RESEARCH ARTICLE

Economic Evaluation and Budget Impact Analysis of the Surveillance Program for Hepatocellular Carcinoma in Thai Chronic Hepatitis B Patients

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Abstract

Background: The incidence rate and the treatment costs of hepatocellular carcinoma (HCC) are high, especially in Thailand. Previous studies indicated that early detection by a surveillance program could help by down-staging. This study aimed to compare the costs and health outcomes associated with the introduction of a HCC surveillance program with no program and to estimate the budget impact if the HCC surveillance program were implemented. Materials and Methods: A cost utility analysis using a decision tree and Markov models was used to compare costs and outcomes during the lifetime period based on a societal perspective between alternative HCC surveillance strategies with no program. Costs included direct medical, direct non-medical, and indirect costs. Health outcomes were measured as life years (LYs), and quality adjusted life years (QALYs). The results were presented in terms of the incremental cost-effectiveness ratio (ICER) in Thai THB per QALY gained. One-way and probabilistic sensitivity analyses were applied to investigate parameter uncertainties. Budget impact analysis (BIA) was performed based on the governmental perspective. Results: Semi-annual ultrasonography (US) and semi-annual ultrasonography plus alpha-fetoprotein (US plus AFP) as the first screening for HCC surveillance would be cost-effective options at the willingness to pay (WTP) threshold of 160,000 THB per QALY gained compared with no surveillance program (ICER=118,796 and ICER=123,451 THB/QALY), respectively. The semi-annual US plus AFP yielded more net monetary benefit, but caused a substantially higher budget (237 to 502 million THB) than semi-annual US (81 to 201 million THB) during the next ten fiscal years. Conclusions: Our results suggested that a semi-annual US program should be used as the first screening for HCC surveillance and included in the benefit package of Thai health insurance schemes for both chronic hepatitis B males and females aged between 40-50 years. In addition, policy makers considered the program could be feasible, but additional evidence is needed to support the whole prevention system before the implementation of a strategic plan.

Keywords: Cost-utility analysis - HCC - hepatitis B - early detection - policy formulation - budget impact analysis

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Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancers with the greatest portion worldwide. It is the sixth most prevalent of cancer and the third leading cause of cancer-related mortality (Ferlay et al., 2010). It has been estimated that approximately 650,000 persons died each year from HCC, among whom at least two-thirds live in the Asia-Pacific region (Farrell et al., 2010). In addition, HCC is the most common cancer in Thailand. The assessment of the incidence of HCC from the database of the Khon Kaen Registry (KKCR) indicated that overall age-standardized rates (ASR) were 30.3 per 100,000 in males (95%CI: 25.9 to 34.6) and 13.1 per 100,000 (95%CI: 10.4 to 15.8) in females (Wiangnon et al., 2012). In Asia including Thailand, most HCC cases are associated with cirrhosis related to chronic hepatitis B (CHB) viruses (El-Serag 2012; Somboon et al., 2014). Some CHB patients who develop liver diseases would receive treatment, and finally might successfully suppress the viruses, while others would proceed to cirrhosis and/or HCC (Hutton et al., 2011).

To detect whether CHB patients would develop to HCC, many current clinical practice guidelines have

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recommended the use of ultrasonography (US) with or without serum alpha-fetoprotein (AFP) determination for screening and surveillance (Patel et al., 2012; Songdo and Bae, 2012). Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) have been recommended in case of positive finding at US surveillance in order to confirm the test's result more definitively (Tang et al., 2013). CT and MRI could help establish noninvasive diagnosis, assess therapeutic response and provide treatment decision (Chamadol et al., 2013). Moreover, if the lesion shows atypical findings of HCC, biopsy should be performed for diagnosis (Song do and Bae, 2012).

After CHB patients were diagnosed with HCC, curative therapies such as ablation, surgical resection and transplantation should be provided. A meta-analysis study associated with the resection revealed that the overall survival improved over the years with an expected 5-year survival of more than 60% (Lim et al., 2012). However, a very limited number of HCC patients are eligible for curative therapies (Han et al., 2011; Somboon et al., 2014), since most HCC patients are usually diagnosed at late stages which treatment options including potential novel agents with systemic therapy or palliative care result in low survival rate (Flores and Marrero, 2014).

Furthermore, the costs of systemic therapy are currently very high. Based on the cost-effectiveness study conducted by the National Institute for Health and Clinical Excellent (NICE), it was recommended that a systemic agent (i.e., Sorafenib) should not be reimbursed by the United Kingdom (UK) National Health Services (Ma and Palmer, 2012). In addition, the burden of HCC causes not only significant morbidity or mortality, but also substantial health care costs such as direct health care expenditures for HCC treatment as well as indirect costs related to productivity loss from disability or premature death due to HCC (Hu and Chen, 2009; Ma et al., 2011; Mantovani and Strazzabosco, 2013).

There has been an effort to develop primary, secondary prevention or screening program which is the key to minimize HCC incidence and reduce morbidity and mortality (Yeo et al., 2013; Somboon et al., 2014). According to the Asia-Pacific Working Party for Prevention of HCC, the HCC surveillance program, a recall procedure of screening test and interval program for diagnosis (Bruix and Sherman, 2005; Sherman, 2007) has been recommended to detect early HCC in at-risk asymptomatic persons (Farrell et al., 2010). Screening diagnostics in surveillance program consisted of using US, AFP and diagnostic imaging such as CT and MRI every 6-12 months. The aim of the HCC surveillance program is to detect HCC at an earlier stage as well as allow prompt and sufficient curative therapy with survival benefit (Amarapurkar et al., 2009; Giannini et al., 2013). However, the application of HCC surveillance in Asia-Pacific countries still depends on economic factors and healthcare priorities (Farrell et al., 2010). Interestingly, there has been a consensus statement from the Asian Oncology Summit 2009 regarding the need to develop resources-based strategies to reduce the burden of HCC (Poon et al., 2009). In Thailand, screening policy in patients who are at high risk has been increasingly encouraged (Somboon et al., 2014).

