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Original article

Clinical presentation, diagnosis, and survival in cholangiocarcinoma: A prospective study

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ABSTRACT

Background and study aims: The diagnosis of cholangiocarcinoma (CCA) is difficult. The present study aimed to assess the clinical features, diagnosis, and survival in CCA.
Patients and methods: This is a prospective study on 46 patients with CCA who underwent endoscopic retrograde cholangiopancreatography (ERCP) or surgical resection and 20 controls with a clinical and ERCP suspicion for CCA in whom surgical biopsy and/or 4-year follow-up showed a benign biliary stricture.
Results: The median age at presentation was 71 years (range 44–88). Thirty-four patients (73.9%) presented with painless jaundice. Median CA 19-9 value was 188 IU/L (range 1–49,138), with a level of <100 IU/L in 13 patients (28%). Total bilirubin was 11.9 (0.6–36.3) mg/dL. The tumour was intrahepatic in 3 (6.5%), hilar (Klatskin) in 25 (54.3%), and located in the lower third of the bile duct in 18 (39.1%) patients. The diagnosis was confirmed by positive cytology in 10 (21.7%), biopsy in 20 (43.5%), cholangioscopy in five (10.9%), and imaging and clinical grounds in 11 (23.9%) patients. Cytology was feasible in 36 patients; it was positive in 10 and "highly indicative" in two patients (33.3% sensitivity). Twenty-two patients (47.8%) were treated by surgical resection, and the rest were offered palliative biliary drainage. Mean estimated survival for the entire group of CCA patients was 21.5 ± 3.3 months. Survival was slightly longer in patients who underwent surgical resection than those who had palliative treatment; the estimated mean survival rates were 26.2 ± 4.2 vs. 17.1 ± 3.3 months, respectively, but the difference was not statistically significant ($p = 0.115$).
Conclusion: The diagnosis of CCA is difficult and often delayed. The outcome is generally poor.

Introduction

Cholangiocarcinoma (CCA) is a malignant neoplasm that originates from the epithelium of the biliary tree [1]. CCA accounts for 3% of gastrointestinal cancers and is the second most common primary liver tumour, following hepatocellular carcinoma [2]. CCA is distinguished into intrahepatic (10%) and extrahepatic CCA. The latter is further characterized as perihilar (Klatskin) tumour (50%), originating at the bifurcation of the common hepatic duct [3], or tumour of the distal bile duct (40%) [1]. Initial symptoms depend on the tumour location. Intrahepatic CCA usually manifests at an advanced stage with nonspecific complaints [4]. In 90% of the patients with extrahepatic CCA, obstructive jaundice is present. [5] A pathological documentation of CCA is not always feasible because of the difficulty in accessing the tumour site. Diagnosis usually relies on imaging modalities such as endoscopic retrograde cholangiopancreatography (ERCP), which offers the option of tumour sampling for cytology, or magnetic resonance

Abbreviations: CCA, cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; CT, computerized tomography; MRI, magnetic resonance imaging; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

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cholangiopancreatography (MRCP) [6]. In general, a cytologic diagnosis is achieved in only a minority of cases (15%–30%) [7,8].

In hilar tumours, the choice of surgical treatment depends on the specific features of CCA. Extrahepatic inoperable cases are usually treated with drainage of the biliary tree by inserting a plastic or metal stent [9]. In general, fatality is high, because of the advanced stage of the disease at the time of diagnosis [10]. It is therefore mandatory that a vigorous diagnostic approach is adopted to ensure timely confirmation of the disease to maximize the patient's benefit from the therapeutic intervention in terms of overall survival and quality of life. In this report, we share our experience of a series of patients with documented CCA. We aimed to assess the clinical features, diagnosis, treatment, and survival in CCA. In addition, we aimed to determine the appropriate laboratory features that may be used to differentiate CCA from benign biliary strictures.

Patients and methods

Patients with CCA in 2006–2010 were included. The tumour was diagnosed by a positive cytology on brushing samples collected during ERCP, a positive surgical biopsy, and/or compatible clinical, imaging, and laboratory findings. Acute onset of painless jaundice was the main clinical manifestation. Presence of a dominant stricture persistent in magnetic resonance imaging (MRI)/MRCP and ERCP with or without upstream biliary duct dilatation and CA 19-9 elevation were the main imaging and laboratory findings. Evidence of hepatocellular carcinoma or metastatic liver tumour, history or findings substantiating sclerosing cholangitis; a pancreatic head mass on computerized tomography (CT) or MRI; and, finally, any deformation of the ampulla of Vater in ERCP were criteria for exclusion. For the purposes of the study, a control group was also selected, which included patients with a clinical and ERCP suspicion for CCA, in whom surgical biopsy and/or 4-year follow-up showed a benign biliary stricture.

