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Analysis of metastasis and survival between extrahepatic and intrahepatic cholangiocarcinoma

A large population-based study

Peng Liao, MD[a], Li Cao, MD[a], Hang Chen, MD[b], Shui-Zi Pang, MD[c,*]

Abstract

To date, extrahepatic cholangiocarcinoma (ECCA) and intrahepatic cholangiocarcinoma (ICCA) have rarely been compared; therefore, we attempted to learn more about the rates of metastasis and survival in both ICCA and ECCA.

Data of patients in the SEER database diagnosed with ICCA or ECCA were extracted to analyse the rate of metastasis and survival. Univariate and multivariate logistic regression analyses were performed to identify the risk factors for metastasis. Propensity score matching (PSM) was used to compare survival rates between ECCA and ICCA.

Data from a total of 15,751 patients diagnosed with ICCA or ECCA were extracted to analyse the rate of metastasis. Metastasis was more common in ECCA than ICCA (42.62% vs. 31.46%, $P < .05$), while ICCA in the T1 stage had a lower rate of metastasis (25.35% vs. 30.61%, $P < .05$). Age, pathology grade, tumour size, lymph node metastasis and T stage were independent risk factors for metastasis in both ECCA and ICCA. There was an inverse correlation between age and metastasis in both ICCA and ECCA. Moreover, PSM demonstrated that patients with ECCA had a better prognosis than patients with ICCA. Patients with ICCA in the T1 stage had better survival than those with ECCA in the T1 stage.

Our study was the first to compare the rates of metastasis and survival between ECCA and ICCA. We observed an inverse association between age and metastasis, that patients with ECCA had a better prognosis than patients with ICCA, and that patients with ECCA in the T1 stage had worse survival than patients with ICCA in the T1 stage.

Abbreviations: CSS = cancer-specific survival, ECCA = extrahepatic cholangiocarcinoma, ICCA = intrahepatic cholangiocarcinoma, LNM = Lymph node metastasis, OS = overall survival (OS), SMD = standardized mean difference.

Keywords: extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma, metastasis, SEER, survival

1. Introduction

Cholangiocarcinoma (CCA) is a highly aggressive cancer derived from the biliary duct epithelium that accounts for approximately 3 to 5% of malignant gastrointestinal tumours.[1] According to the World Health Organization (WHO) categorization based on anatomical location, CCAs are divided into intrahepatic CCA (ICCA) and perihilar and distal CCA, among which the latter two are considered extrahepatic CCA (ECCA).[2] ECCA accounts for 70–90% of all CCAs, while ICCA accounts for 10–20%.[3] There are both similarities and differences between the two types of cholangiocarcinoma. Regarding risk factors, choledochal cysts are strongly associated with both ICCA and ECCA, while cirrhosis is more strongly associated with ICCA than ECCA, and choledocholithiasis is more strongly associated with ECCA than ICCA.[4] With regard to epidemiological profiles, rates of ECCA have been stable in recent decades, whereas the incidence rate of ICCA has increased and reached a plateau in the past decade.[5] The findings of one study, however, were inconsistent with those of the other studies and posited that the incidence rates of both ECCA and ICCA have increased and that the ICD classification system has led to this discrepancy.[6] To date, surgery is the only curative treatment for patients with CCA; however, complete resection (R0) differs between the types. ICCA has a higher probability of achieving R0 than ECCA (81% vs 65%) as a result of tumour extension and microvascular invasion.[7] Moreover, with regard to the genetic alterations between ICCA and ECCA, ICCA is more likely to have mutations of PBMR1 and BAP1, while ECCA is more frequently correlated with KRAS and TP53

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The datasets generated during and/or analyzed during the present study are publicly available.

[a] Department of Integration of Traditional Chinese and Western Medicine and Anorectum, The First Affiliated Hospital of Nanchang University, [b] Department of Day-Care Unit, The First Affiliated Hospital of Nanchang University, [c] Department of Infection Prevention and Control, The First Affiliated Hospital of Nanchang University, Nanchang University, Nanchang, China.

[*] Correspondence: Shui-Zi Pang, Department of Infection Prevention and Control, The First Affiliated Hospital of Nanchang University, 17 Yongwaizheng Street, Nanchang 330006, Jiangxi, China (e-mail: 372650869@qq.com).

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mutations, significantly impacting patient survival.[8] In general, the 5-year survival for ICCA ranges from 14–34%, while patients with ECCA have a 5-year survival of 11–31%, depending on the presence of vascular invasion, lymph node metastasis and other metastases.[9] It has been estimated that, at CCA diagnosis, only one-third of patients are eligible for tumour resection because local infiltration and metastasis are so common.[9] Despite these disparities, few studies have examined and compared these differences. In addition, many clinicians lack a comprehensive understanding of the malignancy of CCA. To date, there is little knowledge about the metastatic rate of CCA and its related risk factors; additionally, it is unknown whether the anatomical location is related to the prognosis of patients. Therefore, we focused on metastasis and survival to investigate whether the disparities were associated with anatomical location.

In our study, we extracted 15,751 patients from the Surveillance, Epidemiology, and End Results (SEER) database to investigate the metastasis and survival of patients with CCA. Furthermore, we performed a heat plot of the metastasis rate according to age group and conducted propensity score matching (PSM) to provide evidence demonstrating the association between survival and anatomical location.

2. Methods

2.1. Patients

Data of all patients with cholangiocarcinoma were retrieved from the SEER database with the National Cancer Institute's SEER*Stat software (version 8.3.6). The patients did not give informed consent because the SEER database is free for public use. According to the International Classification of Diseases in Oncology (ICD-O-3), tumours with codes 8010, 8020, 8041, 8070, 8140, 8144, 8160, 8161, 8260, 8310, 8480, 8490, 8560 and 8162 are identified as ECCA (C24.0), while those with codes 8010, 8020, 8140, 8160 and 8161 are considered ICCA (C22.1).[10] All patients underwent surgery without preoperative adjuvant chemoradiotherapy because adjuvant treatment would affect the assessment of the TNM stage. The surgical methods included both common and laparoscopic surgery, although the detailed information was unknown. In our study, patients with CCA were included according to the following criteria:

1. patients older than 20 who were diagnosed with CCA by positive histology from 2004 through 2015;
2. patients with CCA localized in the extrahepatic and intrahepatic bile duct;
3. patients with metastasis information; and
4. patients with detailed information, including age, sex, race, grade, tumour size, N stage and T stage (used only when we conducted PSM).

2.2. Clinicopathological factors

The clinicopathological variables extracted from the SEER database in our study included age, race, sex, pathology grade, LNM, M stage, tumour size, N stage, and primary site. The patients were divided into six age groups: 20–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years and ≥80 years. Race was classified into three types: white, black and other. Sex included male and female. Pathology grade was categorized as well/moderately differentiated type and poorly differentiated/undifferentiated type. LNM was described as N1 (Yes) or N0 (No). M1 (Yes) indicated positive M stage. Tumour size was categorized into 2 groups: ≤5 cm and >5 cm. In our study, the main observation indicators were metastasis status, overall survival (OS) and cancer-specific survival (CSS), of which OS included CSS and death attributable to other causes.

