

RESEARCH ARTICLE

Cholangiocarcinoma: An-eight-year Experience in a Tertiary-Center in Iran

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Abstract

Background and Aim: Cholangiocarcinoma (CCA) is an uncommon malignancy of the bile duct, occurring in nearly 2 out of 100,000 people. It is a type of adenocarcinoma that originates in the mucous glands of the epithelium, or surface layers of the bile ducts. The aim of this study was to evaluate the clinical features, diagnostic results and factors associated with survival, morbidity and mortality of cholangiocarcinoma cases in Iranian patients. **Method:** In this retrospective study the hospital medical records of 283 patients with a primary or final diagnosis of cholangiocarcinoma who had been admitted to gastroenterology ward of our hospital from 2004 to 2011 were retrospectively reviewed. **Results:** 283 patients (180 male, 63%, and 103 female, 38.6%) with a mean age of 59.7 ± 14.4 years were studied. The most frequent symptoms were painless jaundice (190, 66.9%), abdominal pain (77, 27%), pruritus 133 (46.8%) and weight loss (169, 59.5%). The most frequent associated risk factors and diseases were as follows: gallstones (72, 25.4%), diabetes (70, 24.6%), HBV infection (52 (18.3%), HCV infection 43 (15%), primary sclerosing cholangitis (16, 5.6%) and smoking (120, 42.3%). The most frequent type of cholangiocarcinoma in ERCP and MRCP was hilar. The mean survival time was 7.42 ± 5.76 months. **Conclusion:** The mean survival time in our study was lower than one year. Moreover the most frequent risk factors and associated diseases were smoking, gallstones and diabetes. Painless jaundice, abdominal pain and weight loss were the most clinical features related to cholangiocarcinoma. Additionally survival time did not correlate with risk factors, associated diseases and clinical presentations, but was linked to biliary metallic stenting and surgery.

Keywords: Cholangiocarcinoma - clinical features - risk factors - diagnosis - treatment - survival - ERCP - MRCP

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Introduction

Cholangiocarcinoma (CCA) is an uncommon malignancy of the bile duct, occurring in nearly 2 out of 100,000 people (Carriaga, 1995; Alvaro, 2008; Blechacz and Gores, 2008; Yachimski, 2008). It is a type of adenocarcinoma that originates in the mucous glands of the epithelium, or surface layer of the bile ducts. Female and male are equally affected and most patients are over 65 years old (Carriaga, 1995; Burke et al., 1998). When the tumor obstructs the biliary drainage system, cholangiocarcinoma usually become symptomatic and leads to painless jaundice. Pruritus, abdominal pain, weight loss, fever and hepatomegaly or a right upper quadrant mass are common symptoms in patients (Nagorney et al., 1993; Nakeeb et al., 1996). The cholangiocarcinoma can appear as intrahepatic, hilar, and extrahepatic (Nagorney et al., 1993; Nakeeb et al., 1996; Blechacz and Gores, 2008). By the time, a diagnosis is usually made, intrahepatic cholangiocarcinoma is

demonstrated as a large mass because the tumor does not cause clinical symptoms in its early stages, while, extrahepatic cholangiocarcinoma is commonly small at the time of presentation because the bile ducts are sealed in its early stage and patients present with jaundice (Nagorney et al., 1993; Nakeeb et al., 1996; Ahrendt et al., 2001). The precise reason of cholangiocarcinoma is unknown; however there are several conditions as primary sclerosing cholangitis (PSC), bile duct cysts and chronic biliary irritation that can increase risk of cholangiocarcinoma (Boberg et al., 2002). This study aimed to evaluate the etiologies, clinical features, diagnostic results, factors associated with survival, morbidity and mortality related to cholangiocarcinoma in our hospital in Tehran-Iran.

