Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis

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 technology studied was screening patients with cirrhosis of the liver (LC) to establish whether they have hepatocellular carcinoma (HCC). The screening programme consisted of ultrasonography (US) and analysis of a fetoprotein (AFP) every 6 months.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The population comprised patients with LC, referred to in the Department of Internal Medicine. The following were excluded:

(1) patients aged over 60 years in Child-Pugh class C;

(2) patients who had, in the past, received a diagnosis of a focal liver lesion using ultrasound; and

(3) patients with a serum AFP level of greater than 200 ng/dl.

(4) If, during the course of the study, a patient's health status changed to category (1) above, they were withdrawn from the study. Patients were also withdrawn if they developed other neoplasms or underwent orthotopic liver transplantation (OLT). All patients gave their informed consent.

Setting
The study setting was secondary care. The economic study was carried out in the University Hospital in Bologna Italy.

Dates to which data relate
The effectiveness evidence was collected during the period 1989-1997. The dates for the resource use were 1989-1997. The price year was not reported.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out on the same patient sample as that used in the effectiveness study, but it is not clear whether it was carried out prospectively or retrospectively.

**Study sample**

313 patients with LC were enrolled on to the screening programme (193 were men and 120 women). The mean age was 56.8 years (SD 11.97). The average age was 61.8 years (SD 10.3). Their health status was as follows:

- 64.2% had hepatitis C;
- 17.6% had hepatitis B;
- 29.7% had antibodies to the hepatitis B virus;
- 25.2% abused ethanol;
- 4.2% had primary biliary cirrhosis;
- 63.3% were in Child-Pugh class A;
- 32.9% were in Child-Pugh class B;
- 3.8% were in Child-Pugh class C;
- 82.4% had AFP less than 20ng/dl; and
- 17.6% had AFP greater than 20ng/dl.

When the study finished, 111 patients were still under surveillance, of whom 61 had developed HCC, and the others had died, were lost to follow-up or had entered category 4 above (see Study Population).

The patients in the surveillance programme were compared with 104 patients who had already been diagnosed with HCC. Their average age was 63.8 years (SD 11.1). No power calculations were carried out.

**Study design**

This was a non-randomised trial with concurrent controls, carried out in a single centre. The method of selection of patients per group was not stated. Patients were followed up until December 1997 unless they died or were lost to follow-up (24 patients).

**Analysis of effectiveness**

The analysis was based on treatment completers only. The following health outcomes were used:

1. number and size of HCC nodules detected;
2. eligibility of patients, detected with HCC, for treatment; and
3. survival of patients with HCC.

In terms of health status, age and sex ratio the control group patients differed from those in the surveillance group who turned out to have HCC. The differences in health status (in terms of HCC), were shown to be statistically significant. The authors did not compare the characteristics of the whole surveillance group with those of the control group.

**Effectiveness results**

The effectiveness results were as follows:
number of patients with HCC: surveillance group 61 (19.5% of total surveillance group), control group 104;
unifocal HCC at US: surveillance group 49, control group 55, (p<0.001);
diffuse HCC: surveillance group 6, control group 30, (p<0.01);
mean diameter (SD) (cm): surveillance group 2.73 (1.08), control group 3.34 (3.20);
eligible for treatment: surveillance group 42, control group 61;
number of deaths from HCC : surveillance group 37;
number of deaths from other causes: surveillance group 75;
median survival of HCC patients: surveillance group 30 months, control group 15 months, (p<0.02);
three-year survival of HCC patients: surveillance group 45%, control group 31.7%; and
median survival of all patients was: 92% versus 66% for Child-Pugh Class A, (p<0.05) and 71% versus 34% for Child-Pugh Class B/C, (p<0.05). However, it appears that this did not control for tumour staging, which was shown by multivariate analysis to have a coefficient with p<0.001. Also there appeared to be no statistically significant independent contribution of treatment group, as evidenced by the statement "if tumour staging was removed from the analysis, inclusion in the surveillance programme became significantly associated."

Clinical conclusions
The effectiveness measures used showed that surveillance had patients with statistically significantly fewer lesions, which were, on average, smaller, and that more patients who had undergone surveillance were eligible for treatment. It was also shown that those with HCC lived statistically significantly longer if they had been surveyed. Finally, surveillance seemed to have no independent, statistically significant effect on the whole group, after controlling for staging.

Modelling
Survival was calculated using life tables by the method of Kaplan Meyer. A multivariate model was used to control for variables associated with survival using input variables chosen by first using a univariate model. However, the multivariate model does not seem to have been used to control for prognostic factors for HCC patients only.

Measure of benefits used in the economic analysis
The measures of benefits used were number of treatable cases of HCC detected and number of years of life saved.

Direct costs
The following unit costs were given:

measuring APF;
ultrasound scan;
computed tomography;
echo guided biopsy;
transarterial chemoembolisation (TACE);
percutaneous ethanol injection (PEI); and orthotopic liver transplant (OLT).

