Cost-Effectiveness Analysis of Ultrasound Surveillance for Resectable Cholangiocarcinoma in an Endemic Area

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Abstract

Cholangiocarcinoma (CCA) is common cancer in the northern and northeastern regions of Thailand. Abdominal ultrasound surveillance for CCA is a standard non-invasive imaging study for detecting an early stage of malignancy, which could potentially aim for curative treatment. From 2011 to 2017, Chulabhorn Hospital conducted a cohort on the "Study and treatment project for CCA" in the endemic area of Nan Province, Northern Thailand. The outcome proved that patients who received ultrasound surveillance had a better chance to detect in the resectable stage and eventually had a better survival outcome. However, there is limited data on the cost-effectiveness analysis of using ultrasound surveillance of CCA to be the important information for government reimbursement schemes. This research aimed to study the cost-effectiveness of the ultrasound surveillance program of CCA for high-risk populations in the northern region of Thailand. By analyzing historical data from a societal perspective, a decision tree model was applied to evaluate the cost-effectiveness of ultrasound surveillance programs in populations with high risk for CCA. The results from the cost-effectiveness analysis showed that the population who received ultrasound surveillance for resectable CCA maintained the quality-adjusted life-year gained (QALY gained) of 0.13 years and the incremental cost-effectiveness ratio (ICER) of 58,242 THB/QALY gained as compared with the non-surveillance group. The ICER of 58,242 THB/QALY gained is considered within the threshold of the willingness to pay in Thailand, which is about 160,000 THB/QALY gained; therefore, ultrasound surveillance for resectable CCA is considered cost-effective and affordable. This analytic result may be useful to consider a policy to provide ultrasound surveillance for CCA in the population at risk for reimbursement.

Keywords*: Cost-effectiveness analysis, Ultrasound surveillance, Cholangiocarcinoma*

1. Introduction

CCA is a common malignancy in northern and northeastern parts of Thailand. These two regions of Thailand are endemic because the population in both regions has high incidents of liver fluke infestation by the habit of raw food consumption such as fermented fish and pickled fish, which are potentially contaminated with the parasite (Chaitheerakit, 2018). The main symptoms of CCA are fatigue, loss of appetite, weight loss, right upper quadrant pain, yellow eye jaundice caused by an obstruction of the bile duct, and probably ascites. CCA death was estimated to be approximately 14,000 cases per year which were extremely high compared with the developing countries ("CCA mortality rate in Thailand.," 2019). Moreover, most of the patients carry a poor prognosis with a dismal survival rate. CCA also leads to severe disabilities and decreases the ability to perform daily life.

Abdominal ultrasound surveillance for CCA is the common imaging surveillance tool that can detect small cancer lesions causing patients could receive diagnosis and treatment before the disease progression. Generally, ultrasound is harmless because there is no radiation and also has an accuracy of up to 84% in surveillance and diagnosing CCA. (Saengdidtha, 2015) It is an inexpensive diagnostic tool when compared to other imaging methods. Besides, ultrasound surveillance has proved to have a survival benefit from CCA deaths.

From 2011 to 2017, a cohort of “Study and treatment project for CCA” was conducted by Chulabhorn Hospital in Ban Luang District, Nan Province using abdominal ultrasound examination. The local population living in Ban Luang District, Nan Province, had the highest incidence of CCA in the northern region (cancer-incidence-nan-2012-2014., 2015). The risk factors of the population included the consumption of raw freshwater fish, agricultural chemical use, alcohol drinking, smoking, etc. Kunlayanee Akkarachinorate (2016) conducted an epidemiological study of CCA based on a surveillance cohort by Chulabhorn Hospital in 4,225 populations aged 30-60 years who were at high risk for CCA, which could help diagnose CCA and premalignant lesions. The study found that CCA was the most common cancer in Ban Luang District, Nan. The CCA patients detected by ultrasound and received surgical treatment resulted in an increased survival rate and more disease-free periods (Akkarachinorate, 2018).

