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ORIGINAL RESEARCH

FGFR2-Rearrangement in Intrahepatic and Extrahepatic Cholangiocarcinoma and Prognostic Analysis

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Aim: To investigate the clinicopathological features and prognostic factors of intrahepatic and extrahepatic cholangiocarcinoma.

Methods: Clinicopathological and follow-up data of 328 cholangiocarcinoma patients treated at Shanxi Cancer Hospital from November 7, 2016, to August 11, 2021, were retrospectively reviewed. All samples were tested for Fibroblast growth factor receptor 2 (FGFR2) fusion by FISH. The expression of the proliferative marker Ki67 in patients with intrahepatic cholangiocarcinomas (iCCA) was evaluated by immunohistochemistry. All patients were followed up from the date of surgery to the time of death or August 31, 2023. Pathological specimens from patients with recurrence were collected and FGFR2 was tested again.

Results: The positivity rates for FGFR2 fusion in intrahepatic, perihilar, and distal cholangiocarcinomas were 15%, 2.73%, and 1.69%, respectively. The chi-square test showed that tumor diameter, perineural invasion, complications, and FGFR2 fusion were statistically significant. Immunohistochemistry showed that patients with low expression of Ki67 accounted for 30% of iCCA, low expression of Ki67 and FGFR2 fusion was statistically significant. Relapse specimens were collected from 13 patients, and FISH showed that the expression of FGFR2 was consistent with that of the primary lesion. Multivariate analysis showed that lymph node metastasis was an independent factor for the prognosis of cholangiocarcinoma ($P<0.05$).

Conclusion: CCA is an aggressive tumor with high mortality and low survival rates, especially for perihilar cholangiocarcinoma (pCCA). Therefore, it is necessary to understand the clinicopathological features and prognostic factors of iCCA, pCCA and distal cholangiocarcinoma (dCCA). In addition, lymph node status is likely to be an independent and important prognostic factor.

Keywords: cholangiocarcinoma, FGFR2, prognosis

Introduction

Cholangiocarcinoma (CCA) is a rare cancer; however, it is the second most prevalent type of primary malignancy of the liver after primary hepatocellular carcinoma. It is estimated that approximately 10–15% of primary hepatic epithelial malignancies and 3% of all gastrointestinal malignancies are CCA.[1–3] CCA is a diverse collection of malignant cancers that occur in various parts of the biliary tree. CCA is categorized into iCCA and extrahepatic cholangiocarcinomas (eCCA), according to their anatomical location, eCCA can be further divided into pCCA and dCCA. ICCA originates from the epithelium of intrahepatic bile ducts of the second order or higher. pCCA refers to cholangiocarcinoma involving the bile duct between the level of the cystic duct orifice and the second-order bifurcation of the left and right hepatic ducts, while dCCA begins in the choledochus below the confluence of the cystic duct. The three types of CCA differ in clinical characteristics, natural history, and prognosis, reflecting geographical variations and different risk factors. However, the pathological features of different types of CCA have not been accurately analyzed in the literature, especially in Shanxi, China. For example, studies suggest that iCCA and pCCA comprise 90% of all CCA, but this needs

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to be confirmed by observations in clinical practice.[4] ICCA is a malignant tumor arising from the intrahepatic bile duct epithelium that has an insidious onset and a high degree of malignancy. There are no obvious clinical symptoms in the early stages of iCCA, and many patients are diagnosed at an advanced stage, resulting in a dismal prognosis.[5]

In recent years, progress has been made in the diagnosis and treatment of CCA. Tumor staging methods are constantly being updated, and adjuvant chemotherapy, targeted therapy, and immunotherapy can be applied to patients with advanced or metastatic CCA. Fibroblast growth factor receptor 2 (FGFR2), a member of the fibroblast growth factor receptor family (FGFR1–FGFR4), can bind to fibroblast growth factor to initiate a series of downstream signals that ultimately play critical roles in mitosis and differentiation.[6] Recent studies have shown that gene amplification, abnormal activation, and single nucleotide polymorphisms (SNPs) in FGFR2 play important roles in the migration, invasion, and growth of cancer.[7–11] Therefore, FGFR2 is recognized as a novel therapeutic target for cancer.[12] Patients with metastatic or advanced CCA harboring FGFR2 fusion are clinically treated with pemigatinib as second-line treatment.

As a proliferative marker, Ki67 is broadly used in routinely pathological investigations. Ki67 is a classic prognostic and predictive indicator that is regularly used to assess biopsies from patients with cancer, especially breast, gastric, and colorectal cancer. The proportion of Ki67-positive tumor cells is often correlated with cancer progression. However, a relationship between the expression of Ki67 and FGFR2 fusion has not yet been reported.