For statistical evaluation, all quantitative parameters were considered as nonparametric data, and their values in the two groups were compared using the Mann–Whitney *U* test. The distribution of categorical variables was assessed using the chi-square test. Overall survival was graphically depicted with the Kaplan–Meier curve, while the difference between the groups was evaluated using a log-rank test. All tests were performed on the SPSS 21 software, with significance assumed at $p < 0.05$.

Results

Forty-six consecutive patients (32 men, 14 women) with a documented CCA and 20 consecutive control cases (14 men, 6 women) with benign biliary strictures with a clinical and ERCP suspicion for CCA were included. The latter were followed up for more than 4 years and had an uneventful course. In three patients, the diagnosis of the benign stricture was confirmed by surgical biopsy. Age was largely comparable between the two groups (Table 1). None of the 46 CCA patients had evidence of a previous HBV or HCV infection. Family history was not relevant, and no risk factor could be identified. However, in two female patients, one with intrahepatic CCA and one with hilar tumour, there was a history of primary biliary cirrhosis.

The clinical and laboratory features of the patients in the two groups upon presentation are summarized in Table 1. Of the three patients with intrahepatic disease, none presented with jaundice but were diagnosed incidentally. Of the 43 patients with extrahepatic CCA, 34 (79%) presented with painless obstructive jaundice, seven reported nonspecific symptoms, and the last two patients were asymptomatic and were diagnosed incidentally.

Table 1
Comparison of demographic, clinical, and laboratory characteristics between patients with cholangiocarcinoma and those with benign bile strictures.

	Cholangiocarcinoma	Benign bile strictures	*p*
Age (years)	71 (44–38)	71 (35–87)	0.840
Sex (M/F) (n, %)	32 (69.6)/14 (30.4)	14 (70)/6 (30)	0.972
Tumour location (n, %)	–	–	–
Intrahepatic	3 (6.5)	–	–
Hilar (Klatskin)	25 (54.3)	–	–
Distal extrahepatic)	18 (39.1)	–	–
Jaundice (n, %)	34 (73.9)	14 (70)	0.743
Diabetes mellitus (n, %)	14 (30.4)	2 (10)	0.075
CA 19-9 (U/mL)	188 (1–49,138)	7.4 (2–5000)	0.703
Glucose (mg/dL)	113 (71–330)	104 (59–219)	0.264
AST (IU/L)	105 (23–495)	52 (15–639)	**0.012**
ALT (IU/L)	107 (16–847)	77 (10–370)	0.134
ALP (IU/L)	329.5 (66–1182)	152 (44–901)	**0.014**
g-GT (IU/L)	576.5 (44–2854)	310 (22–1063)	0.076
Amylase (IU/L)	55 (8–604)	80 (23–713)	**0.017**
Total bilirubin (mg/dL)	11.9 (0.6–36.3)	3.5 (0.3–24.7)	**0.007**
Direct bilirubin (mg/dL)	8.8 (0.2–25.8)	1.8 (0.2–15.7)	**0.017**

Quantitative variables are shown as median, followed by range in parentheses. P values in bold indicate a statistically significant difference (AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, g-GT: gamma-glutamyl transpeptidase).

When compared to those with benign strictures, CCA patients had significantly higher aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin values (both total and conjugated) (Table 1, Fig. 1). Difference in CA 19-9 levels did not reach statistical significance (Table 1); the median value for CCA patients was 188 IU/L, and in 13 of them (28.4%), it was below 100 IU/L. A very high value (reaching 20,000 and 50,000 IU/L) was found in two patients. All the CCA patients underwent ERCP at least once, and a brushing cytology specimen was collected from 36 of them. Cytology was positive in 10 patients and highly indicative for malignancy in 2 patients. In contrast, all the 20 control patients had a negative brushing cytology. Thus, the sensitivity, specificity, positive predictive value, and negative predictive value of the cytological confirmation were estimated to be 33.3%, 100%, 100%, and