There was a study to support the idea that ultrasound surveillance is helpful in the diagnosis of CCA. For example, Sungkasubun et al. (2016) compared using upper abdominal ultrasound surveillance every 6 months compared to blood and stool test results, most CCAs were found in patients with a mean age of 51.9 years and a prevalence of 165.7 cases per 100,000 populations. The study has shown the potential for detection of CCA at the premalignant stage in 11 cases. All patients diagnosed with premalignant had good postoperative outcomes. Thus, ultrasound surveillance could help diagnose CCA at the premalignant and early cancer stages (Sungkasubun et al., 2016). A study has also proved a survival benefit of using ultrasound for CCA surveillance (Siripongsakun et al., 2018), which has proved an increased median survival from 6.7 months to 31.8 months.

There has been a quality of life evaluation of the CCA patient after various treatment interventions including surgery, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic biliary drainage (PTBD), and palliative care to incorporate into the cost analysis. Mairiang et al. (2015) conducted a comparative study of the quality of life in hepatic bile duct cancer patients before and after treatment. The Thai version of the Health Quality of Life Questionnaire (EQ-5D) was used to study a total of 261 CCA patients likely to receive one of those treatments, with an assessment of 2-4 weeks before and after treatment. The study found that the group with ERCP plus stent placement significantly improved their quality of life. In the surgical and PTBD groups, there was also an improvement in the quality of life, but not statistically significant. Thus, patients with hepatic bile duct cancer treated with ERCP combined with PTBD had an improved quality of life (Mairiang, 2015).

Currently, there is no cost-effective analysis data on CCA surveillance; however, there was economic cost-effectiveness of hepatocellular carcinoma (HCC), a primary liver cancer that could be related. Sangmala et al (2014) conducted a study on economic cost-effectiveness and budgetary impact analysis of HCC project in patients with chronic hepatitis B virus in Thailand by using the decision tree and the Markov models to assess utility costs. The results showed that the ultrasound surveillance every half year and the ultrasound surveillance every half year combined with alpha-fetoprotein: AFP for tumor marker was the surveillance with incremental cost-effectiveness ratio (ICER) equal to 118,796 THB/QALY gained. Using ultrasound every 6 months and ultrasound every 6 months plus AFP was considered a cost-effective alternative to the willingness to pay (WTP) at 160,000 THB/QALY gained compared to the no surveillance program (Sangmala, Chaikledkaew, Tanwandee, & Pongchareonsuk, 2014).

From the above literature review, Ultrasound surveillance of HCC has proved a survival benefit and cost-effective; however, the study on the economics of CCA surveillance in Thailand remained limited. Therefore, this study aimed to determine the cost-effectiveness of ultrasound surveillance for resectable CCA among high-risk populations in the northern region of Thailand from 2011 to 2017. The result could be valuable information for determining if ultrasound surveillance of CCA is cost-effective to use among larger populations at risk in the endemic areas of Thailand.

2. Objectives

To study the cost-effectiveness of ultrasound surveillance for resectable CCA among high-risk populations in the northern region of Thailand

3. Materials and Methods

3.1 Study design

This was a retrospective descriptive study with data collection to compare the two groups: the non-ultrasound surveillance and the ultrasound surveillance groups.

The non-ultrasound surveillance group included patients with treatment for CCA at Chulabhorn Hospital from 2009 to 2015 (Siripongsakun et al., 2018). Whereas, the ultrasound surveillance group comprised patients in the cohort of "Study and treatment project for CCA" of Chulabhorn Hospital from 2011to 2017 (Sungkasubun et al., 2016).