This study retrospectively analyzed the clinicopathological data of 328 patients with iCCA, pCCA, or dCCA to explore the clinicopathological features and prognostic factors of iCCA, pCCA, or dCCA, investigate the correlation between FGFR2 and Ki67 levels in iCCA, and provide new insights into an in-depth understanding of CCA.

Materials and Methods

Patients and Clinicopathological Data

A total of 328 patients who underwent surgery for cholangiocarcinoma between November 7, 2016, and August 11, 2021, were retrospectively reviewed. The exclusion criteria included: (a). Patients under the age of 18; (b). Contamination of the sample paraffin blocks; (c). Participants requesting to withdraw after enrollment. All enrolled patients were divided into three groups based on their anatomical location: iCCA (n=40), pCCA (n=110), and dCCA (n=178). Clinicopathologic information was available for all patients.

Molecular Analysis

FGFR2 rearrangement for the 328 cases was performed using an FGFR2 dual-colored break-apart FISH probe (AmoyDx, Xiamen, China), following the manufacturer's instructions. All enrolled samples need to be prepared with H&E-stained sections to ensure that the number of cancer cells is sufficient. The cells to be counted must be tumor cells with clear and distinguishable red and green signals. Cells with indistinct nuclear contours or overlapping nuclei are not analyzed. Areas with uneven hybridization are not analyzed. If the signals are too weak in more than 25% of the nuclei or absent in more than 10% of the nuclei, retesting is required. There is still no unified interpretation standard for FGFR2. In many hospitals in China, the interpretation of FISH break-apart probes is currently based on the interpretation criteria for ALK-FISH. Interpretation criteria: Ratio value = number of broken cells / total number of cells counted × 100% (100 × under the oil mirror). If the ratio is ≥ 15% (15/100), it is considered positive, and if the ratio is<15% (15/100), it is considered negative. Pathological specimens were collected from patients with recurrences. KRAS, NRAS, BRAF, EGFR, ALK, ROS1, PIK3CA, HER2, RET, and MET mutations were detected using a polygenic test kit (AmoyDx, Xiamen, China) and analyzed using polymerase chain reaction (PCR) amplification in two patients who presented with other cancers (rectal cancer and lung cancer) during follow-up.

IHC in iCCA

Immunohistochemistry for Ki67 was performed according to the manufacturer's described protocol. Immunohistochemistry for Ki67 (mouse monoclonal antibody, clone M1B1) was performed using a kit from ZSGB-Bio (Beijing, China). The automated procedure was performed using the VENTANA® BenchMark ULTRA.

Morphological and immunohistochemical features, as well as FGFR2 rearrangement in the patients in this study were assessed by two pathologists who have been engaged in the pathology for more than ten years.

Follow-up

Follow-up data on disease progression were obtained from 328 patients through re-examination and telephone interviews. Overall survival (OS) was defined as the time interval between surgery and death. The follow-up period ended on August 31, 2023.

Statistical Analysis

SPSS 27.0 and GraphPad Prism 9.0 were used for statistical analysis. The chi-square test was used to evaluate the associations between different patient groups and clinicopathological features in the univariate analysis. Univariate analyses of OS were performed using the Kaplan-Meier method and Log rank test to identify the influencing factors. Multivariate analysis was performed to identify the independent prognostic factors. Statistical significance was set at $P < 0.05$.

Results

Patient Description

The study included 328 patients who were diagnosed with iCCA, pCCA, and dCCA respectively. The median age of the 328 patients was 64 years (range, 36–82 years). Among them, 199 were male and 129 were female.

Clinicopathological Features

There were 40 (12.2%) patients with iCCA, 110 (33.5%) patients with pCCA, and 178 (54.3%) patients with dCCA. Microscopic morphology showed that the glands were dysplastic, irregular, and angulated, the polarity was disordered, nucleoli were enlarged, and the ratio of nucleus to cytoplasm visibly increased, as shown in Figure 1.

Significant differences were observed between iCCA, pCCA, and dCCA in tumor diameter, perineural invasion, complications, and FGFR2 rearrangement ($P < 0.001$, $P < 0.001$, $P = 0.014$, and $P < 0.001$). patients with iCCA had larger tumor diameters than those with pCCA or dCCA ($P < 0.001$). Additionally, iCCA patients exhibited a lower proportion of perineural invasion than did pCCA or dCCA patients ($P < 0.01$). Moreover, patients with iCCA showed a lower incidence of complications than those with pCCA or dCCA. Furthermore, iCCA patients showed a higher frequency of FGFR2 rearrangement than pCCA or dCCA patients did. The clinicopathological features of all patients are summarized in Tables 1 and 2.

