Original Article

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Systematic Review of Economic Evaluation of the Surveillance Programs for Hepatocellular Carcinoma (HCC) in Chronic Hepatitis B Patients

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Abstract

Liver cancer is the sixth most frequent form of cancer worldwide and is the third leading cause of cancer-related mortality. Many current surveillance programs for HCC have continuously shown to reduce the burden of HCC. However, the cost-effectiveness information of such programs has been still limited. The objective of this study was to systematically review the studies related to economic evaluation of the surveillance program for HCC in chronic hepatitis B patients. Studies comparing cost and outcomes of surveillance program related to HCC in patients with hepatitis B were searched through Pubmed and Cochrane databases during 2001 and 2011. One-hundred and fifteen articles were reviewed and only eligible five full-text articles were included. Five studies were conducted in Italy, the United Kingdom, Taiwan, the Netherlands and the United State. Alternative surveillance strategies were compared with no surveillance program or usual clinical practice. The perspective of healthcare provider, government, or health system was used. Costs were collected based on the perspective used in the Most studies used model based approach (i.e., decision tree model and/or Markov model), while the study in Italy did not. Incremental cost-effectiveness ratio (i.e., cost per quality-adjusted life year or cost per life year gained) was used to present the cost-effectiveness results. Our systematic review results indicated that the surveillance program related to HCC in patients with hepatitis B would be cost-effective in most developed countries. However, further study should be investigated whether such program would be cost-effective in Thailand, a high prevalence area of hepatitis B.

Key words: Economic evaluation, Surveillance program, Liver, Neoplasm, Hepatitis B virus, Hepatocellular carcinoma

INTRODUCTION

Liver cancer is the sixth most frequent form of cancer worldwide and is the third leading cause of cancer-related mortality. It has been estimated that approximately 650,000 persons die each year from hepatocellular carcinoma (HCC) and at least two-thirds live in the Asia-Pacific region especially low or middle-income countries.

The screening of patients at risk group seems logical and has been widely embraced by hepatologists around the world. The most proven survival benefit in large randomized studies was in China[1]. It was indicated that the surveillance programs could

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detect tumors at an earlier stage, could increase the chances of performing a potentially curative or radical therapy and finally could gain the patients' survival.

The range of available screen modalities for HCC has expanded. They consisted of the measurement of alpha-fetoprotein (AFP) concentration, ultrasonography (US), computed tomography (CT) and/or magnetic resonance imaging (MRI) every 3-12 months. The relative performance and cost-effectiveness of these tests in surveillance programs of HCC have not been evaluated in low or middle income countries in Asia yet. The economic evaluation information of such programs has been still very limited. Therefore, the objective of this study aimed to systematically review the economic evaluation studies of the surveillance programs for HCC in chronic hepatitis B patients.

MATERIALS AND METHODS

Studies comparing cost and outcomes of surveillance program related to HCC in patients with hepatitis B were searched through Pubmed and Cochrane databases during 2001 and 2011. The different keywords and Mesh terms were used to identify the relevant economic evaluation studies. The searching keywords and Mesh terms contained hepatocellular carcinoma, epidemiology, SEER program, early detection of cancer, mass screening, diagnosis, surveillance, screening, cancer prevention, cost benefit analysis, cost utility analysis, cost effectiveness analysis, CUA, CBA, CEA and economic evaluation. English and human studies were included. Studies that were not cost-effectiveness or cost-utility analyses and studies that did not contain original analyses were excluded. Only studies with hepatitis B-related populations were included, so that the studies conducted in other HCC risk groups such as hepatitis C or alcoholic individuals were excluded. Both the choices of method used and results of economic evaluation were reviewed.

RESULTS AND DISCUSSION

One-hundred and fifteen articles were reviewed and only eligible five full-text articles were included. Five studies were conducted in Italy[2], the United Kingdom (UK)[3], Taiwan[4], the Netherlands[5] and the United State (US)[6]. The perspective of healthcare provider, government, or health system was used. Costs were collected based on the perspective used in the study. The research design of most studies was a model-based approach (i.e., decision tree model and/or Markov model). The studies in the United Kingdom (UK)[3], the Netherlands[5] and the United State (US)[6] used Markov model, whereas the study of Taiwan[4] used both a 1-year decision tree and 60-year Markov cohort simulation model to assess the short and long-term costs and outcomes. Effectiveness data of most studies using a model based approach were derived from the previous published studies. Both costs and effectiveness were discounted at 3-5%. However, only study of Italy used a cohort study of Italian patients with liver cirrhosis enrolled in the surveillance program during 1989-1991 and compared with the consecutive patients with incidentally detected at the same period. The economic evaluation was measured in term of cost per treatable HCC and cost per life year saved from the charge of the hospital and eligibility for treatment or survival of patients at the end of cohort study (Table 1).