3.2 Study population

It was a comparison between 2 groups:

1) The non-ultrasound surveillance group of CCA patients at Chulabhorn Hospital

Inclusion criteria:

- Patients diagnosed with CCA from Chulabhorn Hospital, 2009-2015
- Tissue diagnostic of CCA

Exclusion criteria:

- Imaging diagnostic of CCA only
- Diagnosed with or undergoing treatment for another cancer

2) The ultrasound surveillance group among the population diagnosed with or undergoing treatment for another cancer in 4 sub-districts of Ban Luang District, Nan Province (Siripongsakun et al., 2019)

Inclusion criteria:

- Population aged 30-60 years, based on a database in the cohort of Chulabhorn Hospital
- Living in Ban Luang District, Nan Province

Exclusion criteria:

- Pregnant or breastfeeding
- Diagnosed with or undergoing treatment for another cancer
- Not complete the project as specified

3.3 Study procedures:

1) Request for historical data on the "Study and treatment project for CCA" of Chulabhorn Hospital from the Chalerm Phrakiat 60th Birthday Celebration Research and Learning Center

2)Find out more from the Medical Records and Medical Statistics Department and Picture Archiving and Communication System (PACs) from the database of Chulabhorn Hospital

3) Use the data obtained to analyze the cost-effectiveness

4) Study report

3.4 Materials and methods

A case record form was used for data collection. The study was based on ultrasound results from the upper abdomen of populations at high risk of CCA in the northern area of Thailand to compare with the non-ultrasound surveillance group of patients with CCA in Chulabhorn Hospital.

3.5 Data collection

This study obtained data from two sources:

Data from the Medical Records and Medical Statistics Department, Chulabhorn Hospital during 2009-2015 for patients without ultrasound surveillance: 121 cases of CCA were treated at Chulabhorn Hospital, including 48 females and 73 males.

Data on the cohort of "Study and treatment project for CCA" of Chulabhorn Hospital during 2011-2017: 4,225 cases (2,306 females and 1,919 males) with 42 CCA and 21 premalignant lesions were included (Siripongsakun et al., 2019)

3.6 Statistical analysis

The decision tree model was used to simulate the evaluation of outcomes closer to the actual value and determine the consumption of resources according to the likelihood of occurrence. The decision tree model paradigms were based on a cross-sectional observational period in both the non-ultrasound surveillance group (Figure 1) and the ultrasound surveillance group (Figure 2).

The cost-effectiveness analysis (CEA) was used to assess cost-effectiveness in public health from a societal perspective to allocate limited resources for maximum efficiency. CEA was a method of comparison between monetary costs and effectiveness. The results of all alternatives must be in the same types to measure the differences.

Sensitivity analysis (SA) considered the change in point estimates. The results from the base case analysis were divided into two methods: 1) Deterministic sensitivity analysis (DSA), which was a one-way sensitivity analysis of changes in outcomes when one of the data values was changed. This method was widely used and logical as presented with the Tornado diagram, 2) Probabilistic sensitivity analysis (PSA), a sensitivity analysis of simultaneous data changes when every change in the data changes was at the same time on probabilities (Chaikledkaew & Teerawattanon, 2014). The study used variables to analyze events' sensitivity and likelihood, as shown in Table 1 below.

Two large cohorts in Thailand conducted a surveillance program for CCA, which are the Chulabhorn cohort and Cholangiocarcinoma Screening and Care Program (CASCAP) (Cholangiocarcinoma Screening and Care Program., 2018). These two programs used 6-month intervals of ultrasound surveillance as a standard protocol. Therefore, the analysis will be based on six months surveillance interval to calculate the cost. After detecting CCA, the patient will receive a standard treatment depending on the cancer staging, including hepatic resection or chemotherapy, palliative treatment, or a combination of treatments. After treatment, patients received utilities or satisfaction with different health conditions. The utilities of this study came from a literature review, as shown in Table 2 below.

