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Cholangiocarcinoma: A Single-center Western Experience

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Abstract

Background: The purpose of this study was to summarize the surgical management and to evaluate survival rate and clinical outcome of cholangiocarcinoma, in patients hospitalized in our Unit of Oncology and General Surgery.

Methods: This is a retrospective analysis of 76 consecutive patients with diagnosis of cholangiocarcinoma. The surgical procedure was selected based on the origin of the neoplasia. Tumor stage was defined according to the pathological tumour-node-metastasis classification (TNM 7th edtn, 2010). After resection, all patients underwent regular follow-up.

Results: During the study period, 58 patients underwent explorative laparotomy. Forty-six patients were submitted to respective surgery with curative intent. A curative resection (R0) was achieved in 42/46 resected patients. The overall median survival time was 14.2 months, with 1, 3 and 5 year survival rates of 53.6%, 37.7%, and 19.6%, respectively. The survival rates, for the patients underwent R0 resection, was respectively 69%, 47.8% and 32.6% at 1, 3 and 5 years, with median survival time of 20.1 months.

Conclusions: Our experience confirms the main role of R0 surgery in the curative treatment of cholangiocarcinoma.

Keywords: Cholangiocarcinoma; Hepato-biliary cancer; Surgery

Introduction

Cholangiocarcinoma is a devastating cancer arising from the epithelium of the biliary tree, and it accounts for approximately 10% to 15% of all hepatobiliary tract malignancies [1]. Cancer can develop at any location along the biliary tree from the ampulla of Vater up to the smallest intrahepatic ductules and the gall bladder. Intrahepatic cholangiocarcinoma is defined as carcinoma arising from the intrahepatic bile ducts. Extrahepatic cholangiocarcinoma is defined as cancer arising from the common bile duct, the hepatic duct bifurcation, and/or the first order left and right hepatic ducts. Gall bladder cancer is defined as cancer arising from the gall bladder and the cystic duct. For the classification of hilar cholangiocarcinoma, not only the classification of biliary tract carcinoma [2] but also the Bismuth classification [3] is often employed.

Cholangiocarcinoma mostly arises from the extra-hepatic biliary tree (50%-60% hilar "Klatskin" tumors), spreads slowly and infiltrates periductal tissues [1]. Cholangiocarcinoma characteristically presents with signs of liver failure, cachexia, malnutrition, biliary obstruction, vascular obliteration and biliary tract sepsis. These signs are unspecific and the malignancy progresses insidiously. The diagnosis usually is late and it has a severe prognosis. It often occurs in male at seventh decade [4,5]. Fortunately, this tumor is a relatively rare kind of malignancy, since it represents 3% of all gastrointestinal system cancers [6]. Of concern, some reports indicate that the incidence and mortality of intra-hepatic cholangiocarcinoma are increasing worldwide [7-10], while those of extrahepatic cholangiocarcinoma are decreasing [7-9]. To date the reasons of these interesting epidemiologic datas are unknown and the main ipotesis are disputable. The aim of this study was to summarize the surgical management in our experience during the past 10 years and to evaluate survival rates and clinical outcomes of cholangiocarcinoma.

Materials and Methods

Patients

This is a retrospective analysis of 76 consecutive patients with diagnosis of cholangiocarcinoma hospitalized in the Unit of Oncologic and General Surgery, Department of Medicine, Surgery and Neurosciences, University of Siena, Italy, between June 1999 and May 2009. The mean age was 67 years (range 36-83) with a male/female ratio of 1.1:1 (males 40). The diagnosis of cholangiocarcinoma was based upon clinical, imaging, cytologic and histopathologic findings. Cholangiocarcinoma was classified as intrahepatic, extrahepatic and gall bladder cancer. Extrahepatic tumors were further classified in accord with classification of biliary tract carcinoma [2] in proximal, middle and distal tract tumors: Distal cholangiocarcinoma arising from the intrapancreatic portion of the common bile duct, middle cholangiocarcinoma arising from the tract between the confluence of the cystic duct and the suprapancratic margin of the common bile duct, and proximal, or hilar cholangiocarcinoma, which arises from the hepatic duct bifurcation and first order hepatic ducts.