Moreover, the alternative HCC surveillance strategies used in all studies as well as the results of cost-effectiveness analysis are presented in Table 2. All studies compared alternative HCC surveillance strategies with no surveillance program or usual clinical practice. Incremental cost-effectiveness ratio (ICER) was used to present the cost-effectiveness results in terms of cost per treatable HCC, cost per life year saved (LYS), cost per quality-adjusted life year (QALY) or cost per life year gained (LYG).

Table 1. Results of a systematic review

Study	Country	Research design	Target populations	Perspective
Bolondi et al (2001)[2]	Italy	Cohort study	Patients with liver cirrhosis without HCC	Provider
Thompson et al (2008)[3]	UK	Model-based	Patients with cirrhosis (separate cohort for alcoholic liver disease, Hepatitis B and C)	Government
Shih et al (2010)[4]	Taiwan	Model-based	Taiwanese individuals born before 1984a	Government
Veldhuijzen et al (2010)[5]	The Netherlands	Model-based	Migrants born in intermediate to high-prevalence HBV countries	Health system
Andersson et al (2010)[6]	US	Model-based	50-year-old patients with cirrhosis	Health system

[a]The year when the national hepatitis B vaccination program was implemented

It was found that the HCC surveillance programs seemed cost-effective particularly in screening individuals with hepatitis B-related cirrhosis. The economic evaluation results of each surveillance strategy were quite varied among all studies. The result of Italy study did not represent an exact ICER but offered the idea of the expenditure requested. Although, the cumulative survival rate of the patients with liver tumors detected in the surveillance program was significantly longer than that of no surveillance program and the results seemed beneficial in term of the cost per treatable HCC and the cost per life year saved, the study still provided the policy recommendation that the adoption of HCC surveillance program should rely on the prevalence of the disease and healthcare resources in the country.

For those studies representing the ICER values, if the ICER values of the intervention are below the societal willingness to pay of the country, it means that the intervention would be cost-effective. Based on the results from the study in UK, having alpha-fetoprotein (AFP) triage every year or every six months seemed cost-effective. However, the addition of ultrasound would increase the ICER value and would not be cost-effective in the UK. On the contrary, having annual ultrasound and every six months in the United State would be more cost-effective than other alternative strategies. Furthermore, a two-phase economic model of the mass screening campaign and subsequent continuing surveillance for HCC in Taiwan demonstrated that having AFP every 3-6 months would be potentially cost-effective compared to usual clinical practice. Correspondingly, the systematic screening for chronic hepatitis B infection followed by additional diagnostics and treatment among migrants with the goal of improving chronic hepatitis B outcome included HCC was cost-effective in the Netherlands.

One-way, two-way and probabilistic sensitivity analyses were applied to test the parameter uncertainty. The analyses showed that the influential factors on ICERs were probability of disease progression (tumor growth rate), mortality rate, disease prevalence, the mean age at diagnosis in individuals with hepatitis B-related cirrhosis, patient compliance, discounting rate, probability of liver transplantation and probability of HCC treatment in compensated cirrhosis.

Table 2. Cost-effectiveness analysis results summarized from a systematic review

Country (Willingness to pay per QALY gained)	Alternative HCC surveillance strategies	ICER results
Bolondi et al (2001)[2]	No surveillance	
	AFP+US every 6 months	No ICER represented
Thompson et al (2008)[3]	No surveillance	
(£ 20,000)	Annual AFP-triage	£ 10,200 per QALY gained
	Annual US	Dominated by no surveillance
	Annual AFP+US	Extendedly dominated by no surveillance
	AFP-triage every 6 months	£ 12,700 per QALY gained
	US every 6 months	Dominated by no surveillance
	AFP+US every 6 months	£ 26,800 per QALY gained
Shih et al (2010)[4]	Usual clinical practice	
(NT$ 1,070,000)	AFP every 3-6 months	NT$ 402,000 per LYS
Veldhuijzen et al (2010)[5]	The status quo (no screening)	
(euros 20,000)	Systematic hepatitis B screening + diagnostics	euros 8,966 per QALY gained
Andersson et al (2010)[6]	No surveillance	
(US$ 50,000)	Annual US	US$ 21,200 per QALY gained
	Annual CT scan	Dominated by US every 6 months
	Annual MRI	Dominated by US every 6 months
	US every 6 months	US$ 30,700 per QALY gained
	AFP/US every 6 months	US$ 73,500 per QALY gained
	CT scan every 6 months	US$ 331,800 per QALY gained

CONCLUSION

Our systematic review results suggested that the surveillance program related to HCC in patients with hepatitis B appeared to be cost-effective in most developed countries. A particular country had to take a consideration about choosing the alternative strategy that demonstrated the economic efficiency in their contexts. Nevertheless, further study should be investigated whether such program would be cost-effective in Thailand, a high prevalence area of hepatitis B.

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