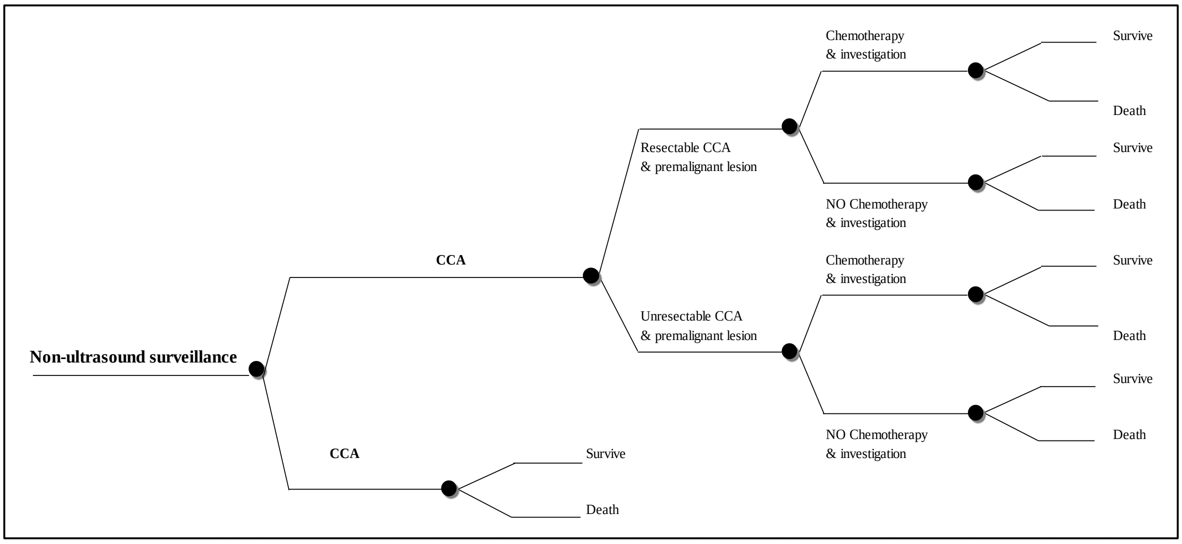

Figure 1 Decision tree model of Non-ultrasound surveillance

The cost parameters, were used in the analysis of both groups, consisting of 1) Direct medical costs: All diagnostic radiological examinations included Ultrasound (US), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography-Computed Tomography (PET-CT), and pathological examination. The costs included in this study are based on only definite standard treatment, including surgery and chemotherapy. The palliative intervention costs, which are adjunct to the standard treatment, such as endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic biliary drainage (PTBD) since these palliative interventions have no impact on survival benefits. 2) Direct non-medical costs were travel expenses, foods, and surplus expenses, and 3) Indirect costs were loss of income or time as shown in Table 3 below (Permsuwan, 2020).