Based on the systematic review of economic evaluation of HCC surveillance program in CHB patients (Sangmala et al., 2012), five eligible studies were conducted in Italy (Thompson Coon et al., 2008), the UK (Bolondi et al., 2001), Taiwan (Shih et al., 2010), the Netherlands (Veldhuijzen et al., 2010) and the United State (US) (Andersson et al., 2008). It was found that the HCC surveillance program seemed cost-effective particularly in screening individuals with hepatitis hepatitis B-related cirrhosis in the UK. Screening by US every six months in the US would be more cost-effective than other alternative strategies. However, the study of Thai National Institute of Cancer (NCI) in 2008 indicated that AFP and US for semi-annual HCC screening in patients with hepatitis B surface antigen positive would not be cost-effective at the societal willingness to pay (WTP) in Thailand. The limitations of this study were that this study considered only two health states (i.e., resectable and unresectable HCC), did not take into account HCC treatment costs, and obtained the clinical and cost data from NCI only. Therefore, the study on economic evaluation in Thailand should be further reinvestigated to overcome the limitations.

Since July 2010, there has been the preliminary project for the HCC surveillance in Thai patients with CHB infection initiated and organized by Chulabhorn hospital. This project aimed to prevent the incidence of HCC by screening high risk group as well as providing appropriate care and treatment throughout the period of five years (2010-2015). Clinical outcome data were obtained from 2,293 patients participating in this cohort study. However, in order to implement the HCC surveillance as the national program in Thai healthcare setting, policy makers require the information related to cost-effectiveness, budget impact, and feasibility of the program in addition to the program's effectiveness. Thus, the objectives of this study were to compare the costs and health outcomes associated with the introduction of HCC surveillance program with no program based on a societal perspective using a cost-utility analysis as well as to estimate the budget impact of HCC surveillance program based on a governmental perspective whether it would be cost-effective in Thai context. The results obtained from this study could be used as the information for policy decision making whether HCC surveillance program should be included as the national program in the benefit package of health insurance schemes or implemented in healthcare settings.

Materials and Methods

Analytic overview

Cost-utility analysis using both decision tree and Markov models was applied to compare the costs and outcomes of each diagnostic strategy as the first screening in a surveillance program with no program in CHB patients in a lifetime period based on a societal perspective. The population of interest was both males and females aged from 40 to 60 years with HBsAg positive or the CHB carriers without antiviral treatment. Eight diagnostic strategy alternatives included (i) semi-annual

ultrasonography (US), (ii) semi-annual alpha-fetoprotein plus ultrasonography (AFP plus US), (iii) semi-annual computed tomography (CT), (iv) semi-annual magnetic resonance imaging (MRI), (v) annual ultrasonography (US), (vi) annual alpha-fetoprotein plus ultrasonography (AFP plus US), (vii) annual computed tomography (CT), and (viii) annual magnetic resonance imaging (MRI). Effectiveness data were obtained from observational studies and existing trials of treatment effectiveness. The results were presented in term of the incremental cost effectiveness ratio (ICER) or cost per quality-adjusted life year (QALY) gained. The budget impact of the most cost-effective treatment was also estimated during the fiscal year 2013 to 2022 based on a governmental perspective. Study protocol was approved by the Committee on Human Rights Related to Research Involving Human Subjects Chulabhorn Research Institute on February 19, 2013 as well as the Human Research Ethics Committee of Faculty of Dentistry/Faculty of Pharmacy, Mahidol University on January 9, 2013.

Model structure

A decision tree and Markov models were constructed to assess the long-term costs and outcomes associated to the introduction of the HCC surveillance program in lifetime period. A decision tree model of the alternative surveillance for HCC is shown in Figure 1a-1d. The diagnosis of HCC was based on the additional confirmed tests according to diagnostic algorithm for HCC (Bruix and Sherman, 2011; Forner, et al., 2012). Figure 1a shows that US was used as the first screening and if the mass was found, AFP test would be performed. Among individuals achieving a level of AFP≥200 ng/ml, they would be diagnosed with HCC, if only one imaging of CT or MRI showed positive result. For those who had a level of AFP<200 ng/ml, both CT and MRI must be positive in order to be diagnosed with HCC. In case of no mass was found, the program of surveillance with US every six months or one year would be done. Figure 1b shows that US and AFP tests were used as the first screening. A 20 ng/ml of AFP was used as a cut-off value for screening, while a 200 ng/ml cut-off value of AFP and one or two imaging were used to confirm the HCC diagnosis, the same as the strategy in Figure 1a. The individuals who had no mass and AFP level less than 20 ng/ml would be followed with the surveillance program with US plus a 20 ng/ml cut-off of AFP every six months or one year. Figure 1c demonstrates that CT was used as the first screening. If the result was positive, AFP test would be performed. If AFP level ≥200 ng/ml, then they would be diagnosed with HCC. If AFP level <200 ng/ml, MRI or biopsy test must be positive to be diagnosed as HCC. The surveillance with CT every six months or one year would be performed in case of the no mass of CT screening was shown. Figure 1d demonstrates that MRI was used as the first screening. If AFP level <200 ng/ml with positive MRI, CT or biopsy test must be positive to be diagnosed as HCC as well as AFP≥200 ng/ml. If MRI result was no mass, the surveillance with MRI every six months or one year would be performed.

A Markov model simulated the disease progression for individuals with CHB after HCC was detected (Figure 2). A number of health states and transition pathways in this model were developed on the basis of literature

