Prognostic Factors of Cholangiocarcinoma After Surgical Resection: A Retrospective Study of 293 Patients

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Background: Cholangiocarcinoma is one of the most common malignancies in China. Surgical resection is the only treatment option; however, diagnosis at advanced stage precludes surgery. Comprehensive knowledge of prognostic markers is missing. Hence, the aim of this study was to determine clinicopathological indexes that would be indicative of prognosis in post-operative cases of cholangiocarcinoma.

Material/Methods: A retrospective analysis of 293 cases of cholangiocarcinoma patients attending the 301 Military Hospital in Beijing, China between January 2004 and December 2010 were included in the study. The patients had follow-up history until August 2012. Cox proportional hazards model analysis was performed to identify indexes of prognosis. All indicators were analyzed by univariate and multivariate analysis.

Results: The median follow-up time was 55.90 months, with recurrence and metastasis in 162 cases (55.3%) and death in 223 cases (76.1%). The 1-year, 3-year, and 5-year survival rates were 71.7%, 38.2%, and 10.6%, respectively. The independent risk factors of overall survival were degree of tumor differentiation, TNM stage, surgical margin, intraoperative blood transfusion, tumor location, alkaline phosphatase levels in blood, and relapse.

Conclusions: Good prognosis in cholangiocarcinoma patients is indicated by highly differentiated tumor, early stages of TNM staging, no resection margin invaded, no intraoperative blood transfusion, intrahepatic tumor, normal alkaline phosphatase levels, and no relapse.

MeSH Keywords: Ambulatory Surgical Procedures • Cholangiocarcinoma • Prognosis

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Background

Cholangiocarcinoma, a rare form neoplasm originating from the intra- or extra-hepatic bile duct epithelium, accounts for about 3% of gastroenteric tumors and is the second most common primary hepatic neoplasia [1,2]; however, its incidence rate is increasing [3]. Cholangiocarcinoma is also one of the most common cancers in China [4]. Surgical resection is the only curative approach [3]; however, due to delayed diagnosis, resection rates are low.

Although some patients undergo surgical therapy, the recurrence rate in those patients is very high [5,6]. The poor prognosis is dependent on a multitude of factors, including tumor differentiation, tumor staging, lymph node metastasis, nerve invasion, intravascular cancer emboli, the depth and distribution of infiltration, tumor size, successful tumor resection, and location of tumor. It has been shown that perioperative blood transfusion is a strong predictor of poor survival after radical hepatectomy for hilar cholangiocarcinoma [7]. Another study showed that a positive resection margin is associated with poor overall survival in peripheral cholangiocarcinoma patients undergoing hepatectomy [8]. In a population-based study, poor performance status, primary tumor location, and sites of advanced disease were found to be relevant to prognosis [9]. Furthermore, patients with unresectable cholangiocarcinoma have limited treatment options with only modest survival advantages [10,11].

All of the aforementioned indices can thus be important indicators for chemotherapeutic decision-making post-surgery. Hence, investigating biological characteristics of cholangiocarcinoma and the associated factors that would inform successful therapeutic regimen is of paramount importance.

Material and Methods

Patients

The study was approved by the Institutional Review Board of the General Hospital of the Chinese PLA, Beijing, China. Between 2004 and 2010, a total of 397 consecutive patients diagnosed with cholangiocarcinoma underwent surgery in the General Hospital of the Chinese PLA. Of the 397 patients, a total of 293 had follow-up results available and were enrolled in the current study.

Statistical analyses

Unless designated otherwise, results are presented as mean ± standard error of mean (SEM). SPSS19.0 software was used for data analysis. Log-rank test was used for single-factor analysis and Cox regression analysis was used for multivariable survival analysis. $P < 0.05$ was considered statistically significant.

Results

The 293 enrolled patients included 202 men and 91 women (average 64 years old) with age of onset of cholangiocarcinoma ranging between 40 and 85 years. The clinicopathological characteristics of the enrolled patients are summarized in Table 1. The peak of the onset age was from 50 to 60 years old. Men were comparatively more predisposed to cholangiocarcinoma than females (sex ratio of male to female ranged from 1.5 to 3.0). There were 74 and 219 cases of intra- and extrahepatic tumors, respectively. Classified according to TMN stage, there were 150 in stage 1, 88 in stage 2, 41 in stage 3, and 14 in stage 4. There were 19 cases of well-differentiated, 159 cases of moderately differentiated and 115 cases of poorly differentiated tumors.

