Original Article

Cost Utility Analysis of Biliary Drainage and Palliative Care in Unresectable Hilar Cholangiocarcinoma: Decision Analytic Modeling Approach

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ABSTRACT

Background: Endoscopic biliary drainage (EBD) using metal stent, percutaneous transhepatic biliary drainage (PTBD) and palliative care are treatment options for patients with unresectable hilar cholangiocarcinoma (HCA). The information about their cost effectiveness is not available. The aim of this study was to compare the cost utility of EBD or PTBD to palliative care.

Methodology: Cost and quality-adjusted life year (QALY) of EBD, PTBD and palliative care group were evaluated by decision analytic model (Markov model). Cost of treatment and utility of each Markov state were derived from hospital charges and previous quality of life study respectively. Transition probabilities were derived from international literature and cholangiocarcinoma registry database from tertiary care hospitals in Thailand. Base-case and sensitivity analyses were performed.

Results: Compared with palliative care, an incremental cost per additional QALY gained of EBD and PTBD were 655,520 baht (US$19,976) and 6,548,398 baht (US$199,549), respectively. From probabilistic sensitivity analysis, EBD is preferable than palliative care if the willingness to pay (WTP) is higher than 650,000 baht (US$19,807). PTBD is not cost-effective compared with palliative care at any WTP threshold.

Conclusion: EBD is more cost effective than PTBD when compared with palliative care in unresectable HCA.

Key words : Hilar cholangiocarcinoma, Drainage, Palliative, Cost effectiveness, Decision theory, Markov model.

[Thai J Gastroenterol 2015; 16(3):144-150.]

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Introduction

Hilar cholangiocarcinoma (HCA) is the most common hepatobiliary cancer in Northeast Thailand. The incidence in female and male is 39.4 and 94.8 per 100,000 respectively[1,2]. The major risk factor of HCA in Aseans related to the culture of eating raw fish ingested with *Opisthorchis viverini,* whereas HCA in Western countries is related to primary sclerosing cholangitis (PSC)[3,4].

Unfortunately, only one-third of HCA patients are eligible to curative resection as patients often present in an advanced stage[5,6]. Symptomatic unresectable cases require some form of palliative biliary drainage, such as endoscopic biliary drainage (EBD) using metal stent, percutaneous transhepatic biliary drainage (PTBD) or biliary bypass surgery[7,8]. Because surgical bypass carries a high complication and mortality rate, non-surgical drainage is preferable[23,24].

Previous studies reported not only the efficacy of biliary drainage options[9-15] but also quality of life improvement[16-18,26]. EBD is cost effective than surgery[19]. Two randomized controlled trial and cost utility analyses indicated that metal stent was better than plastic stent in terms of adequacy of drainage and cost-effectiveness[9,20]. However, no study about cost-effectiveness of palliative biliary drainage option is available. The aim of this study was to compare the cost utility of EBD and PTBD to palliative care.

Methodology

We use the Markov model to evaluate the cost-effectiveness of EBD or PTBD compare to palliative care alone in patients with complex unresectable HCA (Figure 1). The Markov model is designed to mimic natural history of this disease by projecting the life time outcomes including costs and quality-adjusted life years (QALYs)[8].

Patients who choose EBD entered the model at endoscopic biliary drainage (EBD) state to have endoscopic metal stent insertion. In case of successful stent drainage, patients will move to and stay at post endoscopic biliary drainage (Post-EBD) state. If stent is occluded, the patient will return to EBD state for stent exchange. Percutaneous transhepatic biliary drainage (PTBD) is a rescue therapy for patients who failed EBD or preferred PTBD for first line. If drainage is adequate after PTBD, patients will move to and stay at post percutaneous transhepatic biliary drainage (Post-PTBD) state and return to PTBD state in case of PTBD malfunction. All patients who refuse biliary drainage receive palliative treatment (Palliative care state). Patients who failed PTBD or failed EBD or choose only palliative care will move to and stay at Post palliative care state. Patients who died at any states will moved to Death state.

