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Improving postoperative survival in cholangiocarcinoma: development of surgical strategies with a screening program in the epidemic region

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Abstract

Background The Cholangiocarcinoma Screening and Care Program (CASCAP) has been launched since 2013 to detect early-stage cholangiocarcinoma and reduce the disease death. However, the clinical utility of the CASCAP remains unclear. To compare survival outcomes between two time periods: before and after 2013, when significant changes in treatment strategies were implemented, and to evaluate the efficacy of the ultrasound-based screening program, in an Asian region endemic for cholangiocarcinoma.

Methods A single-center retrospective review was conducted in curative-intended resection cholangiocarcinoma from 2002 to 2021. Patents characteristics and survival outcomes were compared between 2002 and 2013 (early period) and 2014 to 2021 (later period).

Results A total of 1091 patients with intrahepatic ($n=624$) or perihilar ($n=467$) cholangiocarcinoma was included (early period, $n=658$; later period, $n=433$). Of 66 (15.2%) patients in the later period were referred by the CASCAP. The incidence of early-staged disease (Stage 0 and 1) was lower in early period compared to later period 16.0% versus 29.1% ($p<0.001$); that of positive surgical margin was higher in early period 53.7% versus 40.0% ($p<0.001$). A median survival time (MST) was 14 months in early and 40 months in later period ($p<0.001$). Subgroup analysis by tumor location, the MST was 13 versus 60 months in early and late periods for intrahepatic tumor ($p<0.001$), respectively. While MST in perihilar tumor was 18 versus 31 months in early and late periods($p<0.001$), respectively. By presentation, the MST was 51 vs. 38 months, respectively, with screening and usual presentation ($p=0.06$).

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Conclusion Postoperative survival in CCA patients improved more than doubled during the study period. Moreover, the late period demonstrated enhanced early-stage detection, a higher rate of negative surgical margins, and improved survival outcomes.

Keywords Cholangiocarcinoma, Cholangiocarcinoma Screening and Care Program, Surgical strategies, Screening program, Survival outcome

Introduction

Cholangiocarcinoma (CCA) is an insidious primary bile duct cancer characterized by a relatively rare disease with an incidence of 0.3 to 6 per 100,000 inhabitants per year worldwide [1, 2]. As most patients have advanced stage of the disease at initial presentation of jaundice, a sole curative option is unfrequently applied for CCA; furthermore, postoperative survival is generally poor survival with a 5-year survival rate of 10 to 20% even after curatively-intended resection [1, 3, 4]. Subsequently, a global mortality rate of this disease has been reported as 1–6 per 100,000 inhabitants per year. The almost same number between prevalence and mortality suggests an intractable disease nature. Although a combination of chemotherapy and immunotherapy has recently developed for CCA, a therapeutic option remains limited and challenging in the world [1, 5–7].

The northeast region of Thailand is a watershed of the Mekong River tributary, small river fish in which is a famous host of liver fluke, *Opisthorchis viverrini* (OV) [8, 9]. As people in this area consume raw fish for protein intake; subsequently OV parasitizes within the biliary system, ending in CCA development. The CCA incidence reaches as high as 36.3 to 43.0 in female and 87.7 to 135.4 in male per 100,000 population [10–12]. Thus, OV is a well-known trigger to CCA [8, 13, 14], working as a serious local health problem. Therefore, early detection of CCA is a key factor to improve survival of CCA patients in endemic area. Srinagarind Hospital, Khon Kaen University is a tertiary referral center specialized for hepatobiliary disease in the northeastern region of Thailand. For over the past two decades, our center has adopted many improvements in CCA treatment including preoperative biliary drainage for resectable CCA with obstructive jaundice, evaluation of liver volume, and volume modification by portal vein embolization. We also have launched an abdominal ultrasound screening program for CCA, named "Cholangiocarcinoma Screening and Care Program (CASCAP)", in August 2013 on the initiative of the deceased Professor Narong Khuntikeo [12].

The authors hypothesized that the development of surgical strategies and the initiation of CASCAP would improve surgical outcomes over time. Therefore, we reviewed surgical treatment outcomes at our center, comparing data from before and after the launch of CASCAP.

Methods

Patients and data collection

Database for CASCAP program (Isan cohort) [15] and medical records in Srinagarind Hospital was reviewed. CASCAP Program comprised of 2 independent cohorts, screening and patient cohorts. Informed consent was obtained before registering subjects in the cohort. In the screening cohort, abdominal ultrasound examination was performed regularly in population at risk for CCA at least annually aiming for detection of early-stage CCA and other intra-abdominal disease. Population at risk included subjects aged over 40 years who were ever infected with OV or had ever self-treated for parasites with over-the-counter anthelmintic drugs. Patients with suspected CCA finding referred to treatment centers as appropriate. In patient cohort, 15 secondary and tertiary hospitals in Thailand were registered with CASCAP program for CCA patient's data collection who entering treatment process of each hospital [12]. Srinagarind Hospital is a main referral center of all centers received suspected CCA into treatment.