2.3. Statistical analysis

For the basic statistics, patients were divided into two groups, i.e., ECCA and ICCA, and Pearson's chi-squared test was utilized to investigate the associations among the categorical variables. To explore the potential risk factors for metastasis, we performed univariate and multivariate logistical regression, and we present the results as the odds ratio (OR) with 95% confidence interval (CI). With respect to the OS and CSS of patients with ECCA and ICCA, we generated survival curves using the survminer package in R software. Regarding the imbalance between the ECCA and ICCA groups, we performed PSM and inverse probability of treatment weighting (IPTW) to obtain new data for analysis with the MatchIt package in R software. The value of the calliper was set at 0.02, and the effect was evaluated based on the standardized mean difference (SMD). The effect was balanced when the SMD was less than 0.1.[11] The detailed process was as follows. First, we calculated the propensity scores of each patient according to the primary site (ECCA and ICCA) with the multivariate logistic regression model. Then, we matched patients between the two groups at a ratio of 1:1. Next, we analysed the differences in all variables between the ECCA and ICCA groups with SMD, as shown in Supplementary Figures 2 and 3, http://links.lww.com/MD2/A74. Finally, we explored the correlation between survival and primary site using the univariate Cox regression model. Additionally, a plot of the survival curve was also constructed.

All statistical analyses were performed with R software (version 3.6.1, StataCorp LLC, College Station, Texas). The main packages used in our study included the ggplot2, MatchIt, survival, rms, survminer and forest packages. The chi-squared test was performed with SPSS (version 24.0). The results were considered to be statistically significant when the P value was less than 0.05.

3. Results

3.1. Basic information of extracted patients with ICCA and ECCA

As shown in Supplementary Figure 1, http://links.lww.com/MD2/A74, we extracted 15,751 patients in total, including 6891 patients with ICCA and 8860 patients with ECCA. Detailed information related to the extracted patients is listed in Table 1; both ECCA and ICCA patients were more likely to be older (ECCA, >50 years vs. <50 years, 79.58% vs. 21.42%; ICCA, >50 years vs. <50 years, 71.59% vs. 28.41%, $P < .001$) and white (ECCA vs. ICCA, 78.25% vs. 78.48%, $P = 0.924$). Regarding sex distributions, the proportions of male and female patients with ICCA were very similar (51.4% vs. 48.6%), while patients with ECCA were more likely to be male (68.87% vs. 38.13%). The pathology grades of ECCA and ICCA tended to be well or moderately differentiated. The rate of lymph node metastasis for ECCA was higher than that of ICCA (26.66% vs. 23.16%, $P = .000$), while the rate of metastasis for ECCA was lower than that of ICCA (31.46% vs.

Table 1.

Patients' demographics, clinical characteristics at diagnosis.

Variables	Total (%)	Intraductal cholangiocarcinoma	Extraductal cholangiocarcinoma	*P* Value
N	15751	6891	8860	
Age				.000
20–39	334 (2.12%)	173 (2.51%)	161 (1.82%)	
40–49	852 (5.41%)	452 (6.56%)	400 (4.51%)	
50–59	2581 (16.39%)	1333 (19.34%)	1248 (14.09%)	
60–69	4185 (26.57%)	1985 (28.81%)	2200 (24.83%)	
70–79	4285 (27.2%)	1795 (26.05%)	2490 (28.1%)	
>=80	3514 (22.31%)	1153 (16.73%)	2361 (26.65%)	
Race				.924
White	12341 (78.35%)	5408 (78.48%)	6933 (78.25%)	
Black	1287 (8.17%)	557 (8.08%)	730 (8.24%)	
Other	2123 (13.48%)	926 (13.43%)	1197 (13.51%)	
Sex				.000
Male	8320 (52,82%)	3489 (51.4%)	4831 (61.87%)	
Female	7431 (47.18%)	3402 (48.6%)	4029 (38.13%)	
Pathology Grade				.036
Well/moderately differentiated	3670 (23.3%)	1579 (22.91%)	2091 (23.6%)	
Poorly/Undifferentiated	2698 (17.13%)	1240 (18%)	1458 (16.46%)	
Unknown	9383 (59.57%)	4072 (59.09%)	5311 (59.94%)	
Lymph node Metastasis				.000
No	10108 (64.17%)	4662 (67.65%)	5446 (61.47%)	
Yes	3958 (25.13%)	1596 (23.16%)	2362 (26.66%)	
Unknown	1685 (10.7%)	633 (9.19%)	1052 (11.87%)	
Metastasis				.000
No	10027 (63.66%)	3954 (57.38%)	6073 (68.54%)	
Yes	5724 (36.34%)	2937 (42.62%)	2787 (31.46%)	
Tumor size				.000
≤5cm	5435 (34.5%)	1759 (25.52%)	3676 (41.49%)	
>5cm	3667 (23.28%)	2535 (36.79%)	1132 (12.78%)	
Unknown	6649 (42.21%)	2597 (37.69%)	4052 (45.73%)	
T stage				.000
T1	4356 (27.66%)	2109 (30.61%)	2247 (25.35%)	
T2	1679 (10.66%)	794 (11.52%)	885 (10%)	
T3	3912 (24.84%)	1432 (20.78%)	2480 (27.99%)	
T4	2059 (13.07%)	833 (12.09%)	1226 (13.84%)	
Unknown	3745 (23.78%)	1723 (25%)	2022 (22.82%)	

42.62%, $P < .001$). Tumour size tended to be smaller than 5 cm in ECCA (>5 cm vs. < 5 cm, 12.78% vs. 41.49%), whereas ICCA tumours were more often larger than 5 cm (>5 cm vs. <5 cm, 36.79% vs. 25.52%).

3.2. Identifying risk factors for metastasis

To investigate the risk factors for metastasis, we performed univariate and multivariate logistic regression analyses, and the results are shown in Tables 2 and 3. For ICCA patients (Table 2), univariate analysis results showed that younger patients (<50 years), those with poorly differentiated or undifferentiated disease, positive lymph nodes, larger tumour size (>5 cm) and advanced tumours (stages T3 and T4) were more likely to have metastasis ($P < .001$). Race and sex were not associated with metastasis ($P > .05$). Consistent with the results of the univariate analysis, the multivariate analysis showed that age, pathology grade, tumour size, lymph node metastasis and T stage were independent risk factors for metastasis (Table 2). Compared to ICCA, apart from those risk factors, female patients with ECCA had a higher probability of metastasis (OR = 1.27, 95% CI, 1.161–1.39, $P < .0001$), as demonstrated by multivariate analysis (OR = 1.258, 95% CI, 1.135–1.395, $P < .0001$) (Table 3).