Patients were followed up until August 31, 2012, with an interval of 6 months. The 1-year, 3-year, and 5-year survival rates were 71.7%, 38.2%, and 10.9%, respectively. We next determined the relationship of all observed indexes and postoperative prognosis using log-rank single-factor analysis (Table 2). Thirteen indexes were significantly correlated ($P < 0.05$): depth of invasion, lymphatic metastasis, tumor differentiation, TNM staging, resection margin invasion, blood transfusion during surgery, total bilirubin (TBIL), conjugated or direct bilirubin (DBIL), alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT), and relapse status (Table 2).

The risk of death with poor differentiation was 1.356 times that of medium differentiation, while the latter is 1.356 times that of high differentiation. The risk of death increased by 1.379 times as TNM staging increases a level. The risk of death on patients with positive resection margins was 1.404 times that of patients with negative resection margins. Intrahepatic tumors caused a risk of death 0.594 times that of extrahepatic ones. Patients who received blood transfusion during the operation had a risk of death 1.493 times that of those who did not receive a transfusion. Relapsed patients had a risk of death 1.962 times that of those who did not exhibit a relapse. Patients who had high ALP in blood had a risk of death 1.954 times that of those who had normal ALP.

All 13 indexes were used in Cox model regression analysis. With α=0.05, we were able to import independent factors related to cholangiocarcinoma postoperative prognosis because all variables passed the Cox multivariable analysis (Table 3).

Table 1. Clinicopathological characteristics of the enrolled patients.

Program	Group	Patients	Percentage
Gender	Male	202	68.9
	Female	91	31.1
Age	<64	136	46.4
	≥64	157	53.6
Tumor location	Intrahepatic	74	25.3
	Extrahepatic	219	74.7
Tumor Size	<3 cm	161	54.9
	≥3 cm	132	45.1
Depth of Invasion	Total infiltration	167	57.0
	Local infiltration	126	43.0
Lymphatic metastasis	Yes	51	17.4
	No	242	82.6
Differentiation	High	19	6.5
	Medium	159	54.3
	Low	115	39.2
Nerve Invasion	Yes	93	31.7
	No	200	68.3
Vascular cancer embolus	Yes	17	5.8
	No	276	94.2
TNM Staging	I	150	51.2
	II	88	30.0
	III	41	14.0
	IV	14	4.8
Resection Margin	Positive	74	25.3
	Negative	219	74.7
Intraoperative blood loss	<500 ml	186	63.5
	≥500 ml	107	36.5
Blood transfusion	Yes	89	30.4
	No	204	69.6
Relapse	Yes	158	53.9
	No	135	46.1
Chemotherapy	Yes	4	1.4
	No	289	98.6
TBIL	Normal	83	28.3
	High	210	71.7

Table 1 continued. Clinicopathological characteristics of the enrolled patients.

Program	Group	Patients	Percentage
DBIL	Normal	85	29.0
	High	208	71.0
ALP	Normal	82	28.0
	High	211	72.0
ALT	Normal	82	28.0
	High	211	72.0
Aspartate Transaminase	Normal	87	29.7
	High	206	70.3
GGT	Normal	73	24.9
	High	220	75.1
Surgical method	Not combined with portal vein resection and repair	284	96.9
	Combined with portal vein resection and repair	9	3.1
History of hepatitis	Yes	18	6.1
	No	275	93.9
Stone	Yes	31	10.6
	No	262	89.4
Cholecystectomy before the illness	Yes	36	12.3
	No	257	87.7

Table 2. Single factor analysis for cholangiocarcinoma clinical data and treatment characteristics.