The cycle length of 2 weeks was chosen because it was close to the shortest time frame that could cap-

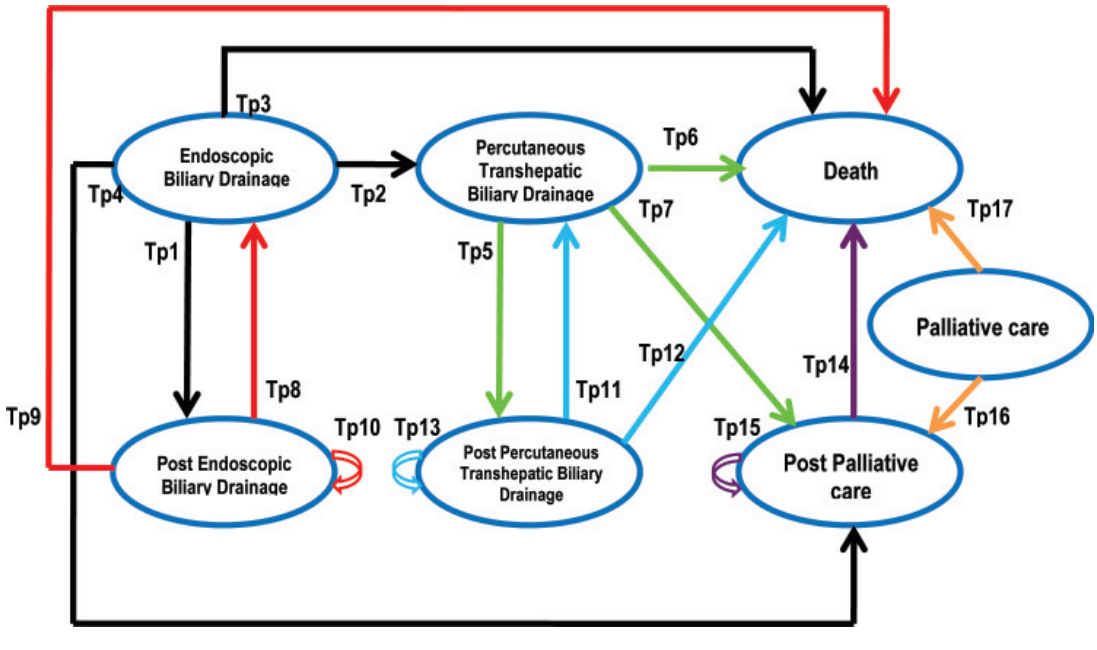

Figure1. Markov model disease states for the treatment of complex unresectable hilar CCA.

ture the clinical courses of disease. All costs, utility and transition probabilities were adjusted to 2 weeks cycle. The model calculates outcomes by taking into account clinical effectiveness, utilities and costs of each Markov state and final outcome is reported in terms of incremental cost per incremental QALY of EBD and PTBD compared with Palliative care. All costs and consequences that occurred beyond one year were discounted with a rate of 3 percent.

Transition probabilities

Transition probabilities (Tps) were derived from systematic searching of international literature and cholangiocarcinoma registry database from tertiary care hospitals in Thailand[28]. Tps relating to EBD were obtained from an open-label RCT[9]. Two-week Tps derived from this RCT were Tp from EBD to Post-EBD (Tp1), Tp from EBD to PTBD (Tp2), Tp from EBD to Death(Tp3) and Tp from Post-EBD to EBD (Tp8).

The Tp from PTBD to Post-PTBD (Tp5), PTBD to Death (Tp6) and Post-PTBD to Death (Tp12) were derived from a retrospective study of 168 inoperable HCA[25]. Post-PTBD to PTBD (Tp11) were derived from a retrospective study of 134 inoperable Bismuth type II-IV HCA[27]. Tp from Post-EBD to Death (Tp9), Palliative care to Death (Tp17), and Post palliative care to Death (Tp14) were derived from cholangiocarcinoma registry database[28]. Table 1 summarizes the transition probabilities of each disease state.

