Original Article

Economic Evaluation of Palliative Biliary Drainage in Unresectable Hilar Cholangiocarcinoma

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Objective: The current treatment options available for patients with unresectable hilar cholangiocarcinoma [CCA] are endoscopic biliary drainage [EBD] using a metal stent, percutaneous transhepaticbiliary drainage [PTBD], and palliative care. However, information regarding their cost-effectiveness is not available.This study aimed to compare the cost utility between palliative biliary drainage [EBD or PTBD] and palliative care.

Materials and Methods: We used 2 methods for evaluation, direct calculation and the Markov decision analysis model. The cost of treatment and quality-adjusted life years [QALY] in the EBD, PTBD and palliative care groups were collected from the cohorts of unresectable hilar CCA database at a tertiary care hospital in Thailand. Transition probabilities were derived from international literature and the cohorts. Base-case and sensitivity analysis was also performed.

Results: Compared with palliative care, the incremental cost per additional QALY gained from EBD and PTBD using the direct calculation method were 422,822 baht (US$ 12,622) and 490,578 baht (US$ 14,644) per QALY gained, respectively. This result was in concordance with the Markov model. The ICER from EBD and PTBD were 655,520 baht (US$19,568) and 6,548,398 baht (US$195,475) per QALY gained, respectively. According to probabilistic sensitivity analysis using the Markov model, EBD is preferable to palliative care if the willingness to pay [WTP] is higher than 650,000 baht (US$19,403) per QALY gained. PTBD is not cost-effective compared to palliative care at any WTP threshold. At a WTP threshold of 160,000 Thai baht (the threshold of Thailand; US$ 4,776 per QALY gained) neither EBD nor PTBD were found to be cost-effective. At this threshold, only palliative care is cost-effective.

Conclusion: EBD is more cost-effective than PTBD when compared with palliative care in cases of unresectable hilar CCA, but at the WTP threshold of Thailand only palliative care is cost-effective.

Keywords: Cost-effectiveness, Cost utility, Endoscopic biliary drainage, Hilar cholangiocarcinoma, Percutaneoustranshepatic biliary drainage, Palliative

J Med Assoc Thai 2018; 101 [Suppl. 4]: S44-S52
Full text. e-Journal: http://www.jmatonline.com

Cholangiocarcinoma [CCA] is a primary bile duct cancer and the most common cause of malignant hilar strictures[1]. Cholangiocarcinoma accounts for approximately 10% to 20% of all cases primary liver cancer worldwide[2]. The highest age-standardized incidence rates of CCA are found in the northeast provinces of Thailand where the liver fluke *Opisthorchis viverrini* is endemic. In this area, 89% of primary liver cancers are CCA[3-5]. The incidence rates are 94.8 and 39.4 per 100,000 people in the male and

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How to cite this article: Suttichaimongkol T, Borntrakulpipat S, Sangchan A, Mairiang P, Mairiang E, Sukeepaisarnjaroen W, Chunlertlith K, Sawadpanich K. Economic evaluation of palliative biliary drainage in unresectable hilar cholangiocarcinoma. J Med Assoc Thai 2018;101;Suppl.4:S44-S52.

female populations, respectively[6].

The only curative treatment available for hilar CCA is surgery. Unfortunately, only one-third of patients are eligible for surgery, as they often present at an advanced stage[7,8]. The primary aim of palliative treatment is to improve quality of life by providing biliary drainage with long-term relief of jaundice, pruritus, pain, and cholangitis. Stent placement that results in adequate biliary drainage improves survival and quality of life[9,10]. Due to the fact that surgical bypass has high complication and mortality rates, either palliative percutaneous transhepaticbiliary drainage [PTBD] or endoscopic biliary drainage [EBD] is preferable[11-13].

Both a randomized controlled trial and a cost-utility analysis have shown that a metal stent is both more adequate in terms of drainage and more cost-effective compared to a plastic stent[14,15]. However, there have, thus far, been no studies examining the cost-effectiveness of palliative biliary drainage options. The aim of this study is to compare the cost utility between palliative biliary drainage [EBD or PTBD] and palliative care.