Factor	Group	Patients	Median survival time (months)	95%CI	P-value
Gender	Male	202	21.20	15.629~26.771	0.981
	Female	91	20.67	11.662~29.678	
Age	<64	136	21.20	15.649~26.751	0.585
	≥64	157	20.97	14.108~27.832	
Tumor location	Intrahepatic	74	21.20	11.863~30.537	0.725
	Extrahepatic	219	20.97	15.377~26.563	
Tumor size	<3 cm	161	25.00	17.225~32.775	0.328
	≥3 cm	132	17.43	12.146~22.714	
Depth of invasion	Total infiltration	167	27.47	17.339~37.601	0.012
	Local infiltration	126	15.83	14.078~17.582	
Lymphatic metastasis	Yes	51	26.23	20.032~32.428	0.000
	No	242	14.27	11.711~16.829	
Differentiation	High	19	49.77	28.916~70.624	0.001
	Medium	159	27.47	19.620~35.320	
	Low	115	15.23	13.128~17.332	

Table 2 continued. Single factor analysis for cholangiocarcinoma clinical data and treatment characteristics.

Factor	Group	Patients	Median survival time (months)	95%CI	P-value
Nerve Invasion	Yes	93	17.47	12.229~22.711	0.157
	No	200	24.03	16.733~31.327	
Vascular cancer embolus	Yes	17	14.67	6.737~22.603	0.227
	No	276	21.50	16.151~26.849	
TNM staging	I	150	37.33	29.075~45.585	0.000
	II	88	15.67	13.372~17.968	
	III	41	16.93	7.232~26.628	
	IV	14	7.40	1.955~12.845	
Resection Margin	Positive	74	20.67	14.365~26.975	0.010
	Negative	219	22.40	15.055~29.745	
Intraoperative blood loss	<500 ml	186	26.27	18.545~33.995	0.199
	≥500 ml	107	15.90	10.131~21.669	
Blood transfusion	Yes	89	13.43	11.037~15.823	0.001
	No	204	27.93	20.505~35.355	
Relapse	Yes	158	18.10	14.458~21.742	0.000
	No	135	31.50	3.236~59.764	
Chemotherapy	Yes	4	18.10	0.000~41.747	0.745
	No	289	21.20	16.030~26.370	
TBIL	Normal	83	28.93	15.172~42.688	0.025
	High	210	18.10	14.466~21.734	
DBIL	Normal	85	28.93	15.007~42.853	0.032
	High	208	18.10	14.483~21.717	
ALP	Normal	82	36.53	18.820~54.240	0.002
	High	211	17.43	14.230~20.630	
ALT	Normal	82	36.90	19.399~54.401	0.002
	High	211	18.10	14.105~21.795	
AST	Normal	87	30.57	11.745~49.395	0.014
	High	206	18.13	13.635~22.625	
GGT	Normal	73	41.30	22.698~59.902	0.003
	High	220	17.43	14.034~20.826	
Surgical method	Not combined with portal vein resection and repair	284	20.97	16.048~25.892	0.320
	Combined with portal vein resection and repair	9	25.37	0.000~80.796	
History of hepatitis	Yes	18	41.30	15.171~67.429	0.072
	No	275	20.53	16.086~24.974	
Stone	Yes	31	15.90	11.646~20.154	0.099
	No	262	21.50	16.418~26.582	
Cholecystectomy before the illness	Yes	36	16.40	14.783~18.017	0.243
	No	257	21.73	16.743~26.717	

Table 3. Multivariable regression analysis of cholangiocarcinoma using Cox proportional hazard model.

Parameter	Regression parameter estimation (B)	Standard errors (BE)	Wald	Degree of freedom	P-value (Sig)	Relative risk (B)	95% CI for Exp (B)
Differentiation	0.304	0.115	6.953	1	0.008	1.356	1.081~1.699
TNM staging	0.322	0.079	16.548	1	0.000	1.379	1.181~1.610
Resection margin	0.339	0.154	4.832	1	0.028	1.404	1.037~1.899
Tumor location	−0.520	0.190	7.496	1	0.006	0.594	0.410~0.863
Blood transfusion	0.401	0.144	7.704	1	0.006	1.493	1.125~1.982
Relapse	0.674	0.149	20.511	1	0.000	1.962	1.466~2.627
ALP	0.670	0.192	12.235	1	0.000	1.954	1.342~2.844

Discussion

The morbidity of cholangiocarcinoma has been increasing in recent years. The prognoses of advanced cholangiocarcinoma cases are very poor, with median survival time less than 1 year [12]. Thus, it is imperative to develop comprehensive treatment strategies that consider all 13 factors that affect treatment outcome. Most cholangiocarcinoma patients are diagnosed at an advanced, unresectable stage. Even in those who can receive resection, there is high risk of relapse. We thus performed the initial single-factor analysis, which would allow subsequent multi-factor analysis with a subset of indicator indexes.