Materials and Methods

The hospital medical records of 283 patients with the primary or final diagnosis of cholangiocarcinoma who had been admitted to gastroenterology ward of our

hospital (a tertiary academic center in Tehran-Iran) from 2004-2011 were retrospectively reviewed. Since this study was retrospective, the ethical committee approval was not required. Patients with cholangiocarcinoma diagnosis who had been admitted to other units of our hospital with complaints other than related to cholangiocarcinoma were excluded. Medical records of included patients were evaluated regarding epidemiologic characteristics, predisposing factors, initial manifestations of the disease, method of diagnosis, laboratory findings, surgical or palliative therapy and overall survival. The staging of the tumor was performed based on the TNM staging system and or the Bismuth classification. Moreover demographic data as Age, Sex, and BMI and risk factors and associated diseases as PSC, diabetes, PBC, chronic hepatitis B, chronic hepatitis C, cirrhosis and IBD, as well biomarkers as CA 19-9, CEA were collected. Furthermore Imaging modalities and therapeutic procedures were recorded in data collection form. To evaluate the Survival time and outcome of therapy, we called the patients or their families by phone and filled the questionnaire. All data were presented as percentage of patients or mean±standard deviation. Linear regression used to evaluate the correlation between different variables and survival time. All statistical analyses were performed using SPSS computer software (version 20.00; SPSS, Chicago, Illinois). Pearson chi square test used to show the correlation between survival time and risks factors, associated diseases and clinical features. A p-value<0.05 was considered to be statistically significant.

Results

In this study we evaluated medical records of 283 patients (180 male (63%) and 103 female (38.6%)) with mean age of 59.67±14.44 years (range 18-89 years). Using linear regression, risks factors and associated diseases did not correlate to CCA. The clinical features, associated diseases and risk factors related to CCA are detailed in Table 1.

All patients were evaluated using MRCP and ERCP. In this case, Hilar CCA was more frequent finding in MRCP and ERCP evaluation. The MRCP and ERCP findings and related procedures such as stenting have been described in Table 2.

The mean of survival <6 months was reported in 138 patients (3.66±1.175 months); survival about 6 months was reported in 10 patients, moreover survival >6 and <12 months was reported in 93 patients (8.76±1.48 months) and survival >12 and <24 months was reported in 39 patients (15.4±2.88 months).

The correlation between survival time and metallic biliary stenting (P=0.05), surgery treatment (P=0.001), also with presenting symptoms of abdominal pain (0.001) and painless jaundice (0.008) was significant. However the correlation between survival time and biliary plastic stenting (P=0.19), bismuth corlette type (P=0.341), TNM stage (P=0.66), Moreover cholangitis (P=0.57), diabetes (P=0.72), HBV infection (P=0.16), HCV infection (P=0.38), Cancer Associated Antigen 19.9: CA 19.9 (P=0.1), Carcinoembryonic Antigen: CEA (P=0.4),

Table 1. Clinical Manifestations and Associated Diseases and Risk Factors

Associated diseases	N	(%)
PSC	16	(5.6%)
Choledocolithiasis	7	(2.5%)
Gallstone	72	(25.4%)
Diabetes mellitus	70	(24.6%)
Chronic hepatitis B	43	(15.0%)
Chronic hepatitis C	31	(11.0%)
Cirrhosis	31	(11.0%)
History of cholecystectomy	13	(4.6%)
History of choledocal cyst surgery	2	(0.7%)
Ulcerative colitis	10	(3.5%)
Crohn's disease	1	(0.4%)
Painless jaundice	190	(66.9%)
Pruritus	133	(46.8%)
Abdominal pain	77	(27.0%)
Weight loss	169	(59.5%)
Fever	66	(23.3%)
Cholangitis	45	(15.8%)
Icter	233	(82.0%)
Positive HBS Ag	52	(18.3%)
Positive HCV Ab and PCR	43	(15.0%)
Smoking	120	(42.3%)
Alcohol consumption	21	(7.4%)
Opiate addiction	57	(20.1%)

Table 2. MRCP and ERCP Findings

MRCP	Intrahepatic	10	(3.5%)
	Hilar	203	(71.5%)
	Distal	62	(21.8%)
	Ascites	37	(13.0%)
	Liver metastasis	63	(22.2%)
	Not performed	5	(1.8%)
ERCP	Intrahepatic	4	(1.4%)
	Hilar	173	(60.9%)
	Distal	54	(19.0%)
	Plastic stent	94	(33.1%)
	Metallic stent	105	(37.0%)
	Failed	28	(9.9%)
	Not Performed	33	(11.6%)
ERCP-guided brush cytology	Negative	1	(0.4%)
	Positive	4	(1.4%)
	Not Performed	278	(97.9%)
ERCP-guided forceps biopsy	Positive	1	(0.4%)
	Not Performed	282	(99.0%)

cirrhosis (P=0.10), cholecystectomy (P=0.97), IBD (P=0.44), weight loss (P=0.21), cholangitis (P=0.26), Icter (P=0.90), pruritus (0.27), opiate addiction (0.75), alcohol consumption (0.88), smoking (0.23) and gallstone (0.86) was not significant.