Preoperative evaluation

The aim of the preoperative staging was to define the stage of the tumor and to identify its exact location. The computed tomography (CT) of the thorax and abdomen was performed in all the patients in order to exclude metastatic disease localized at peritoneum or in other organs, and to evaluate the local extension of the neoplasia, in particular the localization of the tumor and the lymph nodes involvement. The magnetic resonance imaging (MR) of the upper abdomen was useful for intrahephatic malignancy, to differentiate intrahepatic cholangiocarcinoma especially from hepatocellular carcinoma. Magnetic resonance cholangiography (MRCP) was used, in particular, in case of tumours of extrahepatic origin, to define the localization of the cancer. During the preoperative assessment, all the patients with obstructive jaundice were submitted to endoscopic stent placement or internal-external biliary drainage.

The patients were submitted to hepatic functionality blood test (bilirubin, alkaline phosphatase, transaminases, albumin, and prothrombin time), tumor markers (CEA, CA 19-9), standard blood assay, dosage of serum levels of creatinine, chest x-ray, electrocardiogram and accurate anaesthesiologist evaluation.

Surgery

The aim of the surgical procedure was to obtain a complete resection of the cancer. During the operations intraoperative ultrasound was routinely used to confirm the preoperative diagnosis, evaluate the relation between the tumor and blood vessels, and evaluate the presence of intrahepatic metastases not otherwise specified. Curative resection (R0) was defined as a negative resection margin at histopathological definitive examination. Criteria for unresectability were the presence of distant metastases, peritoneal carcinomatosis, extensive vascular involvement, multiple intrahepatic metastases, or severe liver cirrhosis in patients who required major liver resection [11].

The surgical procedures were based on the origin of the neoplasia: for intrahepatic cholangiocarcinoma the hepatic resection; for extrahepatic cholangiocarcinoma localized at proximal tract a complete excision of the extrahepatic biliary tract with a biliary-enteric Roux-en-Y anastomosis; the complete resection of the choledocus and a biliary-enteric anastomosis with a Roux-en-Y reconstruction was performed for tumors arising from the middle biliary tract; the pancreatoduodenectomy (PD) for cancer of the distal biliary tract; cholecystectomy and atypical resections of the gall bladder bed for gall bladder cancer. Explorative laparotomy with biopsy was performed to discern the doubt cases and when a surgical procedure with a curative intent cannot be executed. In patients where a curative resection could be achieved, a loco-regional lymphadenctomy was performed too, with the excision of the lymph-nodes localized at hepatic hilum and at hepato-duodenal ligament.

For the cholangiocarcinoma localized at distal biliary tract a further lymphadenectomy was executed, and the lymph-nodes at common hepatic artery, celiac axis and para-aortic were completely removed.

Tumor staging

Tumor stage was defined according to the pathological tumor node metastasis classification (pTMN staging system) proposed by the International Union against Cancer (UICC/AJCC, 7th edition, 2010) [12]. All the cases before 2010 were revised and the pTNM classification has been updated at the 7th edtn.

Follow up

After resection, all the patients underwent regular follow-up with clinical check every 6 months. Vital status was investigated also by telephonic interview. During the follow-up check blood tests, tumor markers tests (CA 19.9, CEA), clinical examinations, and CT scan of the abdomen were performed. Suspected recurrences were confirmed with CT or MR with MRCP. Chest CT scan or bone scanning was performed in case of recurrence or clinical suspect of distant metastases.

Statistical analysis

Organization and preliminary evaluation of the data were fundamental in this study. An appropriate database was created and all data were classified in 57 variables. Data were analyzed with SPSS statistical software (version 16.0; SPSS, Chicago, IL, USA). Survival analyses were carried out with the Kaplan-Meier method. Mantel-Cox test was used to compare subgroups in the univariate analysis.