3.3. Inverse association of age with risk of metastasis

Interestingly, we found an inverse association between age and metastasis. A previous study showed that the median age at diagnosis progressively decreased for both ICCA and ECCA from 1973 to 2012,[12,13] which suggested that we should pay more attention to younger patients. Therefore, we divided all patients into six groups according to age and determined the detailed ratios of metastasis in the different groups. For ICCA (Fig. 1), patients aged 20–39 years had the highest rate of 50.29%, followed by patients aged 40–49 years, patients aged 50–59 years and patients aged 60–69 years, while the oldest patients aged 80+ years had the lowest rate of 35.47%. Moreover, analysis of the linear trend suggested that an increased age at diagnosis was correlated with a lower risk of LNM ($P = .019$) (Fig. 2). Subgroup analysis was performed to evaluate whether a similar trend existed in other groups stratified by sex, race, tumour size, pathology grade, LNM and T stage (Fig. 1). As shown in Figure 1, in the male and female subgroups, we found that the rate of metastasis decreased as age increased. In addition to white race, there was also an inverse association between age and the risk of metastasis. Consistent with the pathology grade and tumour size subgroups, younger patients had a higher probability of metastasis. For patients with stages T3 and T4 ICCA, patients

Table 2.

Univariate and multivariate logistic regression analysis of intrahepatic cholangiocarcinoma's patients for metastasis.

Variables	Univariate analysis		Multivariate analysis	
Age		0.000		0.000
20–39	Reference	–	Reference	–
40–49	0.905 (0.637–1.285)	0.576	1.208 (0.688–1.537)	0.523
50–59	0.862 (0.628–1.018)	0.035	0.988 (0.686–1.022)	0.298
60–69	0.756 (0.554–1.001)	0.041	0.89 (0.622–1.003)	0.041
70–79	0.7 (0.512–0.956)	0.025	0.826 (0.576–0.985)	0.026
>=80	0.543 (0.394–0.749)	0.000	0.528 (0.364–0.767)	0.001
Race				
White	Reference	–		
Black	0.938 (0.785–1.12)	0.477		
Other	1.021 (0.887–1.176)	0.768		
Sex		0.039		
Male	Reference	–		
Female	0.929 (0.844–1.022)	0.131		
Pathology Grade				
Well/moderately differentiated	Reference	–	Reference	–
Poorly/Undifferentiated	1.532 (1.308–1.795)	0.000	1.302 (1.092–1.554)	0.003
Lymph node Metastasis				
No	Reference	–	Reference	–
Yes	2.402 (2.139–2.697)	0.000	2.169 (1.917–2.455)	0.000
Tumor size				0.000
≤5cm	Reference	–	Reference	–
>5cm	1.932 (1.689–2.21)	0.000	1.695 (1.448–1.984)	
T stage				
T1	Reference	–	Reference	–
T2	1.011 (0.801–1.215)	0.91	1.133 (0.928–1.385)	0.221
T3	1.914 (1.659–2.208)	0.000	1.465 (1.245–1.724)	0.000
T4	2.423 (2.051–2.863)	0.000	1.873 (1.562–2.246)	0.000

Table 3.

Univariate and multivariate logistic regression analysis of extrahepatic cholangiocarcinoma's patients for metastasis.

Variables	Univariate analysis		Multivariate analysis	
Age				
20–39	Reference	–	Reference	–
40–49	0.805 (0.523–1.124)	0.325	0.694 (0.421–1.143)	0.151
50–59	0.701 (0.472–1.046)	0.023	0.634 (0.401–1.004)	0.042
60–69	0.601 (0.406–0.888)	0.011	0.568 (0.362–0.891)	0.01
70–79	0.509 (0.344–0.752)	0.001	0.464 (0.295–0.728)	0.001
>=80	0.32 (0.216–0.475)	0.000	0.211 (0134–0.332)	0.000
Race		0.124		
White	Reference	–		
Black	1.083 (0.921–1.273)	0.333		
Other	0.840 (0.734–0.962)	0.012		
Sex				
Male	Reference	–	Reference	–
Female	1.27 (1.161–1.39)	0.0001	1.258 (1.135–1.395)	0.000
Pathology Grade				
Well/moderately differentiated	Reference	–	Reference	–
Poorly/Undifferentiated	2.022 (1.702–2.402)	0.000	1.744 (1.45–2.098)	0.000
Lymph node Metastasis				
No	Reference	–	Reference	–
Yes	1.661 (1.494–1.845)	0.000	1.932 (1.706–2.188)	0.000
Tumor size				
≤5cm	Reference	–	Reference	–
>5cm	3.103 (2.541–3.789)	0.000	2.177 (1.93–2.456)	0.000
T stage				
T1	Reference	–	Reference	–
T2	0.468 (0.367–0.597)	0.000	0.65 (0.56–0.843)	0.05
T3	1.5 (1.307–1.722)	0.000	1.429 (1.225–1.666)	0.000
T4	2.152 (1.837–2.52)	0.000	1.836 (1.541–2.188)	0.000

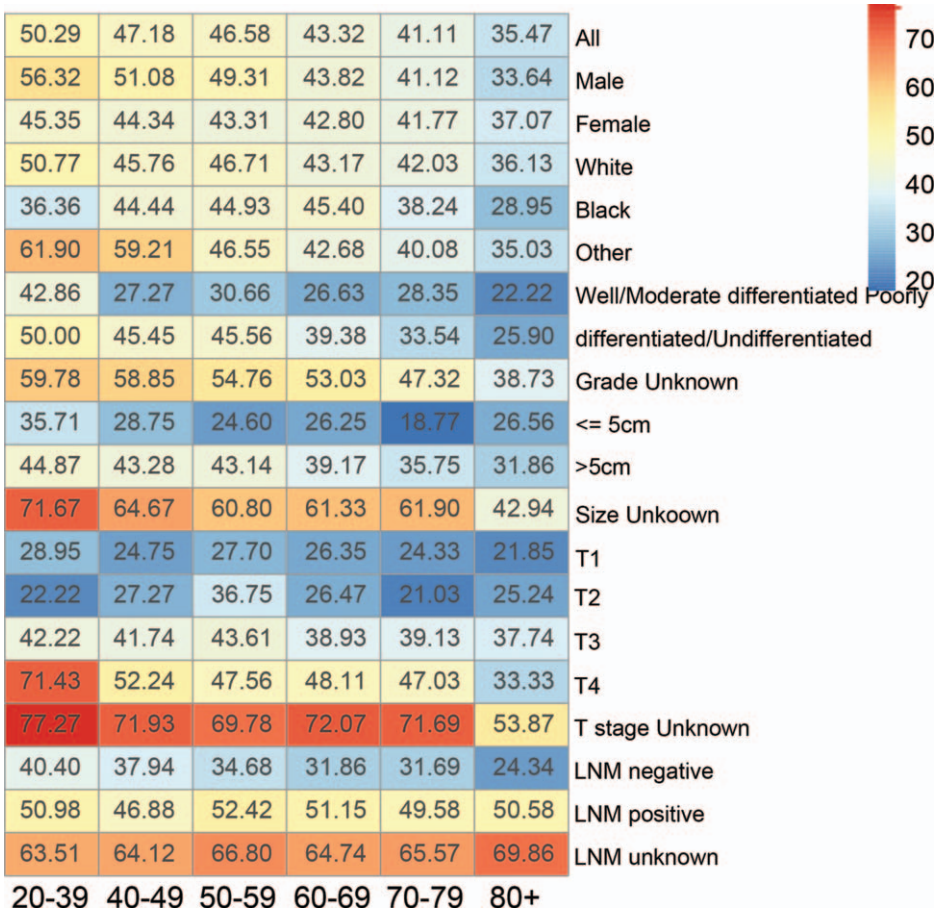

Figure 1. Heatmap showing the rate of metastasis of patients with ICCA among patients aged 20–39, 40–49, 50–59, 60–69, 70-79 and 80+ years stratified by different characteristics.