Quantities and unit costs, as charges, were reported separately by procedure. The source was the costs given to the Bologna University Hospital by the National Public Health Service. The source of quantities was the University Hospital. The costs were converted from lire to US dollars, but a common price year was not used. No discounting took place. The following costs were not calculated: the cost of clinic visits for the surveilled group and the costs of tests which may have been performed for the unsurveilled group prior to the study.

**Indirect Costs**
No indirect costs were calculated.

**Currency**
US dollars ($), having been converted from Italian lire (L).

**Sensitivity analysis**
No sensitivity analysis was carried out.

**Estimated benefits used in the economic analysis**
The estimated benefits used in the economic analysis were as follows:

number of treatable cases of HCC detected by surveillance: 42 (69%);

number of treatable cases of HCC detected in the control group: 61 (59%);

median survival of HCC patients in the surveillance programme: 30 months; and

median survival of HCC patients the in control group: 15 months;

The side-effects of treatment were not considered.

**Cost results**
The total costs for diagnosis and treatment of patients in the surveillance programme and in the unsurveilled group were as follows:

APF: unit cost $14, surveilled group total $40,236, unsurveilled group total $1,456;

US: unit cost $47, surveilled group total $135,078, unsurveilled group total $4,888;

computed tomography: unit cost $1,530, surveilled group total $11,322, unsurveilled group total $15,912;

echo guided biopsy: unit cost $95, surveilled group total $5,700, unsurveilled group total $9,025;

PEI: unit cost $1,610, surveilled group total $22,540, unsurveilled group total $32,200;

TACE: unit cost $3,250, surveilled group total $165,750, unsurveilled group total $292,500;

hepatic resection: unit cost $11,970, surveilled group total $47,880, unsurveilled group total $99,850; and

OLT: unit cost $54,120, surveilled group total $324,720, unsurveilled group total $432,960.
Total Cost: surveilled group $753,226, unsurveilled group $858,791.

Synthesis of costs and benefits
Cost per treatable HCC: surveilled group $17,934, unsurveilled group $14,555.

The cost of an extra year of life saved as a result of the surveillance programme was $112,996 for HCC patients only.

Authors' conclusions
The authors concluded that although the surveillance programme increased the number of years lived, the cost of this gain was rather high. They compared the cost per year saved of $112,996 with that of the breast screening programme which gives a result of $13,000-28,000 per year of life saved, the implication being that only a wealthy country would consider this a cost worth paying.

CRD COMMENTARY - Selection of comparators
The selection of no screening would be justifiable where this is current practice. However, the criteria by which patients were referred to the clinic, including the symptoms with which they presented, were not clear.

Validity of estimate of measure of effectiveness
The study design was limited in several ways. The average age in the unsurveilled group was 2 years greater than that in the surveilled group. The authors did not show that the two groups were comparable in terms of characteristics other than their HCC status. The authors stated that a randomised study comparing survival from HCC in surveilled and unsurveilled patients would be unrealistic and possibly unethical. However, the effects of the surveillance programme could only be properly identified if the two groups were at the same stage in their illness as well as being comparable in other respects. The control group was clearly at a later stage of the disease and so one would expect survival from diagnosis to be longer in the surveilled group. However, it is still possible that some selection bias was present, not in terms of stage of disease, given that it is by this mechanism that surveillance is expected to work, but because it is impossible to know whether, independent of staging, the groups differed in terms of prognosis, since it is not clear that there was any control for prognostic factors independent both of staging and technology.

The estimate of effectiveness was incomplete in that the side-effects and indirect costs of surveillance were not included.

Validity of estimate of measure of benefit
As the authors acknowledge, by using treatable cases, one is disregarding the benefit of avoiding false positives. Also, having an adjustment for quality of life might have been useful.

Validity of estimate of costs
Unfortunately, no discounting took place, no adjustment to a common price year was made and the authors did not give details of how the conversion from Italian lire to US dollars took place. Although the authors correctly stated that resource quantities are more generalisable and that others can apply their own unit costs, sensitivity analysis on the different components of costs would have been useful for decision makers in other locations. The authors stated that costs for the control group might have been underestimated, as not all the procedures undertaken before the study began were known; this underestimation would have acted against the cost-effectiveness of the surveillance programme. On the other hand some costs in the surveillance programme were not calculated either. The indirect costs of the surveillance programme were obviously large and should have been calculated.

Other issues
The authors made appropriate comparisons of their results with those from other studies. As stated, they were aware of
many of the limitations of their study and do not appear to have been selective in the presentation of the results. Given that the selection bias has not been clearly controlled for, it is difficult to fully accept the author's conclusions regarding this population.

**Implications of the study**
The authors state that their study would not provide a strong case in favour of surveillance because of its high cost. However, although it is not surprising that surveillance increases benefit through early detection and better treatment, the extent of this is unclear from this paper and much of the costing is not available. Comment In: Gut 2001; 48(2):149-50.

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