Results

The study included 76 patients. Preoperative diagnosis, based on the anatomical origin of the tumor, are showed in Table 1. Preoperative biliary drainage was performed, by internal-external biliary drainage or endoscopic stent placement, in 19 (82.6%) of the 23 patients presented with obstructive jaundice. Of these, 4 patients were considered unresectable, and 19 were submitted to resective surgery. During the study period, 58/76 patients (76.3%) underwent explorative laparotomy, whereas in the other 18 (23.7%) patients surgery was not indicated because of advanced disease or poor general conditions.

Fourty-six of 58 patients (79.3%) were submitted to resective surgery with curative intent, whereas in the other 12 patients (20.7%) resection was not indicated because of peritoneal carcinomatosis, extensive vascular involvement, or liver metastases not detected in preoperative staging. A curative resection (R0), with negative resection margins, was achieved in 42/46 resected patients (91.3% of patients submitted to resection, 55.3% of complete populations in study) (Figure 1).

The following surgical procedures, based on the anatomical origin of the neoplasia, were performed (Table 2): Hepatic resection 15.5% (9 patients), for intrahepatic cholangiocarcinoma; complete excision of the extrahepatic biliary tract with a biliary-enteric Roux-en-Y anastomosis, 6.9% (4 patients) for the cancer localized at proximal tract; complete resection of the choledocus and anastomosis biliary-enteric with a Roux-en-Y anastomosis 8.6% (5 patients), for the tumor originated from the middle tract; pancreatoduodenectomy 29.4% (17 cases) for the cancer of the distal biliary tract; cholecystectomy and atypical hepatic resection 18.9% (11 cases), for cholangiocarcinoma originated from gall bladder; explorative laparotomy with biopsy 20.7% (12 cases), to discern doubt cases at preoperative evaluation. There were 4 in-hospital deaths (6.9%).

Postoperative complications occurred in 41.4% of cases (24 patients) and the most common observed were: Hemoperitoneum (4), abdominal abscess (3), pleural effusions (3), anastomotic dehiscence (3), biliary fistula (2), wound infection (2), slow gastric emptying (2) and intestinal perforation (1). Histological examination of the biopsy,

effectuated during the surgical procedure, deposed in any case, for adenocarcinoma.

Characteristic Parameters		No
Sex	Male	40 (52.6%)
	Female	36 (47.4%)
Age	Range	36-83
	Mean	67 years
	Male/female ratio	1.1:1 (males 40)
Tumor location	Intrahepatic	24 (32%)
	Extrahepatic	22 (29%)
	proximal tract	3 (13.5%)
	middle tract	3 (13.5%)
	distal tract	16 (73%)
	Gall bladder	30 (39%)
Surgery	Yes	58 (76.3%)
	No	18 (23.7%)
Resection	Yes	46 (79.3%)
	No	12 (20.7%)
Radicality	R0	42 (91.3%)
	R+	4 (8.7%)
Morbidity		24 (41.4%)
Mortality		4 (6.9%)

Table 1: Clinico-pathological characteristics of the patients.

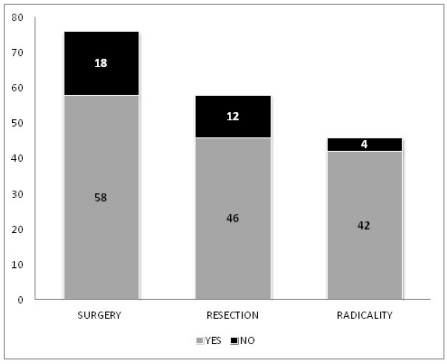

Figure 1: Surgical indications and results.

The T stage and lymph-nodal involvement (based on TNM 7th edtn) observed in our cases with the relative UICC stage are showed in Table 3, and the respective survival curves are showed in Figure 2. The overall median survival time was 14.2 months, with 1, 3 and 5 years survival rates of 53.6%, 37.7%, and 19.6%, respectively (Figure 3A).

