the first 6 months to 11% in the fourth and later 6-month cycles.
The perioperative mortality from CLT was 5%.
The annual mortality after CLT was 8%.
The perioperative mortality from LDLT was 0.2% for the donor and 5% for the recipient.
The annual mortality after LDLT was 8%.
The sensitivity of AFP plus US was 79% and the specificity was 87%.
The follow-up CT sensitivity was 100%.
The utilities derived from the review were:
0.8 for compensated cirrhosis;
0.5 for decompensated cirrhosis;
0.3 for untreatable HCC; and
0.8 for post-resection, post-CLT and post-LDLT health states.
Methods used to derive estimates of effectiveness
The authors made several assumptions in order to derive outcomes.

Estimates of effectiveness and key assumptions
The authors assumed a sensitivity and specificity of 100% when CT was used as a confirmatory test.
The authors assumed an equal likelihood of CLT for HCC or decompensated cirrhosis.
The authors assumed identical HCC risk with decompensated cirrhosis.
The authors assumed that HCC caused mortality only once it was large.
The mortality rates for LDLT and CLT were assumed to be the same.

Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-years (QALYs) gained. The utilities for each of the health
states identified in the modelled were derived from the literature and from the authors' assumptions. The authors
assumed that asymptomatic HCC did not affect quality of life, and that quality of life was the same after successful
CLT or LDLT. They also assumed that quality of life after successful resection, CLT or LDLT was equivalent to
quality of life with compensated cirrhosis, and that LDLT donors had optimal health. The health benefits were
discounted at an annual rate of 3%.

Direct costs
The direct costs included in the analysis were those of the health care service or third-party payer. This included the
costs of screening, care of compensated, decompensated or untreatable HCC, treatment (i.e. resection, CLT and LDLT)
and care after treatment. The costs were derived from the literature and Medicare schedules. The authors assumed
equivalent costs for post-CLT and post-LDLT care. As costs could be incurred until the patients were 80 years old,
future costs were discounted at an annual rate of 3%. The study reported the average costs. The price year was 2000.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The indirect costs were not included.

Currency
US dollars (US $).

Sensitivity analysis
The authors examined the effect of changing the value of each variable in one-way and multi-way sensitivity analyses,
using ranges derived from the literature. They also undertook a probabilistic analysis (Monte Carlo simulation), in
which all model inputs were varied simultaneously and randomly for 3,000 iterations. The results were reported as
medians and with interquartile ranges (IQRs).

Estimated benefits used in the economic analysis
The QALYs gained per person were:
with natural history, 14.754 QALYs;
with surveillance/resection, 15.243 QALYs;
with surveillance/CLT, 17.334 QALYs; and
with surveillance/LDLT, 18.561 QALYs.

**Cost results**
The average cost per person was:
with natural history, $53,200;
with surveillance/resection, $63,500;
with surveillance/CLT, $173,500; and
with surveillance/LDLT, $245,400.

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the additional cost per QALY gained). When strategies were compared with natural history, the incremental cost per QALY gained was $26,100 for surveillance resection, $46,700 for surveillance/CLT and $50,400 for surveillance/LDLT. When surveillance/CLT was compared with surveillance/resection, the incremental cost-utility ratio was $51,400 per QALY gained. When surveillance/LDLT was compared with surveillance/CLT, the incremental cost per QALY gained was $58,400.

In the sensitivity analysis, the authors found that the results were dependent primarily on the benefits and costs of the radical therapies. The results also depended on the epidemiology and natural history of cirrhosis and HCC, and the routine costs of care for these conditions. The results were not sensitive, however, to changes in the sensitivity, specificity and costs of the surveillance tests. When the analysis was performed without quality of life adjustments, the costs per life-year gained increased by less than 7%.

The Monte Carlo simulation showed that the results did not differ significantly from the base-case. Compared with natural history, the additional costs per QALY gained for surveillance/resection were $18,000 (IQR: 11,200 - 30,300). Compared with surveillance/resection, surveillance/CLT gained QALYs in 2,525 out of the 3,000 iterations, at a median cost of $69,600 (IQR: 49,600 - 106,000) per QALY gained. Compared with surveillance/CLT, the additional costs per QALY gained for surveillance/LDLT were $58,400 (IQR: 44,100 - 79,200).

**Authors' conclusions**
Surveillance for hepatocellular carcinoma (HCC) in patients with compensated hepatitis C virus (HCV)-related cirrhosis had the potential to substantially increase quality-adjusted life expectancy at acceptable costs, irrespective of the treatment strategy adopted.

**CRD COMMENTARY - Selection of comparators**
The authors reported that they investigated the potential consequences of the most commonly used surveillance strategy (AFP and US every 6 months) followed by competing HCC treatments. However, the authors reported they did not model alternative surveillance methods explicitly (e.g. CT and magnetic resonance imaging), nor did they include all potentially relevant interventions (e.g. interferon therapy). You should decide if the interventions under study are current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The authors did not perform a systematic review of the literature to identify relevant research and minimise biases. However, they reported the sources searched to identify relevant research and the criteria for inclusion in the review. The review of MEDLINE appears to have been exhaustive and up to date, with over 45 studies published between 1980 and 2003 being included in the review. The authors, however, did not report how the estimates of effectiveness from the studies were combined, nor did they report if there were significant differences between relevant studies. Data from the trials were supplemented with the authors’ own assumptions. All assumptions and parameters used were appropriately varied in the sensitivity analyses using very wide ranges.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled using a decision analytic Markov model. As benefits could be accrued over a long time, future benefits were appropriately discounted at an annual rate of 3%.

**Validity of estimate of costs**
The perspective adopted in the economic analysis was not explicitly reported, but it appears to have been that of a third-party payer such as Medicare. All the categories of cost relevant to this perspective were included in the study. Further, all major cost components appear to have been included in the analysis. The costs and the quantities were not reported separately, which will limit the generalisability of the authors’ results. However, the total costs were itemised by resource category. The costs were derived from the literature or Medicare schedules. Appropriate sensitivity analyses (one-way and multi-way) and Monte Carlo simulations were performed. Since the costs could be incurred over a long time, the future costs were discounted appropriately. The price year was reported, which will aid any possible inflation exercises.

**Other issues**
The authors made appropriate comparisons of their findings with those from other studies that also found the outcomes of HCC surveillance were likely to depend on treatments and on population characteristics. The issue of generalisability to other settings was partially addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors reported a number of further limitations to their study. For example, they did not include all potentially relevant interventions, and there remained uncertainties about in vivo HCC growth characteristics and the comparison between CLT and LDLT.

**Implications of the study**
The authors reported that by diminishing delay until definitive treatment, LDLT might achieve the greatest gain in life expectancy in patients with HCV-related cirrhosis undergoing HCC surveillance. Prioritising HCC for CLT would increase the overall benefits for the population under surveillance.

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**Other publications of related interest**


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