Original Article

Predictive Factors for Survival Time of 273 Inoperable Hilar Cholangiocarcinoma Patients: Disease Registry Analyses

Srikhajonjit S, MD[1], Mairiang P, MD[1], Mairiang E, MD[2], Sawadpanitch K, MD[1], Sangchan A, MD[1], Sukeepaisarnjaroen W, MD[1], Chunlertrith K, MD[1]

[1] Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[2] Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Background: Cholangiocarcinoma (CCA) is a rare primary liver cancer in most parts of the world; however, it is the major liver cancer in the Northeast region of Thailand. Hilar cholangiocarcinoma (HCA), is the most common type of CCA, commonly presents with cholestasis; a majority of HCA is in an inoperable stage. This study aimed to analyze factors that predict survival of inoperable HCA in the high patient-loaded-center.

Materials and Methods: The study analyzed the data from hilar cholangiocarcinoma registry of 273 HCA. The survival time (Kaplan-Meier) was analyzed in association with age, sex, underlying diseases, liver function tests, level of CEA and CA19-9, Bismuth-Corlette type, staging and methods of treatment. Univariate and multivariate analyses were performed.

Results: The poor prognostic factors were clinical presentation with jaundice, ECOG performance status ≥3, serum CA19-9 >100 U/mL, serum CEA >30 ng/mL. Patients who had biliary drainage with ERCP and PTBD had reduced risk of death (hazard ratio [HR] 0.48, 95% confidence interval [CI] 0.25 to 0.90 and HR 0.40, 95% CI 0.24 to 0.69, respectively).

Conclusion: Inoperable HCA has poor prognosis. Biliary drainage with either ERCP or PTBD can prolong the survival time.

Keywords: Hilar cholangiocarcinoma, Survival analyses, Prognostic factors

J Med Assoc Thai 2019;102(Suppl.10): 43-9
Website: http://www.jmatonline.com

Cholangiocarcinoma (CCA) accounts around 10 to 25% of the primary liver cancers in most parts of the world. It is a rare in Western countries, whereas it is more seen in Asia, with highest incidence in the Northeast region of Thailand[1]. *Opisthorchis viverrini* infestation is the major risk factor in Thai patients[2,3], while primary sclerosing cholangitis is the major risk factor in Western countries[4]. Other risk factors are biliary-duct cysts, hepatolithiasis[5] and toxins (Thorotrast)[6]. Other less-established potential risk factors include inflammatory bowel disease, hepatitis C virus, hepatitis B virus, cirrhosis, diabetes mellitus, obesity, alcohol, smoking[7] and host genetic polymorphisms[8]. CCA is commonly classified based on the location of the tumor into intrahepatic (20%), hilar (50 to 60%), distal types (20%), and combine type (10%)[9].

Hilar cholangiocarcinoma (HCA) is the most common type of CCA. HCA is difficult to early diagnose owing to its silent clinical symptoms. The majority of patients develop symptoms only at an advanced stage of disease[10]. The clinical presentation depends upon tumor stage, tumor location and growth patterns. The commonly presenting symptoms are jaundice, abdominal pain, weight loss and cholangitis. Surgery is the only curative treatment for patients with cholangiocarcinoma. Less than one-third of patients are resectable at diagnosis. The biliary tract obstruction in unresectable disease is treated by biliary stenting rather than a surgical bypass. Stent placement resulting in adequate biliary drainage improves survival[7,9,11-16]. Many potential factors had been statistically analyzed to predict survival. These factors had been classified according to whether they are tumor-related, patient-related, or treatment-related[17-19]. These including age, sex, comorbidities, performance status, nutritional status (body mass index, albumin, hemoglobin), clinical signs and symptoms, tumor staging, tumor marker level and treatment modalities.

Previous studies of survival in CCA patients show many significant prognostic factors, including endoscopic biliary drainage by using metal stents in HCA[20,25], CEA level >30 ng/mL[21], Bismuth-Corlette stage, bilirubin >10 mg/dL[22,23] and CA19-9 level >100 U/mL[27], CEA level >2.5 ng/mL advance stage, presentation with jaundice, presentation with ascites, and standard treatment compared to palliative treatment[28], lymph node metastasis[29], comorbidities (Charlson comorbidity index score ≥2)[30]. Data about predictive factors in Thai patients with HCA, however, are still limited. This study aimed to determine predictive factors in inoperable HCA in Thai patients.