Patients who underwent curative resection between 2002 and 2021 in Srinagarind Hospital, Khon Kaen University were included in the present study and divided into two period groups on the basis of CASCAP initiation: early period (2002–2013) and later period (2014–2021). Age, gender, location of CCA, type of surgical procedure, date of surgery, and death dated were collected for demographic data. Type of liver resection data was collected according to The Brisbane 2000 and The "New World" Terminology of Liver Anatomy and Resections [16, 17]. All processes of this study were accepted and approved by the Khon Kaen University Ethics Committee for Human Research under the reference number HE671317.

Preoperative management

Computed tomography (CT) or magnetic resonance imaging (MRI) was performed for disease staging and resectability assessment. Preoperative biliary drainage via percutaneous or endoscopic approach had been proactively used in jaundiced patients since 2012 [18]. Future liver remnant volume was calculated on the basis of CT images. Portal vein embolization was performed in patients with insufficient future remnant volume, 2–4 weeks before scheduled surgery since 2013 [19]. Thus, even jaundice patients had undergone definitive resection without preoperative biliary drainage and portal embolization before 2012 [20].

Surgical procedure

Surgery was performed after the total bilirubin decreased to less than 3 mg/dL. The procedure was individually planned, considering the patient's risk and the extent of hepatectomy. Generally, intrahepatic cholangiocarcinoma (iCCA) was treated with left or right hepatectomy alone according to tumor's location. Limited resection was performed in selected high-risk patients. For perihilar cholangiocarcinoma (pCCA), type of liver resection was designed according to Bismuth type and future liver remnant volume. In principle, caudate lobe and extrahepatic bile duct resection were routinely performed. In some cases where the hilar tumor infiltrated down to the intrapancreatic part, combined pancreaticoduodenectomy was performed. Extrahepatic bile duct resection alone was exceptionally performed in high-risk patients with Bismuth type 1 tumor. Bilio-enteric anastomosis was performed for reconstruction of biliary tract. Roux-en-Y hepaticojejunostomy was usually performed with 4−0 or 5−0 absorbable sutures. Two or three surgical drains were routinely placed near the anastomosis and surgical site.

Pathological diagnosis

Specimens and relevant tissue blocks were collected for routine tissue processing. Formalin-fixed paraffin-embedded (FFPE) tissue blocks were sectioned at 5 microns and stained with H&E [21]. Pathological diagnosis and staging was documented according to the 2019 WHO classification criteria [22] and American Joint Committee on Cancer (AJCC) 8th edition [23]. Histomorphological data recorded under light microscopy included growth patterns, histological type, histological grade, surgical margin, lymphovascular invasion, and lymph node metastasis.

Four major histological types were identified: papillary adenocarcinoma, tubular adenocarcinoma, papillotubular adenocarcinoma, and adenocarcinoma (NOS) [22].

The gross tumor type was classified into three broad categories into intraductal growth (IG), periductal infiltrating (PI), and mass-forming (MF) patterns by the predominant morphology [24–27]. Sectioned specimen was surveyed for parasitizing OV in the biliary system.

Postoperative management and follow-up

Patients who underwent surgery were admitted to the intensive care unit for monitoring immediate postoperative complications such as respiratory complications and bleeding. Surgical drain fluids were checked for bleeding, bile leakage, and pancreatic leakage and were removed between day 3 to day 5 if there were no signs of intra-abdominal complications. Undrained and symptomatic collection was managed with ultrasound-guided percutaneous drainage. After patients recovered without immediate postoperative complications, they were discharged from the hospital.

Adjuvant chemotherapy with gemcitabine-based regimen or 5-fluorouracil based regimen was given since around 2010, provided in patients with good general condition. Surveillance for recurrent disease was conducted by monitoring CA19-9 levels and performing CT scans every 3 months during the 1st year after resection, followed by assessments every 6 to 12 months thereafter. Patients with disease relapse were considered systemic chemotherapy as appropriated.