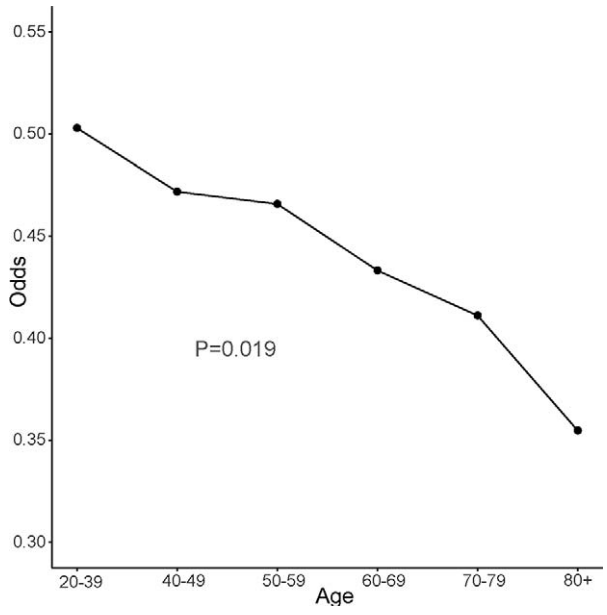

Figure 2. Association between odds of metastasis and age at diagnosis in patients with ICCA. The *P* value for the linear trend of the log odds of lymph node metastasis was tested using score statistics and variance.

aged 20–39 years had the highest metastasis rate, while patients aged >=80 had the lowest rate. However, compared to patients with negative LNM, patients with positive LNM had an extremely high rate of metastasis that was not associated with age; patients with ECCA demonstrated a similar trend. As shown in Figure 3, the highest LNM rate was 47.66% in patients aged 20–39 years old, which deceased with increasing age, finally reaching 22.23% for patients aged 80+ years. This correlation was also statistically significant, as demonstrated by analysis of the linear trend (Fig. 4, $P = .0035$). Analysis of subgroups also showed that patients aged 20–39 years had the highest metastasis rate, and patients aged 80+ had the lowest rate. Unlike ICCA, ECCA patients with positive LNM had a higher rate of metastasis than patients with negative LNM, and this rate also decreased with increasing age.

3.4. Comparison of the survival of patients between ICCA and ECCA

To further compare the survival of patients with ICCA and ECCA, we performed K-M curves to show the OS and CSS of patients. The results showed that patients with ICCA had a 1-year CSS of 37.5% and a 3-year CSS of 14.6%, while patients with ECCA had a 1-year CSS of 36.4% and a 3-year CSS of 14.3%, which were not significantly different between ICCA and ECCA,

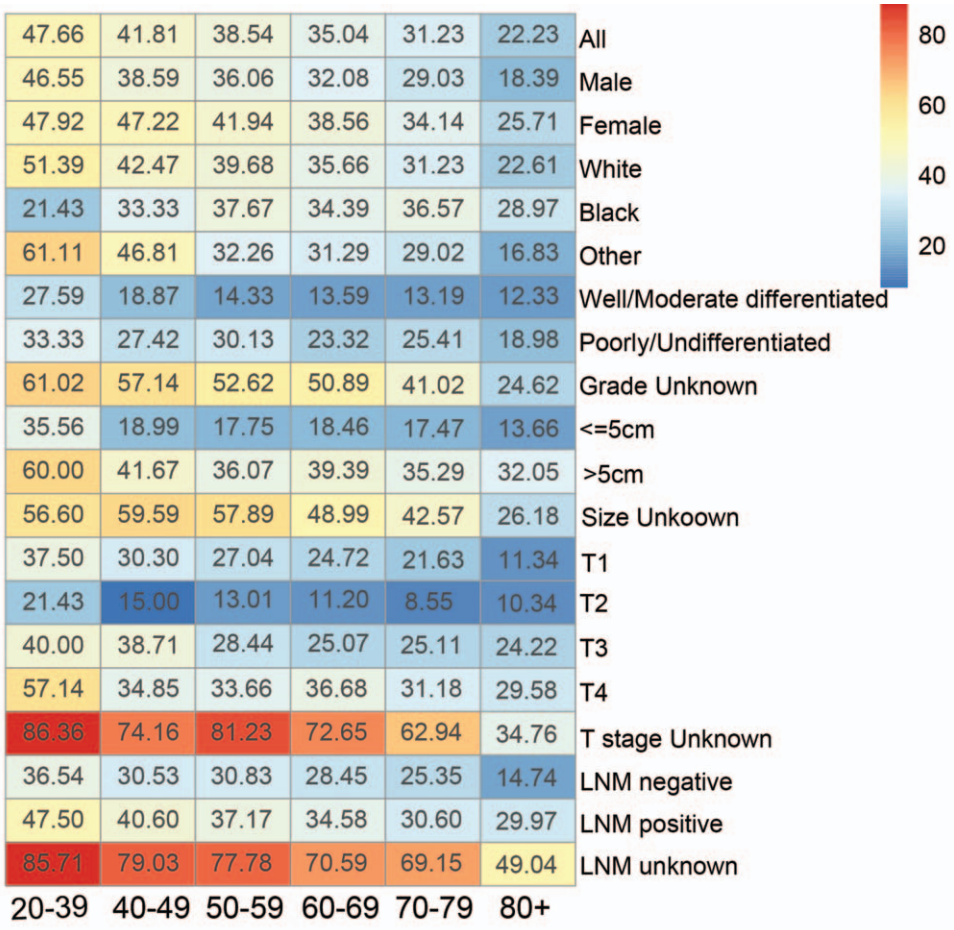

Figure 3. Heatmap showing the rate of metastasis in patients with ECCA among patients aged 20–39, 40–49, 50–59, 60–69, 70–79 and 80+ years stratified by different characteristics.