Correspondence to:
Mairiang P.
Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
Phone: +66-86-2250846, **Fax:** +66-43-202628
E-mail: pisaln_m@hotmail.com

How to cite this article: Srikhajonjit S, Mairiang P, Mairiang E, Sawadpanitch K, Sangchan A, Sukeepaisarnjaroen W, Chunlertrith K. Predictive Factors for Survival Time of 273 Inoperable Hilar Cholangiocarcinoma Patients: Disease Registry Analyses. J Med Assoc Thai 2019;102(Suppl.10): 43-9.

Materials and Methods

The authors reviewed data from 273 HCA disease registry started from October 2011 to July 2014. The patients attended at Cholangiocarcinoma Clinic, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. The study was approved by the institutional review board (HE581342).

HCA was diagnosed by histopathology or presumed diagnosis using detailed clinical evaluation, serum biochemistry, and hepato-biliary imaging studies that included computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP). Demographic, clinical and biochemical data collected at the time of diagnosis ,which included age, sex, underlying diseases (especially type 2 diabetes), body weight, height, clinical manifestations, prothrombin time (INR), hemoglobin, serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and tumor data (staging classification by the Bismuth-Corlette classification, lymph node metastasis and distance metastasis) were analyzed. Criteria of inoperable HCA[31] are: 1) medical comorbidities limiting the patient's ability to undergo major surgery 2) significant underlying liver disease prohibiting liver resection necessary for curative surgery based on pre-operative imaging 3) bilateral tumor extension to secondary biliary radicals 4) encasement or occlusion of the main portal vein 5) lobar atrophy with contralateral portal vein involvement 6) contralateral tumor extension to secondary biliary radicals 7) evidence of metastases to N2 level lymph nodes 8) presence of distant metastases.

Statistical analysis

The survival time was defined as date of diagnosis to date of death from any cause. Demographic and tumor data were summarized as percentage. The cumulative survival rate is presented by the Kaplan-Meier curve. All the variable factors mentioned earlier were analyzed. Univariate analysis was performed with the Kaplan-Meier method. Significant factors on univariate analysis were then evaluated by multivariate analysis using the Cox proportional hazard model (backward selection). The statistical analyses were performed by using STATA software version 10.1. A *p*-value <0.05 was considered statistically significant.

Results

A total of 273 consecutive patients diagnosed as HCA were analyzed. Baseline characteristics were presented in Table 1. There were 201 males and 72 females (ratio 2.8: 1), with a mean age of 63.9 (range 37 to 87) years. The majority of the patients had normal BMI (49.6%) and impaired performance status (45% had ECOG3). A history of underlying disease was recognized in 111 cases (40.7%), and diabetes was reported in 34 case (12.3%).

Major clinical presentations were jaundice (93.4%), pruritus (75.5%), abdominal pain (46.2%), fever (42.9%)

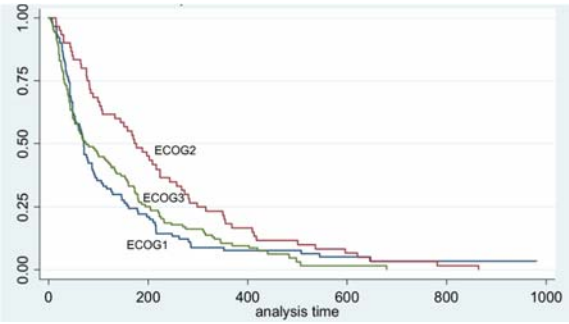

Figure 1. Median survival depending on patients' performance status.

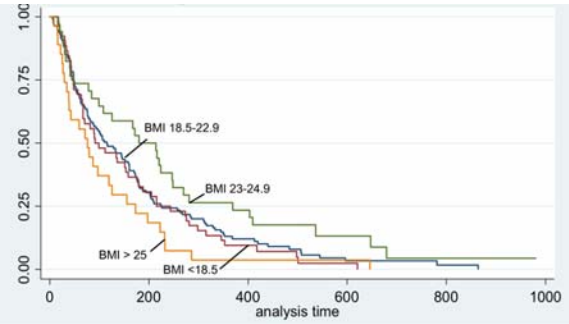

Figure 2. Median survival depending on patients' body mass index.