Statistical analysis

Continuous data are presented as the median (IQR) and categorical data are presented as percentage. The statistical analysis was performed using Mann-Whitney U test for continuous data and chi-square tests (χ2-Test) for catagorical data. Survival analysis was calculated by Kaplan-Meier method. Survival time was defined as the interval from the date of surgery to that of the patient's death. The end of study was 31st December 2023, patients who survived after the end of study were defined as censored. Median survival time (MST) and overall survival (OS) rates are presented and test of statistically difference between groups was analyzed by log-rank test. Univariable and multivariable analyses were performed to identify prognostic factors using the Cox regression model. In the Cox regression model, we selected a *p*-value threshold of $p<0.20$, which was derived from the univariate analysis [28]. A *p-value* of less than 0.05 was deemed statistically significant. All analyses were performed using the Stata/SE program version 17 (StataCorp LLC., Texas, USA).

Results

Overall population characteristics and pathological outcome

A total of 1091 consecutive patients with iCCA ($n=624$) or pCCA ($n=467$) were included in the study. There were 658 (60.3%) patients in the early period and 433 (39.7%) patients in the later period, with a median age of 60 (54–66) years. Tumor location significantly changed over time ($p<0.001$). The incidence of iCCA decreased from 65.2% in the early period down to 45.0% in the later period; conversely, pCCA increased from 34.8% up to 55.0%. Surgical strategy significantly differed during the study period; hepatectomy with bile duct resection and adjuvant chemotherapy accounted for 54.5% and 40.7%, respectively, in the later period. Early-staged tumor was more common and positive surgical margin was less frequent in the later period, compared to the early period ($p<0.001$) (Table 1).

Subgroup analysis according to tumor location

Characteristics and pathological outcome of 624 patients with iCCA are summarized in Table 2. Early-staged disease was more common in the later period than in the early period 35.4% vs. 17.5% ($p<0.001$). Additionally, positive margin rate significantly decreased from 51.8% in the early period down to 34.4% in the later period ($p<0.001$); similarly, lymph node metastasis reduced from 36.8 to 23.1% cases ($p=0.001$).

Clinical background and pathological findings of 467 patients with pCCA are demonstrated in Table 3. The same trend with iCCA was observed in the pCCA subpopulation in terms of early-staged disease and positive surgical margin. In later period, there was also a higher proportion of early-stage cases in pCCA compared to early period 13.1% vs. 24.0%, ($p<0.001$). The proportion of cases with positive margins was also lower in later period than in early period 57.2% vs. 44.5%, ($p=0.006$) as in iCCA group. However, the proportion of lymph node metastasis cases had no difference between both periods 42.8% vs. 42.9% ($p=0.989$) in early and later period, respectively.

In later period, extended lobectomy and trisectionectomy were more likely to be performed for older patients with pCCA compared to early period. The 90-day mortality rate, however, showed no difference between periods (27 (11.8%) vs. 18 (7.6%) cases in early and later period respectively, $p=0.122$).

Survival analysis

Median follow up time of all patients ($n=1091$) and censored patients ($n=207$) were 19 and 64 months respectively. Postoperative overall survival for the whole cohort was 63.6% at 1 year, 34.7% at 3 years, 23.3% at 5 years, and 14.3% at 10 years with an MST of 21 months. Stratified by study period (Fig. 1), survival for the 658 patients in the early period was 22.8% at 3 years and 12.6% at 5 years with an MST of 14 months; whereas that for the 433 patients in the later period 52.8% at 3 years and 40.2% at 5 years with an MST of 40 months ($p<0.001$). When the later period was divided by mode of presentation (Figs. 2), 66 patients entering treatment process by screening program had a longer survival than 367 patients who visit hospital in later period with usual presentation but did not reach statistical significance: MST of 51 months vs. 38 months and 5-year OS 49.5% vs. 39.3% ($p=0.06$). A better survival outcome in later

Table 1 Population characteristics*

Characteristic	All $n=1091$	2002 to 2013 (Early period) $n=658$	2014 to 2021 (Later period) $n=433$	p
Age, years., (median; IQR)	60 (54–66)	58 (52–63)	64 (58–69)	< 0.001
Gender				
Male	735 (67.4)	448 (68.1)	287 (66.3)	0.534
Female	356 (32.6)	210 (31.9)	146 (33.7)	
Present by screening program	66 (6.1)	0 (0.0)	66 (15.2)	< 0.001
Tumor location				
Intrahepatic	624 (57.2)	429 (65.2)	195 (45.0)	< 0.001
Perihilar	467 (42.8)	229 (34.8)	238 (55.0)	
Operation				
Hepatectomy	624 (57.2)	429 (65.2)	195 (45.0)	< 0.001
Hepatectomy with BDR	417 (38.2)	181 (27.5)	236 (54.5)	
BDR alone	48 (4.4)	47 (7.1)	1 (0.2)	
HPD	2 (0.2)	1 (0.2)	1 (0.2)	
90-day mortality	107 (9.8)	83 (12.6)	24 (5.5)	< 0.001
Pathological staging†				
Early (Stage 0, 1)	231 (21.2)	105 (16.0)	126 (29.1)	< 0.001
Locally advance (Stage 2, 3)	792 (72.6)	509 (77.4)	283 (65.4)	
Metastatic (Stage 4)	68 (6.2)	44 (6.7)	24 (5.6)	
Positive surgical margin	526 (48.2)	353 (53.7)	173 (40.0)	< 0.001
Lymph node metastasis	403 (36.9)	256 (38.9)	147 (34.0)	0.097
Presence of Opisthorchis viverrini	17 (1.6)	2 (0.3)	15 (3.5)	< 0.001
Adjuvant chemotherapy	180 (16.5)	4 (0.6)	176 (40.7)	< 0.001