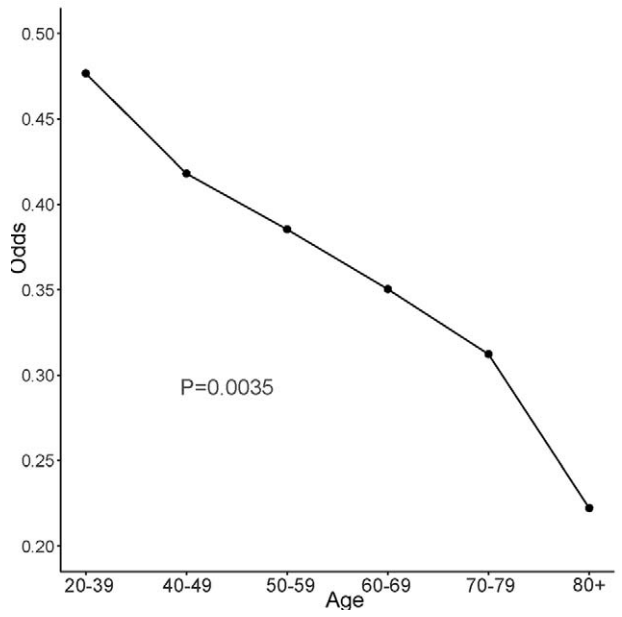

Figure 4. Association between odds of metastasis and age at diagnosis in patients with ECCA. The *P* value for the linear trend of the log odds of lymph node metastasis was tested using score statistics and variance.

regardless of OS or CSS ($P > .05$, Fig. 5). However, we found that the basic characteristics between the two groups were not balanced, which could affect the analysis of survival. Hence, we performed PSM to adjust the imbalance. As shown in Supplementary Figure 3, http://links.lww.com/MD2/A74, the baseline data were obviously imbalanced (SMD>0.1). After deleting some unknown information and then matching 881 ICCA patients with 881 ECCA patients, we found that all data were comparable because the SMD was lower than 0.1. As the K-M curve of the OS and CSS revealed, patients with ECCA had better survival than ICCA patients ($P < .05$, Fig. 6). Moreover, while analysing the rate of metastasis, we found that patients with ECCA in the T1 stage had a higher probability than patients with ICCA in the T1 stage, causing us to compare the survival of patients in the T1 stage between the two types of CCA. In our preliminary analysis, we found that patients with ECCA had worse OS and CSS than those with ICCA, which was contrary to the overall analysis results ($P < .0001$, Fig. 7). To further test our findings, we performed PSM to adjust for confounding factors. As demonstrated in Supplementary Figure 3, http://links.lww.com/MD2/A74, we balanced the imbalance inherent in the basic data (SMD<0.01). The K–M survival curve of OS and CSS indicated that ICCA patients had a lower survival rate than ECCA patients ($P < .05$, Fig. 8).

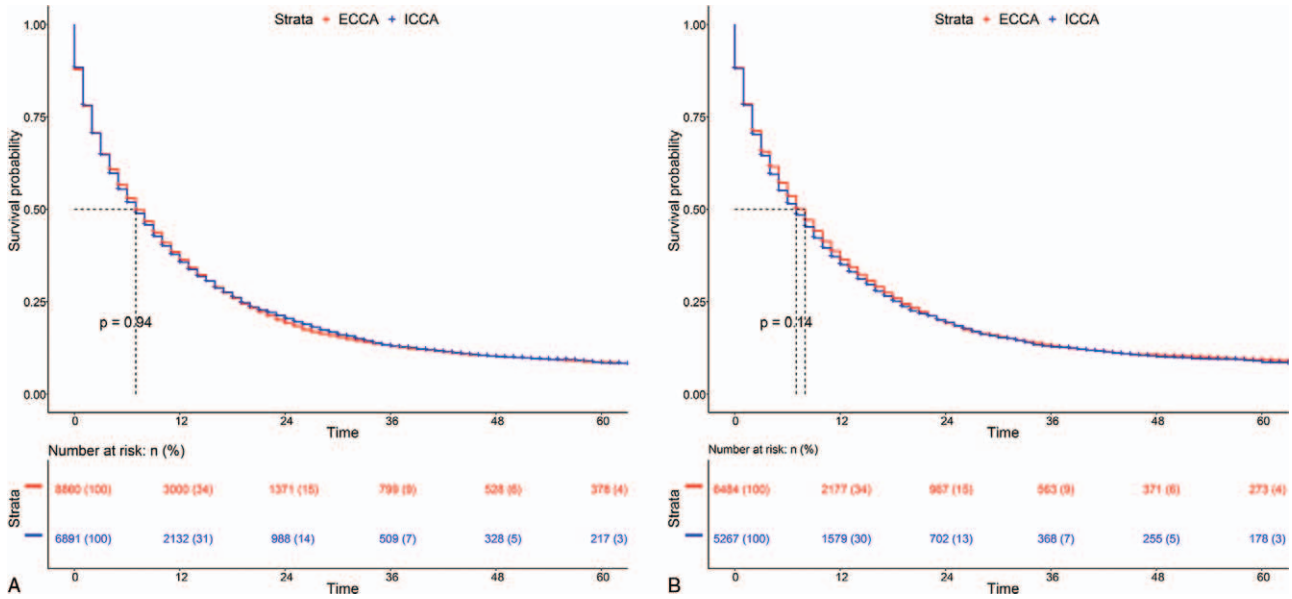

Figure 5. Comparison of OS (A) and CSS (B) among patients diagnosed with ECCA and ICCA.

4. Discussion

To the best of our knowledge, ECCA and ICCA are quite different types of CCA in terms of risk factors and clinical manifestations. Furthermore, the incidence and mortality rate of CCA increased between 2000–2015.[14] To date, however, ICCA and ECCA have rarely been compared because of difficulties in diagnosis and follow-up.[15] Concerning the CCA guidelines, an evaluation found that some current guidelines had poor applicability and lacked rigor in their development, although the proportion was small.[16,17] Especially regarding the surgical management of CCA, the quality of the guidelines needs to be improved.[17] Therefore, some clinical data about ECCA and ICCA that were unknown, such as the survival rates, LNM rates and probability of metastasis, should be discussed. In our study, we extracted a total of 15,751 patients with CCA from the SEER database and analysed the different rates of metastasis between ECCA and ICCA; we found that patients with ECCA had a lower probability of metastasis than patients with ICCA (31.46% vs. 42.62%, $P < .001$). In addition, there was an inverse association between age and metastasis, and the ratios of metastasis in different age groups with ICCA were higher than those in the corresponding age group with ECCA. For survival analysis, patients diagnosed at an older age had a worse prognosis. Additionally, patients with ICCA had worse survival than patients with ECCA, which was demonstrated by performing