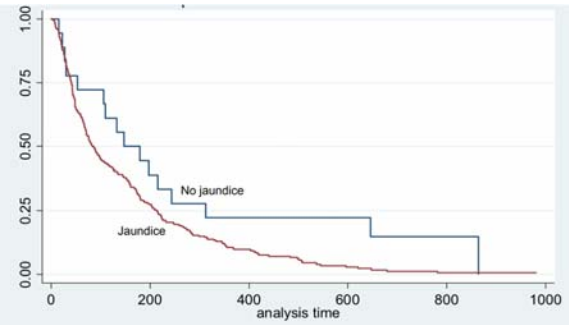

Figure 3. Median survival depending on patients with jaundice.

and ascites (13.2%). Tumor data are present in Table 2. There were 64.1% with Bismuth-Corlette type IV and 27.5% with type III. About one-third of the cases had portal vein involvement, lymph node metastasis, or distant metastasis.

The overall median survival was 89 (range 71 to 115 days). On univariate analysis, several clinical factors showed a statistically significant associated with survival time, as shown in Table 1. That included patients age, performance status, body mass index, clinical presentation, higher serum total bilirubin (>10 mg/dL), lower serum albumin

Table 1. Baseline characteristics of 273 unresectable hilarcholangiocarcinoma patients

	n (%)	Median survival (day)	Crude hazard ratio	95% confidence interval	*p*-value
Age (years)					
<60	97 (35.5)	115	Reference		
60 to 69	95 (35.8)	82	1.04	0.78 to 1.39	0.794
>70	81 (29.7)	80	1.04	0.77 to 1.40	0.809
Sex					
Female	72 (26.4)	76	Reference		
Male	201 (73.6)	91	1.12	0.885 to 1.48	0.437
Performance status					
ECOG 0	0				
ECOG 1	90 (33.0)	70	Reference		
ECOG 2	60 (22.0)	172	0.64	0.46 to 0.89	0.009
ECOG 3	123 (45.0)	75	0.98	0.74 to 1.29	0.87
ECOG 4	0				
Body mass index (kg/m^2)					
<18.5	53 (23.3)	91	1.11	0.79 to 1.55	0.547
18.5 to 22.9	113 (49.6)	115	Reference		
23 to 24.9	34 (14.9)	180	0.69	0.46 to 1.03	0.074
>25	28 (12.3)	76	1.53	1.00 to 2.33	0.05
Clinical presentations					
Pruritus	206 (75.5)	102	0.95	0.72 to 1.28	0.766
Jaundice	255 (93.4)	84	1.73	1.04 to 2.90	0.036
Fever	117 (42.9)	87	0.95	0.74 to 1.21	0.657
Abdominal pain	126 (46.2)	75	1.16	0.91 to 1.48	0.23
Ascites	36 (13.2)	54	1.77	1.24 to 2.53	0.002
Diabetes mellitus	34 (12.3)	78	0.86	0.60 to 1.25	0.436
Underlying diseases	111 (40.7)	72	1.04	0.81 to 1.32	0.787
Anemia	186 (86.5)	102	1.05	0.70 to 1.58	0.801
Total bilirubin >10 mg/dL	195 (75.3)	79	1.47	1.09 to 1.99	0.011
INR >1.5	80 (36.9)	89	1.07	0.81 to 1.42	0.634
ALT >30 U/L	198 (81.8)	87	1.32	0.94 to 1.85	0.11
AST >30 U/L	227 (93.8)	99	1.72	0.97 to 3.03	0.061
ALP >121 U/L	233 (96.7)	99	1.56	0.76 to 3.22	0.221
CA19-9 >100 U/mL	160 (72.7)	71	1.7	1.24 to 2.32	0.001
CEA >30 ng/mL	160 (75.8)	69	1.75	1.27 to 1.43	0.001
Creatinine >1.5 mg/dL	29 (11.2)	89	1.79	1.21 to 2.64	0.001

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = alanine aminotransferase, CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen

(<3.5 g/ dL), higher serum CA19-9 (>100 U/ml), higher serum CEA (>30 ng/mL), Bismuth Corlette classification type III or IV, portal vein involvement, lymph node metastasis, distant metastasis, treatment with biliary drainage by ERCP or PTBD and adequate biliary drainage.