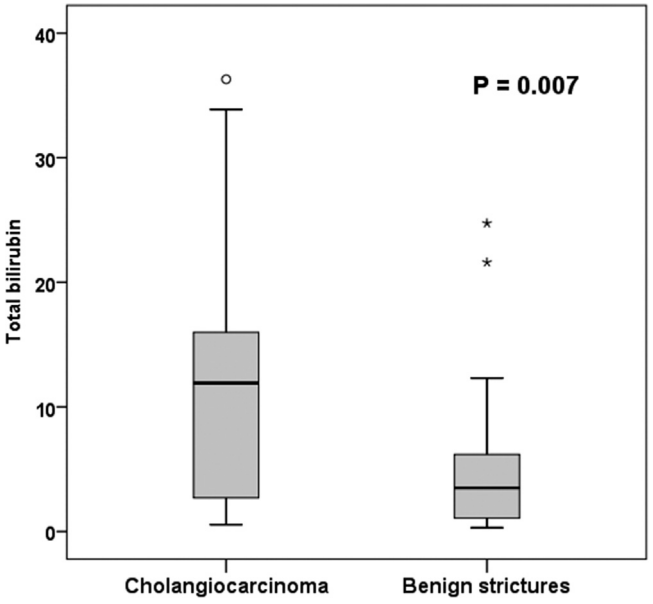

Fig. 1. Comparison of total bilirubin values (mg/dL) between patients with cholangiocarcinoma and those with benign bile strictures.

45%, respectively. In summary, among the 46 patients with documented CCA, the diagnosis was established by cytology in 10 (21.7%), surgical biopsy in 20 (43.5%), and cholangioscopy in 5 (10.9%, including the two cases with an indicative cytology) and on clinical grounds only in 11 cases (23.9%). Cholangioscopy was performed by a single-operator cholangioscopy system (SpyGlass Direct Visualization System; Boston Scientific Corporation, Boston, MA, USA).

Most CCA patients underwent endoscopic drainage with a stent inserted. Up to 9 plastic and metal stents were placed in each patient during the course of the disease. Nearly half the CCA patients (22; 47.8%) underwent surgical resection including hepatectomy or Whipple procedure depending on the tumour location. Surgical resection with negative tumour margins were achieved in 5 of 22 patients (22.7%). Mean estimated survival for the whole group of CCA patients was 21.5 ± 3.3 months. Although the outcomes in resected patients is better than in those treated conservatively (26.2 ± 4.2 vs. 17.1 ± 3.3), the difference did not reach significance (log rank, $p = 0.117$) (Fig. 2). More specifically, the survival rate at 1, 2, and 3 years was 70%, 53%, and 47%, respectively, for those who underwent resection and 57%, 29%, and 21%, respectively, for those who received conservative treatment.

Discussion

CCA was considered a rare tumour, mainly affecting the elderly; however, during the last decade, an increase in the incidence of the disease was observed [11], particularly in younger patients with no history of primary sclerosing cholangitis or any other recognized predisposing factors. Consistently, no risk factor could be identified in any of the CCA patients enroled in our study, and the youngest patient was 44 years old. No satisfactory explanation was given for this change in the epidemiology of CCA, and the aetiology of the disease remains largely unknown. The proposed models of pathogenesis indicate the presence of cholestasis and the resulting chronic inflammation, together with genetic aberrations [12], but there are several points that require further clarification.

Painless jaundice along with increased CA 19-9 levels are usually reported as the most common initial manifestation of CCA. However, nine of the 43 patients with extrahepatic disease in our cohort did not present with jaundice, and in some of them, the tumour was rather an incidental finding. Moreover, in several patients, there was no excessive CA 19-9 increase, and 13 of them (28.4%) had levels below 100 IU/L. However, one of the control patients presented with a CA 19-9 value of 5000 IU/mL. In this patient, total bilirubin and CA 19-9 levels returned to normal after ERCP, and the jaundice subsided permanently after laparoscopic cholecystectomy. In our study, statistically significant differences were found for serum amylase (higher values in the control group), AST, and ALP levels (both elevated in CCA patients). The former may be explained by the presence of chronic pancreatitis, often underlying a benign biliary stricture or injury to the biliary tree due to the passage of stones. The increase in AST and ALP values in cancer patients confirms previous findings and may be attributed to the release of the enzymes from tumour cells. These findings, however, are not very helpful in predicting malignancy [13]. Therefore, no single laboratory test may differentiate between malignant and benign causes in cases with bile strictures with confidence, and a proper diagnostic approach requires a full evaluation of clinical, laboratory, and imaging data.