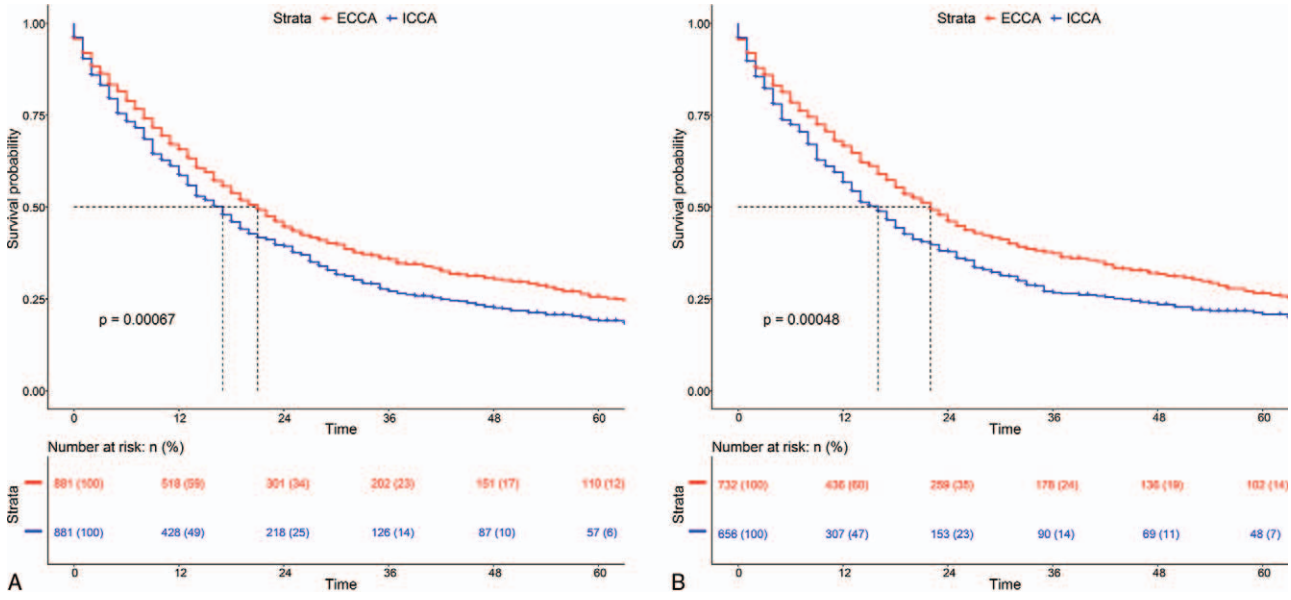

Figure 6. Comparison of OS (A) and CSS (A) among patients diagnosed with ECCA and ICCA after performing PSM.

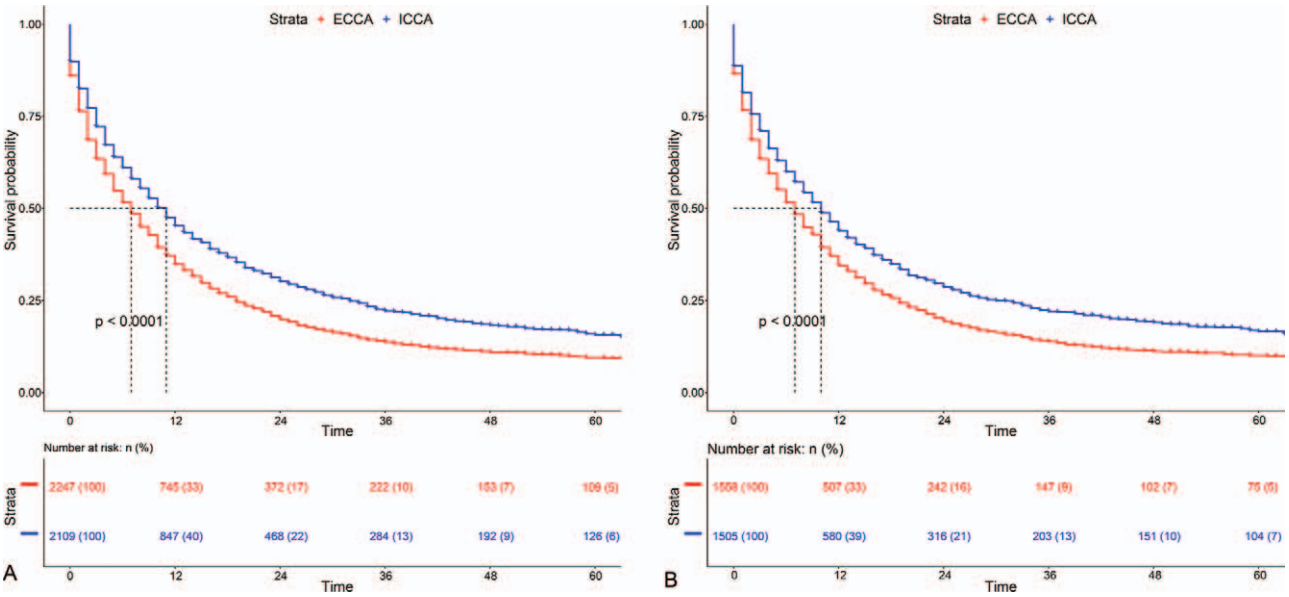

Figure 7. Comparison of OS (A) and CSS (B) among patients diagnosed with ECCA and ICCA in the T1 stage.

PSM. In contrast, before or after performing PSM, we found that patients with ICCA in the T1 stage had better survival.

Regarding the basic characteristics of ICCA and ECCA, consistent with our results, a previous study found that the majority of CCA cases were well/moderately differentiated, while other histological tumours accounted for only a small proportion.[18] For both ECCA and ICCA, there were more male patients than female patients.[19] Moreover, the median age at diagnosis of patients with ECCA or ICCA was over 65 years, which was consistent with our results.[10,12] Lymph node metastasis (LNM) has been considered an independent prognostic factor for CCA; patients with ICCA have an LNM rate of 30–50%, while patients with ECCA have an LNM rate of 20%–50%.[20–22] In contrast, our results showed that the proportion of patients with LNM was 20%–30%, for which a potential explanation was the different sample sizes.

The aggressiveness of CCA is due to its propensity to spread to other places, such as to regional lymph nodes, the liver or the lungs. Our results suggested that the rate of metastasis in patients with ECCA was 31.46%, while that for patients with ICCA was 42.62%. Other studies have reported the rates of metastasis in ECCA and ICCA to be 30%–50% and 30–40%, respectively.[20,23,24] Knowledge about metastasis significantly decreased the duration of the hospital stay and prolonged survival,[25] suggesting that patients with ICCA should be provided more inpatient care. With regard to the factors of metastasis, we found