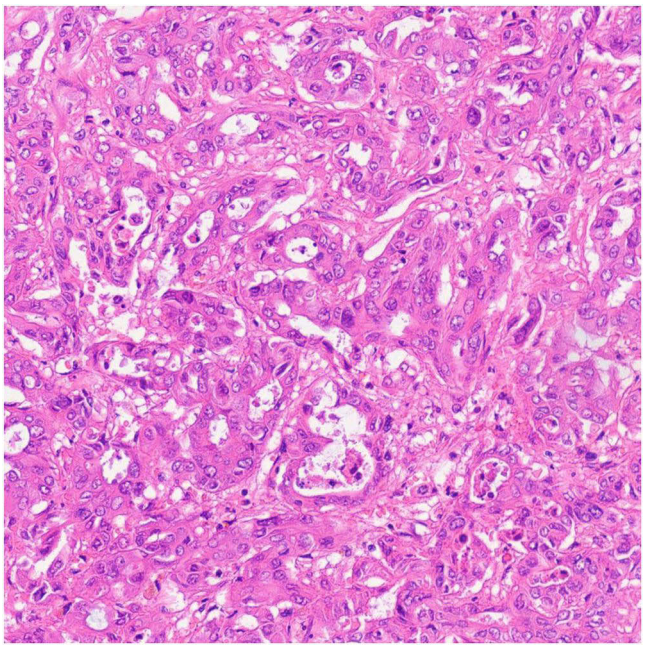

Figure 1 Morphologic feature of cholangiocarcinoma (HE, 20X).

Table 1 Comparison of Clinicopathological Features Between iCCA, pCCA and dCCA

Pathological Parameters	Tumor Location			χ^2	*P*-value
	iCCA (n=40)	pCCA (n=110)	dCCA (n=178)		
Sex				0.387	0.824
Male	23(57.5%)	69(62.7%)	107(60.1%)		
Female	17(42.5%)	41(37.3%)	71(39.9%)		
Age in years				2.466	0.291
≤60	19(47.5%)	41(37.3%)	61(34.3%)		
>60	21(52.5%)	69(62.7%)	117(65.7%)		
Tumor diameter				128.597	<0.001***
≤4 (cm)	15(37.5%)	105(95.5%)	173(97.2%)		
>4 (cm)	25(62.5%)	5(4.5%)	5(2.8%)		
Lymph node metastasis				4.857	0.088
No	33(82.5%)	75(68.2%)	139(78.1%)		
Yes	7(17.5%)	35(31.8%)	39(21.9%)		
Vascular invasion				5.966	0.051
No	37(92.5%)	91(82.7%)	163(91.6%)		
Yes	3(7.5%)	19(17.3%)	15(8.4%)		
Perineural invasion				48.592	<0.001***
No	30(75.0%)	20(18.2%)	45(25.3%)		
Yes	10(25.0%)	90(81.8%)	133(74.7%)		
Complication				8.490	0.014*
No	16(40.0%)	19(17.3%)	47(26.4%)		
Yes	24(60.0%)	91(82.7%)	131(73.6%)		
FGFR2				16.834	<0.001***
Negative	34(85.0%)	107(97.3%)	175(98.3%)		
Positive	6(15.0%)	3(2.7%)	3(1.7%)		

Notes: *P<0.05; ***P<0.001.

Table 2 Comparison of Clinicopathological Features Between FGFR2-Positive and FGFR2-Negative

Clinicopathological Characteristics	FGFR2		*P*-value
	Negative (n=316)	Positive (n=12)	
Sex			0.378
Male	190(95.5%)	9(4.5%)	
Female	126(97.7%)	3(2.3%)	
Age in years			0.370
≤60	115(95.0%)	6(5.0%)	
>60	201(97.1%	6(2.9%)	
Tumor diameter			<0.001***
≤4(cm)	287(98.0%)	6(2.0%)	
>4(cm)	29(82.9%)	6(17.1%)	
Lymph node metastasis			0.737
No	237(96.0%)	10(4.0%)	
Yes	79(97.5%)	2(2.5%)	
Vascular invasion			
No	279(95.9%)	12(4.1%)	0.374
Yes	37(100.0%)	0(0.0%)	
Penineural invasion			0.113
No	89(93.7%)	6(6.3%)	
Yes	227(97.4%)	6(2.6%)	

(*Continued*)

Table 2 (Continued).