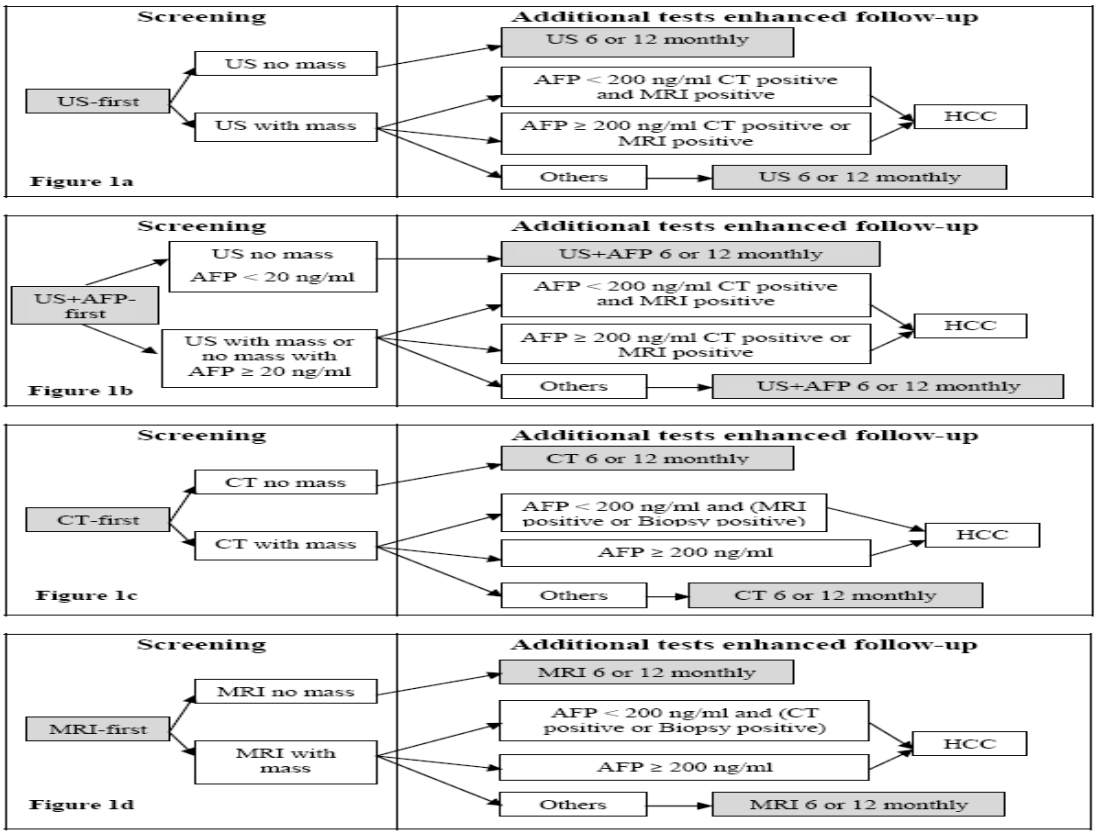

Figure 1. The Decision Tree Model of Each Alternative Surveillance Strategy

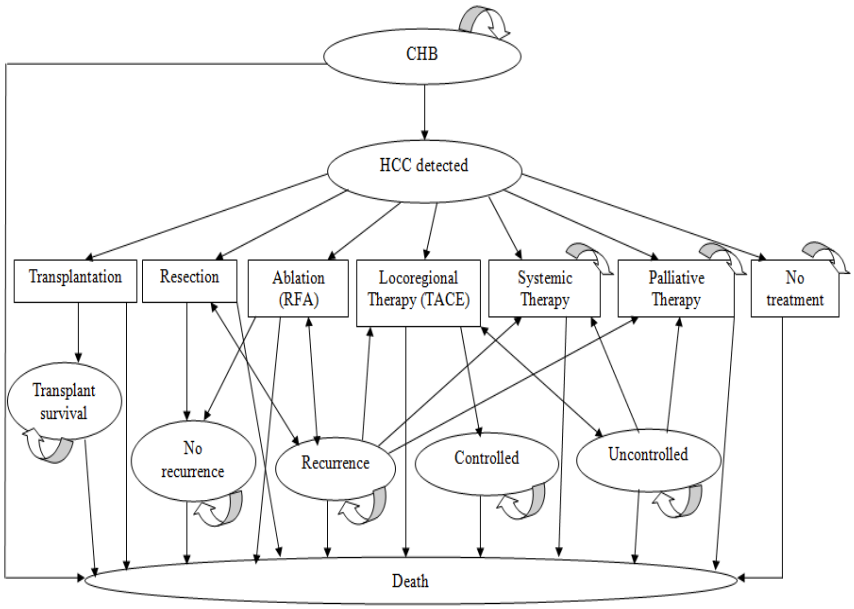

Figure 2. Markov Model Used in this Study

reviews and clinical expert opinions. Health states were represented in the oval and rectangular shapes. The transition pathways from one state to other states were shown as arrows. Death was applied to patients in all health states. The cycle length in this study was six months and one year for the semi-annual and annual strategies, respectively.

Figure 2 presents the Markov model used in this study. Oval shapes represent health states used in the model and rectangular shapes indicate health states related to alternative treatments for HCC. Arrows demonstrates the transition from one state to another. After selecting a diagnostic strategy for HCC surveillance as the first screening (see Figure 1), in case that HCC patients were detected, they would enter a Markov model in order to simulate that they would receive each alternative treatment (i.e., transplantation, resection, radiofrequency ablation (RFA), trans-arterial chemoembolization (TACE), systemic therapy (i.e., Sorafenib), palliative care or no treatment. The patients who were treated by each alternative treatment in the model could be moved to any other health states due to recurrent or uncontrolled conditions upon disease progression. The patients in CHB, systemic therapy, palliative care, no treatment, transplant survival, no recurrence, recurrence, controlled and uncontrolled health states could stay at the same state. The patients in all health states would move to death state.

A number of assumptions were made in the base case analysis as follows. First, we did not consider the incidence and prevalence of the inactive carriers, since we focused on the incidence and prevalence of active carriers in HBV patients. Second, the sensitivity and specificity were assumed to be 100%, therefore false positive and false negative were not considered in this model. Third, the transition probabilities and recurrent rates after treatments as well as mortality rate of all health states were the same in surveillance and no surveillance groups. Fourth, it was assumed that all HCC patients who were detected would receive treatment. Last, patient follow-up was assumed to be fully compliant.

Transitional probabilities

All parameters used in the model are summarized in Table 1. The estimated probability of the CHB patients accidental detected or symptomatic detected was assumed to be 0.0019 (SE=0.0004) in the base case analysis as well as the number of patients in no surveillance group was obtained from the study of Yang et al. (1997). To calculate the transition probabilities, all values of average annual transition probabilities for one year-cycle length were changed to semi-annual probabilities by the survival curve function and put into six month-cycle length estimation. Transition probabilities were obtained from published studies (Lee et al., 2002; Chung, 2005; Yeung et al., 2005; Chen et al., 2006; 2009; Fattovich et al., 2008; Bouza et al., 2009; Cheng et al., 2009; Kim et al., 2009; 2013; Cabibbo et al., 2010; Tong et al., 2010; Zhou et al., 2010a; 2010b; Chun et al., 2011; Kao, et al., 2011; Sawhney et al., 2011; Thein et al., 2012).