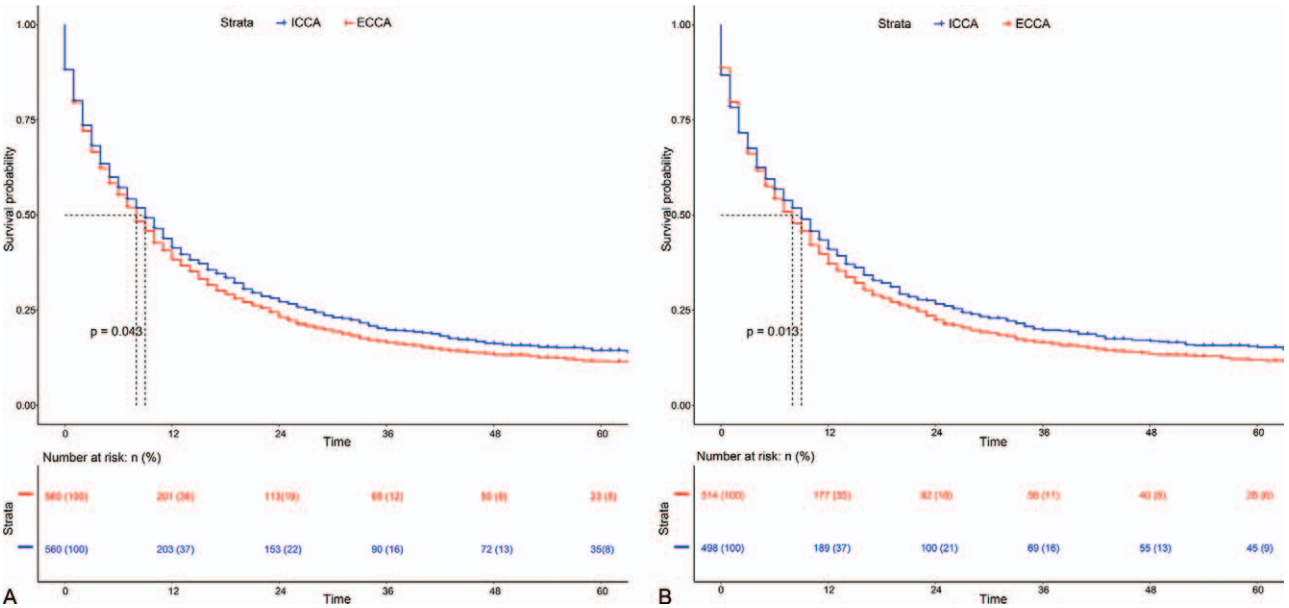

Figure 8. Comparison of OS (A) and CSS (B) among patients diagnosed with ECCA and ICCA in the T1 stage after performing PSM.

that age, pathology grade, tumour size, LNM and T stage were independent factors of metastasis for both ECCA and ICCA. Consistent with some studies, tumour size >5 cm, LNM and T stage were independent factors for metastasis.[26] Knowing the independent factors was of great help for predicting patients with advanced disease, which could improve treatment by applying multimodal therapies, such as chemotherapy and radiation.[27,28] A high incidence of recurrence up to 70% was also a feature of CCA, which was associated with the stage of the tumour.[29] The clinical information we found could provide opportunities for the management of patients with recurrent disease. Interestingly, we found an unexpected phenomenon in which younger patients were more likely to have metastasis than older patients, and ours was the first study to elucidate this trend. According to epidemiological data regarding incidence, fewer patients >75 years of age were found to have either ICCA or ECCA, and the median age at diagnosis has gotten progressively younger in recent decades.[12,30] CCA has received great attention among older patients (>50 years), whereas patients diagnosed before age 50 have rarely been studied.[31] Moreover, due to the higher resistance to surgery for younger patients, younger patients tended to have a better prognosis than older patients, leading to some neglect of younger patients.[31] According to our results, younger patients had a higher risk of metastasis, implying that younger patients should be treated differently, as Hughes N et al suggested.[32] For the inverse association between age and metastasis, some potential explanations, such as molecular mechanisms and physiological changes, should be considered.[33,34] For instance, most patients with early-onset (age <50 years) disease present with a lower prevalence of microsatellite instability and an enhanced frequency of KMT2C and ASXL1 mutations in comparison with late-onset patients.[35] Although to date, there remains an insufficient explanation for this issue, we hope there will be more research following our results, and we will also perform research on this mechanism.

As a malignant tumour, the 1- and 3-year survival rates for patients with CCA are only 30–47% and 15%-30%, respectively, while the difference in survival between ICCA and ECCA is controversial.[2,9,33] Our extracted data showed that there was no difference in survival between them; however, after performing PSM, we found that patients with ICCA had a worse prognosis than those with ECCA ($P < .05$). Many causes could result in different survival rates between ECCA and ICCA, such as different genetic factors, different risk factors and different methods of surgery.[15,36] For instance, the chance of having surgery for patients with ECCA was 36–37%, while that for patients with ICCA was 18.5%, which was associated with the rate of distant metastasis (ECCA vs ICCA, 30% vs 43.5%).[37] In addition, we found that older patients (>=50 years) had worse survival than younger patients (<50 years) in both ECCA and ICCA, which may be somewhat associated with better tolerance of the operation itself and fewer complications in younger patients.[7,9,38] With regard to CCA in the T1 stage, we found that patients with ICCA had better survival than those with ECCA before or after performing PSM. Some studies reported that patients with ICCA in the early stage had a larger probability of having R0 than those with ECCA, which could explain our results.[7] For example, patients with ICCA in the T1 stage had an R0 rate of 81.7%, while the R0 rate was 74.4% for patients with ECCA in the T1 stage.[39,40] Moreover, we also found that the rate of metastasis for ICCA in the T1 stage was lower than that for ECCA (Figs. 1 and 3). Indeed, different treatments made a large difference in survival. For instance, adjuvant radiotherapy after resection of ECCA was associated with a survival benefit in patients, even in patients with margin-negative or node-negative resections.[41] Moreover, the safety and feasibility of laparoscopic versus open liver resection-associated lymphadenectomy for intrahepatic cholangiocarcinoma are still controversial.[42,43] Of course, this was also a limitation of our study; however, we will collect patient data from our hospital to further demonstrate our results.

5. Conclusions

This study is the first to compare the rate of metastasis and survival between ECCA and ICCA, and we found that there was an inverse association between age and metastasis; patients with ECCA had a better prognosis than patients with ICCA, while patients with stage T1 ECCA had worse survival. Our results suggested that patients diagnosed at a younger age need more attention, and the survival of patients with ECCA and ICCA should be recognized according at different stages, enhancing the knowledge of CCA for clinicians. Additionally, clinicians should treat CCA in different anatomic positions with different methods.

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Author contributions

PL was responsible for collecting data and writing manuscript. LC and HC were responsible for data analysis. SZP designed and supervised the study.
Conceptualization: Peng Liao.
Data curation: Peng Liao.
Formal analysis: Peng Liao.
Methodology: Li Cao.
Validation: Li Cao.
Investigation: Hang Chen.
Resources: Hang Chen.
Project administration: Shui-Zi Pang.
Writing – review & editing: Shui-Zi Pang.