Clinicopathological Characteristics	FGFR2		*P*-value
	Negative (n=316)	Positive (n=12)	
Complication			
No	77(93.9%)	5(6.1%)	0.183
Yes	239(97.2%)	7(2.8%)	
Tumor location			
iCCA	34(85.0%)	6(15.0%)	<0.001***
pCCA	107(97.3%)	3(2.7%)	
dCCA	175(98.3%)	3(1.7%)	

Note: ***$P<0.001$.

Molecular Features

According to the FISH interpretation criteria in this study, 6 of the 40 cases of iCCA (15.0%), 3 of the 110 cases of pCCA(2.7%), and 3 of the 178 cases of dCCA (1.7%) were positive (Figure 2 and Table 2).

Only 11 pathological samples from patients with recurrence were obtained and two of these patients had concurrent other cancers (rectal cancer and lung cancer, respectively). Specimens were collected from 13 patients, and the FISH results showed that the expression of FGFR2 was consistent with that of the primary lesion. KRAS, NRAS, and BRAF were wild-type in patients with concurrent rectal cancer. EGFR, ALK, ROS1, KRAS, NRAS, BRAF, PIK3CA, HER2, RET, and MET were detected using PCR in the concurrent lung cancer and showing KRAS mutations.

IHC of iCCA

Ki67 protein is localized to the nucleus. All patients with iCCA were Ki67 positive. The proportion of positive cells for Ki67 ranging from 10% to 80%. Currently, there is no unified threshold for defining low or high Ki67 expression. We selected 40%, which is half of the highest expression of Ki67 (80%) observed in this study, as the threshold. Less than 40% was considered low expression, while 40% or higher was considered high expression.

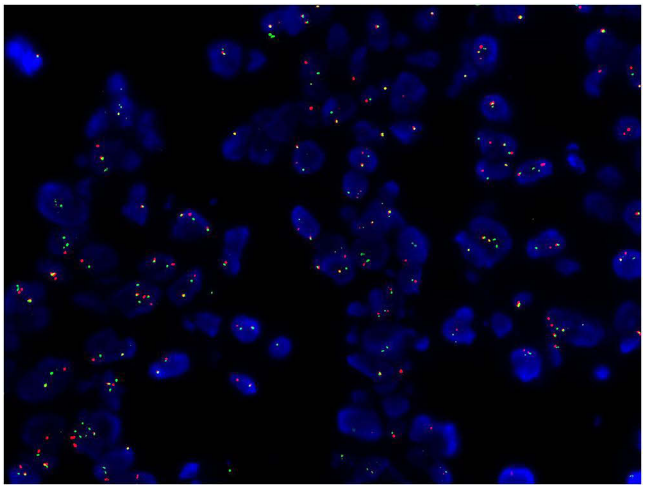

Figure 2 FISH showed FGFR2 rearrangement positive.

Table 3 The Relationship Between FGFR2 Fusion and Ki67 Expression in iCCA

FGFR2	Ki67		χ2	*P*-value
	High Expression (n=28)	Low Expression (n=12)		
Negative(n=34)	27(96.4%)	7(58.3%)	6.807	0.009**
Positive(n=6)	1(3.6%)	5(41.7%)		

Note: **$P<0.01$.

Patients with low expression of Ki67 accounted for 30.0% (12/40) in iCCA. Low expression of Ki67 was statistically significant associated with FGFR2 fusion. The relationship between FGFR2 fusion and Ki67 expression is shown in Table 3.

Follow-up

The overall survival rate of the 328 patients was 66.8%, with a median survival of 22 months. The median survival times of patients with iCCA, pCCA, and dCCA were 18, 13, and 29 months, respectively. The median follow-up duration for the 328 patients was 44 months (range: 22–89 months). During the follow-up period, 24 out of 40 patients (60.0%) with iCCA died, 92 out of 110 patients (83.6%) with pCCA died, and 103 out of 178 patients (57.9%) with dCCA died.

Kaplan–Meier analysis and univariate and multivariate Cox analyses of prognostic factors in patients with iCCA, pCCA, and dCCA.