*Values in the table represent the number of patients (percentage) unless indicated otherwise

† According to American Joint Committee on Cancer (AJCC) 8th edition

BDR, bile duct resection; HPD, hepatopancreatoduodenectomy

Table 2 Intrahepatic cholangiocarcinoma subgroup characteristics*

Characteristic	2002 to 2013 (period 1) $n = 429$	2014 to 2021 (period 2) $n = 195$	p-value
Age, yr., (median, range)	57 (32–82)	64 (41–85)	< 0.001
Gender			
Male	277 (64.6)	123 (63.1)	0.719
Female	152 (35.4)	72 (36.9)	
Present by screening program	0 (0.0)	31 (15.9)	< 0.001
Portal vein embolization	0 (0.0)	10 (5.1)	< 0.001
Operation[†]			
H5678	290 (67.6)	123 (63.1)	0.013
H4'5678	3 (0.7)	2 (1.0)	
H234	124 (28.9)	52 (26.7)	
H2345'8'	2 (0.5)	2 (1.0)	
Segmentectomy	10 (2.3)	16 (8.2)	
90-day mortality	56 (13.1)	6 (3.1)	< 0.001
Pathologic staging[‡]			
Early (Stage 0, 1)	75 (17.5)	69 (35.4)	< 0.001
Locally advance (Stage 2, 3)	353 (82.3)	125 (64.1)	
Metastatic (Stage 4)	1 (0.2)	1 (0.5)	
Positive surgical margin	222 (51.8)	67 (34.4)	< 0.001
Lymph node metastasis	158 (36.8)	45 (23.1)	0.001
Opisthorchis viverrini seen in specimen	1 (0.2)	8 (4.1)	< 0.001
Growth Pattern[§]			
Intraductal growth (IG)	50 (11.7)	52 (26.7)	< 0.001
Periductal infiltration (PI)	61 (14.2)	2 (1.0)	
Mass forming (MF)	196 (45.7)	66 (33.9)	
Mixed	122 (28.4)	75 (38.5)	
Histological type			
Tubular	226 (52.7)	109 (55.9)	0.105
Papillary	170 (39.6)	73 (37.4)	
Mixed	18 (4.2)	12 (6.2)	
Undifferentiated	15 (3.5)	1 (0.5)	
Adjuvant chemotherapy	1 (0.2)	74 (38.0)	< 0.001

*Values in the table represent the number of patients (percentage) or median (range) unless indicated otherwise

† According to "New World" Terminology of hepatic anatomy and resections

‡ According to American Joint Committee on Cancer (AJCC) 8th edition

period was observed in the subgroup of iCCA with MST 13 months vs. 60 months ($p < 0.001$) and 5-year OS 12.6% vs. 49.1% ($p < 0.001$) (Fig. 3). Survival outcome was also better in later period in pCCA subgroup with MST 18 months vs. 31 months ($p < 0.001$) and 5-year OS 12.5% vs. 33.9% ($p < 0.001$) (Fig. 4).

Multivariable analysis for OS (Table 4) demonstrated that later period, IG growth pattern, papillary histological type and adjuvant chemotherapy were significantly associated with favorable survival whereas positive surgical margin and lymph node metastasis significantly worsened OS. Screening presentation was a marginal factor for better survival, compared to usual presentation.

Discussion

As most patients with CCA were symptomatic with advanced disease at initial presentation [1, 29], resectability rate is relatively low, ranging from 20 to 50% [30–33]. Even after resection, positive surgical margin, a robust deteriorator for survival [33–35], is often faced with an incidence of 30 to 60% [34, 36, 37]. A previous study clearly showed that greater tumor size or advanced tumor increased the chance of tumor exposure, nodal metastasis and vascular invasion [38], all these features led to poor survival outcome [39–41] with MST of 30–37 months and with 5-year OS of 30 –35% [30, 42–46]. Thus, extend surgical resection as well as early detection of disease were two top priorities to improve the outcome of surgical patients with CCA. The present study focused on the comparison between the two periods in