The sensitivity and specificity of each diagnostic test were used to estimate the probability of positive test or the transitional probability from CHB to HCC. We conducted a meta-analysis of the sensitivity and specificity of AFP, US, spiral CT and MRI for HCC diagnosis in CHB patients using Meta-Disc (Zamora et al., 2006). A total of 19 studies were considered for the analysis (Maringhini et al., 1984; Okazaki et al., 1984; Kobayashi et al., 1985; Gambarin-Gelwan et al., 2000; Lim et al., 2000; Peterson et al., 2000; Kim, et al., 2001; Krinsky, et al., 2001; Rode et al., 2001; Tong et al., 2001; Trevisani et al., 2001; Bennett et al., 2002; de Ledinghen et al., 2002; Libbrecht et al., 2002; Mori et al., 2002; Zacherl et al., 2002; Bhartia et al., 2003; Burrel et al., 2003; Marrero et al., 2003).

Cost measurement

Based on a societal perspective, direct medical, direct non-medical and indirect costs were included. Direct medical costs consisted of the costs associated with diagnostic tests and treatments used in the screening and enhanced follow-up of the surveillance. Diagnostic test costs were derived from 2009 standard cost list for Health

Table 1. All Parameters Used in this Study

Parameters	Distribution	Baseline	Standard Error	Source
Probability				
Average mortality rate estimated from survival rate				
Following transplantation	Beta	0.0767	0.0077	(Chen, et al., 2009)
Following resection	Beta	0.1056	0.0106	(Chen, et al., 2006)
Fol lowing ablation (RFA)	Beta	0.1126	0.0113	(Bouza, et al., 2009)
Following loco-regional treatment (TACE)	Beta	0.3852	0.2461	(Sawhney, et al., 2011)
Following systemic therapy (Sorafenib)	Beta	0.7219	0.1066	(Cheng, et al., 2009)
Following palliative treatment	Beta	0.825	0.1568	(Cabibbo, et al., 2010)
Controlled HCC	Beta	0.017	0.0017	(Lee, et al., 2002)
Uncontrolled HCC	Beta	0.2394	0.0239	(Lee, et al., 2002)
No treatment	Beta	0.9051	0.0905	(Yeung, et al., 2005)
Recurrent HCC	Beta	0.3699	0.037	(Chun, et al., 2011)
Chronic hepatitis B patients	Beta	0.006	0.0051	(Fattovich, et al., 2008)
Average mortality rate estimated from recurrent/disease free survival				
Following transplant survival	Beta	0.2441	0.2722	(Chen, et al., 2009)
No recurrent	Beta	0.2679	-	(Zhou, et al., 2010b)
Average transition probability				
From resection to recurrent	Beta	0.1279	0.0128	(Kao, et al., 2011)
Fom ablation to recurrent	Beta	0.0342	0.0357	(Bouza, et al., 2009)
From TACE to uncontrolled	Beta	0.3381	0.0338	(Chung, 2005)
From recurrent to systemic therapy	Beta	0.0409	-	(Kao, et al., 2011, Kim, et al., 2013)
From recurrent to palliative therapy	Beta	0.053	-	(Kao, et al., 2011, Kim, et al., 2013)
Repeated hepatectomy	Beta	0.1341	0.0134	(Zhou, et al., 2010a)
Recurrent to ablation	Beta	0.1	0.01	Expert
Recurrent to loco-regional treatment	Beta	0.2	0.02	Expert
Repeated TACE	Beta	0.3803	0.038	(Kim, et al., 2009)
From uncontrolled to systemic therapy	Beta	0.1	0.01	Expert opinion
From uncontrolled to palliative	Beta	0.1	0.01	Expert opinion
Treatment related transition rate for surveillance group				
Transition rate to liver transplantation	Beta	0.3077	0.0888	(Tong, et al., 2010)
Transition rate to resection	Beta	0.1923	0.0758	(Tong, et al., 2010)
Transition rate to ablation (RFA)	Beta	0.1154	0.0615	(Tong, et al., 2010)
Transition rate to locoregional therapy (TACE)	Beta	0.1538	0.0694	(Tong, et al., 2010)
Transition rate to systemic therapy (Sorafenib)	Beta	0	0	(Tong, et al., 2010)
Transition rate to palliative treatment	Beta	0.2308	0.0811	(Tong, et al., 2010)
Transition rate to no treatment	Beta	0	0	Assumed
Treatment related transition rate for no surveillance group				
Transition rate to liver transplantation	Beta	0.0406	0.032	(Tong, et al., 2010)
Transition rate to resection	Beta	0.1219	0.052	(Tong, et al., 2010)
Transition rate to ablation (RFA)	Beta	0.0813	0.0439	(Tong, et al., 2010)
Transition rate to locoregional therapy (TACE)	Beta	0.0812	0.0439	(Tong, et al., 2010)
Transition rate to systemic therapy (Sorafenib)	Beta	0.0677	0.0405	(Tong, et al., 2010)
Transition rate to palliative treatment	Beta	0.3115	0.0682	(Tong, et al., 2010)
Transition rate to no treatment	Beta	0.2958	0.0258	(Thein, et al., 2012)
Sensitivity (%)				
Ultrasonography	Beta	64	56-71	Meta-analysis results*
Alpha-fetoprotein	Beta	49	45-53	Meta-analysis results*
Computed tomography	Beta	58	50-66	Meta-analysis results*
Magnetic resonance imaging	Beta	85	77-91	Meta-analysis results*
Specificity (%)				
Ultrasonography	Beta	97	96-98	Meta-analysis results*
Alpha-fetoprotein	Beta	92	91-93	Meta-analysis results*
Computed tomography	Beta	91	89-93	Meta-analysis results*
Magnetic resonance imaging	Beta	79	73-84	Meta-analysis results*
Costs				
Diagnostic tests**				
Alpha-fetoprotein (AFP)	Gamma	373	373	(Riewpaiboon, 2009)
Abdominal ultrasonography (US)	Gamma	897	897	(Riewpaiboon, 2009)
Computerized tomography (CT)	Gamma	6,906	6,906	(Riewpaiboon, 2009)
Magnetic resonance imaging (MRI)	Gamma	11, 048	11,048	(Riewpaiboon, 2009)
Treatments and additional procedures				
Transplantation	Gamma	494,026	494,026	Chulabhorn DRG
Post-transplantation (year 1+)	Gamma	82,105	82,105	Siriraj, (DMSIC, 2013)
Resection	Gamma	61,286	61,286	Chulabhorn DRG
Radiofrequency ablation (RFA)	Gamma	61,286	61,286	Chulabhorn DRG
Locoregional therapy (TACE)	Gamma	22,326	22,326	Chulabhorn DRG
Post-resection, Post-RFA or Post TACE (first year)	Gamma	30,270	30,270	Expert, (Riewpaiboon, 2009)
Post-resection, Post-RFA or Post TACE (year 2+)	Gamma	15,136	15,136	Expert, (Riewpaiboon, 2009)
Systemic therapy (Sorafenib)	Gamma	2,243,529	2,243,529	MOPH***
Palliative care	Gamma	565,562	98,059	Chulabhorn medical record****
Direct non-medical costs				
Transportation cost	Gamma	71	5.8	Standard costing (Riewpaiboon, 2009)
Total costs of food, residence, out of pocket, and productivity loss of care giver	Gamma	141	29.24	Chulabhorn cohort Program survey
Utility				
Chronic hepatitis B	Beta	0.68	0.66-0.70	(Levy, et al., 2008)
All known HCC	Beta	0.38	0.36-0.41	(Levy, et al., 2008)
Post liver transplant (year 1)	Beta	0.57	0.54-0.60	(Levy, et al., 2008)
Post liver transplant (year2+)	Beta	0.67	0.64-0.69	(Levy, et al., 2008)