The overall survival rates, for the patients who underwent to surgical procedure with an R0 resection, was respectively 69%, 47.8% and 32.6% at 1, 3 and 5 years (Figure 3B). In patients with free-margins and no residual tumor detected macroscopically and microscopically, the median overall survival was 20.1 months. The 1, 3 and 5 years survival rates for intrahepatic cholangiocarcinoma were 61.4%, 42.1%, and 10% respectively and the median survival was 20.1 months. While the 1, 3 and 5 year overall survival rates for extrahepatic cholangiocarcinoma were 66.7%, 50% and 25% respectively, with median survival of 18.1 months. Gall bladder cancer was the 1, 3 and 5 years overall survival rates of 34.6%, 20.8% and 13.9%, and median survival of 5.4 months (Figures 4A and 4B).

Surgical procedures	No.	%
Hepatic resection	9	15.6
Cholecistectomy+Atypical hepatic resection	11	19.1
Pancreatoduodenectomy	17	29.4
Excision of the extrahepatic biliary tract and biliary-enteric anastomosis	5	8.6
Excision of the choledocus and biliary-enteric anastomosis	4	6.9
Explorative laparotomy	12	20.7

Table 2: Summary of the surgical procedures.

Intrahepatic cholangiocarcinoma	Extrahepatic biliary tract cholangiocarcinoma T stage (n)	Gallbladder cholangiocarcinoma
T1 28.6% (2)	T1 15.0% (3)	T1 15.8% (3)
T2 14% (1)	T2 35.0% (7)	T2 10.5% (2)
T3 28.6% (2)	T3 35.0% (7)	T3 57.9% (11)
T4 28.6% (2)	T4 15.0% (3)	T4 15.8% (3)
N Stage (n)		
N0 42.9% (3)	N0 50% (10)	N0 57.9% (11)
N+57.1% (4)	N+50% (10)	N+42.1% (8)
UICC Stage (n)		
I-II 42.90% (3)	I-II 60% (12)	I-II 26.3% (5)
III-IV 57.10% (4)	III-IV 40% (8)	III-IV 73.7% (14)

Table 3: TNM and UICC staging of the patients treated with curative intent.

Discussion

There are well-recognized risk factors for cholangiocarcinoma, such as primary sclerosing cholangitis (especially in western countries), parasitic infections (liver flukes *Clonorchis sinensis* and *Opisthorchis viverrini* in asian countries), hepatolithiasis, congenital biliary anomalies, chronic typhoid carriage, bile duct adenoma, biliary papillomatosis, obesity, drug exposure and genetic risks [6,10,13].

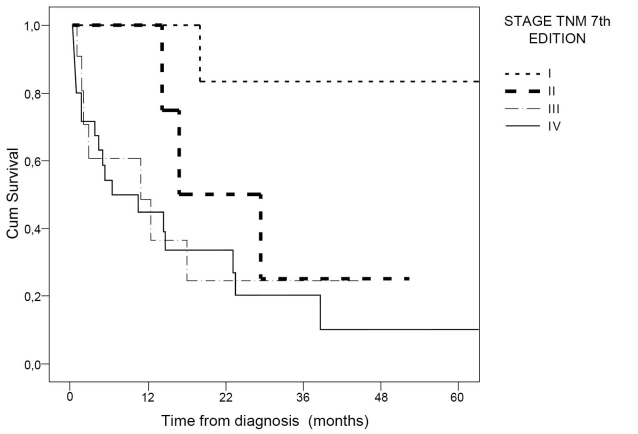

Figure 2: Survival curves of the patients classified by the TNM stage (7th edtn).

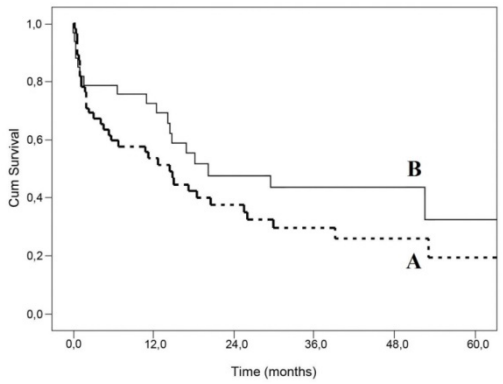

Figure 3: Overall survival curve for all 76 patients observed (A) and survival curve of 42 patients with R0 margins (B).