Twenty eight patients were managed with surgery and R0 resection was done in 14 cases and the most frequent histologic type was well differentiated (Table 3). The mean survival time was 7.42±5.76 months (range 1-52) and the most frequent cause of death was infectious complications (Table 3). The frequency of tumor margin, biliary drainage procedures, diagnostic base, TNM staging, Bismuth corlette type, treatments and mean±SD of survival time have been described in Table 3. The mean and standard deviation of laboratory data were described in Table 4.

Table 3. The Frequency of Tumor Margin, Biliary Drainage Procedure, Diagnostic Base, TNM Staging, Treatments and Mean±SD of Survival Time

Variables		N	(%)
Tumor margin	R0	14	(4.9%)
	R1	10	(3.5%)
	R2	4	(1.4%)
Tumor histology	Well differentiated	7	(2.5%)
	Moderate differentiated	6	(2.1%)
	Poor differentiated	15	(5.3%)
Biliary drainage procedure	ERCP guided	192	(67.6%)
	Percutaneous	30	(10.6%)
	Surgical Procedure	19	(6.7%)
	None	34	(12%)
	ERCP guided & surgical procedure	8	(2.8%)
Diagnostic base	Diagnostic criteria	250	(88.1%)
	Brush Cytology	4	(1.4%)
	Forceps Biopsy	1	(0.3%)
	Surgery	28	(9.9%)
Bismuth corlette type	I	15	(5.3%)
	II	66	(23%)
	IIIa	41	(14.4%)
	IIIb	42	(14.8%)
	IV	53	(18.7%)
TNM staging	IA	10	(3.5%)
	IB	6	(2.1%)
	IIA	8	(2.8%)
	IIB	4	(1.4%)
Therapy	Supportive therapy	155	(54.6%)
	Chemotherapy	121	(42.6%)
	Curative surgery	14	(4.9%)
	Palliative surgery	14	(4.9%)
Survival time	7.42±5.76 months (range 1-52)		
Cause of death	Infection	221	(78%)
	Hepatic failure	12	(4.2%)
	Myocardial infarction	8	(2.8%)
	Infection & Hepatic failure	30	(10.6%)
	Others	12	(4.2%)
ERCP-guided forceps biopsy	Positive	1	(0.4%)
	Not Performed	282	(99.0%)

Table 4. Mean and Standard Deviation of Laboratory Data

Laboratory data	Mean±SD	
Alpha phyto protein	952±352	IU/ml
Direct Bilirubin	12±4	mg/dl
Total Bilirubin	23±7	mg/dl
ALT	141±55	IU/L
AST	128±66	IU/L
Serum Albumin	3.94±0.54	g/dl
CEA	5.75±2.91	ng/ml
CA 19.9	400±295	U/ml
Platelet count	355550±77794	
Leukocyte count	9205±2339	
Hemoglobin	12.63±1.45	g/dl

Discussion

Cholangiocarcinoma (CCA) is an uncommon malignant neoplasm including 3% of all gastrointestinal cancers (Vauthey and Blumgart, 1994). The incidence of cholangiocarcinoma in the United States of America is 2/100,000 (Shaib et al., 2005) but in Iran, the exact