*see detail in method; **adjusted by customer price index (CPI); ***MOPH = Ministry of Public Health; ****cost to charge ratio (1.63) adjusted

Technology Assessment of Thailand (Riewpaiboon, 2009) and valued according to the type and the number of tests used in each alternative strategy as presented in the decision tree model.

Treatment costs of liver transplantation, resection, RFA, and TACE costs were obtained from the reimbursement claims data of the diagnosis-related groups (DRGs) of C22.0 or HCC for National Health Security Office (NHSO) at the Chulabhorn hospital. Post-transplantation medication use and amount were obtained from doctor order sheet template at a university hospital and valued as the first and second year of post-transplantation costs. The medication costs were manufacturer's price estimate obtained from the Center of Essential Information for All Health Officers, Thailand (DMSIC) (DMSIC, 2013). In case of systemic therapy, the price of Sorafenib usual dose was used (Llovet et al., 2008) and obtained from the Thai Ministry of Public Health in 2007 (Misnistry of public health, 2007). Palliative care costs were collected from the charge data of inpatient care services and treatments at the Chulabhorn hospital. Amount of additional procedures regarding to post treatment of resection, RFA, and TACE were estimated by the expert opinion. They were assumed as the consistency screening by the diagnostic US every one month for the first year and then US every three months from the second year after receiving the post treatment procedure.

Direct non-medical costs in this study included the costs of travelling to and from the hospital, food, and lodging required for the patients and their families during out-of-town follow-up process. Indirect costs were the productivity losses of caregivers also included. However, the productivity loss of patients due to going to the hospital for surveillance was not included, because it would be double counting in the utility valuation. Direct non-medical costs and indirect costs were collected using data collection form including all questions related to out-of-pocket expenses and productivity loss of patients and caregivers. One hundred patients or caregivers at the HCC surveillance program of Chulabhorn hospital were interviewed. However, we obtained the transportation costs from standard costing menu (Riewpaiboon, 2009). The cost to charge ratio equal to 1.63 was used to adjust the costs (Riewpaiboon, 2009). Discounting rate for costs and outcomes used in this study was equal to 3% based on the recommendation from Thai Health Technology Assessment Guidelines (Health Intervention and Technology Assessment Program, 2009; Permsuwan, et al., 2014). All costs were adjusted and expressed in Thai THB (2013) using Consumer Price Index (CPI) (Bureau of Trade and Economic Indices-Ministry of Commerce, 2013) and the exchange rate was 30.73 THB per one US dollar ($1 PPP = 0.4) (World Bank, 2013).

Health outcomes

Health outcomes were life years (LYs) and quality adjusted life years (QALYs) gained, calculated from the life years (LYs) multiplied by health utility scores or quality of life weights. Health utilities were retrieved from international published studies due to the lack of data in Thailand. The utility weight of CHB patients progressing to the liver health status were reviewed and obtained from one study (Levy et al., 2008). The results were presented as the incremental cost-effectiveness ratio (ICER) in Thai THB per LY or QALY gained which calculated by the incremental costs divided by the incremental effectiveness.

Uncertainty analysis

One way sensitivity and probabilistic sensitivity analyses were applied to test the uncertainty of all parameters. One-way sensitivity analysis results were presented as Tornado diagram. We also tested whether the increase in age of patients at the beginning of the surveillance program had an impact on the ICER values. Furthermore, at the base case analysis, we assumed that treatment rate was 100% meaning that all HCC patients detected would receive treatment. Therefore, treatment rates were varied from 0 to 100% in order to investigate the impact on the ICER values.

In addition, probabilistic sensitivity analysis (PSA) was undertaken. One thousand Monte Carlo simulations were run with key inputted values randomly drawn from probabilistic density functions. To perform PSA, Microsoft Office Excel 2010 (Microsoft Corp., Redmond, WA) was used. The distribution of parameters was beta distribution assigned to transitional probabilities and utilities (value in range zero to 1). The gamma distribution was assigned to costs which were attributed to the positive values and the log-normal distribution was model for ancillary parameters of death and failure events. The simulations by sampling from the distribution of each parameter with 1,000 iterations could provide the feasible values series of total costs, life years (LY), QALYs, and the estimation of the ICER in THB per LY or in THB per QALY gained. In addition, cost-effectiveness acceptability curves were presented to explore the strategies giving the maximum expected net monetary benefit for each level of ceiling ratio or willingness to pay (WTP), the amount that the society was willing to pay for the intervention in order to gain one QALY. In late 2013, the National List of Essential Medicine (NLEM) committee recommended raising the Thai GNI to 160,000 THB/QALY) (Thavorncharoensap et al., 2013).