Materials and Methods

We used 2 methods for economic evaluation, direct calculation and the Markov decision analysis model.

Direct calculation method

All of the data were retrieved from a cohort study that was conducted at Khon Kaen University's Srinagarind Hospital in Khon Kaen, Thailand. The study was approved by the Khon Kaen University Ethics Committee for Human Research, and written informed consent was obtained from the patients before enrollment.

Patients

All patients at Srinagarind Hospital who were diagnosed with hilar CCA from August 2011 to January 2015 were recruited for the study. The inclusion criteria were that the patients were 18 years old or older and had unresectable Bismuth type I-IV hilar CCA. The diagnosis of hilar CCA was made based on clinical signs and symptoms, as well as radiologic images (Computed tomography [CT] or magnetic resonance cholangiopancreatography [MRCP]). The criteria for unresectability were based on a study by Jarnagin et al[16]. The exclusion criteria were class 4 and 5 of American Society of Anesthesiologist Physical Status classification, previous biliary stent, previous PTBD, previous surgery, previous chemotherapy, underlying ischemic heart disease, and unwillingness to participate in the study.

A total of 274 patients were enrolled and voluntarily assigned 1 of 3 groups: the EBD group, PTBD group, or palliative care group, in which 50, 118, and 106 patients were enrolled, respectively. Participants were followed until death or end of study. There were 2, 2, and 3 patients who survived until the end of the study in the EBD group, PTBD group, and palliative group, respectively. Baseline characteristics among the groups were comparable, as shown in Table 1. However, lymph node N2 metastasis and portal vein involvement occurred less frequently in the EBD group compared with the PTBD and palliative care groups.

Interventions

Patients in the EBD and PTBD groups were given prophylactic intravenous antibiotics, 2g of ceftriaxone, or 400 mg ciprofloxacin 1 hour before the procedure. Endoscopic retrograde cholangiopancreatography [ERCP] was carried out under general anesthe sia by an experienced endoscopist [AS]. PTBD was carried out under local anesthesia by an experienced intervention radiologist [EM]. The palliative care group received medications from gastroenterological staff in order to relieve symptoms such as itching, pain, insomnia, poor appetite, and depression. All patients attended an outpatient clinic at regular intervals for about 4 to 8 weeks in order that symptoms and complications following EBD, PTBD or palliative care could be assessed.

Cost and perspective

As this study was undertaken using patient perspective, the inpatient and outpatient costs involved in hilar CCA treatment with EBD, PTBD, and palliative care were retrieved from the Srinagarind Hospital database. Cost refers to the actual cost for each visit, which includes both (1) direct medical costs (medication, investigations, interventions, and management of complications) and (2) direct non-medical costs (transportation, food, and accommodation) in Thai baht. The average exchange rate was 33.5 Thai baht per US dollar[17].

Utility and quality-adjusted life year [QALY]

The health state utilities were obtained from the Thai version of the EuroQolfive-dimensions questionnaire (EQ-5D-3L)[18]. The results of the

Table 1. Baseline characteristics of patients from the Srinagarind Hospital database

Demographic and clinical basal data	EBD (n = 50)	PTBD (n = 118)	Palliative care (n = 106)
Age (years)	62.2±9.9	62.3±10.2	66.5±10
Male gender	38 (76)	85 (72)	79 (75)
Income (baht)	4,664±10,110	3,856±6,883	3,489±6,205
Bismuth's classification I/II/IIIa/IIIb/IV (n)	5/3/6/9/27	1/2/10/10/95	4/8/26/14/54
Albumin (g/dL)	2.99±1.35	2.97±1.05	2.47±1.54
Total bilirubin (mg/dL)	17.6±13.3	21.2±11.9	12±12.9
Creatinine (mg/dL)	0.8±0.5	1.0±1.2	0.9±1.4
CA19-9 (IU/mL)	2,530.5±12,220.5	373.8±472.9	420±467.6
CEA (IU/mL)	35.2±101.4	24.9±80.5	26.4±75.2
INR	1.06±0.93	1.77±2.06	1.24±1.89
PV encasement or occlusion: left/right/main/none (n)	1/4/5/40	22/24/4/68	17/11/9/69
N2 LN metastasis*	13 (26)	35 (30)	43 (46)
Distant metastasis	20 (40)	22 (18)	51 (48)
Number of visit	5±3	4±3	1

