Klatskin Tumor: A Population-Based Study of Incidence and Survival

ABEF 1 Xinying Zhang
ABE 2 Hui Liu

Background: Klatskin tumor (KCC) is a rare type of tumor, with an annual incidence rate of no more than 1: 100 000. Because of its rarity, KCC is difficult to investigate. The present study provides new insights into KCC by using public database.

Material/Methods: We used the Surveillance, Epidemiology, and End Results (SEER) database to conduct the analysis. Klatskin tumor patients were identified and compared with patients that had other kinds of cholangiocarcinomas (OCC). We identified differences between the 2 groups of patients and assessed tumor characteristics. We used Cox regression analysis to identify the prognostic indicators for KCC. The propensity score 1-to-1 matching method was used to compare the survival difference between KCC and OCC.

Result: We extracted data on 26 137 patients diagnosed with cholangiocarcinomas between 1973 and 2014 from the SEER database: 1341 cases were diagnosed with KCC and 24 796 cases were diagnosed with OCC. The number of diagnoses has gradually increased in both groups. There were significant differences in pathology grades, T stage, N stage, M stage, and SEER historic stage between the KCC and OCC groups. Survival analysis showed that the OCC group had better survival compared to the KCC group, both in matched and unmatched cohorts. The Cox regression results showed that older age, higher M stages, and higher pathology grades were associated with worse prognosis for KCC patients.

Conclusions: Klatskin patients have worse survival compared to OCC patients. Older age, higher M stages, and higher pathology grades were associated with worse survival in KCC patients.

MeSH Keywords: Cholangiocarcinoma • Klatskin's Tumor • SEER Program

Abbreviations: KCC – Klatskin tumor; OCC – other kinds of cholangiocarcinomas; SEER – Surveillance, Epidemiology, and End Results database; CSS – cancer-specific survival; OS – overall survival; AJCC – American Joint Committee on Cancer

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/914987
Background

Klatskin tumor ( hilar cholangiocarcinoma or central bile duct carcinoma, KCC) is a rare type of tumor, with an annual incidence of no more than 1: 100 000 [1]. It originates from the bifurcation of the extrahepatic bile duct and was first described in 1965 by Gerald Klatskin who reported 15 cases and defined some features in these cholangiocarcinomas [2–4]. Most KCCs are adenocarcinomas with poor differentiation degree, spreading along the duct and nerve sheath [5]. There are some risk factors, including primary sclerosing cholangitis (PSC), liver fluke infection (C. sinensis and Opisthorchis viverrini), and intrahepatic bile duct stones, but most KCCs are sporadic with no obvious predisposing factors [6]. The symptoms are usually fatigue, jaundice, and cachexia, indicating metastatic or advanced tumors. Most patients have biliary symptoms, including painless jaundice. About 10% of patients also simultaneously present with cholangitis [7].

The only curative treatment is a complete surgical resection with histologically negative margins. Current surgical strategies usually include choledochectomy, extended hepatectomy, and portal resection. Due to the local anatomy, the proximal and lateral safety margin R0 resection is a surgery that demands excellent technique [5]. Molina et al. reported that lymph node involvement and metastasis were important prognostic factors. The median survival of inoperable patients is 6 to 12 months, and the most common causes of death are liver failure and septic complications [8].

To investigate KCC was quite difficult in the past because of its rarity in the general population. The present study gives new insights into KCC by using population data in the Surveillance, Epidemiology, and End Results (SEER) database. The aim of our study was to analyze a large sample and to compare the data between patients with KCC and those with other kinds of cholangiocarcinomas (OCC) to clarify the epidemiologic characteristics, frequency, and survival rates patients with this rare malignant tumor.

Material and Methods

We used SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (1973–2014 varying) to conduct the analysis, which contained patient information from 18 cancer registries. Institutional review board (IRB) approval was not needed because no patient identifiers were used. To obtain the necessary data, International Classification of Diseases and Oncology, third edition (ICD-O-3), codes was used. We used histology codes (8162/3) to obtain the KCC data. We also used topography codes corresponding to the bile biliary tract (22.1, 24.0, 24.1, 24.8, and 24.9) to obtain OCC except for KCC and made a comparison. We excluded patients whose first tumor was not biliary duct-derived, and patients for whom the tumor was not histologically confirmed. We report 2000–2014 incidence data (per 100 000 people) adjusted to the standard 2000 population US Census. Cancer-specific survival (CSS) and overall survival (OS) were selected as the endpoints.