Table 3 Perihilar cholangiocarcinoma subgroup characteristics*

Characteristic	2002 to 2013 (period 1) *n* = 229	2014 to 2021 (period 2) *n* = 238	*p*-value
Age, years, (median, range)	58 (34–88)	63 (31–83)	< 0.001
Gender			
Male	171 (74.7)	164 (68.9)	0.167
Female	58 (25.3)	74 (31.1)	
Present by screening program	0 (0.0)	35 (14.7)	< 0.001
Portal vein embolization	0 (0.0)	30 (12.6)	< 0.001
Operation†			
H15678-B	117 (51.1)	84 (35.3)	< 0.001
H14'5678-B	7 (3.1)	50 (21.0)	
H145678-B	2 (0.9)	23 (9.7)	
H1234-B	49 (21.4)	52 (21.9)	
H12345'8'-B	6 (2.6)	24 (10.1)	
H145678-B	0 (0.0)	2 (0.8)	
H1458-B	0 (0.0)	1 (0.4)	
Bile duct resection alone	47 (20.5)	1 (0.4)	
Hepatopancreatoduodenectomy	1 (0.4)	1 (0.4)	
90-day mortality	27 (11.8)	18 (7.6)	0.122
Pathological staging‡			
Early (Stage 0, 1)	30 (13.1)	57 (24.0)	0.001
Locally advance (Stage 2, 3)	156 (68.1)	158 (66.4)	
Metastatic (Stage 4)	43 (18.8)	23 (9.7)	
Positive surgical margin	131 (57.2)	106 (44.5)	0.006
Lymph node metastasis	98 (42.8)	102 (42.9)	0.989
Presence of Opisthorchis viverrini	1 (0.4)	7 (2.9)	0.037
Growth Pattern			
Intraductal growth	43 (18.8)	54 (22.7)	< 0.001
Periductal infiltration	82 (35.8)	20 (8.4)	
Mass forming	33 (14.4)	17 (7.1)	
Mixed	71 (31.0)	147 (61.8)	
Histologic type			
Tubular	143 (62.5)	127 (53.4)	0.124
Papillary	75 (32.8)	94 (39.5)	
Mixed	10 (4.4)	12 (5.0)	
Undifferentiated	1 (0.4)	5 (2.1)	
Adjuvant chemotherapy	3 (1.3)	102 (42.9)	< 0.001

*Values in the table represent the number of patients (percentage) unless indicated otherwise

† According to "New World" Terminology of hepatic anatomy and resections

‡ According to American Joint Committee on Cancer (AJCC) 8th edition

an Asian CCA-endemic area, observing several findings. First, survival ameliorated over time, both in iCCA and pCCA. Second, surgical and presurgical strategies have moved gradually with reference to international standard practices. Third, patients with CASCAP screening showed better survival than those with usual symptomatic presentation but not reach statistically significant.

The most impressive observation of the present study was raising 5-year survival rate by approximately 30%: from 12.6% in the early period up to 40.1% in the later period ($p<0.001$). This drastic improvement during approximately 20 years was explained by several factors. The increase in treatment experience at the institute may be a contributing factor to the improved survival outcomes.

Previously, preoperative biliary drainage had not been used for resectable pCCA but has been proactively used in CCA patients with obstructive jaundice or intrahepatic bile duct dilatation since around 2012. Also, the volume of FLR was calculated, and PVE was applied when needed. Thus, the concept of liver optimization prior to surgery has been involved in our daily practice. In addition, extended surgical approach including caudate lobectomy, regional lymphadenectomy and vascular