Kaplan-Meier survival curve analysis showed that iCCA and dCCA had better overall survival than pCCA ($P < 0.05$, Figure 3). CCAs with FGFR2 rearrangement positivity exhibited better overall survival ($P < 0.05$, Figure 4). The effects of clinicopathological features on OS were analyzed using univariate and multivariate Cox regression analyses. Cox regression analysis demonstrated that lymph node metastasis, vascular invasion, and perineural invasion increased the possibility of shorter OS (HR = 1.840, 95% CI:1.380 to 2.452, P<0.001; HR = 1.857, 95% CI: 1.274 to 2.708, P = 0.001; HR = 1.486, 95% CI:1.087 to 2.030, P = 0.013). FGFR2 rearrangement was associated with a decreased risk of shorter

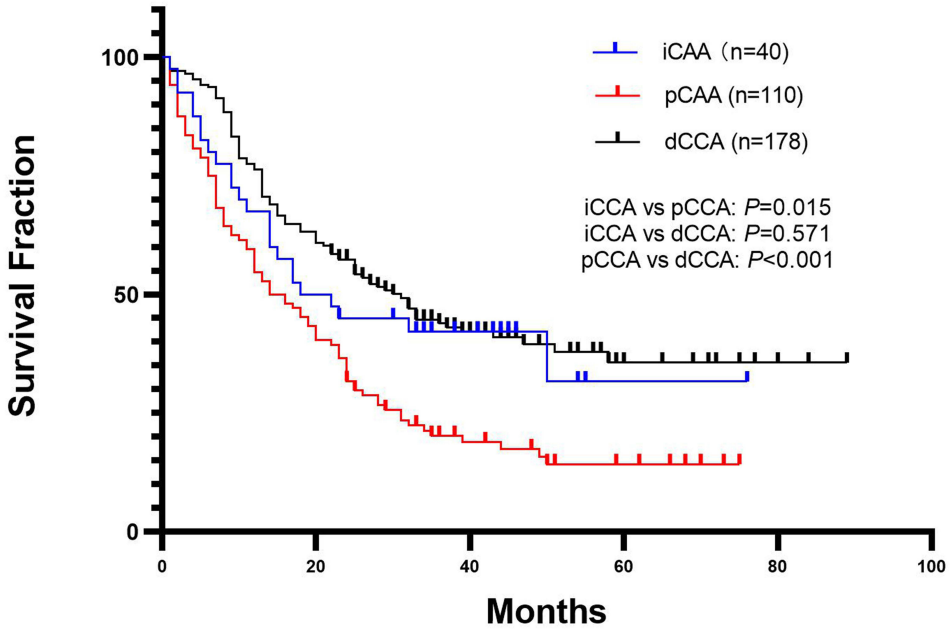

Figure 3 Kaplan-Meier survival curve analysis showed that iCCA and dCCA had better overall survival than pCCA.

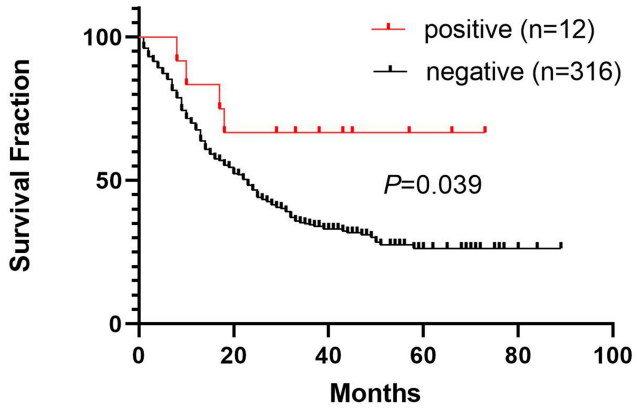

Figure 4 CCAs with FGFR2 rearrangement positivity exhibited better overall survival.

OS (HR = 0.359, 95% CI:0.134 to 0.967; P = 0.043). Furthermore, in the multivariate Cox regression analysis, the lymph node metastasis remained a factor that shortened OS (HR = 1.619, 95% CI:1.201 to 2.184; P = 0.002). In the iCCA group, lymph node metastasis and vascular invasion increased the risk of progression in univariate analysis (HR = 3.419, 95% CI:1.298 to 9.004; P = 0.013; HR = 3.525, 95% CI:0.994 to 12.506, P = 0.050). Multivariate Cox regression analysis revealed that lymph node metastasis was a significant predictor of disease progression (HR = 3.284, 95% CI:1.231 to 8.764, P = 0.018). For pCCA patients, univariate analysis showed that tumor diameter and lymph node metastasis increased the risk of disease progression (HR = 2.896, 95% CI]: 1.157 to 7.247, P = 0.023; HR = 1.747, 95% CI: 1.134 to 2.691, P = 0.011). In the multivariate Cox regression analysis, tumor diameter remained a significant factor associated with shorter OS (HR = 1.114, 95% CI:1.037 to 6.543; P = 0.042). In the dCCA group, three factors-lymph node metastasis, vascular invasion, and perineural invasion-increased the risk of disease progression in univariate analysis (HR = 1.585, 95% CI: 1.031 to 2.438, P = 0.036; HR = 1.929, 95% CI: 1.054 to 3.530, P = 0.011; HR = 1.768, 95% CI:1.073 to 2.914, P = 0.025). However, these differences were not significant in the multivariate Cox regression analysis. The results are summarized in Table 4.