Multivariate analysis using Cox's proportional hazard model are shown in Table 3. The results showed significant poor prognosis factors including clinical presentation with jaundice (hazard ratio [HR] 3.5, 95% CI 1.71 to 7.18), patients with impaired performance status (ECOG3 compared with ECOG1, HR 1.75, 95% CI 1.08 to 2.83), serum CA19-9 >100 U/mL (HR 1.74, 95% CI 1.16 to 2.63), serum CEA >30 ng/mL (HR 2.37, 95% CI 1.57 to 3.59) and patients who had inadequate biliary drainage (HR 1.84, 95% CI 1.15 to 2.95). Whereas, having biliary drainage with ERCP or PTBD were good prognostic factors (HR 0.48, 95% CI 0.25 to 0.90 and HR 0.4, 95% CI 0.24 to 0.69, respectively).

Discussion

The present study was the biggest report on predictive factors for survival time of 273 advanced HCA from a single center. The majority of the patients were elderly, poor performance status (ECOG2 and 3), locally advanced disease (portal vein invasion and Bismuth Corlette type III/ IV) and metastasis. The possible treatment options among these patients could be 1) palliative resection with or without adjuvant chemotherapy 2) non-surgical biliary drainage (ERCP or PTBD) 3) palliative end of life care. In the past patients tended to accept palliative end of life care at home if the surgery gave them no hope for cure. However our previous study showed that endoscopic self-expandable metallic stent

Table 2. Tumor data and treatment modalities and outcome

	n (%)	Median survival (day)	Crude hazard ratio	95% confidence interval	*p*-value
Bismuth-Corlette classification					
Type I	10 (3.6)	33	Reference		
Type II	13 (4.8)	152	0.58	0.25 to 1.33	0.199
Type III	75 (27.5)	75	0.48	0.24 to 0.93	0.03
Type IV	175 (64.1)	93	0.5	0.26 to 0.95	0.035
Portal vein involvement	97 (35.5)	69	1.31	1.02 to 1.69	0.037
Lymph node metastasis	91 (33.3)	65	1.35	1.04 to 1.74	0.023
Distant metastasis	93 (34.1)	64	1.54	1.19 to 1.99	0.001
Inadequate drainage	177 (72.8)	69	2.01	1.51 to 2.71	<0.001
Treatment					
Palliative care	106 (38.8)	48	Reference		
PTBD	117 (42.9)	158	0.57	0.43 to 0.74	<0.001
ERCP	50 (18.3)	153	0.5	0.35 to 0.71	<0.001

ERCP = endoscopic retrograde cholangiopancreatography, PTBD = percutaneous transhepatic biliary drainage

Table 3. Significant prognostic factors by multivariate analysis

	Crude hazard ratio	Adjusted hazard ratio	95% confidence interval	*p*-value
Performance status				
ECOG1	Reference	Reference		
ECOG2	0.64	1.66	0.89 to 3.12	0.113
ECOG3	0.98	1.75	1.08 to 2.83	0.024
Body mass index (kg/m^2)				
<18.5	1.11	1.31	0.83 to 2.07	0.239
18.5 to 22.9	Reference	Reference		
23 to 24.9	0.69	0.52	0.32 to 0.85	0.009
>25	1.53	1.38	0.76 to 2.48	0.289
Jaundice	1.73	3.5	1.71 to 7.18	0.001
CA19-9 >100 U/ml	1.7	1.74	1.16 to 2.63	0.008
CEA >30 ng/mL	1.75	2.37	1.57 to 3.59	<0.001
Inadequate biliary drainage	2.02	1.84	1.15 to 2.95	0.011
Treatments				
Palliative	1	1		
PTBD	0.57	0.4	0.24 to 0.69	0.001
ERCP	0.5	0.48	0.25 to 0.90	0.021

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ERCP, endoscopic retrograde cholangiopancreatography; PTBD, percutaneous transhepatic biliary drainage

(SEMS) placement improved survival of unresectable HCA[25] and the treatment was cost-effective as well as improved quality of life[32]. It is very important to predict HCA whom will be most benefit from non- surgical biliary drainage since the SEMS placement did have significant complications. We performed this study to confirm the improvement of survival after biliary drainage by ERCP and/or PTBD compared to symptomatic palliative treatment and also explored the predictive factors for survival of these inoperable HCA.