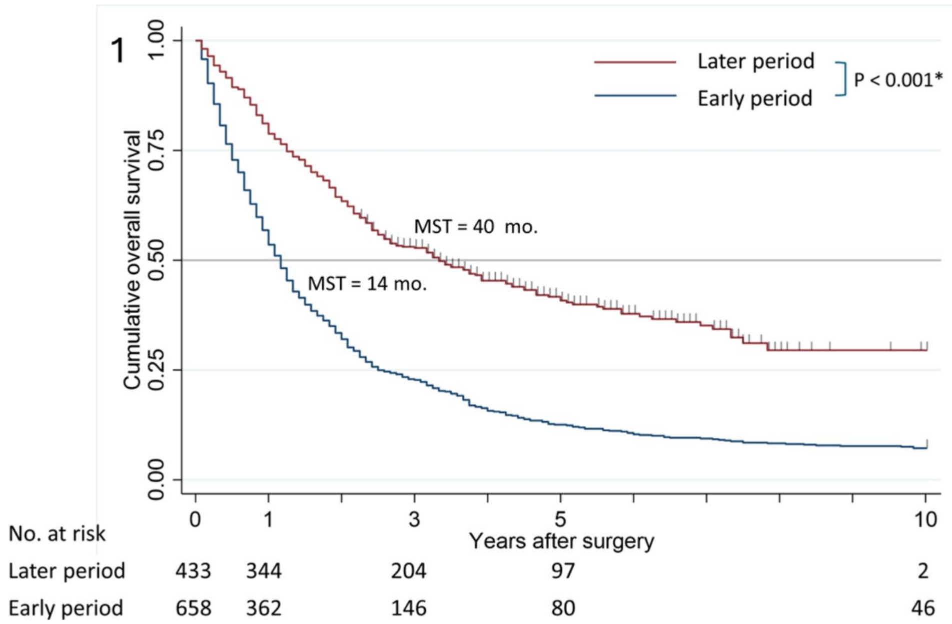

Fig. 1 Overall survival according to time periods: 2002 to 2013 (early period) and 2014 to 2021 (later period). *Log-rank test

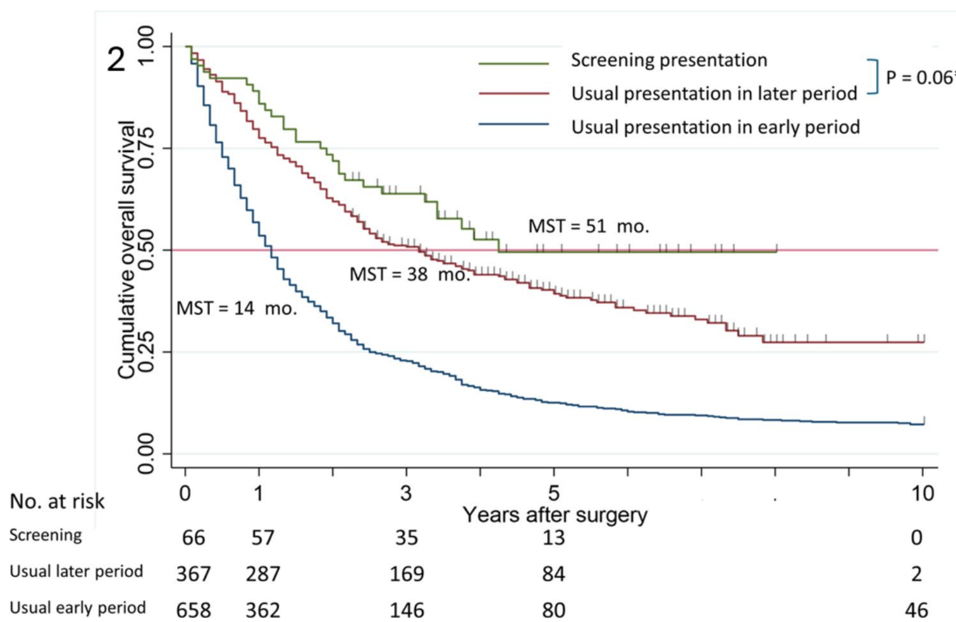

Fig. 2 Overall survival according to time periods with subdivision of the later group into screening program and usual presentation. *Log-rank test

resection on demand has been used recently. In fact, limited hepatectomy for iCCA and bile duct resection for pCCA remarkably reduced between two periods. Instead, extended right hepatectomy (H156784'-B) or right trisectionectomy (H145678-B) has been preferentially applied. All these changes lead to decreasing rate of involved surgical margin and surgical death, improving survival outcome in our institution.

The CASCAP was probably another attributor to favorable survival in the later period. Particularly, the prognostic improvement was impressive in the iCCA group, with a more than 4-fold increase in the five-year survival rate and an almost 5-fold longer MST. This improvement may be attributed to the more frequent diagnosis of early-stage disease through ultrasound screening. Unfortunately, this study failed to show a significant predictive power for OS in multivariable analysis, which the authors think underpowered analysis with a sample size of only 66.

Only large tumor causes abdominal pain and small tumor leaves patients asymptomatic in iCCA. Previous studies showed that only 25 to 33.4% of iCCA patients