Table 4 Univariate and Multivariate Cox Regression Analysis of Cholangiocarcinoma

Pathological Parameters	CCA HR (95% CI)	*P*-value	iCCA HR (95% CI)	*P*-value	pCCA HR (95% CI)	*P*-value	dCCA HR (95% CI)	*P*-value
Univariate analysis								
Sex	1.189(0.909 to 1.555)	0.206	1.110(0.493 to 2.497)	0.801	1.050(0.690 to 1.598)	0.820	1.337(0.906 to 1.972)	0.144
Age	1.264(0.956 to 1.671)	0.100	1.003(0.449 to 2.239)	0.995	1.385(0.898 to 2.136)	0.141	1.271(0.840 to 1.923)	0.256
Tumor diameter	0.923(0.589 to 1.448)	0.728	0.834(0.370 to 1.883)	0.663	2.896(1.157 to 7.247)	0.023*	0.660(0.162 to 2.679)	0.561
Lymph node metastasis	1.840(1.380 to 2.452)	<0.001***	3.419(1.298 to 9.004)	0.013*	1.747(1.134 to 2.691)	0.011*	1.585(1.031 to 2.438)	0.036*
Vascular invasion	1.857(1.274 to 2.708)	0.001***	3.525(0.994 to 12.506)	0.050*	1.279(0.753 to 2.172)	0.363	1.929(1.054 to 3.530)	0.033*
Perineural invasion	1.486(1.087 to 2.030)	0.013*	1.311(0.541 to 3.174)	0.549	1.114(0.648 to 1.913)	0.697	1.768(1.073 to 2.914)	0.025*
Complication	0.963(0.710 to 1.309)	0.816	0.871(0.386 to 1.965)	0.739	0.670(0.394 to 1.140)	0.140	0.977(0.632 to 1.510)	0.917
FGFR2	0.359(0.134 to 0.967)	0.043*	0.680(0.202 to 2.293)	0.534	0.217(0.030 to 1.567)	0.130	0.048(0.000 to 13.320)	0.290
Multivariable								
Tumor diameter	-	-	-	-	1.114(1.037 to 6.543)	0.042*	-	-
Lymph node metastasis	1.619(1.201 to 2.184)	0.002**	3.284(1.231 to 8.764)	0.018*	1.217(1.098 to 2.617)	0.130	1.353(0.859 to 2.131)	0.193
Vascular invasion	1.465(0.989 to 2.170)	0.057	3.225(0.895 to 11.629)	0.074	-	-	1.576(0.837 to 2.970)	0.159
Perineural invasion	1.300(0.945 to 1.788)	0.107	-	-	-	-	1.627(0.980 to 2.703)	0.060
FGFR2	0.429(0.159 to 1.157)	0.095	-	-	-	-	-	-

Notes: *$P<0.05$; **$P<0.01$; ***$P<0.001$.

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Discussion

CCA has a high degree of malignancy and a poor prognosis. The clinical presentation, natural history, molecular features, and therapeutic strategies of iCCA, pCCA, and dCCA vary. It is reported that iCCA and pCCA account for more than 90% of all CCAs worldwide.[4] However, the proportion of iCCA and pCCA in our study was only 45.7%, which may be influenced by regional disparities. Patients with CCA are mostly elderly, with slightly more men than women, regardless of whether liver flukes are endemic in the area. In this study, the three groups (iCCA, pCCA, and dCCA) were observed more frequently in men and older patients. This finding is consistent with previous studies. Lymph node metastasis and vascular invasion did not show statistically significant differences, but the trends were the same; both were in a minority proportion. In this study, tumor diameter, nerve invasion, and FGFR2 fusion were considered practical clinicopathological characteristics for the evaluation of CCA. Moreover, CCAs with FGFR2 rearrangement positivity tended to exhibit more favorable prognostic behavior, consistent with a previous report.[13]

Although the pathogenesis of certain CCAs has long been debated, some cases have been associated with prior biliary or hepatocellular disease. In the present study, complications were a clinicopathological feature with statistical significance, with cholecystitis accounting for the highest proportion of complications. Therefore, patients with cholecystitis should be treated regularly to improve the early detection, diagnosis, and treatment of CCA and to further improve the overall survival of CCA.