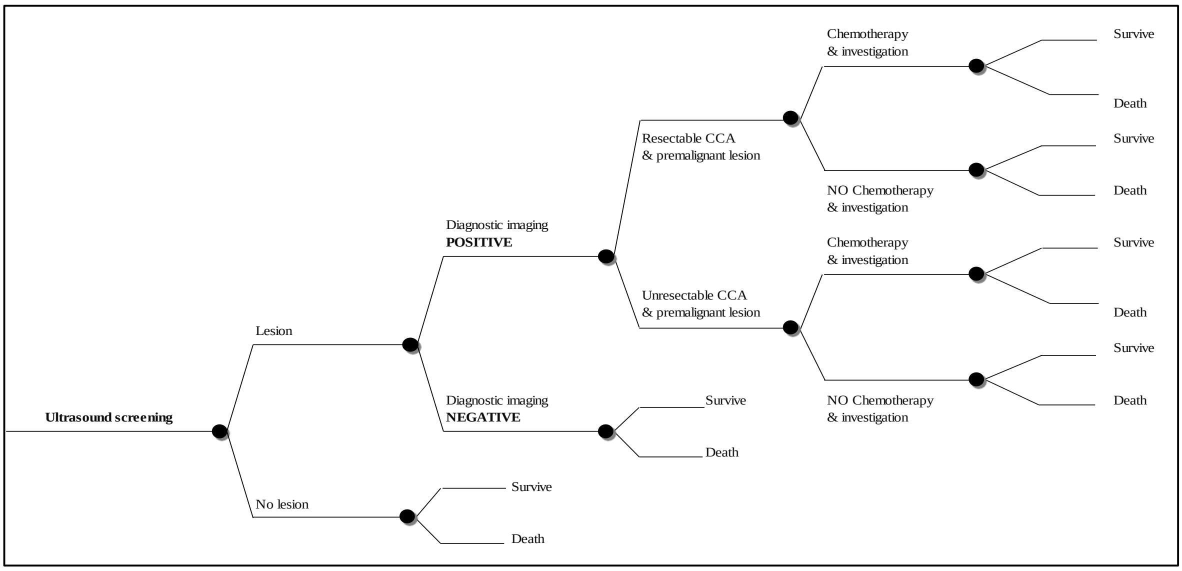

Figure 2 Decision tree model of Ultrasound surveillance

4. Results and Discussion

This study divided the treatment of CCA into four types: surgery, surgery combined with chemotherapy, chemotherapy, and supportive treatment. The demographics of both groups were those with and without ultrasound surveillance. The mean age of those without and with ultrasound surveillance was 59.6 years and 53.6 years, respectively, with statistical significance. Gender had no statistical significance in both groups.

This study could explain the results of a one-way sensitivity analysis presented as a Tornado diagram. The variables were divided into two groups: 1) Probability and utility parameters, including the top 3 factors or variables affecting ICER, such as the probability of diagnostic CCA from imaging positive, Probability of survival of untreated CCA, and Probability of unresectable CCA or premalignant lesion needed chemotherapy (Figures 3) and 2) The cost parameter group had the top 3 factors or variables affecting ICER, namely the cost of chemotherapy drugs requiring hospitalization for those who did not undergo ultrasound surveillance (Chemotherapy IPD cost of Non-US surveillance), ultrasound upper abdomen and ultrasound liver cost, and PET-CT cost, respectively shown in Figure 4 below.

The results revealed that the group who received ultrasound surveillance for CCA had increased QALY gained by 0.13 years with an incremental cost-effectiveness ratio (ICER) of 58,242 THB/QALY gained as compared with the non-surveillance group (Table4).

Overall surveillance of CCA is considered cost-effective in Thailand since the ICER is within the threshold of the willingness to pay in Thailand, which is less than 160,000 THB/QALY gained.

Table1 Probability parameters

Outcome parameter description Non-US surveillance	**Distribution**	**Probabilistic**	**Mean**	**SE**	**Alpha**	**Beta**
Probability of diagnostic CCA from imaging positive	beta	0.0723	0.1000	0.0300	9.9000	89.1000
Probability of resectable CCA or premalignant lesion from imaging positive	beta	0.1847	0.1653	0.0338	19.8363	100.1657
Probability of resectable CCA or premalignant lesion needed chemotherapy	beta	0.6291	0.6500	0.1067	12.3502	6.6501
Probability of unresectable CCA or premalignant lesion needed chemotherapy	beta	0.5991	0.6238	0.0482	62.3818	37.6211
Probability of survive of resectable CCA with treatment	beta	0.4023	0.2308	0.1169	2.7697	9.2306
Probability of survive of resectable CCA without treatment	beta	0.3682	0.4286	0.1870	2.5716	3.4284
Probability of survive of unresectable CCA with treatment	beta	0.0426	0.0317	0.0221	1.9654	60.0354
Probability of survive of unresectable CCA without treatment	beta	0.0000	0.0000	0.0000	1.0000	99,997.0000
Probability of survive of untreated CCA	beta	0.9673	0.9500	0.0218	94.054	4.9502
Outcome parameter description US surveillance	**Distribution**	**Probabilistic**	**Mean**	**SE**	**Alpha**	**Beta**
Probability of US surveillance positive	beta	0.0496	0.0473	0.0033	200.5122	4,038.6464
Probability of diagnostic surveillance positive	beta	0.2955	0.3150	0.0328	62.6859	136.3169
Probability of resectable CCA or premalignant lesion from imaging positive	beta	0.6681	0.7460	0.0548	46.2526	15.7482
Probability of resectable CCA or premalignant lesion needed chemotherapy	**beta**	**0.2640**	**0.3191**	**0.0680**	**14.6789**	**31.3221**
Probability of unresectable CCA or premalignant lesion needed chemotherapy	beta	0.4370	0.5625	0.1240	8.4376	6.5626
Probability of survive of resectable CCA with treatment	beta	0.4133	0.2667	0.1142	3.7338	10.2663
Probability of survive of resectable CCA without treatment	beta	0.8899	0.9063	0.0515	28.0960	2.9048
Probability of survive of unresectable CCA with treatment	beta	0.0000	0.0000	0.0000	1.0000	99,997.0000
Probability of survive of unresectable CCA without treatment	beta	0.3251	0.2857	0.1707	1.7142	4.2858