EBD = endoscopic biliary drainage; PTBD = percutaneous transhepatic biliary drainage; CEA = carcinoembrionic antigen; INR = international normalized ratio; LN = lymph node
* N2 LN metastasis is metastatic disease to peripancreatic, periduodenal, celiac, superior mesenteric or posterior pancreati coduodenal lymph nodes. Data are expressed as mean ± standard deviation, number, or number (%)

questionnaires were represented as a 0 to 1 utility score, as calculated using the formula below: Thai preference score for EQ-5D-3L health state

Utility = 1 - 0.202 - (0.121 xmo)-(0.121 xsc)-(0.059 xua)-(0.072 xpd)-(0.032 x ad)-(0.190 x m2) - (0.065 x p2) - (0.046 x a2) - (0.139 x N3)

Where mo = motility, sc = self-care, ua = usual activities, pd = pain/discomfort, ad = anxiety/ depression[19].

A utility weight represents the value placed on the presence of a medical condition by a patient, where 1 represents perfect health and 0 represents death. Negative values represent states worse than death. We estimated the benefit of treatment as QALY using the trapezium rule for calculating the area under the curve [AUC] of utility and life-year gain.

Measuring cost-effectiveness

For each patient, we calculated the EQ-5D-3L utilities followed by the AUC of utility and survival (year) to ascertain QALY. In base-case analysis, results were calculated from the mean values of the parameters and presented in terms of incremental cost-effectiveness ratio [ICER] per additional QALY.

The data obtained through the direct calculation method was analyzed using the bootstrap technique to handle the uncertainty of the results[20]. This is the method used to derive robust estimates of standard errors and confidence intervals, and was performed using STATA version 10. We randomized both 50 values total cost and 50 values QALY for each randomization with replacement then repeated this process for 1,000 replications.

Markov decision analysis model

We used the Markov model to evaluate the cost-effectiveness of EBD and PTBD compared to palliative care alone in patients with complex unresectablehilar CCA (Figure 1). The Markov model is designed to mimic the natural history of this disease by projecting the lifetime outcomes including costs and QALYs[11].

Patients who chose EBD entered the model at the EBD state to undergo endoscopic metal stent insertion. In cases of successful stent drainage, patients were moved to the post-EBD state. If the stent was occluded, the patient was returned to the EBD state for stent exchange. PTBD is a rescue therapy for patients who fail EBD or who opt for PTBD to begin with. If drainage was adequate after PTBD, patients were moved to the post PTBD state. They were returned to the PTBD state in cases of PTBD malfunction. All patients who refused biliary drainage received palliative treatment (palliative care state). Patients who failed

PTBD, failed EBD, or chose only palliative care were moved to the post palliative care state. Patients who died at any state were moved to the death state, where they remained.

A cycle length of 2 weeks was chosen because it was close to the shortest time frame in which the clinical course of the disease could be observed. All cost, utility, and transition probabilities were adjusted to a 2-week cycle. The model calculates outcomes by taking into account clinical effectiveness, as well as cost and utility at each Markov state. The final outcome is reported in terms of incremental cost per incremental QALY in cases of EBD and PTBD compared with palliative care. All costs and consequences that occurred beyond 1 year were discounted at a rate of 3%.

Transition probabilities [TPs] were derived from systematic review of international literature and the cohort. Table 2 summarizes the transition probabilities of each disease state.