Weber, et al[22] reported 76 HCA patients who had endoscopic biliary drainage with or without PTBD. The study showed that only serum bilirubin >10 mg/dL was the poor predictive factor. Mihalache, et al[20] showed that palliative resection alone had no survival benefit than patients receiving SEMS at one year. They suggested that unresectable HCA whom survival less than 4 months should be treated with endoscopic biliary drainage. Wirasorn, et al[29] reported that serum CEA >2.5 ng/mL, lymph node metastasis and positive surgical margin were the poor prognostic factors of resectable CCA. They also showed that patients received adjuvant chemotherapy had better median survival. However, they did not mention about prognostic factors of unresectable HCA. Recently, Sumiyoshi, et al[33] reported that chemoradiotherapy for initially unresectable local advanced

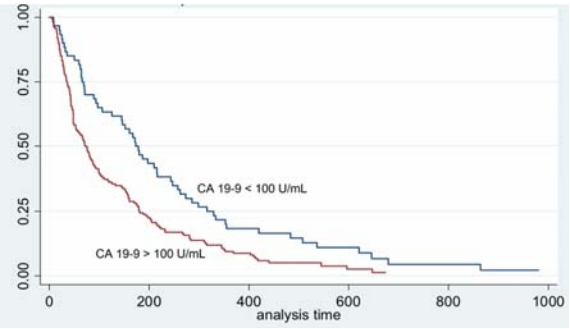

Figure 4. Median survival depending on patients with high level of serum CA19-9.

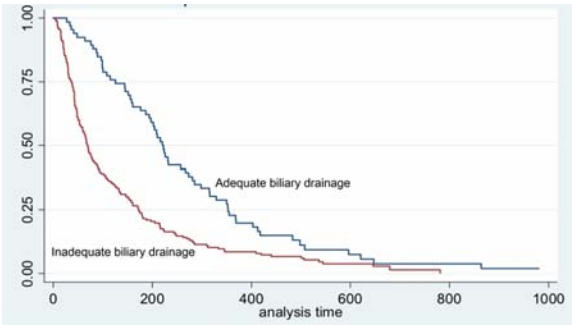

Figure 6. Median survival depending on biliary drainage outcome.

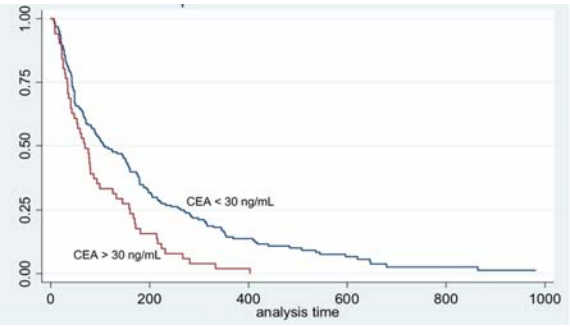

Figure 5. Median survival decreased among patients with high level of serum CEA.

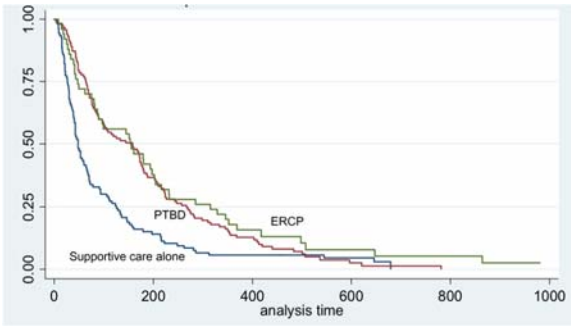

Figure 7. Median survival depending on patient treatment modalities; ERCP with SEMS and PTBD gave significant longer survival than supportive care alone.

CCA could down stage and increased resectability. This report is to be confirmed due to the small sample size. Li, et al[34] reported that combined gemcitabine and S1 chemotherapy for treating unresectable HCA could prolong survival but they did not evaluate the quality of life in their study.

In our study, several factors were found to be predictors of worse outcome. With respect to clinical factors, patients who were poor performance status at diagnosis, or presented with jaundice were more likely to die early. All these reflect late presentation and more advanced disease. In our study, Bismuth-Corlette type III and IV did not relate to poor survival time. Many authors have showed an association between serum tumors marker and outcomes of CCA, by using different value cut-off[21,26-30]. Our study demonstrated patients who have base line serum CA19-9 >100 U/mL or CEA >30 ng/mL were independent poor prognostic factors.