** CCA: Cholangiocarcinoma*

Table 2 Utility parameters

Utility index	Mean	Source
Utility of resectable CCA with chemotherapy	0.4500	Ref. (Cillo et al., 2015; Njei et al., 2017)
Utility of resectable CCA without chemotherapy	0.5300	Ref. (Mairiang, 2015)
Utility of unresectable CCA with chemotherapy	0.2600	Ref. (Cillo et al., 2015; Njei et al., 2017)
Utility of unresectable CCA without chemotherapy	0.4370	Ref. (Suttichaimongkol T, 2018)
Utility of palliative care CCA	0.3540	Ref. (Suttichaimongkol T, 2018)

* CCA: Cholangiocarcinoma

Table 3 Cost parameters

Cost parameter description	Distribution	Source
Ultrasound upper abdomen and Ultrasound liver	gamma	GFPrice (CGD)
Ultrasound-Guided for biopsy and Ultrasound Needle Core Biopsy	gamma	GFPrice (CGD)
Fine Needle Aspiration under ultrasound	gamma	GFPrice (CGD)
Ultrasound intraoperative / Use ultrasound	gamma	GFPrice (CGD)
CT Upper abdomen for diagnotic	gamma	GFPrice (CGD)
CT Whole abdomen for diagnotic	gamma	GFPrice (CGD)
CT Chest non contrast for diagnotic	gamma	GFPrice (CGD)
CT Upper abdomen for investigation	gamma	GFPrice (CGD)
PET-CT	gamma	Chulabhorn hospital
MRI Upper abdomen	gamma	GFPrice (CGD)
MRI Liver	gamma	GFPrice (CGD)
MRI Bilitary system (MRCP)	gamma	GFPrice (CGD)
MRI Whole abdomen	gamma	GFPrice (CGD)
Resectable of Non-US surveillance	gamma	Chulabhorn DRG
Resectable of US surveillance	gamma	Chulabhorn DRG
Biopsy	gamma	GFPrice (CGD)
Chemotherapy OPD cost of Non-US surveillance	gamma	Chulabhorn hospital
Chemotherapy OPD cost of US surveillance	gamma	Chulabhorn hospital
Chemotherapy IPD cost of Non-US surveillance	gamma	Chulabhorn DRG
Chemotherapy IPD cost of US surveillance	gamma	Chulabhorn DRG
Palliative care	gamma	Ref. (Suttichaimongkol T, 2018)
Travelling expense	gamma	Ref. (Riewpaiboon, 2011)
Food	gamma	Ref. (Riewpaiboon, 2011)
Loss of earned income for CCA patient	gamma	Ref. (Riewpaiboon, 2011)
Loss of earned income for relative	gamma	Ref. (Riewpaiboon, 2011)

** CGD: The Comptroller General's Department, DRG: Diagnosis Related Group, OPD: Out-Patient Department, and IPD: In-Patient Department*