Budget impact analysis

The budget impact analysis (BIA) was performed based on the governmental perspective using Markov model. The amount of budget required was calculated if HCC surveillance program would be implemented at the national level. Only the most cost-effectiveness strategy was compared with no surveillance program. The size of population affected by the HCC surveillance program was identified by the incidence and prevalence of Thai CHB patients for the new cases and the remained cases, respectively in the following 10 years. Based on the 2013 Thai population of 68.79 million (National Economic and Social Development Board, 2013) and the incidence of CHB patients were 7.62 per 100,000, the updated disease surveillance report 2013 from Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health (Bureau of Epidemiology-Department of Disease Control

Ministry of Public Health, 2013). It was assumed that only 15% of all CHB patients were at-risk group (i.e., both males and females aged 40-50 years) (National Economic and Social Development Board, 2013) and 10% of these at-risk group could access to the surveillance program and receive treatment based on expert opinion.

Results

Cost-utility analysis

The total lifetime costs for each alternative strategy are shown in Table 2. The costs for each CHB patient aged 40 years who enrolled in the surveillance program for lifetime period were considered. The results showed semi-annual MRI as the first screening had the highest costs (362,131 THB) followed by annual MRI (271,534 THB), whereas annual US had the lowest costs (45,657 THB).

CHB patients entered the HCC surveillance had more LYs and QALYs compared with those not entering the program. Semi-annual MRI had the highest LYs (17.09) and QALYs (10.72), whereas no surveillance group had the lowest LYs (13.11) and QALYs (8.89). Annual MRI had the highest LYs (10.66) and QALYs (6.86), while no surveillance group had the lowest (LYs=9.20, QALYs=6.24).

Table 3 demonstrates the cost-utility analysis results. The costs and QALYs of different alternative strategies were compared with those of no surveillance program. The annual MRI yielded the highest ICER value (407,143 THB/QALY gained), while semi-annual US yielded the lowest ICER value (118,796 THB/QALY gained). In addition, the cost-effectiveness plane which Y-axis was incremental costs and X-axis represented incremental QALYs when compared with no surveillance is shown in Figure 3. The ICER values of all strategies were located on the upper right-hand quadrant of the plane indicated extended QALYs with higher costs. The semi-annual

Table 2. Estimated Lifetime Costs and Health Outcomes of Each Screening Strategy

Strategy	Total costs (THB)	Life year (years)	Quality adjusted life year (QALYs)
Semi-annual Ultrasonography	58,370	13.8	9.21
Semi-annual Computed tomography	248,084	15.93	10.19
Semi-annual Magnetic resonance imaging	362,131	17.09	10.72
Semi-annual Utrasonography plus Alpha-fetoprotein	109,575	14.68	9.62
Annual Ultrasonography	45,657	9.44	6.34
Annual Computed tomography	188,279	10.23	6.69
Annual Magnetic resonance imaging	271,534	10.66	6.86
Annual Utrasonography plus Alpha-fetoprotein	85,900	9.77	6.48
No surveillance 6-month interval	20,487	13.11	8.89
No surveillance 1-year interval	20,067	9.2	6.24

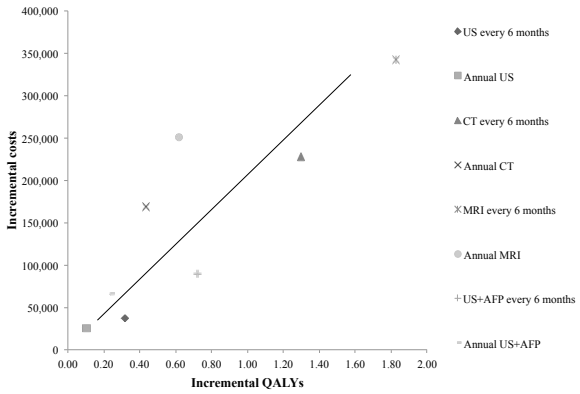

Figure 3. Cosy-Effectiveness Plane

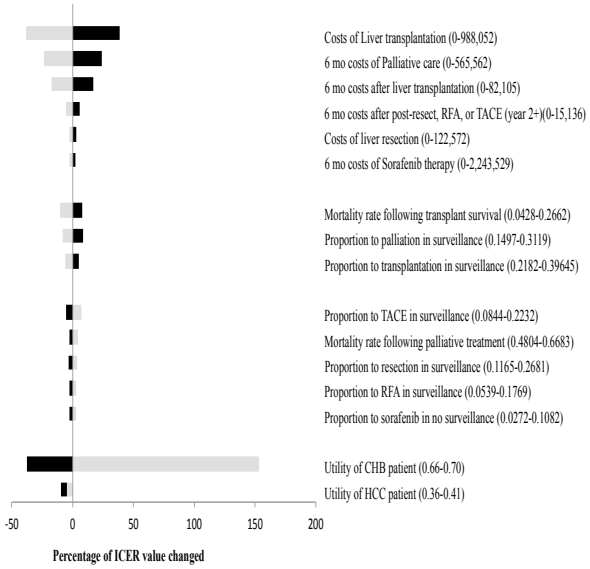

Figure 4. Tornado Diagram

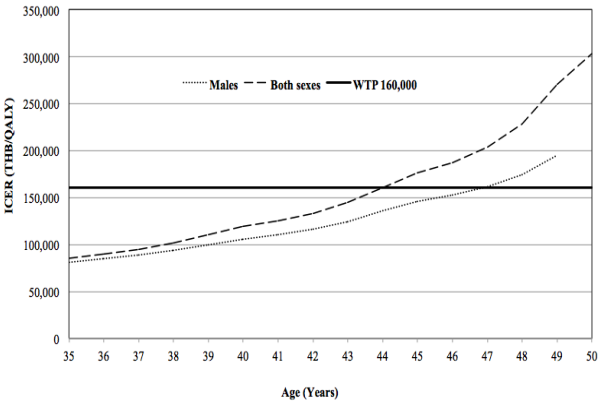

Figure 5. ICER Values of Semi-Annual US for Patient Aged 35-50 at theStart of the HCC Program

Table 3. The ICER Results of Eight Alternative Strategies Compared with No Surveillance

Strategy	US-first		CT-first		MRI-first		US+AFP-first	
	6-month interval	12-month interval	6-month interval	12-month interval	6-month interval	12-month interval	6-month interval	12-month interval
Incremental costs (THB)	37,823	25,581	227,596	168,212	341,643	251,471	89,088	65,833
Incremental life years gained (year)	0.69	0.23	2.83	1.03	3.99	1.46	1.57	0.57
Incremental QALYs gained (year)	0.32	0.1	1.3	0.44	1.83	0.62	0.72	0.24
ICER per LYs	54,697	109,201	80,442	162,961	85,690	172,574	56,616	116,445
ICER per QALYs gained	118,796	252,921	175,583	384,236	187,064	407,143	123,451	273,568