Statistical analysis

We used Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat) version 8.3.4 to conduct frequency analysis and extract data, as well as to determine the incidence annual percentage change based on 1-year end-points. Continuous data are shown as means and standard deviations and were compared using the t test. We used frequencies and percentages to display the categorical variables and compared them using the chi-square test or Fisher’s exact test. Kaplan-Meier method with log-rank test was used to conduct survival analysis. Univariate and multivariate Cox regression were conducted to identify the prognostic indicators for KCC. We conducted propensity score 1-to-1 matching to decrease the selection bias and mimic the randomized controlled trials. We divided patients into a KCC group and an OCC group, and baseline characteristics were entered into the logistic model using nearest-neighbor matching with a stringent caliper of 0.05 [9]. After we generated the matched datasets, we used them to compare the survival difference between KCC and OCC patients. We used SPSS, version 24.0 (SPSS Inc., Chicago, IL) to conduct the analysis, and 2-sided P<0.05 was considered statistically significant.

Results

Demographics

In total, 26 137 patients diagnosed with cholangiocarcinomas between 1973 and 2014 were extracted from the SEER database. Among them, 1341 cases were diagnosed with KCC and 24 796 cases were diagnosed with OCC (Table 1). The number of diagnoses has gradually increased in recent years for both Klatskin tumor and other cholangiocarcinomas (P<0.001). Males constituted 51.2% of KCC cases and 51.5% of OCC cases, and most patients in both groups were white. Most of the patients in both groups had undergone surgeries (73.4% for KCC and 67.3% for OCC). There was no significant difference in age distribution between the 2 groups of patients (P=0.095), but the difference in survival time was obvious (P<0.001).
Tumor characteristics and incidence trends

As shown in Table 2, there were significant differences between KCC and OCC groups in pathology grades (P<0.001), T stage (P=0.040), N stage (P<0.001), M stage (P<0.001), and SEER historic stage (P<0.001). There was no obvious difference in tumor size. Between 2000 and 2014, the overall incidence rate trend of KCC was decreasing and the trend for OCC was increasing (Figure 1). The annual percent change (APC) for KCC was –2.962 (P=0.001) and 3.688 for OCC (P<0.001).

Survival analysis

In the original groups, as shown in Figure 2A, 2B, the CSS and OS for the OCC group were significantly better than for the KCC group (P<0.001) and the 1-, 3-, and 5-year CSS rates were higher in OCC patients (Table 3). Then, we stratified patient survival using the 6th AJCC staging system. Figure 3 and Table 3 show that the 6th AJCC staging system performs well in classifying OCC patient survival, but did not perform well in KCC patients. Considering the significant differences of baseline characteristics between the KCC and OCC groups, we conducted 1-to-1 propensity score matching; 1046 patients were selected into a matched group and all baseline characteristics were well matched for further analysis (Table 4). We used the matched group to compare survival between the KCC and OCC groups. As shown in Figure 2C, 2D, the OCC group had better survival than the KCC group (P<0.001).

Finally, we used the original cohort to conduct univariate and multivariate Cox analysis. Gender, year of diagnosis, age, race, pathology grades, and T, N, and M stage were entered into analysis. As shown in Table 5, age, M stage, and pathology grades were brought into the final model. Older age, higher M stages, and higher pathology grades were associated with worse prognosis for KCC patients.
Discussion

Cholangiocarcinoma is a malignant tumor of epithelial cells, originating from different locations in the biliary tree, and shows markers of biliary cell differentiation. Cholangiocarcinoma is classified according to anatomical location, including intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, and distal cholangiocarcinoma. About 50% of cholangiocarcinomas are perihilar cholangiocarcinoma, 40% of cholangiocarcinomas are distal cholangiocarcinoma, and less than 10% of cholangiocarcinomas are intrahepatic cholangiocarcinoma [10]. The perihilar cholangiocarcinoma is also called Klatskin tumor. Due to its rarity, there has been little progress in many research aspects of Klatskin tumor. Therefore, we conducted the present study using the SEER database to resolve this problem.

Klatskin tumor is an advanced disease that usually occurs in patients over age 60 years, which is similar to our results

Table 2. Baseline tumor characteristics of the KCC and OCC patients.