Cost and perspective

This model was undertaken from the perspective of public health care providers.The inpatient and outpatient charges involved in treatment of unresectable hilar CCA using an EBD, PTBD, and palliative care from 2011 to 2014 were retrieved from the cohort. The charges examined were the average charges involved in treatment at each disease state in both simple and complicated cases. These charges included the drugs, investigation (such as laboratory and radiologic examination), intervention related to each disease state, and management of complications stem ming from both the disease and interventions at each disease state. These charges were then converted to costs using a cost-to-charge ratio of 0.8, which was derived from the general administration information gathered from hospitals in Thailand[21]. The average exchange rate in 2017 (33.5 baht per US$) was used to convert Thai baht to US dollars[17]. Table 3 summarizes the cost of each disease state.

Utility

The utility of EBD and PTBD states were derived from pre-treatment utility data from a previous quality of life study[22]. Those of other states were collected from the cohort. The post-EBD state and post-PTBD state utility scores were obtained from patients who underwent successful stent drainage and PTBD, respectively. The palliative care state utility scores were obtained from patients who refused drainage therapy. The post-palliative care state utility scores were

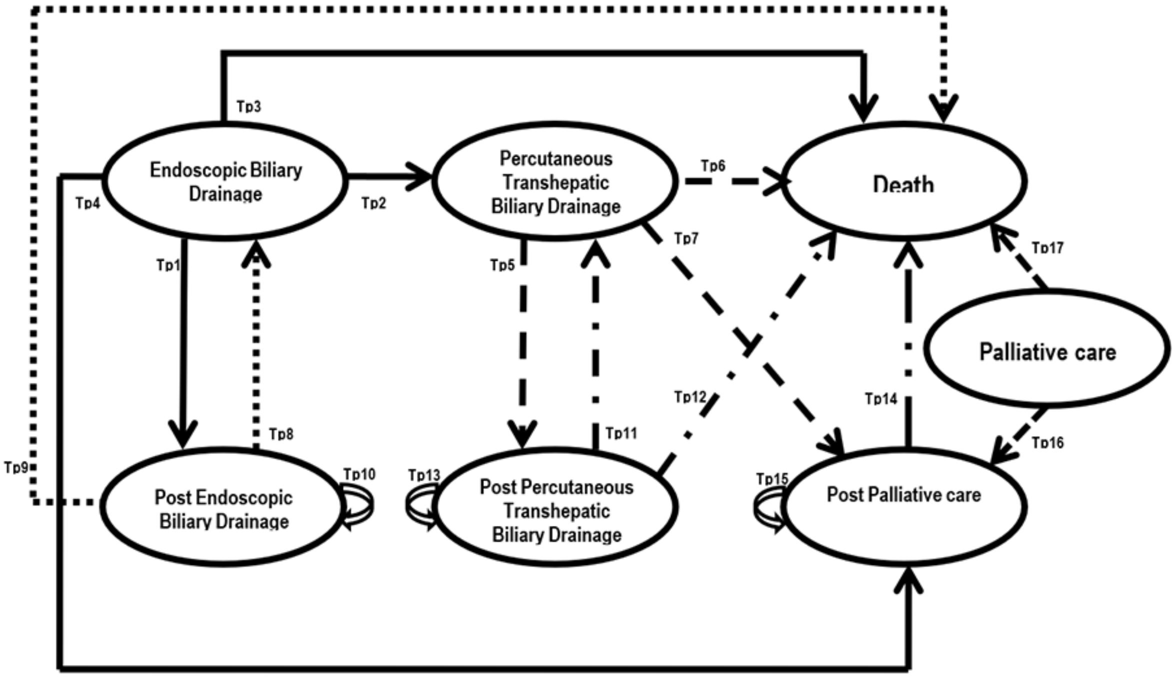

Figure 1. Markov model disease states for the treatment of complex unresectable hilar cholangiocarcinoma.

obtained from patients post ERCP and PTBD with inadequate drainage who either refused further drainage options or received only palliative care and no drainage. Table 4 shows the utility parameters of each disease state.

