Serum Alpha-Fetoprotein (AFP) and/or Ultrasound (US) for Hepatocellular Carcinoma (HCC) Screening
Executive Summary

[Adapted from the report by SYFUL AZLIE MD FUZI]

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Background

Most primary liver cancers are classified as hepatocellular carcinoma (HCC). According to the World Health Organization (WHO) and GLOBOCAN 2008, liver cancer is the seventh most common form of cancer worldwide and the third leading cause of cancer-related death globally. While more recent data is yet to be published, going by the numbers provided in the National Cancer Registry (NCR) in 2006, liver cancer was then already ranked the sixth most frequent cancer, fifth among males and ninth among females in Malaysia. Chronic hepatitis B virus (HBV) affects around a million patients in Malaysia (2004) which accounts for majority of the diagnosed HCC (> 80.0%). However, there is currently no formal/structured national liver cancer screening programme being implemented. Screening for HCC in the high-risk group using test method such as serum alpha-fetoprotein (AFP) and imaging method such as ultrasound (US) on the other hand, has become widely applied despite lack of published evidence of benefit on these various methods used. With the significant burden of liver cancer globally and locally, one of the strategies for early detection of cancer in the Malaysian National Cancer Management Blueprint 2008-2015 is to provide service on liver cancer screening. Therefore, this Health Technology Assessment (HTA) is requested to review evidence on the efficacy/effectiveness and cost-effectiveness of using serum AFP and/or US for HCC detection in the high-risk group in MOH facilities. The high-risk groups for developing HCC include chronic liver infection due to hepatitis and liver cirrhosis. With regards to hepatitis, the common infection is HBV and infrequently common is the HCV infection.

Technical Features

Two commonly used methods for liver cancer screening are serum alpha-fetoprotein (AFP) and ultrasound (US) examination of the liver. However, there are limitations to the usefulness of these methods. It is uncertain which method is better or whether the two should be combined.

Policy Question

i. Should a screening programme for HCC in the high-risk group be established as part of the Malaysian National Cancer Control Programme?
ii. Which methods namely using serum AFP alone or US alone or combined is most suitable to be used for HCC detection in the high-risk group?

Objective

i. To determine the benefits of HCC screening programme in the high-risk group using serum AFP and/or US compared with no screening, with regards to patient outcomes such as detection rate, mortality rate, survival rate, quality of life (QOL) and quality adjusted life years (QALY) gained
ii. To determine the diagnostic accuracy of serum AFP and/or US for HCC detection in the high-risk group
iii. To determine the cost-effectiveness of using serum AFP and/or US for HCC detection in the high-risk group

Methods

The following electronic databases were searched: MEDLINE (1950-Week 3 March 2012), EBM Reviews-Cochrane Database of Systematic Reviews (2005 to May 2012), EBM Reviews-Cochrane Central Register of Controlled Trials (1st Quarter 2012), EBM Reviews-HTA Databases (1st Quarter 2012), EBM Reviews-Cochrane Methodology Register (1st Quarter 2012), EBM Reviews-ACP Journal Club (1991 to May 2012), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2012) via OVID, PubMed, INAHTA database, HTA database and US FDA

database. The last search was run on 10 May 2012. No limits were applied to the search. Detailed search strategy is as in Appendix 4. Additional articles were identified from reviewing the bibliographies of retrieved articles and hand-searching of journals. General search engine was used to get additional web-based information.
Result and conclusion

Results and conclusion:
Effectiveness of HCC screening using serum AFP and/or US

The available evidences on HCC screening for mortality and survival from three large randomised controlled trials and one cohort study were conflicting. However, most studies showed that using serum AFP and/or US were more effective than no screening. Zhang BH et al. trial in Shanghai reported a significantly lower HCC mortality rate in the screened group than in controls, being 83.2 per 100,000 and 131.5 per 100,000 respectively with a mortality rate ratio of 0.63 (95% CI: 0.41 to 0.98). In contrast, two other trials, Yang et al. (Shanghai) and Chen et al. (Qidong) did not differ significantly regarding HCC mortality. Yang et al. and Zhang BH et al. reported the overall survival rate at five-year was better in screened group than in controls (52.7% and 46.4%, respectively), whereas there was no difference in five-year survival between the screened group and the control group in Chen et al. trial. A prospective 16-year population-based cohort study showed a significant survival benefits at five and 10 years in screened hepatitis B surface antigen positive (HBsAg+ve) Alaskan native carriers compared with historical controls (42.0% and 30.0%, respectively).