As summarized in Table 2, our analysis revealed 13 indexes that could affect prognosis in cholangiocarcinoma patients. It has been previously shown that portal involvement by hilar cholangiocarcinoma was not a significant contraindication for surgical resection [13–15]. Given that most diagnosed cases are in advanced stage of the disease and do not receive surgical resection, it is difficult to investigate the true effect of surgical resection and disease prognosis.

Tumor differentiation status was also previously shown to have significant effect on prognosis [14,15]. Prognoses are poorer on low-differentiated tumors than on high-differentiated ones. This is mainly because low-differentiated cancers are prone to early metastasis. Our research also shows that prognoses of cancers with low differentiation are poorer than of those with medium or high differentiation. Thus, making sure about the degree of differentiation as early as possible can help in deciding the best treating method. There are 2 possible methods to help in diagnosis: one is preoperative biopsy diagnosis and the other is intraoperative frozen pathological diagnosis.

Tumor stages have also been related with prognosis [16]. Early stages indicate that tumors are confined to local metastasis,

and late stages indicate that tumors might have already had distant metastasis. Locally-confined tumors are easier to totally resect. However, tumors that have already had distant metastasis are not likely to be totally removed by surgery. Early stages of cholangiocarcinoma do not have obvious clinical manifestation; instead, there could only be jaundice or pruritus. Existence of obvious clinical manifestation means that cholangiocarcinoma is already in advanced stage. Recently, more methods are used to diagnose cholangiocarcinoma. Imaging diagnosis can find cholangiectasis at early stages.

It is widely believed that resection margin infiltrated by cancer cells indicate a poor prognosis [17]. A positive resection margin usually indicates that tumor is removed generally, but not a complete cure when examined microscopically. It has been shown that the length of cholangiocarcinoma cells invaded mucosa are usually shorter than 10 mm [17]. Thus, surgical resects 10 mm away from the tumor could achieve a non-invaded resection margin.

As we performed single-factor analysis, the statistical tests on tumor location have no statistical interpretation. But when doing multi-factor analysis, tumor location has difference in statistical tests, which indicates multi-factor interaction influences. It has been shown that the 1-year, 3-year, and 5-year survival rates for intrahepatic cholangiocarcinoma are 62%, 24%, and 20%, respectively, and the median survival time is 16.9 months. The 1-year, 3-year and 5-year survival rates for hilar cholangiocarcinoma are 49%, 16%, and 8%, respectively, and the median survival time is 11.7 months [3]. Statistical differences exist within the survival time, which corroborates the findings of the current study.

It has been suggested before that intraoperative blood transfusion could increase the chance of relapse of malignant tumors [18]. Whether blood transfusion is taken during the operation indicates intraoperative blood loss or preoperative anemia. The

exact mechanism by which intraoperative blood transfusion effects prognosis is still not clear, but research shows that blood transfusion could cause immune system adjustment by inhibiting the immune function of recipients and causing a drop in antibody level. Thus, if intraoperative blood transfusion is necessary, autologous transfusion, blood component transfusion, and in-need transfusion are available.

Conclusions

Highly differentiated tumor, early stages of TNM staging, no resection margin invaded, no intraoperative blood transfusion,

intrahepatic tumor, normal ALP levels and no relapse are associated with good prognosis of cholangiocarcinoma. Initial results from ongoing clinical trials have indicated that chemotherapy response rate, disease control rate, and overall survival have a significant correlation [19–23]. Thus it is imperative to explore adjuvant, neoadjuvant, and first-line chemotherapy to gain understanding and provide reference value for comprehensive treatment strategies for cholangiocarcinoma.

Conflict of interests

The authors report no conflict of interests.

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