References

[1] O H , H M , C P , et al. A nomogram to predict long-term survival after resection for intrahepatic cholangiocarcinoma: an eastern and western experience. JAMA Surgery 2014;149:432–8.
[2] A N , HA P , TA S , et al. Cholangiocarcinoma. a spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463–73. discussion 473-465.
[3] PV D , SW B . Distal cholangiocarcinoma. Surg Clinics N A 2014;94:325–42.
[4] Clements O, Eliahoo J, Kim JU, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a systematic review and meta-analysis. J Hepatol 2020;72:95–103.
[5] Fitzmaurice C, Abate D, Abbasi N, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol 2019.
[6] Khan SA, Emadossadaty S, Ladep NG, et al. Rising trends in cholangiocarcinoma: is the ICD classification system misleading us? J Hepatol 2012;56:848–54.
[7] Ercolani G, Dazzi A, Giovinazzo F, et al. Intrahepatic, perihilar and distal cholangiocarcinoma: three different locations of the same tumor or three different tumors? Eur J Surg Oncol 2015;41:1162–9.

[8] M S , M F , A R , et al. Multigene mutational profiling of cholangiocarcinomas identifies actionable molecular subgroups. Oncotarget 2014;5:2839–52.
[9] Y C , N C , H Y , et al. The current management of cholangiocarcinoma: a comparison of current guidelines. Bioscience trends 2016;10:92–102.
[10] Welzel TM, Graubard BI, El-Serag HB, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. Clin Gastroenterol Hepatol 2007;5:1221–8.
[11] ST N , MB L , E G , et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol 2001; 54:387–98.
[12] SK S , AX Z , CS F , et al. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. The Oncol 2016;21:594–9.
[13] SA K , S E , NG L , et al. Rising trends in cholangiocarcinoma: is the ICD classification system misleading us? J Hepatol 2012;56:848–54.
[14] Gad MM, Saad AM, Faisaluddin M, et al. Epidemiology of cholangiocarcinoma; United States incidence and mortality trends. Clin Res Hepatol Gastroenterol 2020.
[15] Esnaola NF, Meyer JE, Karachristos A, et al. Evaluation and management of intrahepatic and extrahepatic cholangiocarcinoma. Cancer 2016;122:1349–69.
[16] Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. Clinical Practice Guidelines We Can Trust Washington (DC): National Academies Press (US), Copyright 2011 by the National Academy of Sciences; 2011.
[17] Gavriilidis P, Askari A, Roberts KJ, et al. Appraisal of the current guidelines for management of cholangiocarcinoma-using the Appraisal of Guidelines Research and Evaluation II (AGREE II) Instrument. Hepatobiliary Surg Nutr 2020;9:126–35.
[18] T E , G E , D A , et al. Current status on cholangiocarcinoma and gallbladder cancer. Liver Can 2016;6:59–65.
[19] F B , G S , K M , et al. Intrahepatic cholangiocarcinoma tumor burden: a classification and regression tree model to define prognostic groups after resection. Surgery 2019;166:983–90.
[20] T A , S K , T H , et al. Clinical significance of preoperative CA19-9 and lymph node metastasis in intrahepatic cholangiocarcinoma. Surg Today 2020.
[21] Navarro JG, Lee JH, Kang I, et al. Prognostic significance of and risk prediction model for lymph node metastasis in resectable intrahepatic cholangiocarcinoma: do all require lymph node dissection? Hepatobiliary Pancreat Dis Int 2020.
[22] Aoba T, Ebata T, Yokoyama Y, et al. Assessment of nodal status for perihilar cholangiocarcinoma: location, number, or ratio of involved nodes. Ann Surg 2013;257:718–25.
[23] M A , T A , K U , et al. Benefits and limitations of middle bile duct segmental resection for extrahepatic cholangiocarcinoma. Hepatobiliary Pancreat Dis Int 2020.
[24] Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507–17. discussion 517–509.
[25] Idrees JJ, Merath K, Gani F, et al. Trends in centralization of surgical care and compliance with National Cancer Center Network guidelines for resected cholangiocarcinoma. HPB (Oxford) 2019;21:981–9.
[26] Conci S, Vigano L, Ercolani G, et al. Outcomes of vascular resection associated with curative intent hepatectomy for intrahepatic cholangiocarcinoma. Eur J Surg Oncol 2020.
[27] Reames BN, Bagante F, Ejaz A, et al. Impact of adjuvant chemotherapy on survival in patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis. HPB (Oxford) 2017;19:901–9.
[28] Bergeat D, Turrini O, Courtin-Tanguy L, et al. Impact of adjuvant chemotherapy after pancreaticoduodenectomy for distal cholangiocarcinoma: a propensity score analysis from a French multicentric cohort. Langenbeck's Arch Surg 2018;403:701–9.
[29] Spolverato G, Kim Y, Alexandrescu S, et al. Management and outcomes of patients with recurrent intrahepatic cholangiocarcinoma following previous curative-intent surgical resection. Ann Surg Oncol 2016; 23:235–43.
[30] Tyson GL, Ilyas JA, Duan Z, et al. Secular trends in the incidence of cholangiocarcinoma in the USA and the impact of misclassification. Digest Dis Sci 2014;59:3103–10.
[31] Rizvi S, Khan SA, Hallemeier CL, et al. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol 2018;15:95–111.
[32] Hughes N, Stark D. The management of adolescents and young adults with cancer. Cancer Treat Rev 2018;67:45–53.
[33] Liu XF, Tang K, Sui LL, et al. Cholangiocarcinoma: present status and molecular aspects of diagnosis. Oncol Research 2014;22:177–83.
[34] Labib PL, Goodchild G, Pereira SP. Molecular pathogenesis of cholangiocarcinoma. BMC cancer 2019;19:185.
[35] Feng H, Tong H, Yan J, et al. Genomic features and clinical characteristics of adolescents and young adults with cholangiocarcinoma. Front Oncol 2019;9:1439.
[36] Montal R, Sia D, Montironi C, et al. Molecular classification and therapeutic targets in extrahepatic cholangiocarcinoma. J Hepatol 2020.
[37] Hang H, Jeong S, Sha M, et al. Cholangiocarcinoma: anatomical location-dependent clinical, prognostic, and genetic disparities. Ann Transl Med 2019;7:744.
[38] GG P , F P , JV G , et al. Liver transplantation for cholangiocarcinoma: insights into the prognosis and the evolving indications. Curr Oncol Rep 2020;22:49.
[39] Hwang S, Lee YJ, Song GW, et al. Prognostic impact of Tumor growth Type on 7th AJCC staging system for intrahepatic cholangiocarcinoma: a single-center experience of 659 Cases. J Gastrointest Surg 2015;19:1291–304.
[40] Chen RF, Li ZH, Zhou JJ, et al. Preoperative evaluation with T-staging system for hilar cholangiocarcinoma. W J Gastroenterol 2007;13:5754–9.
[41] Kamarajah SK, Bednar F, Cho CS, et al. Survival benefit with adjuvant radiotherapy after resection of distal cholangiocarcinoma: a propensity-matched National Cancer Database analysis. Cancer 2020.
[42] Wu J, Han J, Zhang Y, et al. Safety and feasibility of laparoscopic versus open liver resection with associated lymphadenectomy for intrahepatic cholangiocarcinoma. Biosci Trends 2020;14:376–83.
[43] Gunasekaran G, Bekki Y, Lourdusamy V, et al. Surgical treatments of hepatobiliary cancers. Hepatology 2020.