Model assumptions

The assumptions of the model in this study were as follows: 1) All patients with unresectable hilar CCA who received EBD, PTBD, or palliative care were included in this study, 2) patients were evaluated every

Table 2. Transition probabilities and parameters of each disease state

14-day transition probabilities	Mean	Standard error	Parameter distribution	Data source
From EBD to Post-EBD (tp1)	0.822	0.058	Beta	Ref. 14
From EBD to PTBD (tp2)	0.063	0.063	Beta	Ref. 14
From EBD to Death (tp3)	0.074	0.036	Beta	Ref. 14
From PTBD to Post PTBD (tp5)	0.247	0.044	Beta	Cohort
From PTBD to Death (tp6)	0.151	0.042	Beta	Cohort
From Post EBD to EBD (tp8)	0.111	0.047	Beta	Ref. 14
From Post EBD to Death (tp9)	0.081	0.045	Beta	Cohort
From Post-PTBD to PTBD (tp11)	0.288	0.056	Beta	Ref. 25
From Post-PTBD to Death (tp12)	0.083	0.058	Beta	Cohort
From Post palliative care to Death (tp14)	0.273	0.079	Beta	Cohort
From Palliative care to Dead (tp17)	0.083	0.047	Beta	Cohort

EBD = Endoscopic biliary drainage; tp = transition probability; PTBD = Percutaneous transhepatic biliary drainage

Table 3. Cost of each disease state from the 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

EBD = Endoscopic biliary drainage; PTBD = Percutaneous transhepatic biliary drainage

Table 4. Utility parameters

Markov state	N	Mean	Standard error	Parameter distribution	Data source
EBD	37	0.303	0.035	Beta	Ref. 22
PTBD	77	0.316	0.022	Beta	Ref. 22
Post-EBD	37	0.565	0.027	Beta	Cohort
Post-PTBD	77	0.402	0.022	Beta	Cohort
Palliative care	104	0.354	0.029	Beta	Cohort
Post palliative care	96	0.437	0.021	Beta	Cohort

EBD = endoscopic biliary drainage; PTBD = percutaneous transhepatic biliary drainage

Table 5. The results of base-case analysis

	EBD	PTBD	Palliative care
Direct calculation method			
Life expectancy (days), mean ± SD	218±222	197±152	89±116
Direct medical cost (baht)	81,471	58,780	1,862
Total cost (baht)	91,422	68,294	3,521
QALY	0.25	0.18	0.05
Incremental cost per QALY (bath per QALY gained)	422,822 (US$12,622)	490,578 (US$14,644)	
Markov decision analysis model			
Total life expectancy (days)	153	66	62
Total lifetime cost (baht)	99,582	29,758	6,287
Total QALYs (years)	0.21	0.07	0.07
Incremental cost per QALY (bath per QALY gained)	655,520 (US$19,568)	6,548,398 (US$195,475)	

EBD = Endoscopic biliary drainage; PTBD = Percutaneoustranshepatic biliary drainage; QALY = Quality adjusted life year; SD = standard deviation

two weeks, 3) stent or PTBD catheter exchange was carried out in cases of stent/catheter occlusion, and 4) the charge at each Markov state was the average charge of treatment for simple and complicated cases.

Measuring cost-effectiveness

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

To handle the uncertainty of the results, proba bilistic sensitivity analysis [PSA] using the Monte Carlo simulation was conducted to eliminate the effects of uncertainty around all parameters that varied simultaneously. The model was simulated for 1,000 iterations, and the cost-effectiveness acceptability curve [CEAC] was graphed based on the results derived from the Monte Carlo simulation. All parameters in the PSA were randomly varied according to their distributions and the ICERs were calculated. The distributions of the parameters were as follows: 1) gamma distribution, which is in the interval between 0 and positive infinity and can be positively skewed, was assigned for cost data and 2) beta distribution, which was constrained to the interval between 0 and 1 and was assigned for probability and utility(23).