| Tumor characteristics | Klatskin tumor (n=1341) | Other biliary tract malignancies (n=24796) | P value |
|-----------------------|-------------------------|------------------------------------------|--------|
| Pathological grade    |                         |                                          | <0.001|
| G1                    | 53 (4.0)                | 1538 (6.2)                               |        |
| G2                    | 227 (16.9)              | 511 (20.6)                               |        |
| G3                    | 223 (16.6)              | 4006 (16.2)                              |        |
| G4                    | 14 (1.0)                | 195 (0.8)                                |        |
| Gx                    | 824 (61.4)              | 13946 (56.2)                             |        |
| T stage               |                         |                                          | 0.040  |
| T0                    | 11 (0.8)                | 165 (0.7)                                |        |
| T1                    | 223 (16.6)              | 4230 (17.1)                              |        |
| T2                    | 104 (7.8)               | 2100 (8.5)                               |        |
| T3                    | 241 (18.0)              | 4149 (16.7)                              |        |
| T4                    | 177 (13.2)              | 2663 (10.7)                              |        |
| Tx                    | 585 (43.6)              | 11489 (46.3)                             |        |
| N stage               |                         |                                          | <0.001 |
| N0                    | 607 (45.3)              | 9921 (40.0)                              |        |
| N1                    | 277 (20.7)              | 4660 (18.8)                              |        |
| Nx                    | 457 (34.1)              | 10215 (41.2)                             |        |
| M stage               |                         |                                          | <0.001 |
| M0                    | 582 (43.4)              | 10810 (43.6)                             |        |
| M1                    | 368 (27.4)              | 5525 (22.3)                              |        |
| Mx                    | 391 (29.2)              | 8461 (34.1)                              |        |
| SEER historic stage   |                         |                                          | <0.001 |
| Localized             | 277 (20.7)              | 4440 (17.9)                              |        |
| Regional              | 401 (29.9)              | 8827 (35.6)                              |        |
| Distant               | 447 (33.3)              | 7129 (28.8)                              |        |
| Unstaged              | 216 (16.1)              | 4400 (17.7)                              |        |
| Size                  |                         |                                          | 0.225  |
| Median                | 4.29                    | 4.05                                     |        |
| Incidence             | 0.097                   | 2.526                                    |        |
| APC                   | ¬2.962 (P=0.001)        | 3.688 (P<0.001)                          |        |
median age: 71 years) [11]. Males and females were affected roughly equally in our study, but some studies have shown that males have a slightly higher incidence. Globally, the highest incidence of Klatskin tumor is in Southeast Asia, and the disease is rare in the United States [12].

The cause of Klatskin tumor is still unclear, but many risk factors have been identified. Infection seems to be closely related to the development of cholangiocarcinoma in Asian countries. Liver flukes, including _Clonorchis_ trematode and Thai liver fluke, can chronically infect the bile duct and cause the development of cholangiocarcinoma [13]. Other risk factors related to Klatskin tumor include alcoholism, hepatitis B and hepatitis...
C viruses, chronic pancreatitis, primary sclerosing cholangitis, choledochal cysts, and cholelithiasis [14].

Current unresectable disease criteria include major portal vein involvement or encapsulation, bilateral spread, bilateral hepatic artery involvement, and the presence of distant lymph nodes or organ metastases [15]. For patients whose tumors are operable, the current primary treatment is surgery. Several studies have shown that patients undergoing resection have significantly longer survival than in non-surgical patients, and the overall 5-year survival rate for highly selected patients is close to 53%.

The resection for Klatskin tumor involves achieving an R0 surgical margin and then trying to improve the survival time. A number of studies have shown that, compared with R1 resection, the overall survival rate of the R0 surgical margin increased significantly [16].

There are also some other surgical factors and tumor features related to longer survival time after surgery. Studies showed that the presence of lymph node metastasis was associated with poor survival [17,18]. Some case analyses showed that elevated preoperative serum bilirubin, histological tumor type, and tumor differentiation in patients are associated with lower survival rates, although these findings vary from study to study [19–21]. In our analysis, older age, higher M stages, and higher pathology grades were related to the worse prognosis.

To the best of our knowledge, this is the first study to investigate the clinical characteristics of KCC and identify the difference between KCC and OCC. Although we used the SEER database, which contains massive patient data, there are still several deficiencies. It cannot provide the risk factors related to the KCC, and the surgical margin status is not available. Also, the recurrence data and detailed therapeutic methods are not provided. Even with these limitations, our study is the first to use a large public database cohort of KCC to investigate the characteristics of patients and tumors.
Table 4. Baseline characteristics of the patients in the matched cohort.