Table 4 ICER results

	Result (Deterministic)	Result (Probabilistic)
Incremental costs (THB)	7,659	8,410
Incremental LY	0.1318	0.1326
Incremental QALY	0.1315	0.1325
ICER (per QALY gained)	58,242	63,492

** ICER: Incremental cost-effectiveness ratio, LY: Life-years, QALY gained: Quality-adjusted life years gained and THB: Thai baht*

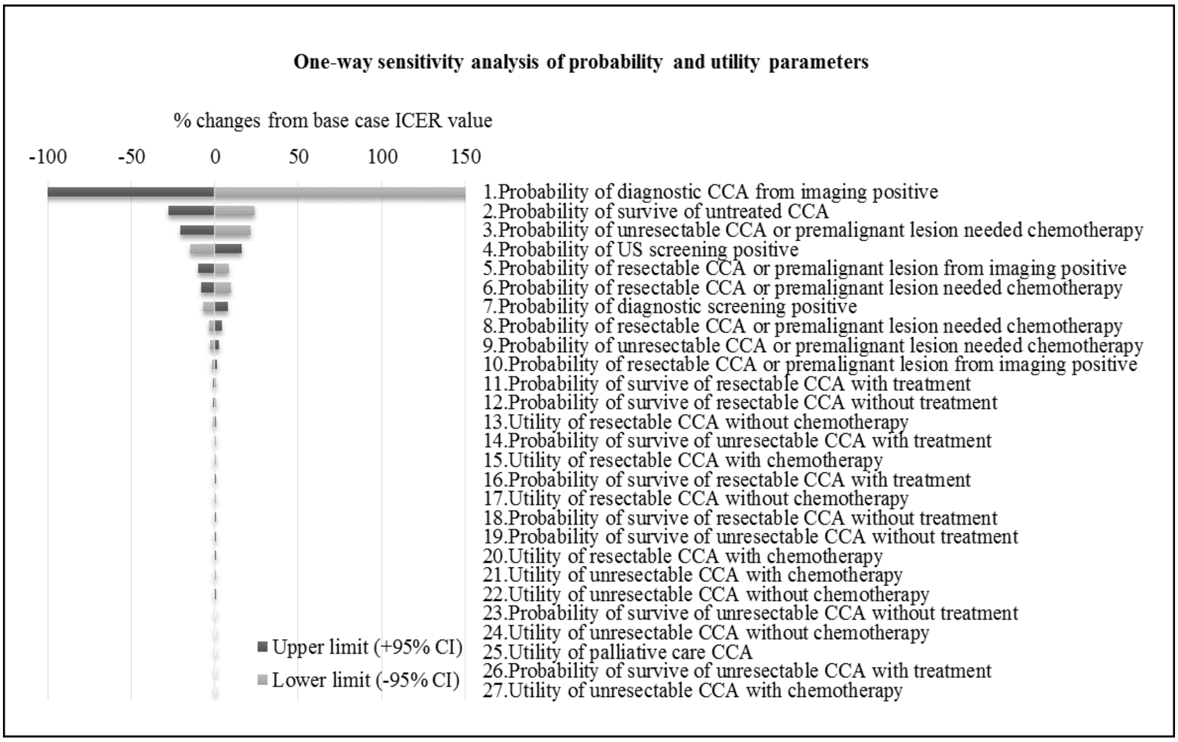

Figure 3 Tornado diagram of ICER transmission probability and utility parameters

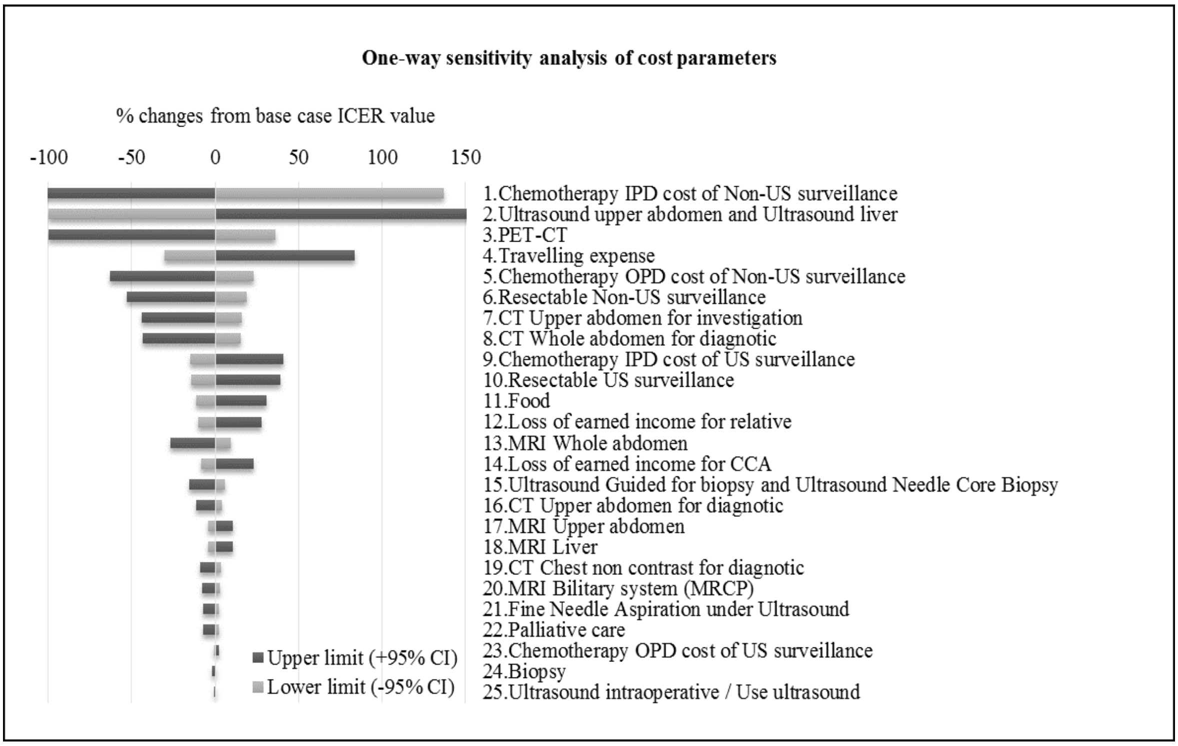

Figure 4 Tornado diagram of ICER transmission cost parameters

5. Conclusion

Some limitations exist in this study. The group with ultrasound surveillance in our cohort had included a population aged between 30-60 years; however, the national guideline recommends the surveillance of CCA should start at 40 years of age due to the starting peak incident of cancer (Chanwas, Ruk-iat, Panchan, Chaiwerawattana, & Aimsamran, 2016) (Khuntikeo et al., 2015). Starting surveillance at a younger age may overestimate the cost of the surveillance group. However, this effect is a positive effect on the surveillance group if apply the surveillance at 40 years of age, the ICER is probably even less.

It is recommended for further study to have more data collection in the case of CCA patients who have disease recurrence or undergo resection since it will increase costs. This study was conducted in populations at high risk of CCA. On the other hand, CCA is the most common endemic in the northern and northeastern regions of Thailand. Nonetheless, areas with a low risk of CCA may have less prevalence with no cost-effectiveness. Thus, it is advisable to also consider additional cost-effectiveness.

In conclusion, ultrasound surveillance of CCA in the endemic area was cost-effective. This information may be useful for considering a policy of surveillance of CCA in the endemic area of Thailand.

6. Acknowledgements

Thanks to the staff of the Medical Records and Medical Statistics Department, Chulabhorn Hospital for the information search, and the Head of the Chalerm Phrakiat 60th Birthday Celebration Research and Learning Center for supporting research data and consulting statistics

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