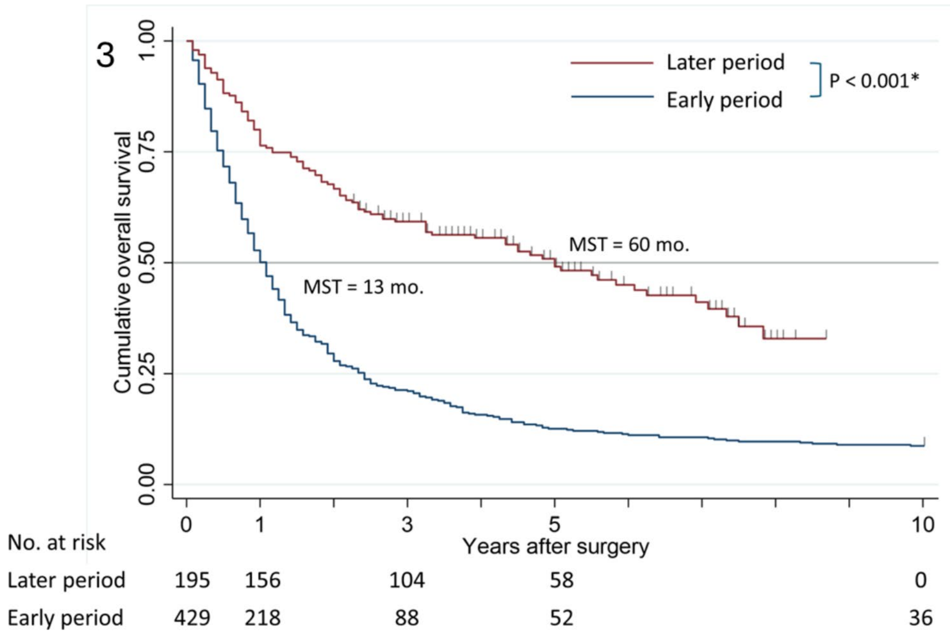

Fig. 3 Overall survival of intrahepatic cholangiocarcinoma patients according to time periods: 2002 to 2013 (early period) and 2014 to 2021 (later period)

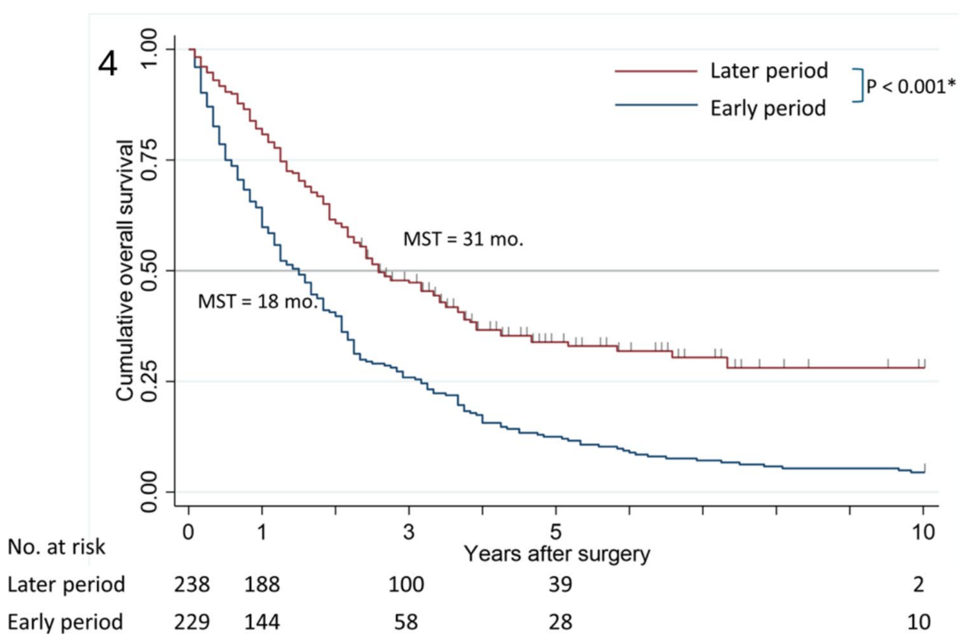

Fig. 4 Overall survival of perihilar cholangiocarcinoma patients according to time periods: 2002 to 2013 (early period) and 2014 to 2021 (later period). *Log-rank test

had symptoms associated with mass effect [6, 7, 47]. Therefore, ultrasound screening is useful for detecting asymptomatic small liver tumor in CCA endemic areas. In fact, the proportion of patients with early stage iCCA was significantly higher, and 66 (15.2%) patients were detected by this screening program in later period. As anticipated, the 66 with screening presentation exhibited a favorable survival with a 5-year survival rate of 49.5%, which surpassed 39.3% in patients with usual presentation in the later period. This result suggests the utility of CASCAP.