Cost and perspective

As this study was undertaken using health system perspective, the inpatient and outpatient charges involved in treatment of unresectable HCA using endoscopic biliary stent, PTBD and palliative care from 2011 to 2014 were retrieved from Srinagarind University Hospital database. These charges were the average charges of treatment of each disease state including simple and complicated cases. These charges included the charges of medicine, the charges of investigations such as laboratory and radiologic investigations, the charges of interventions related to each disease state, and the charges of management of complications from the disease and complications of interventions during each disease state. All such charges were converted to costs using the cost to charge ratio of 0.8, which was derived from the general administration information of hospitals in Thailand[21]. The average exchange rate in 2014, 32.82 baht per US$, was used to convert Thai Baht to US dollar[29]. Table 2 summarizes the costs of each disease state.

Utility

The health state utilities were obtained from unresectable HCA patients at Srinagarind Hospital using Thai version EQ-5D questionnaire. The answers from questionnaires were converted into 0 to 1 utility score using the Thai preference score for EQ-5D health state[22].

Table 1. Transition probabilities and parameters of each disease state.

Parameters	Mean	Standard error	Parameter distribution	Data source
14-day transition probabilities				
From EBD to Post-EBD (Tp1)	0.822	0.058	Beta	(9)
From EBD to PTBD (Tp2)	0.063	0.063	Beta	(9)
From EBD to Death (Tp3)	0.074	0.036	Beta	(9)
From PTBD to PostPTBD (Tp5)	0.247	0.044	Beta	(25)
From PTBD to Death (Tp6)	0.151	0.042	Beta	(25)
From Post EBD to EBD (Tp8)	0.111	0.047	Beta	(9)
From Post EBD to Death (Tp9)	0.081	0.045	Beta	(28)
From Post-PTBD to PTBD (Tp11)	0.288	0.056	Beta	(27)
From Post-PTBD to Death (Tp12)	0.083	0.058	Beta	(25)
From Post palliative care to Death (Tp14)	0.273	0.079	Beta	(28)
From Palliative care to Dead (Tp17)	0.083	0.047	Beta	(28)

EBD: Endoscopic biliary drainage; Tp: Transition probability; PTBD: Percutaneous transhepatic biliary drainage

Utility of EBD and PTBD state were obtained from pre-treatment utility in a previous quality of life study[26] thus other state were collected from cholangiocarcinoma registry database[28]. Utilities of Post-EBD state and Post-PTBD state were obtained from patients who had successful stent drainage and PTBD, respectively. Utility of Palliative care state was obtained from patients who refused drainage therapy. Utility of Post palliative care state was obtained from post ERCP and PTBD patients with inadequate drainage who refused further drainage option or patients who chose only palliative care. Table 3 showed utility parameters of each disease state.

Model assumptions

The assumptions of the model in this study were as follows: 1) All patients with unresectable HCA who received EBD, PTBD or palliative care were included in this study. 2) All patients were evaluated every 2 weeks. 3) Metal stent in stent was chosen in case of metal stent occlusion. 4) PTBD catheter exchange was carried out in case of catheter occlusion. 5) Charge of each Markov state was the average charge of treatment of simple and complicated cases.

Data Analysis

The results of Markov model were calculated using Microsoft Excel 2010®. In base-case analysis, results were calculated from the mean values of the parameters, and presented in terms of incremental cost per additional QALY.

To handle the uncertainty of the results, probabilistic sensitivity analyses (PSA) using Monte Carlo simulation was undertaken to capture the effects of uncertainty around all varied parameters simultaneously. The model was simulated on 1,000 iterations and the cost-effectiveness acceptability curve (CEAC) was graphed based on the results derived from the Monte Carlo simulation. In PSA, all parameters were randomly varied according to their distributions, then the incremental cost-effective ratios were calculated. The distributions of the parameters were as follow: 1) Gamma distribution which is in the interval between 0 to positive infinity and which can be positively skewed was assigned for cost data. 2) Beta distribution constrained on the interval between 0 and 1 was assigned for probabilities and utilities[30].

Table 2. Cost of each disease state from hospital database in years 2011-2014 (Baht).

Markov state	N	Mean	Standard error	Parameter distribution
EBD	57	43,710	3,855	Gamma
PTBD	170	26,473	1,281	Gamma
Post-EBD	41	1,475	592	Gamma
Post-PTBD	109	1,826	560	Gamma
Palliative care	3	4,403	1,536	Gamma
Post palliative care	33	560	128	Gamma

Table 3. Utility parameters.