prevalence of cholangiocarcinoma is unclear. We studied medical records of 283 patients to evaluate risk factors, associated diseases and survival time related to cholangiocarcinoma, as well diagnostic tools in Iran. The mean age of our patients was about 60 years that was lower than previous reports. The most of these studies indicated that the peak age of the patients with cholangiocarcinoma was the seventh decade; However the mean age in our study was in line with study by Yeh et al. (60 years vs 57 years) (Burak et al., 2004). Furthermore some reports designated that the frequency of cholangiocarcinoma in men was greater than women that were in agreement with our findings (Shaib and El-Serag, 2004; Shaib et al., 2005). Primary sclerosing cholangitis (PSC) is the well-known predisposing factor for cholangiocarcinoma (Vauthey et al., 1994; Carriaga, 1995; Boberg et al., 2002; Shaib and El-Serag, 2004; Shaib et al., 2005; Alvaro and Mancino, 2008; Blechacz and Gores, 2008; Yachimski, 2008), in our survey 16 patients (5.6%) had PSC and correlation between CCA and PSC was significant. In study by Boberg et al, CCA was diagnosed within the first year after diagnosis of PSC in 24 (50%) patients. Furthermore, Jaundice, pruritus, abdominal pain and fatigue were significantly more frequent in diagnosis of PSC in the group that developed CCA (Boberg et al., 2002). Moreover et al. in a study indicated that frequency of cholangiocarcinoma was significantly higher in PSC than the rates in the general population and approximately 7% of PSC patients later developed CCA during 11.5-year follow-up (Burak et al., 2004). Several studies indicated that nonbiliary diseases as heavy alcohol use, obesity, nonalcoholic fatty liver disease, chronic hepatitis C and cirrhosis are more frequent in patients with CCA compared to the general population (Nagorney et al., 1993; Vauthey et al., 1994; Carriaga and Henson, 1995; Nakeeb et al., 1996; Burke et al., 1998; 2004; Boberg et al., 2002; Khan et al., 2002; Shaib and El-Serag, 2004; Shaib et al., 2005; 2007; Welzel et al., 2007). In current study smoking, opiate and alcohol use were the most common risk factors in CCA patients respectively, furthermore, other more associated diseases were gallstone, diabetes, chronic hepatitis B infection, chronic hepatitis C infection and cirrhosis. As well more common clinical features comprised: painless jaundice, abdominal pain and icter, weight loss and pruritus. In comparison with our findings the most frequent symptoms in other studies comprised pruritus, abdominal pain, weight loss, and fever, as well physical signs include jaundice, hepatomegaly or a right upper quadrant mass were more common in previous reports (Nagorney et al., 1993; Nakeeb et al., 1996). The survival of untreated patients with advanced intra-hepatic cancers is short and associated with several factors. Tumor-spreading type was a prognostic variable of CCA survival (Jan et al., 1996). Also another study by Suh indicated that Patients with intraductal papillary cholangiocarcinoma (PCC) had significantly better survival rates than those with periductal-infiltrating or mass-forming type PCC (Suh et al., 2000). In a large cohort study by Park et al. (2009) survival rate was about 3.0±5.3 months. Conversely, in other study by Cho et al. (2010) to evaluate the survival rate of intrahepatic

cholangiocarcinoma after resection, the median survival of patients with intrahepatic cancer who were treated with systemic chemotherapy was 8-12 months. Furthermore, after surgical resections with curative intent, 1-year and 5-year survival of 68% and 32%, respectively, have been reported (Cho et al., 2010). In present study 155 (54.6%) patients were taken supportive therapy, 121 (42.6%) chemotherapy, 14 (4.9%) surgery curative and 14 (4.9%) palliative therapy. Regarding survival time our findings were near the other previous reports (mean Survival time 7.42 ± 5.76 months (range 1-52). Moreover, using correlation test the correlation between survival time and metallic biliary stenting ($P=0.05$), surgery treatment ($P=0.001$), also with presenting symptoms of abdominal pain (0.001) and painless jaundice (0.008) was significant. However the correlation between survival time and plastic biliary stenting ($P=0.19$), tumor margin ($P=0.36$), bismuth correlative type ($P=0.341$), TNM stage ($P=0.66$), Moreover cholangitis ($P=0.57$), diabetes ($P=0.72$), HBV infection ($P=0.16$), HCV infection ($P=0.38$), cirrhosis ($P=0.10$), cholecystectomy ($P=0.97$), IBD ($P=0.44$), weight loss ($P=0.21$), cholangitis ($P=0.26$) and icter ($P=0.90$) was not significant.

This was a retrospective uncontrolled study in a small population of a tertiary level referral center and could not reflect the real occurrence of these events in a general population. So, more controlled prospective studies with large sample size are needed to validate findings reported here.

In conclusion, mean survival time in our study was 7.42 ± 5.76 months and the most frequent type of CCA in ERCP and MRCP was hilar. Moreover the most frequent risk factor was smoking, as well gallstone, diabetes. The painless jaundice and weight loss was the most frequent disease and clinical features related to cholangiocarcinoma. Additionally survival time correlated to metallic biliary stenting and surgery treatment.

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