In addition, there was a significant improvement of five-year survival rate and MST also in the pCCA group, but the extent of increase was not as much as that was observed in the iCCA group. This difference can be explained by different nature of disease morphology between iCCA and pCCA. Early staged pCCA may be hard to visualize by abdominal ultrasound. Some studies

Table 4 Univariable and multivariable analyses of survival in CCA patients

Characteristics	N	Median survival time, mo.	Univariable	Multivariable		
			P	Hazard ratio	95% Confidence Interval	*P*
All patients	1091	21	-	-	-	-
Age						
≥ 60 years	521	23	0.003	1.04	0.90–1.20	0.579
< 60 years	570	18		1		
Gender						
Male	735	20	0.463	-	-	-
Female	356	22				
Period						
Later	433	40	< 0.001	0.59	0.48–0.72	< 0.001
Early	658	14		1		
Presentation						
Screening	66	51	< 0.001	0.69	0.47–1.01	0.060
Usual	1025	19		1		
Tumor location						
Intrahepatic	624	16	0.316	-	-	-
Perihilar	467	25				
Portal vein embolization						
Performed	40	70	< 0.001	0.61	0.35–1.04	0.070
Not performed	1051	19		1		
Margin status						
Positive	526	12	< 0.001	1.60	1.38–1.86	< 0.001
Negative	565	32		1		
Nodal metastasis						
Positive	403	12	< 0.001	1.69	1.45–1.95	< 0.001
Negative	688	28		1		
Morphology						
Intraductal growth type	437	51	< 0.001	0.46	0.39–0.55	< 0.001
Other	654	12		1		
Histologic type						
Papillary	573	27	< 0.001	0.84	0.72–0.97	0.021
Non-papillary	518	15		1		
Adjuvant chemotherapy						
Presence	180	39	< 0.001	0.74	0.58–0.95	0.017
Absence	911	17		1		

show that periductal fibrosis (PDF) was an ultrasound finding specific to surveillance CCA was, a representative of chronic inflammation of biliary tract, if PDF founded patients recommended to schedule annual follow op for CCA surveillance because they have evidence of chronic cholangitis [48, 49]. Studies show association between PDF grade III and CCA with odds ratio 2.52 (95% CI, 1.38 to 4.58) [48]. However, a direct ultrasound marker for early-stage pCCA has yet to be established. Another ultrasound finding of pCCA was upstream bile duct dilatation, that may be observed in patients with already obstructive jaundice, indicating that the tumor may no longer be in the early stage. As a result, there was no significant difference in the proportion of node positive pCCA cases, which is a strong prognostic factor, between early and later. But as mentioned improvement of survival outcome finding of pCCA in this study may be result from our peri-surgical management in pCCA in the meantime. As shown in this study, we performed more extensive procedures in later period compared with early period with acceptable rate of severe complications reflected by low 90-day mortality rate. Adopting extended procedures may have reduced the incidence of positive surgical margins, leading to better survival.

This study has some limitations. First, the retrospective study design with a long collection period may introduce many biases such as selection bias, changing trend of surgical strategy and preoperative patients care. Second, a single-center study resulted in a small number of patients from the screening program, which did not reach statistically significant differences in survival outcomes in multivariable analysis. Further study involving all centers registered with CASCAP will overcome the statistical underpower. Third, direct evidence of OV in the specimen was gained only in 1.6%, irrespective of study in the OV-pandemic area. As people in the Northeast region of Thailand self-treated for OV as mentioned in the method section, the incidence was underestimated than the actual incidence of 69.3–73.3% by detecting serum OV IgG in cholangiocarcinoma patients underwent curative resection [50, 51]. Fourth, the diagnostic yield of screening US could not be calculated because the present study collected only the surgical candidates screened by the CASCAP. Nonetheless, the present study clearly shows the recent drastic increase of survival in CCA, indicating the present institutional protocol against CCA should be implement in other center in CCA endemic area.

Conclusion

In summary, improvement of surgical management along with ultrasound screening program considerably improved survival probability in surgical patients with CCA. These attempts should be diffused or shared in the hot spot area of CCA.

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Author contributions
VT, TE and AT provided Conceptualization; AT and WL were Funding acquisition; VT, TS, VL, TT, AJ, KR, KK, NK, JC, TCS, NC, SK, PS, and AT conducted Sample collection and diagnosis; VT, NN, PP, NW, TE and AT performed Analysis and interpretation of data; AT was Project administration; AT, WL and TE were Supervision; VT, TS, VL, TT, AJ, KR, KK, NK, JC, TCS, NC, SK, PS PK, AW, NN, WL, NN, PP, NW, TE and AT conducted Manuscript Validation; VT, NM and PP prepared Writing original draft; All authors reviewed and edited the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study adhered to the principles of Good Clinical Practice, the Declaration of Helsinki, and relevant national regulations governing clinical studies. Informed consent was obtained from all participants, and the study protocol was approved by the Khon Kaen University Ethics Committee for Human Research under reference number HE671317. Clinical data and medical records were anonymized, with participants being identified only by hospital number (HN), ensuring that no individual could be personally identified.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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