Markov state	N	Mean	Standard error	Parameter distribution	Data source
EBD	37	0.303	0.035	Beta	(26)
PTBD	77	0.316	0.022	Beta	(26)
Post-EBD	37	0.565	0.027	Beta	(28)
Post-PTBD	77	0.402	0.022	Beta	(28)
Palliative care	104	0.354	0.029	Beta	(28)
Post palliative care	96	0.437	0.021	Beta	(28)

EBD: Endoscopic biliary drainage; PTBD: Percutaneous transhepatic biliary drainage.

Table 4. The results of base-case analysis.

	EBD	PTBD	Palliative care
Total lifetime cost (baht)	99,582	29,758	6,287
Total life expectancy (years)	0.42	0.18	0.17
Total QALYs (years)	0.21	0.07	0.07
Incremental cost per life expectancy (bath per life year gained)	371,527	1,412,591	
Incremental cost per QALY (bath per QALY gained)	655,520 (US$ 19,976)	6,548,398 (US$ 199,549)	

QALY, Quality adjusted life year, EBD: Endoscopic biliary drainage; PTBD: Percutaneous transhepatic biliary drainage.

RESULTS

Base-case analyses

Results of base-case analyses are shown in Table 4. The total lifetime cost of EBD, PTBD and palliative care in unresectable HCA were 99,582 baht (US$ 3,034), 29,758 baht (US$ 907) and 6,287 baht (US$192) per patient, respectively. The average life expectancy of EBD, PTBD and palliative care were 0.42, 0.18 and 0.17 years, respectively. The average QALYs were 0.21, 0.07 and 0.07 years in EBD, PTBD and palliative care. When compared with palliative care, an incremental cost per additional QALY gained of EBD and PTBD were 655,520 baht (US$19,976) and 6,548,398 baht (US$199,549), respectively.

Sensitivity analyses

The result of probabilistic sensitivity analyses (PSA), and the scatter plots of one thousand simulation processes of incremental cost and incremental QALYs are shown in Figure 2. Most of the scatter plots of EBD compared with palliative care are in the right-upper quadrant of cost-effectiveness plane, which means that EBD was more expensive and more effective than palliative care. Plots of PTBD compared with palliative care are both in the left and the right-upper quadrants, which means that PTBD was more expensive but could be less or more effective than palliative care.

Additionally the results of the PSA were also pre-

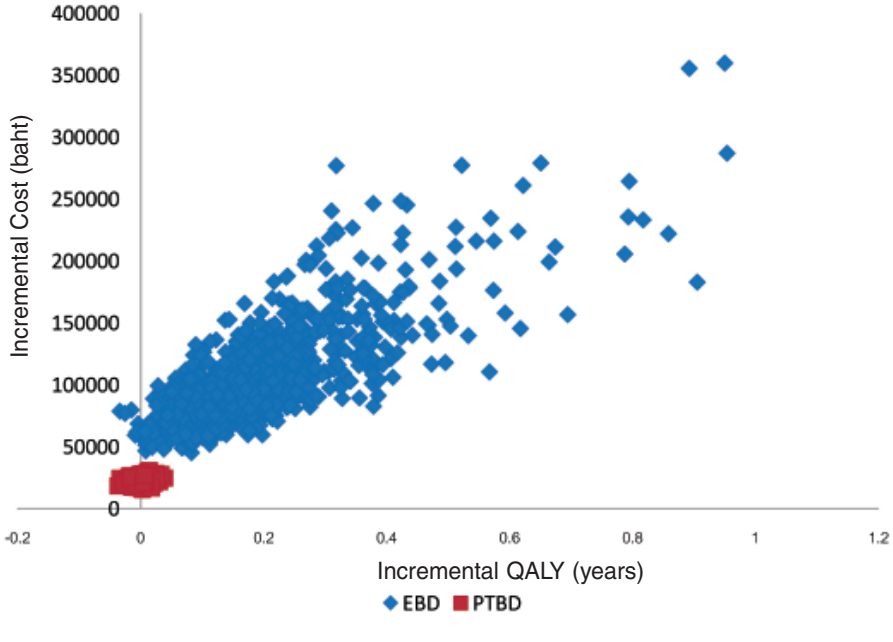

Figure 2.