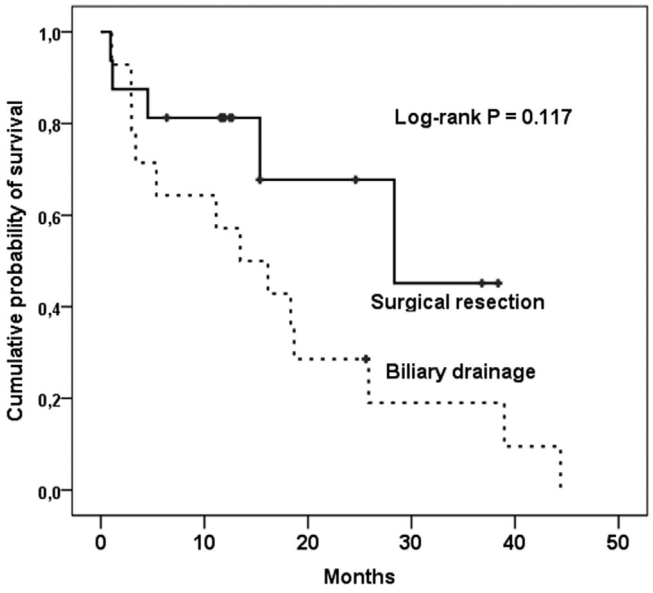

Fig. 2. Comparison of survival between patients receiving tumour resection and those treated conservatively.

Nevertheless, a definite preoperative diagnosis of CCA remains difficult despite the development of new techniques such as cholangioscopy. In the majority of the patients in our study, the diagnosis was documented with a surgical biopsy. Moreover, 2 of the 20 control patients were operated with the suspicion of CCA, but the biopsy of the surgical samples showed a benign condition, namely fibrosis. These figures are in accordance with data from other series in literature showing that among patients with clinical and imaging findings compatible with hilar CCA who were operated upon, 10%–15% were found to have nonmalignant conditions [14–16]. A similar rate of benign histology (13%) was also obtained among patients operated with the suspicion of distal bile duct CCA [17]. It is evident therefore that the distinction between malignant and benign biliary strictures is often difficult and that a significant number of patients are unnecessarily operated upon. For the majority of the patients, the diagnostic documentation relies on the cytological assessment of brushing samples obtained during ERCP. Although it has a high specificity, reaching 100%, this technique is hampered by a low sensitivity rate, ranging between 30% and 88% [12,18–21]. In our study, the corresponding figures were estimated at 100% and 33.3%, respectively.

The outcome after surgery is generally poor. Among surgically treated patients, the 5-year survival was reported to be 30–40% for intrahepatic and hilar disease, whereas for distal bile duct involvement, it was 37% [22]. Prognosis seems to vary according to the disease location and stage and the treatment offered. In a previous study, the survival rates in patients offered radical resection of extrahepatic CCA were 75%, 56%, and 41% at 1, 2, and 5 years, respectively, which are better than those of the patients who had undergone palliative resection (43%, 27%, and 27%, respectively), whereas among those treated with a stent insertion, the survival rate was 23%, 7%, and 0%, respectively [23]. In contrast, only 18% of the patients in whom no surgical or endoscopic intervention was attempted were alive at 12 months, and all of them had succumbed at 3 years [23]. Similarly, survival was poor among patients with inoperable tumour who were treated with endoscopic drainage only: 53%, 19%, 9%, and 4% at 1, 2, 3, and 5 years, respectively [24]. In our study, patients who underwent resection had a better survival rate than those who were offered a palliative drainage; however, the difference in survival between the two groups did not reach statistical significance. This may reflect the advanced stage of the disease at diagnosis.

We conclude that the therapeutic dilemmas in CCA are largely exemplified by the difficult choice between a major operation with significant morbidity and mortality and a palliative approach that relies on endoscopic stent insertion, which often get blocked and

results in episodes of obstructive jaundice and cholangitis. Obviously, radical resection of the tumour can prove helpful and should be attempted in cases where an early diagnosis is obtained. Hopefully, novel molecular approaches such as fluorescent in-situ hybridization applied on ERCP brushing specimens will improve the sensitivity of cytological assessment, leading to a timely diagnosis and, eventually, a better prospect for a significant number of patients [25].

Conflict of interest

None.

Ethical committee

The study was approved by the hospital ethical committee and all subjects provided informed consent for the study.

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