Table 4. Estimated Total Budget Impact of Semi-Annual US and US Plus AFP During 2013-2022

Fiscal year	Estimated Total Budget (million THB)			Incremental Budget (million THB)	
	Semi-annual US	Semi-annual US+AFP	No surveillance	Semi-annual US	Semi-annual US+AFP
2013	215	365	128	87	237
2014	328	615	137	191	478
2015	331	632	130	201	502
2016	321	617	121	200	496
2017	304	589	111	193	478
2018	282	549	99	183	450
2019	256	500	88	168	412
2020	232	452	78	153	374
2021	208	407	70	139	337
2022	187	364	61	125	303

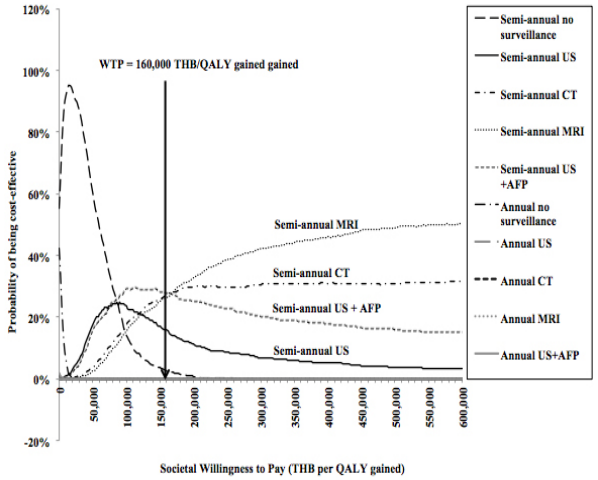

Figure 6. Cost-Effectiveness Acceptability Curves

strategies compared with annual strategies could yield more QALYs but also more costly.

Uncertainty analysis

One-way sensitivity analysis: Since the first screening with semi-annual US yielded the lowest ICER values compared to other alternative strategies, the effect of all parameter uncertainties on the ICERs of semi-annual US were investigated and presented as a tornado diagram (Figure 4). Values in parenthesis indicated upper and lower bounds of confidence interval or ±10% for each parameter. The vertical line indicated the change in the percentage of ICER from the base case value. All parameters (i.e., transition probabilities, cost and utility values) were tested for uncertainty. Among transition probabilities, mortality rate of the patients who were survived after transplantation was the most influential parameter on ICER values followed by the proportion of patients in surveillance program to palliative therapy and to transplantation. Moreover, the liver transplantation cost had the most impact on the ICER values followed by the costs of palliative care and care after liver transplantation. The reduction of these parameters caused the reduction of ICERs. Conversely, the ICER values would be increased if some parameters decreased. A decreased in utility of CHB patients had the most impact on an increase in the ICER values.

The cost-utility analysis results indicated that semi-annual US in both males and females at the starting age of 40 years was the most cost-effective surveillance program at the threshold 160,000 THB per QALY. When varied age of CHB patients from 35 to 50 years, the ICER values of semi-annual US as the first screening compared with no surveillance would increase as age increased. The ICER values were greater than the cost-effectiveness threshold at age greater than 47 years in males and 44 years in both males and females (Figure 5).

Probabilistic sensitivity analysis: Figure 6 shows the cost-effectiveness acceptability curves for all semi-annual and annual strategies. The curves illustrated the probability that each strategy would be cost-effective at the willingness to pay of 160,000 THB for a QALY gained. Semi-annual US plus AFP yielded the highest probability of being cost-effective (28%), slightly followed by semi-annual CT (27%), semi-annual MRI (26.5%). Semi-annual US (17%) at the WTP threshold 160,000 THB/QALY gained. If the WTP per QALY was increased more than 180,000 THB/QALY, semi-annual MRI would have the highest probability to be the cost-effective option.

Budget impact analysis

Based on the cost-utility analysis results, semi-annual US and semi-annual US plus AFP would be the cost-effective options at the WTP threshold in Thailand. However, semi-annual US plus AFP yielded more probability of being cost-effectiveness or more net monetary benefit than semi-annual US. Therefore, the budget impact of both strategies were determined how much impact on future expenditures if these two programs would be implemented compared with no surveillance based on the governmental perspective. Table 4 presents the governmental budget impact of the implementation semi-annual US and semi-annual US plus AFP for CHB patients at the age of 40-50 years compared with no surveillance in next ten fiscal years (2013-2022).

According to the budget impact analysis results, when compared with no surveillance program, the incremental budget of providing semi-annual US was 87 million THB at the first year, increased to 201 million THB at the third year, and decreased to 125 million THB at the tenth year. In addition, the incremental budget of providing semi-annual US plus AFP was higher than those of semi-annual US alone, the budget increased from 237 million to 502 million at the first and second year, then decreased to 303 million THB at the tenth year.

Discussion

Based on the cost-effectiveness results, our study indicated that semi-annual US (ICER=118,796 THB per QALY) and semi-annual US plus AFP (123,451 THB per QALY) as the first screening would be the cost-effective options at the Thai societal willingness to pay of 160,000 THB per QALY. These two diagnostic strategies should be considered as the screening strategies in the HCC surveillance program for CHB patients among Thai population. Generally a particular country should take a consideration about choosing the alternative strategy

which demonstrated the economic efficiency in their context. The results in this study were in accordance with other studies in most developed countries (Bolondi et al., 2001; Andersson et al., 2008; Thompson Coon et al., 2008; Shih et al., 2010; Veldhuijzen et al., 2010). The study in the US found that semi-annual US surveillance was more cost-effective, while US plus AFP would not be cost-effective for HCC in mixed etiology cirrhosis (Andersson et al., 2008). Moreover, the study in the UK indicated that semi-annual US alone or US combined with AFP would be the cost-effective option in the individuals with hepatitis B related cirrhosis (Thompson Coon et al., 2008). In addition, the most intensive surveillance protocol would be US plus AFP every six months. The surveillance program in people with hepatitis B cirrhosis appeared much more likely to be cost-effective than other risk groups.