Results

Base-case analyses

The mean total lifetime cost, average life expectancy, average QALYs in cases of EBD, PTBD, and palliative care in unresectable hilar CCA according to the direct calculation method are shown in Table 5. The incremental cost per additional QALY gained for EBD and PTBD when compared with palliative care were 422,822 baht (US$ 12,622) and 490,578 baht (US$ 14,644) per QALY gained, respectively. At a willingness to pay threshold of 160,000 Thai baht (the threshold used for residents in Thailand; US$ 4,776) per QALY gained both treatment options were not cost-effective when compared with palliative care. However, EBD was more cost-effective than PTBD.

The results of base-case analysis using the Markov model are also shown in Table 5. When compared with palliative care, the incremental cost per additional QALY gained from EBD and PTBD were 655,520 baht (US$19,976) and 6,548,398 baht (US$199,549) per QALY gained, respectively.

Sensitivity analyses

The data obtained through the direct calculation method was analyzed using the bootstrap technique to handle the uncertainty of the results. The results derived from the bootstrap randomization are shown in Figure 2. Axis Y is the mean difference among the costs of intervention and axis X is the mean difference of QALY. Analysis using the bootstrap technique revealed that both EBD and PTBD improved QALY to a greater extent than palliative care. When EBD and PTBD were compared, we found that EBD is associated with a higher QALY score, but at a slight

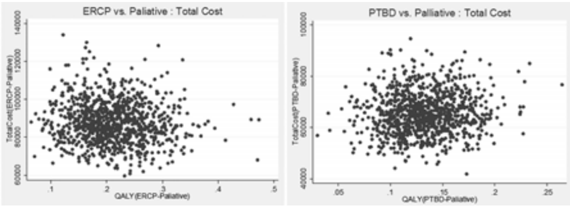

Figure 2. Bootstrap sensitivity analysis using the direct calculation method.

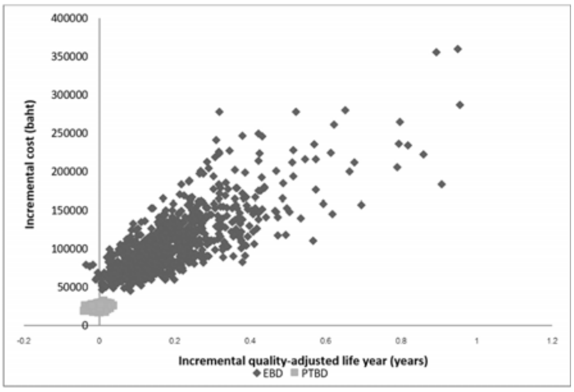

Figure 3. Probabilistic sensitivity analysis [PSA] using the Monte Carlo simulation.

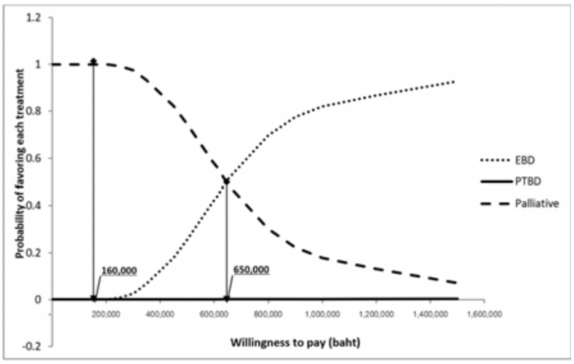

Figure 4. The cost-effectiveness acceptability curve [CEAC] from the Markov model.

increase in cost.

The results of probabilistic sensitivity analysis [PSA] using the Markov model is shown in Figure 3. The scatter plots represent the results of one thousand simulations of incremental cost and incremental QALYs. Most of the scatter plots that show how EBD compares to palliative care are in the right-upper quadrant of the cost-effectiveness plane, which means that EBD was more expensive and effective than palliative care. Despite this, plots representing PTBD compared to palliative care are in both the upper-left and upper-right quadrant, which means that PTBD was more expensive but could be either more or less effective than palliative care. When the simulated ICER of each treatment option is compared with the willingness to pay [WTP] threshold used for residents in Thailand (160,000 baht; [US$ 4,776] per QALY gained), 99.4% of EBD treatments and 69.6% of PTBD treatments were not cost-effective.