Diagnostic accuracy of serum AFP and/or US

There was good level of evidence to suggest that the sensitivity and specificity of serum AFP varies with the cut-off value or positivity threshold. At cut-off value between 20 ng/mL and 200 ng/mL, the sensitivity of AFP alone ranged from 41.0% to 80.0% and 20.0% to 45.0%, whereas specificity ranged from 80.0% to 95.0% and 99.0% to 100.0%, respectively. For US alone, the sensitivity varies from 60.0% to 94.0% and specificity from 94.0% to 97.1% in detecting HCC tumour nodules, varied by characteristics of liver diseases in screened patients, screening frequency, operator expertise as well as on the type of US equipment available. The sensitivity and specificity improved when a combination of AFP and US were used sequentially, at 92.2% and 95.0% respectively, particularly for HCC related with chronic liver infection (HBV). However for HCC related to cirrhosis, the combination of AFP and US gave the sensitivity of 69.0%. The overall positive predictive value (PPV) ranged from 3.0% to 6.6% whereas false positive rate ranged from 2.9% to 7.5%.

Economic evaluation

There was good level of evidence to suggest that:

i. The use of US alone at 6-month intervals in detecting HCC was not only more effective but cheaper than AFP test alone. However, the combined tests not only increased the efficacy of HCC detection but also increased the false positive rate and the cost
ii. The use of US at 12-month intervals and AFP at 6-month intervals was a reasonable strategy, offering the greatest gain in life-expectancy while still maintaining an ICER < USD$50,000 (RM150,000) per QALY
iii. At willingness to pay threshold of £30,000 (RM150,000) per QALY, the most cost-effective strategy is 6-monthly AFP-triage with ICER of £27,600 (RM138,000) per QALY gained

However, economic evaluation review was subjected to several limitations. It must be emphasized that the cost-effectiveness of HCC screening were assessed by

retrospective analysis or by using decision models. Although retrospective studies suffered from selection bias, decision-analysis models were based on simulation of costs and health outcomes and therefore, their results may vary greatly according to different assumptions, such as the incidence of HCC in the screening population, the screening interval, the modality of diagnosis, the type of treatment after diagnosis, the doubling time of tumours, and so forth.

In the Malaysian context, the fees charged by MOH hospital for serum AFP is approximately RM35.00 per test, while US varied from RM17.00 to RM100.00 per imaging. Ultrasound machines cost about USD$10,000 and range up to USD$200,000 (RM30,000 to RM600,000). The price depends largely on the level of complexity of the machine.

Recommendation:
Based on this review, good level of evidence on effectiveness (with respect to mortality and survival rate) showed that there was benefits in screening for HCC using serum AFP and/or US in the high-risk group and hence, can be established as part of the Malaysian National Cancer Control Programme. The decision to enter a patient into a *screening programme is determined by the level of risk for HCC and hence, **surveillance is recommended for the following groups of patients:

i. Hepatitis B carriers:
    - Asian males ≥ 40 years
    - Asian females ≥ 50 years
ii. All cirrhotic hepatitis B regardless of age
iii. Family history of HCC
iv. Liver cirrhosis
    - Hepatitis C
    - Alcoholic cirrhosis
    - Genetic hemochromatosis
    - Primary biliary cirrhosis

There was also good level of evidence to show that the combination of serum AFP and US is the most suitable method to be used for HCC detection, particularly for HCC related with chronic liver infection due to HBV. In addition, the recommended cut-off level of serum AFP was ≥ 20.0 ng/mL, as evidence showed that there was optimal balance between sensitivity and specificity in detecting HCC at this cut-off level.

From the cost-effectiveness perspective, most of the studies in the review indicated that 12-months screening interval using serum AFP plus US was as cost-effective as the 6-months interval using serum AFP alone. Hence, the screening interval of 6 to 12 months was a reasonable cost-effective strategy for surveillance of HCC.

However, before commencing the screening programme for HCC detection, it should be noted that currently in Malaysia, serum AFP test are conducted at laboratory hospitals with immunoassay facilities which covers MOH state hospitals and hospitals with specialist amounting to 36 MOH hospitals (personal communication with Head of Chemical Pathology Activities, MOH). Meanwhile, US examination of the liver is only conducted in 39 MOH hospitals with radiologist (personal communication with Head of Radiology Service, MOH).

Footnote:
*Screening – application of diagnostic tests in patients at risk for HCC, but in whom there is no a priori reason to suspect that HCC is present.
**Surveillance – the repeated application of screening tests.