Analysis of metastasis and survival between extrahepatic and intrahepatic cholangiocarcinoma
A large population-based study

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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 cholestocholithiasis 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.
metastases. 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. 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). 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 caliper 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. 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. 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, 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 = .000). 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.
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 these 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               |                       |
| 20–39                      | Reference           | 0.000                 |
| 40–49                      | 0.905 (0.637–1.285) | 0.576                 |
| 50–59                      | 0.862 (0.628–1.018) | 0.035                 |
| 60–69                      | 0.756 (0.554–1.001) | 0.041                 |
| 70–79                      | 0.7 (0.512–0.956)   | 0.025                 |
| >=80                       | 0.543 (0.394–0.749) | 0.000                 |
| Race                       | 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            | Reference           |                       |
| Well/moderately differentiated | 1.532 (1.308–1.795) | 0.000                 |
| Poorly/Undifferentiated    | 0.694 (0.421–1.143) | 0.151                 |
| Lymph node Metastasis      | Reference           |                       |
| No                         | 2.402 (2.139–2.697) | 0.000                 |
| Yes                        | 2.169 (1.917–2.455) | 0.000                 |
| Tumor size                 | Reference           |                       |
| <=5cm                      | 1.932 (1.689–2.21)  | 0.000                 |
| >5cm                       | 1.695 (1.448–1.984) |                       |
| T stage                    | Reference           |                       |
| T1                         | 1.011 (0.801–1.215) | 0.91                  |
| T2                         | 1.133 (0.928–1.385) | 0.221                 |
| T3                         | 1.465 (1.245–1.724) | 0.000                 |
| T4                         | 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                        | 0.000               |                       |
| 20–39                      | Reference           |                       |
| 40–49                      | 0.805 (0.523–1.124) | 0.325                 |
| 50–59                      | 0.701 (0.472–1.046) | 0.023                 |
| 60–69                      | 0.601 (0.406–0.888) | 0.011                 |
| 70–79                      | 0.509 (0.344–0.752) | 0.001                 |
| >=80                       | 0.32 (0.216–0.475)  | 0.000                 |
| Race                       | Reference           |                       |
| Black                      | 1.083 (0.921–1.273) | 0.333                 |
| Other                      | 0.840 (0.734–0.962) | 0.012                 |
| Sex                        | Reference           |                       |
| Male                       | 1.27 (1.161–1.39)   | 0.0001                |
| Female                     | 1.258 (1.135–1.395) | 0.000                 |
| Pathology Grade            | Reference           |                       |
| Well/moderately differentiated | 2.022 (1.702–2.402) | 0.000                 |
| Poorly/Undifferentiated    | 1.744 (1.45–2.098)  |                       |
| Lymph node Metastasis      | Reference           |                       |
| No                         | 1.661 (1.494–1.845) | 0.000                 |
| Yes                        | 1.932 (1.706–2.188) |                       |
| Tumor size                 | Reference           |                       |
| <=5cm                      | 3.103 (2.541–3.789) | 0.000                 |
| >5cm                       | 2.177 (1.93–2.456)  |                       |
| T stage                    | Reference           |                       |
| T1                         | 0.468 (0.367–0.597) | 0.000                 |
| T2                         | 0.65 (0.56–0.843)   | 0.05                  |
| T3                         | 1.5 (1.307–1.722)   | 0.000                 |
| T4                         | 1.836 (1.541–2.188) | 0.000                 |
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.
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).
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.\(^\text{[14]}\) To date, however, ICCA and ECCA have rarely been compared because of difficulties in diagnosis and follow-up.\(^\text{[15]}\) 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.\(^\text{[16,17]}\) Especially regarding the surgical management of CCA, the quality of the guidelines needs to be improved.\(^\text{[17]}\) 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
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.\cite{18} For both ECCA and ICCA, there were more male patients than female patients.\cite{19} Moreover, the median age at diagnosis of patients with ECCA or ICCA was over 65 years, which was consistent with our results.\cite{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%.\cite{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.\cite{20,23,24} Knowledge about metastasis significantly decreased the duration of the hospital stay and prolonged survival,\cite{23} suggesting that patients with ICCA should be provided more inpatient care. With regard to the factors of metastasis, we found...
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 >5cm, LNM and T stage were independent factors for metastasis. 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. A high incidence of recurrence up to 70% was also a feature of CCA, which was associated with the stage of the tumour. 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. CCA has received great attention among epidemiological data regarding incidence, fewer patients >50 years have rarely been studied. 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. 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. For the inverse association between age and metastasis, some potential explanations, such as molecular mechanisms and physiological changes, should be considered. 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. 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%, respective- ly, while the difference in survival between ICCA and ECCA is controversia. 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. 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%). 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. 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. 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. 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. Moreover, the safety and feasibility of laparoscopic versus open liver resection-associated lymphadenectomy for intrahepatic cholangiocarcinoma are still controversial. 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 the manuscript. LC and HC were responsible for data analysis. SZP designed and supervised the study.

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