Nevertheless, the results in our study was not in accordance with the previous study by the National Institute of Cancer (NCI) in Thailand indicating that semi-annual US plus AFP for HCC screening would not be cost-effective in both males and females with CHB from a societal perspective (Institute of Medical Research and Technology Assessment-Ministry of Public Health, 2008). It could be explained that model assumptions and parameters used in our study were different from those in the NCI study. Furthermore, health states related to HCC treatments (i.e., RFA, TACE, Sorafenib, and palliative care) were considered separately in our study, whereas the NCI study determined transplantation and resection in the state of resectable HCC and all other treatments in the state of unresectable HCC. In addition, the probabilities of sensitivity and specificity of diagnostic tests were obtained from our meta-analysis study. The probability of HCC detected in the surveillance program was also considered in our study. Regarding the cost calculation, all costs in the NCI study were retrieved from the medical records of the patients treated at the NCI only, while our cost data were obtained from the reimbursement list for HCC treatment and standard cost list for Thai population. We also obtained outcome data from systematic reviews and meta-analysis from other countries.

Based on the results of cost-utility and budget impact analyses, semi-annual US as the first screening for HCC surveillance program would be cost-effective when considering long-term outcome such as QALY at a reasonable cost. Although semi-annual US plus AFP seemed to be a cost-effective strategy and yielded more monetary benefit, it had a great influence on the national budget. However, in the long run, the incremental budget would be decreasing, since the incidence of HCC would be lower particularly after the national hepatitis B vaccination program has been obligatory in the Expanded Program on Immunization (EPI) since 1990 (Wichajarn, et al., 2008).

According to the sensitivity analysis results of this study, when varying only age parameter, US would be more cost-effective for CHB patients aged between 40 to 50 years. Therefore, both CHB males and females aged between 40-50 years would be recommended to receive HCC surveillance. The recommendations from our study are in accordance with Thai clinical practice guidelines (National Cancer Institute- Ministry of Public Health, 2011) which adopted the concept of screening and surveillance from World Health Organization (WHO) criteria and other guidelines (Ryder, 2003, Meissner, et al., 2004). Thai clinical practice guidelines have recommended that CHB patients with no cirrhosis who are males aged more than 45 years or females aged more than 50 years are recommended to be screened for HCC every six months.

As indicated by one way sensitivity analysis findings, some important conditions related to HCC therapy management were needed to be addressed. The factors which would make the HCC surveillance program more cost-effective were a decrease in the mortality rate of transplant survival patients and an increase in the proportion of patients receiving TACE, resection, and RFA and a decrease in the costs of treatment particularly the cost of liver transplantation and the cost of palliative. In contrast, an increase in the proportion of patients to transplantation and palliation therapy could lower the cost-effectiveness of HCC surveillance program.

After the cost-effectiveness results revealed that semi-annual US in the HCC surveillance program would be a cost-effective option for Thai CHB patients, we explored whether it would be feasible to implement the HCC surveillance in Thai healthcare settings. The feasibility of the HCC surveillance program at the national level was discussed using a focus group method. The meeting attendants included national policy makers, third party payers or administrators of Thai health insurance schemes (i.e, National Health Security Office, Social Security Office, and the Comptroller General's Department), Ministry of Public Health, National Cancer Institute Foundation and specialists in gastroenterology and medical oncology.

Based on a focus group discussion, there are some limitations related to health care systems which would support the HCC surveillance program. First, HBsAg screening for the at-risk group (i.e., CHB patients or HBsAg positive) has not been included in the national program yet, although screening for HBsAg might represent a worthwhile investment of public funds (Vimolket and Poovorawan, 2005). Furthermore, the concept of HBsAg screening is still controversial whether it should be the right or the responsibility of Thai people to protect their own health. Second, after HCC is detected, the particular treatment process (e.g., the infrastructure of transplantation) has not been widely practiced. This could result in the limitations of healthcare settings where could provide the treatment, the standard quality of the treatment, and the referral system. Third, since we recommended that patients should receive US every six months, it is quite challenging in term of work capacity because the follow-up period of six months would increase the routine workload of physicians and other medical staffs, since the radiologists are the only persons who are qualified to perform the US examination, while trained nurses are not commonly accepted to perform the US test in Thailand. Last, the great concerns in other high diagnostic test expenses such as viral load testing in case that the patients have to pay by their out of pockets. Thus,

all administrators proposed that further studies related to above issues should be explored as well as the cost studies in other populations associated with the HCC surveillance program such as the burden of cholangiocarcinoma and CHB patients receiving antiviral therapy.

Moreover, the barrier for the implementation of the HCC surveillance program as the national policy or the inclusion into the benefit package of Thai health insurance schemes was the unclear national policy related to hepatitis B virus and HCC prevention. This leads to no direction point of the strategy related to HCC prevention. At present, Thailand is the only one country in the South East Asia where has no comprehensive policy in HCC prevention. Currently, there has been only primary prevention strategy (i.e., hepatitis B vaccination at birth). Finally, all administrators expected that HCC surveillance program could be feasible if there is the public health policy emphasizing health prevention in the future. The strategies related to HCC prevention and surveillance program may be further analyzed and considered by the established committees of the Ministry of Public Health.

In this study, our data on clinical parameters mostly were limited. They were derived from systematic review and meta-analysis in from other countries. Some parameters were obtained from expert opinion due to the lack of data in Thailand. Therefore, future research should be further investigated on surveillance rate, impact of surveillance results on survival, quality of life of HCC patients in each particular treatment, and HCC therapy practice pattern to gain more information in real practice for Thai population.

In conclusion, based on our cost-effectiveness findings, policy recommendations are proposed for HCC surveillance program. Semi-annual US would be a cost-effective option at the societal WTP in Thailand. Therefore it should be used as the first screening for HCC surveillance program. Although semi-annual US plus AFP would also be a cost-effective strategy, it had a significant impact on the national budget. It was recommended that both CHB males and females aged between 40-50 years should receive HCC surveillance. The inclusion of HCC surveillance program into the benefit package of Thai health insurance schemes would be feasible if there is a clear policy direction for HCC prevention in the future. However, the most significant needs for HCC control policy in Asia-Pacific Region were also included other factors such as political awareness, public awareness, and lifestyle risk factors. Thus, to expand the surveillance program to the national policy, some related evidences have to be further studied.

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