|                          | Klatskin tumor | Other biliary tract Malignancies | P value |
|--------------------------|----------------|----------------------------------|---------|
| **Year of diagnosis**    |                |                                  | 0.990   |
| 2000–2004                | 77             | 77                               |         |
| 2005–2009                | 164            | 162                              |         |
| 2010–2014                | 282            | 284                              |         |
| **Gender**               |                |                                  | 0.620   |
| Male                     | 253            | 245                              |         |
| Female                   | 270            | 278                              |         |
| **Race**                 |                |                                  | 0.875   |
| White                    | 441            | 450                              |         |
| Black                    | 72             | 63                               |         |
| Other                    | 9              | 9                                |         |
| Unknown                  | 1              | 1                                |         |
| **Treatment**            |                |                                  | 0.194   |
| No surgery               | 302            | 285                              |         |
| Surgical treatment       | 219            | 238                              |         |
| Unknown                  | 2              | 0                                |         |
| **Pathological grade**   |                |                                  | 0.653   |
| G1                       | 18             | 13                               |         |
| G2                       | 132            | 141                              |         |
| G3                       | 134            | 146                              |         |
| G4                       | 6              | 8                                |         |
| Gx                       | 233            | 219                              |         |
| **TNM stage**            |                |                                  | 0.981   |
| I                        | 78             | 76                               |         |
| II                       | 110            | 106                              |         |
| III                      | 117            | 121                              |         |
| IV                       | 124            | 120                              |         |
| Unknown                  | 94             | 100                              |         |
| **T stage**              |                |                                  | 0.995   |
| T0                       | 8              | 8                                |         |
| T1                       | 98             | 94                               |         |
| T2                       | 76             | 74                               |         |
| T3                       | 149            | 153                              |         |
| T4                       | 86             | 82                               |         |
| Tx                       | 106            | 112                              |         |
Table 4 continued. Baseline characteristics of the patients in the matched cohort.

|                          | Klatskin tumor | Other biliary tract Malignancies | P value |
|--------------------------|----------------|---------------------------------|---------|
| N stage                  |                |                                 | 0.788   |
| N0                       | 254            | 243                             |         |
| N1                       | 177            | 183                             |         |
| Nx                       | 92             | 97                              |         |
| M stage                  |                |                                 | 833     |
| M0                       | 317            | 314                             |         |
| M1                       | 124            | 120                             |         |
| Mx                       | 82             | 89                              |         |
| SEER historic stage      |                |                                 | 0.996   |
| Localized                |                |                                 |         |
| Regional                 |                |                                 |         |
| Distant                  |                |                                 |         |
| Unstaged                 |                |                                 |         |

Table 5. Univariate and multivariate analysis of the effect of different factors on survival outcomes in KCC patients.

|                          | CSS |                  |                     |                  |                     |
|--------------------------|-----|------------------|---------------------|------------------|---------------------|
|                          | Univariate analysis | Multivariate analysis |
|                          | HR (95% CI)         | P value             | HR (95% CI)       | P value             |
| Gender                   |                 |                   |                    |                   |
| Female                   | Reference        |                     |                    |                   |
| Male                     | 1.01 (0.90–1.12)  | 0.900              |                    |                   |
| Year of diagnosis        |                 |                   |                    |                   |
| 2000–2004                | Reference        |                     |                    |                   |
| 2005–2009                | 1.00 (0.85–1.16)  | 0.947              |                    |                   |
| 2010–2014                |                 |                     |                    |                   |
| Age at diagnosis         |                 |                   |                    |                   |
| ≤70 years                | Reference        |                     |                    |                   |
| >70 years                | 1.33 (1.19–1.48)  | <0.001             | 1.33 (1.19–1.49)   | <0.001             |
| Race                     |                 |                   |                    |                   |
| White                    | Reference        |                     |                    |                   |
| Black                    | 1.09 (0.94–1.27)  | 0.233              |                    |                   |
| Others                   | 1.11 (0.71–1.73)  | 0.650              |                    |                   |
| Unknown                  | 0.54 (0.13–2.14)  | 0.377              |                    |                   |
| Grade                    |                 |                   |                    |                   |
| Well differentiated      | Reference        |                     |                    |                   |
| Moderately differentiated| 1.03 (0.77–1.40)  | 0.834              | 1.07 (0.79–1.45)   | 0.664              |
Table 5 continued. Univariate and multivariate analysis of the effect of different factors on survival outcomes in KCC patients.

| CSS | HR (95% CI) | P value | HR (95% CI) | P value |
|-----|-------------|---------|-------------|---------|
| Poorly differentiated | 1.47 (1.09–1.99) | 0.012 | 1.55 (1.14–2.10) | 0.005 |
| Undifferentiated | 1.39 (0.77–2.51) | 0.277 | 1.40 (0.78–2.54) | 0.259 |
| Unknown | 2.01 (1.51–2.66) | <0.001 | 1.90 (1.43–2.52) | <0.001 |