For more than a decade, chemotherapy has been the primary treatment for postoperative metastatic CCA. In April 2020, the FDA approved an oral selective FGFR inhibitor, pemigatinib, for the treatment of patients with intractable FGFR2 fusion or rearrangement-positive CCA. Study showed that for patients with locally advanced or metastatic CCA harboring FGFR2 fusion or rearrangements, the overall response rate (ORR) with pemigatinib as a second-line treatment was 35.5%.[14] The most common adverse reaction to pemigatinib is hyperphosphatemia, which can be alleviated by controlling the intake of phosphates, using phosphate binders, or administering diuretics.[14] FGFR-driven cholangiocarcinoma is an important subtype of CCA. In recent years, with advancements in the therapeutic targeting of FGFR2 rearrangements in iCCA, detecting FGFR2 rearrangements in CCA has become necessary. Although FISH offers lower sensitivity and cannot provide specific fusion partners compared with NGS, it can visually observe cell morphology and directly detect the FGFR2 gene break status at the DNA level. Therefore, in this study, a dual-color break-apart FISH probe was used to detect FGFR2 rearrangements throughout the cohort. The incidence of FGFR2 fusion or rearrangement is 13–14% in patients with iCCA and in ~1% in patients with eCCA.[15–18] In this study, FGFR2 rearrangement occurred in 15% of patients with iCCA, slightly higher than previously reported. Similarly, the incidence of FGFR2 rearrangement in eCCA was 2.08% (2.73% for pCCA and 1.69% for dCCA), and also slightly higher than previously reported. According to the follow-up data, none of the patients with FGFR2 rearrangement in this study was able to take pemigatinib, possibly due to financial constraints.

The Ki67 protein has been widely used as a proliferation marker for human tumor cells for decades. Recently, researchers have found that high expression of Ki67 is correlated with vascular infiltration in iCCA.[19] In this study, the chi-squared test showed that FGFR2 fusion and low Ki67 expression in iCCA were statistically significant. Therefore, we speculated that FGFR2 fusion, as a favorable factor, may be related to low expression of Ki67, and that there may be a regulatory relationship between them. However, the specific regulatory mechanisms need to be explored further.

For the three types of CCA, the median survival time for patients who did not undergo surgery was reported to be 5–12 months.[20] In the present study, the median survival time for patients with CCA was 22 months. Thus, surgery can effectively improve the survival of patients with CCA. According to the multivariate analysis in this study, lymph node metastasis was an independent risk factor for CCA. Our study confirmed that patients with pCCA had a poorer prognosis than those with iCCA or dCCA (mortality rate: 83.64% versus 60% or 57.87%). Patients with dCCA had the highest median survival, compared to those with iCCA and pCCA. DeOliveira[21] reported that the median survival time for pCCA was identical (13 vs 13 months) to that in our study, whereas the median survival time for iCCA was greater (28 vs 18 months) and that for dCCA was lower (18 vs 29 months) than that in our cohort. We speculated that these discrepancies might reflect regional divergences among these patients.

As with other retrospective analyses, the present study has several limitations. In particular, pathological specimens were not obtained for some relapsed patients, and thus, the molecular expression in these patients could not be fully detected. Additionally, there is no unified strategy for treating recurrence. Other factors, such as family history, regular review, and patient preferences, also influenced patient prognosis. Although this study provides more accurate practice-based clinicopathological features and prognostic data for each of the three different types of cholangiocarcinoma, a prospective, large cohort study of CCA will be required in the future.

Conclusion

In conclusion, CCA, especially pCCA, is an aggressive tumor characterized by high mortality and a low survival rate. Therefore, understanding the clinicopathological features and prognostic factors of iCCA, pCCA, and dCCA is essential. Additionally, lymph node status is likely to be an independent and important prognostic factor.

Abbreviations

CCA, Cholangiocarcinoma; iCCA, intrahepatic Cholangiocarcinoma; eCCA, extrahepatic Cholangiocarcinoma; pCCA, perihilar Cholangiocarcinoma; dCCA, distal Cholangiocarcinoma; FGFR2, Fibroblast growth factor receptor 2; ORR, overall response rate.

Data Sharing Statement

Raw data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval and Consent to Participate

The use of human tissues was approved by the Ethics Committee of Shanxi Provincial Cancer Hospital (No. QX202003) and patient consent was obtained.

Ethics

All participants provided informed consent before their inclusion in the study. The study protocols were conducted in accordance with the principles of the Declaration of Helsinki and approved by the Scientific and Medical Ethical Committee of the Shanxi Provincial Cancer Hospital.