In the aspect of treatment, the median survival time was higher for patients having received biliary drainage by ERCP (153 days) or by PTBD (158 days) than palliative treatment (48 days). When we focused on the patients with successful drainage, the median survival time was shorter for patients who had inadequate biliary drainage versus adequate biliary drainage. Therefore, biliary drainage treatment (ERCP or PTBD) was an independent good prognostic factor.

One limitation of our study was that the diagnoses of many HCA patients had no pathologic confirmation.

Conclusion

Median survival of inoperable HCA was dismal. Predictors for poor survival were performance status (ECOG3), jaundice, CA19-9 >100 U/mL and CEA >30 ng/mL. Chemoradiotherapy to down-stage advanced HCA before reassessing for resectability is to be confirmed.

What is already known on this topic?

HCA patients commonly present late and generally have poor prognosis. The resectable rate is low, therefore, the treatment outcomes are very disappointing. Unresectable HCA is treated by non-surgical biliary drainage (ERCP or PTBD). High grade hilar obstruction with Bismuth-Corlette type III and IV are difficult to drain by ERCP.

What this study adds?

Among the very advanced HCA, the endoscopic biliary drainage and PTBD can prolong survival even in high grade hilar obstruction (Bismuth-Corlette type III and IV) if the drainage is adequate. The patients with serum CEA >30 ng/mL and/or CA19-9 >100 U/mL with poor performance

status (ECOG3) have poor prognosis. Therefore, palliative treatment may be an alternative treatment to be considered in this subgroup patients.

Acknowledgements

This study was funded by a grant from Faculty of Medicine, Khon Kaen University and the Gastroenterological Association of Thailand.

Potential conflicts of interest

The authors have no conflicts of interest.

References

1. Kamsa-ard S, Wiangnon S, Suwanrungruang K, Promthet S, Khuntikeo N, Kamsa-ard S, et al. Trends in liver cancer incidence between 1985 and 2009, Khon Kaen, Thailand: cholangiocarcinoma. Asian Pac J Cancer Prev 2011;12:2209-13.
2. Sripa B, Pairojkul C. Cholangiocarcinoma: lessons from Thailand. Curr Opin Gastroenterol 2008;24:349-56.
3. Sripa B, Brindley PJ, Mulvenna J, Laha T, Smout MJ, Mairiang E, et al. The tumorigenic liver fluke Opisthorchis viverrini—multiple pathways to cancer. Trends Parasitol 2012;28:395-407.
4. Tyson GL, El Serag HB. Risk factors for cholangiocarcinoma. Hepatology 2011;54:173-84.
5. Shin HR, Oh JK, Lim MK, Shin A, Kong HJ, Jung KW, et al. Descriptive epidemiology of cholangiocarcinoma and clonorchiasis in Korea. J Korean Med Sci 2010;25:1011-6.
6. van Kaick G, Wesch H, Luhrs H, Liebermann D, Kaul A. Neoplastic diseases induced by chronic alpha-irradiation—epidemiological, biophysical and clinical results of the German Thorotrast Study. J Radiat Res 1991;32 Suppl 2:20-33.
7. Khan SA, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. Gut 2012;61:1657-69.
8. Jarnagin WR, Bowne W, Klimstra DS, Ben Porat L, Roggin K, Cymes K, et al. Papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma. Ann Surg 2005;241:703-12.
9. Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463-73.
10. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 2011;8:512-22.
11. Soares KC, Kamel I, Cosgrove DP, Herman JM, Pawlik TM. Hilar cholangiocarcinoma: diagnosis, treatment options, and management. Hepatobiliary Surg Nutr 2014;3:18-34.
12. Zhimin G, Noor H, Jian-Bo Z, Lin W, Jha RK. Advances in diagnosis and treatment of hilar cholangiocarcinoma — a review. Med Sci Monit 2013;19:648-56.
13. Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. Ann Surg 1992;215:31-8.
14. Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BJ, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507-17.
15. Khan SA, Davidson BR, Goldin R, Pereira SP, Rosenberg WM, Taylor-Robinson SD, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. Gut 2002;51 Suppl 6:VI1-9.
16. de Groen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM. Biliary tract cancers. N Engl J Med 1999;341:1368-78.
17. Glare P. Clinical predictors of survival in advanced cancer. J Support Oncol 2005;3:331-9.
18. Menon K, Razak SA, Ismail KA, Krishna BV. Nutrient intake and nutritional status of newly diagnosed patients with cancer from the East Coast of Peninsular Malaysia. BMC Res Notes 2014;7:680.
19. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J 2010;9:69.
20. Mihalache F, Tantau M, Diaconu B, Acalovschi M. Survival and quality of life of cholangiocarcinoma patients: a prospective study over a 4 year period. J Gastrointestin Liver Dis 2010;19:285-90.
21. Park J, Kim MH, Kim KP, Park DH, Moon SH, Song TJ, et al. Natural history and prognostic factors of advanced cholangiocarcinoma without surgery, chemotherapy, or radiotherapy: A large-scale observational study. Gut Liver 2009;3:298-305.
22. Weber A, Landrock S, Schneider J, Stangl M, Neu B, Born P, et al. Long-term outcome and prognostic factors of patients with hilar cholangiocarcinoma. World J Gastroenterol 2007;13:1422-6.
23. Farhat MH, Shamseddine AI, Tawil AN, Berjawi G, Sidani C, Shamseddeen W, et al. Prognostic factors in patients with advanced cholangiocarcinoma: role of surgery, chemotherapy and body mass index. World J Gastroenterol 2008;14:3224-30.
24. Weston BR, Ross WA, Wolff RA, Evans D, Lee JE, Wang X, et al. Rate of bilirubin regression after stenting in malignant biliary obstruction for the initiation of chemotherapy: how soon should we repeat endoscopic retrograde cholangiopancreatography? Cancer 2008;112:2417-23.
25. Sangchan A, Kongkasame W, Pugkhem A, Jenwitheesuk K, Mairiang P. Efficacy of metal and plastic stents in unresectable complex hilar cholangiocarcinoma: a randomized controlled trial. Gastrointest Endosc 2012;76:93-9.
26. Hatzaras I, Schmidt C, Muscarella P, Melvin WS, Ellison EC, Bloomston M. Elevated CA 19-9 portends poor prognosis in patients undergoing resection of biliary malignancies. HPB (Oxford) 2010;12:134-8.
27. Leerapun A, Thaikruea L, Pisespongsa P, Chitapanarux