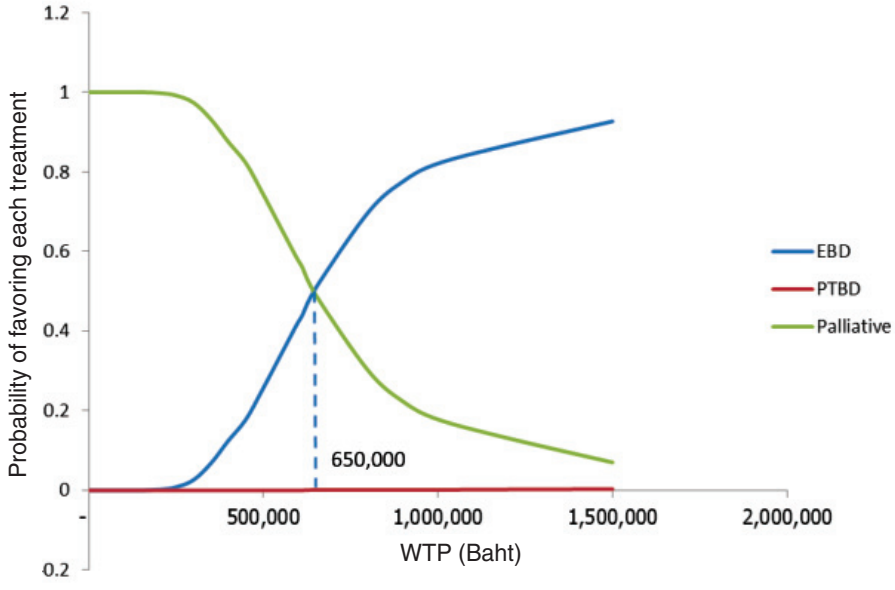

Figure 3.

sented by CEAC (Figure 3). The CEAC illustrates the probability of cost-effectiveness of each drainage type for any particular willingness to pay (WTP) threshold. According to the CEAC, EBD is preferable than palliative care if the WTP is higher than 650,000 baht (US$19,807). However, PTBD is not cost-effective compared to palliative care at any WTP threshold. At the willingness to pay threshold of one and three times GDP per capita of Thailand[32], or 189,667 baht (US$ 5,779) and 569,000 baht (US$ 17,337), no treatment options were cost effective.

Discussion

Our findings showed that among the treatment options for patients with unresectable HCA, EBD was more cost effective than PTBD, when compared with palliative care. To the best of our knowledge, this study is the first cost utility analysis comparing EBD and PTBD with palliative care in unresectable HCA. The WHO recommendation regarding the cost-effectiveness threshold criteria state that an intervention with an ICER less than one or falling between one to three times GDP per capita are highly cost-effective and cost-effective, respectively[31]. When comparing cost effectiveness of each method to GDP per capita based on the WHO recommendation regarding the cost-effectiveness threshold criteria, no treatment options were cost effective, but the trend of EBD was better than PTBD.

This study utilized the best available source of effectiveness parameters from RCT and cholangiocarcinoma registry database from tertiary care hospitals in Thailand[28], which is the largest database.

The reasons why EBD is cost-effective relative to PTBD in this study were as follow: 1) EBD was associated with a higher drainage efficacy, 2) EBD occlusion rate was lower than PTBD; thus patients in the EBD group seemed to have a higher chance of staying in the lower cost and high utility Post-EBD state, compared with the PTBD group, and 3) QALYs gains of patients with EBD was higher than PTBD.

This study had a few limitations regarding the data used in the model. First, there was only a single published RCT efficacy of EBD using metal stent in HCA[9]. Second, cholangiocarcinoma registry database was not published in the official report. Finally, it is well known that the economic analyses should be interpreted carefully within the context of parameters used in the study.

Conclusion

This is the first cost utility analysis providing the evidence that EBD is more cost effective than PTBD when compared with palliative care in unresectable HCA.

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