T stage

| Reference | HR (95% CI) | P value | Reference | HR (95% CI) | P value |
|-----------|-------------|---------|-----------|-------------|---------|
| T0 | Reference | | Reference | |
| T1 | 0.94 (0.51–1.72) | 0.835 | | |
| T2 | 0.72 (0.39–1.35) | 0.306 | | |
| T3 | 1.02 (0.56–1.86) | 0.956 | | |
| T4 | 1.43 (0.78–2.62) | 0.253 | | |
| Unknown | 1.19 (0.66–2.17) | 0.566 | | |

N stage

| Reference | HR (95% CI) | P value | Reference | HR (95% CI) | P value |
|-----------|-------------|---------|-----------|-------------|---------|
| N0 | Reference | | Reference | |
| N1 | 0.80 (0.70–0.93) | 0.002 | 0.88 (0.76–1.02) | 0.090 |
| Unknown | 1.03 (0.91–1.17) | 0.598 | 1.01 (0.80–1.28) | 0.949 |

M stage

| Reference | HR (95% CI) | P value | Reference | HR (95% CI) | P value |
|-----------|-------------|---------|-----------|-------------|---------|
| M0 | Reference | | Reference | |
| M1 | 1.12 (1.05–1.19) | <0.001 | 1.43 (1.24–1.64) | <0.001 |
| Unknown | 1.07 (0.93–1.22) | 0.332 | | |

Conclusions

KCC patients have worse survival compared to OCC patients. Older age, higher M stages, and higher pathology grades were associated with worse KCC patient survival.

References:

1. Seehofer D, Kamphues C, Neuhaus P: Resection of Klatskin tumors. Chirurg, 2012; 83(3): 221–28
2. Burcharth F: Klatskin tumours. Acta Chir Scand Suppl, 1988; 541: 63–69
3. Chamberlain RS, Blumgart LH: Hilar cholangiocarcinoma: A review and commentary. Ann Surg Oncol, 2000; 7(1): 55–66
4. Ryter E: The cheapest synonymous preparations – a proposal with unwanted consequences. Tidskr Nor Laegeforen, 1989; 109(32): 3359–60
5. Stavrou GA, Aloia TA, Crane CH et al: Hilar cholangiocarcinoma: Expert consensus statement. HPB (Oxford), 2015; 17(8): 691–99
6. Jarnagin W, Winston C: Hilar cholangiocarcinoma: Diagnosis and staging. HPB (Oxford), 2005; 7(4): 244–51
7. No conflict of interests

9. Sturmer T, Joshi M, Glynn RJ et al: A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods. J Clin Epidemiol, 2006; 59(5): 437–47
10. DeOliveira ML, Cunningham SC, Cameron JL et al: Cholangiocarcinoma: Thirty-one-year experience with 564 patients at a single institution. Ann Surg, 2007; 245(5): 755–62
11. Everhart JE, Ruhl CE: Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. Gastroenterology, 2009; 136(4): 1134–44
12. Khan SA, Toledano MB, Taylor-Robinson SD: Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. HPB (Oxford), 2008; 10(2): 77–82
13. Shin HR, Oh JK, Masuyer E et al: Epidemiology of cholangiocarcinoma: An update focusing on risk factors. Cancer Sci, 2010; 101(3): 579–85
14. Shab YH, El-Seraf HB, Nooka AK et al: Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: A hospital-based case-control study. Am J Gastroenterol, 2007; 102(5): 1016–21

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]
15. Parikh AA, Abdalla EK, Vauthey JN: Operative considerations in resection of hilar cholangiocarcinoma. HPB (Oxford), 2005; 7(4): 254–58
16. Matsuo K, Rocha FG, Ito K et al: The Blumgart preoperative staging system for hilar cholangiocarcinoma: Analysis of resectability and outcomes in 380 patients. J Am Coll Surg, 2012; 215(3): 343–55
17. de Jong MC, Marques H, Clary BM et al: The impact of portal vein resection on outcomes for hilar cholangiocarcinoma: A multi-institutional analysis of 305 cases. Cancer, 2012; 118(19): 4737–47
18. Song SC, Choi DW, Kow AW et al: Surgical outcomes of 230 resected hilar cholangiocarcinoma in a single centre. ANZ J Surg, 2013; 83(4): 268–74
19. Abdel Wahab M, Fathy O, Elghwalby N et al: Resectability and prognostic factors after resection of hilar cholangiocarcinoma. Hepatogastroenterology, 2006; 53(67): 5–10
20. Cheng Q, Luo X, Zhang B et al: Predictive factors for prognosis of hilar cholangiocarcinoma: Postresection radiotherapy improves survival. Eur J Surg Oncol, 2007; 33(2): 202–7
21. Su CH, Tsay SH, Wu CC et al: Factors influencing postoperative morbidity, mortality, and survival after resection for hilar cholangiocarcinoma. Ann Surg, 1996; 223(4): 384–94