Moreover, the results of the PSA are also represented by a CEAC (Figure 4). The CEAC illustrates the probability of cost-effectiveness of each drainage type for any particular WTP threshold. According to the CEAC, EBD is preferable to palliative care if the willingness to pay WTP is higher than 650,000 baht (US$19,403). However, PTBD is not cost-effective compared to palliative care at any WTP threshold. At the WTP threshold calculated for residents of Thailand, neither treatment option was found to be cost-effective. At this threshold, only palliative care is cost-effective.

Discussion

To the best of our knowledge, this study is the first cost-utility analysis comparing EBD and PTBD with palliative care in cases of unresectable hilar CCA using the direct calculation method from individual patient data and the Markov model that was designed to mimic the natural history of this disease. The results from both methods showed that EBD is a more cost-effective method than PTBD when both are compared with palliative care. However, the ICERs derived from the Markov model were higher than those derived from the direct calculation method. This is especially true of the ICER of PTBD, as the variables that were used in each method to calculate this value came from difference sources. The results of sensitivity analysis also confirm this result. These results were examined from the perspective of patients and public healthcare providers. Based on the Thailand health technology assessment recommendations regarding cost-effectiveness threshold criteria, the results derived from the direct calculation method confirmed neither EBD nor PTBD were cost-effective. At this threshold, only palliative care was cost-effective. However EBD was more cost-effective than PTBD compared to palliative treatment from the perspective of patients in Thailand. Analysis using the Markov model also indicated that no treatment options were cost-effective. Although patients in other regions of Thailand have higher average incomes than those in the northeast, the direct non-medical cost was a small proportion of total cost. The results of this study can, thus, likely be applied in other regions, as well.Although we found that neither EBD nor PTBD were not cost-effective, we still recommend performing biliary drainage on the patient, as it is currently accepted as a standard of care. The results of this study can be used as a basis of comparison if new treatment options for palliative biliary drainage become available in the future.

As a source of effectiveness parameters, this study derived the individual patient data from the largest available database of unresectable hilar CCA from Srinagarind Hospital in northeast Thailand, which has the highest prevalence of CCA in the world[6]. Moreover, we also applied the results of the first randomized controlled trial to the efficacy of EBD using a metal stent in cases of unresectable complex hilar CCA[14].

There were 3 major reasons why this study found EBD to be more cost-effective relative to PTBD. First, EBD has a higher drainage efficacy. Second, the EBD occlusion rate is lower than that of PTBD. Finally, QALY gains for patients in the EBD group were higher than those in the PTBD group. Our findings were consistent with the policy decision made to include EBD with self-expandable metallic stent [SEMS)] in Thailand's Universal Coverage Scheme benefit package.

This study has some limitations. First, the majority of the data were retrieved from a single-center study. Second, lymph node N2 metastasis and portal vein involvement were less prevalent in the EBD group compared with the PTBD and palliative care groups. Finally, it is well known that economic analysis should be interpreted carefully within the context of parameters used in the study. Further economic evaluation is required to assess the costs and benefits in patients who were excluded from the trials such as those with previous PTBD, surgery, or chemotherapy compared with the palliative care group.

Conclusion

EBD is more cost-effective than PTBD when compared with palliative care in cases of unresectable hilar CCA, but at the WTP threshold calculated for residents of Thailand, neither treatment option was cost-effective.

What is already known on this topic?

A randomized controlled trial and a cost utility analysis have both shown that a metal stent is both more adequate in terms of drainage and more cost-effective compared to a plastic stent.

What this study adds?

This is the first study of the cost-effectiveness of palliative biliary drainage options. EBD is more cost-effective than PTBD when compared to palliative care in cases of unresectable hilar CCA.

Acknowledgements

We would like to express our gratitude to Asst. Prof. Yupa Thawornpitak for the statistical analysis and Dylan Southard for English language editing through a grant from the Khon Kaen University Faculty of Medicine (Thailand).

Potential conflicts of interest

None.

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