Patient Consent for Publication

The publication of the clinical datasets in this study did not compromise the anonymity, confidentiality, or breach of local data protection laws.

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Disclosure

The authors declare no conflicts of interest regarding the publication of this article.

References

1. Banales JM, Cardinale V, Carpino G, et al. Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). *Nat Rev Gastroenterol Hepatol*. 2016;13(5):261–280. doi:10.1038/nrgastro.2016.51
2. Fitzmaurice C, Dicker D, Pain A, Global Burden of Disease Cancer Collaboration. The global burden of cancer 2013. *JAMA Oncol*. 2015;1(4):505–527. doi:10.1001/jamaoncol.2015.0735
3. Banales JM, Marin JG, Lamarca A, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol*. 2020;17:557–588.
4. Rizvi S, Khan SA, Hallemeier CL, et al. Cholangiocarcinoma - evolving concepts and therapeutic strategies. *Nat Rev Clin Oncol*. 2018;15(2):95–111. doi:10.1038/nrclinonc.2017.157

5. Pavicevic S, Reichelt S, Uluk D, et al. Prognostic and predictive molecular markers in cholangiocarcinoma. *Cancers*. 2022;14(4):1026. doi:10.3390/cancers14041026
6. Cho SM, Esmail A, Raza A, et al. Timeline of FDA-approved targeted therapy for cholangiocarcinoma. *Cancers*. 2022;14(11):2641. doi:10.3390/cancers14112641
7. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature*. 2007;447(7148):1087–1093. doi:10.1038/nature05887
8. Hunter DJ, Kraft P, Jacobs KB, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nature Genet*. 2007;39(7):870–874. doi:10.1038/ng2075
9. McGrath M, Lee IM, Buring J, et al. Novel breast cancer risk alleles and endometrial cancer risk. International. *J Cancer*. 2008;123(12):2961–2964.
10. Byron SA, Gartside MG, Wellens CL, et al. Inhibition of activated fibroblast growth factor receptor 2 in endometrial cancer cells induces cell death despite PTEN abrogation. *Cancer Res*. 2008;68(17):6902–6907. doi:10.1158/0008-5472.CAN-08-0770
11. Byron SA, Pollock PM. FGFR2 as a molecular target in endometrial cancer. *Future Oncol*. 2009;5(1):27–32. doi:10.2217/14796694.5.1.27
12. Katoh Y, Katoh M. FGFR2-related pathogenesis and FGFR2-targeted therapeutics (review) international. *J Mol Med*. 2009;23(3):307–311.
13. Zou Y, Zhu K, Pang Y, et al. Molecular detection of FGFR2 rearrangements in resected intrahepatic cholangiocarcinomas: FISH could be an ideal method in patients with histological small duct subtype. *J Clin Transl Hepatol*. 2023;11(6):1355–1367. doi:10.14218/JCTH.2022.00060S
14. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020;21(5):671–684. doi:10.1016/S1470-2045(20)30109-1
15. Arai Y, Totoki Y, Hosoda F, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. *Hepatology*. 2014;59(4):1427–1434. doi:10.1002/hep.26890
16. Lowery MA, Ptashkin R, Jordan E, et al. Comprehensive molecular profiling of intrahepatic and extrahepatic cholangiocarcinomas: potential targets for intervention. *Clin Cancer Res*. 2018;24(17):4154–4161. doi:10.1158/1078-0432.CCR-18-0078
17. Silverman IM, Hollebecque A, Friboulet L, et al. Clinicogenomic analysis of FGFR2-rearranged cholangiocarcinoma identifies correlates of response and mechanisms of resistance to pemigatinib. *Cancer Discovery*. 2021;11(2):326–339. doi:10.1158/2159-8290.CD-20-0766
18. Berchuck JE, Facchinetti F, DiToro DF, et al. The clinical landscape of cell-free DNA alterations in 1671 patients with advanced biliary tract cancer. *Ann Oncol*. 2022;33(12):1269–1283. doi:10.1016/j.annonc.2022.09.150
19. Qiang Z, Zhang W, Jin S, et al. Carcinoembryonic antigen, α-fetoprotein, and Ki67 as biomarkers and prognostic factors in intrahepatic cholangiocarcinoma: a retrospective cohort study. *Ann Hepatol*. 2021;20:100242. doi:10.1016/j.aohep.2020.07.010
20. Waseem D, Tushar P. Intrahepatic, perihilar and distal cholangiocarcinoma: management and outcomes. *Ann Hepatol*. 2017;16(1):133–139. doi:10.5604/16652681.1226927
21. 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):755–762. doi:10.1097/01.sla.0000251366.62632.d3