T, Praisontarangkul OA, Thongsawat S. Clinical features and prognostic factors for liver cancer from a referral center in northern Thailand. J Med Assoc Thai 2013;96:531-7.
28. Woradet S, Promthet S, Songserm N, Parkin DM. Factors affecting survival time of cholangiocarcinoma patients: a prospective study in Northeast Thailand. Asian Pac J Cancer Prev 2013;14:1623-7.
29. Wirasorn K, Ngamprasertchai T, Chindaprasirt J, Sookprasert A, Khantikaew N, Pakkhem A, et al. Prognostic factors in resectable cholangiocarcinoma patients: Carcinoembryonic antigen, lymph node, surgical margin and chemotherapy. World J Gastrointest Oncol 2013;5:81-7.
30. Fernandez-Ruiz M, Guerra-Vales JM, Colina-Ruizdelgado F. Comorbidity negatively influences prognosis in patients with extrahepatic cholangiocarcinoma. World J Gastroenterol 2009;15:5279-86.
31. Chamberlain RS, Blumgart LH. Hilar cholangiocarcinoma: a review and commentary. Ann Surg Oncol 2000;7:55-66.
32. Suttichaimongkol T, Borntrekulpipat S, Sangchan A, Mairiang P, Mairiang E, Sukeepaisarnjaroen W, et al. Economic evaluation of palliative biliary drainage in unresectable hilar cholangiocarcinoma. J Med Assoc Thai 2018;101 Suppl 4:S44-52.
33. Sumiyoshi T, Shima Y, Okabayashi T, Negoro Y, Shimada Y, Iwata J, et al. Chemoradiotherapy for initially unresectable locally advanced cholangiocarcinoma. World J Surg 2018;42:2910-8.
34. Li H, Zhang ZY, Zhou ZQ, Guan J, Tong DN, Zhou GW. Combined gemcitabine and S-1 chemotherapy for treating unresectable hilar cholangiocarcinoma: a randomized open-label clinical trial. Oncotarget 2016;7:26888-97.