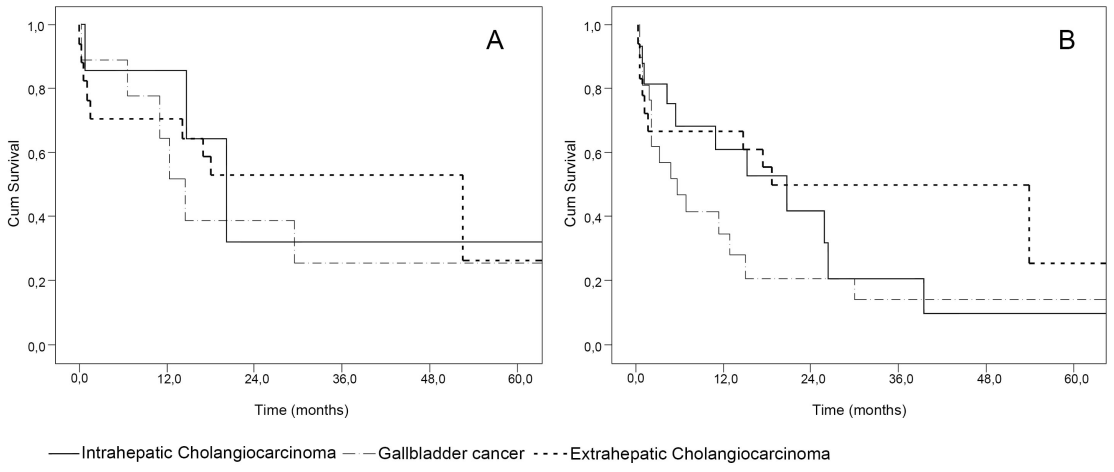

Figure 4: Survival curves of 42 patients with R0 resection margins, further classified on the anatomic origin of the neoplasia (A) and Survival curves of 76 patients classified on the anatomic origin of the neoplasia (B).

Chronic biliary inflammation is the most important risk factor in this pathology and it is also the first step to the carcinogenesis. Indeed the inflammation may modify the expression patterns of growth factors, pro-inflammatory cytokines and their receptors. The cytokines produced by biliary epithelium and activated macrophages can modulate gene expression and lead to activation of carcinogen metabolism [14]. At the time of diagnosis, patients are frequently found to have disease beyond the limits of probably curative surgical therapy (R0), for example in case of multiple intrahepatic metastases, peritoneal carcinomatosis or distant metastases (bones, lungs etc).

The clinical diagnosis of cholangiocarcinoma is challenging due to the lack of specific signs and symptoms, especially in the pre-icteric phase, and as a result of this the diagnosis is often not made until the disease is highly advanced. Many of the presenting features of cholangiocarcinoma overlap with benign biliary and upper gastrointestinal conditions, especially gallstone disease, benign biliary strictures, and other carcinomas. Actually there are no effective screening programs, and a diagnosis in the early stage is very hard. In fact no imaging test or biochemical assay can discover the cholangiocarcinoma in this phase or distinguish between benign and malignant disease [15]. Therefore, multidisciplinary investigative approaches are needed to overcome this problem, in particular an appropriate non-invasive screening program could significantly improve the early diagnosis, the surgical results and consequently the prognosis of the disease. Preoperative study, especially with imaging, is fundamental to confirm the pathology and provide to the surgeon the necessary informations to program the appropriate surgical procedure.

To decrease post-operative mortality and morbidity an adequate preoperative study with biochemical blood tests, cardiologic and anesthesiologic evaluation is mandatory. Even if surgical techniques and postoperative management improved considerably in recent years (biliary drainage, portal vein embolization), the most demolitive procedures, like extended hepatectomy, still entails significant morbidity and mortality. Most surgical series have reported a mortality rate lower than 5%, but the complication rate is still high and it varies from 20% to 85% [16-19]. In our experience, the mortality and morbidity rates were 6.9% and 41.4% respectively. The management of patients with lymph nodes metastases is controversial. The anatomical distribution of the lymphatic drainage is different in relation to the different malignant origin from the biliary tree [12]. Another important topic is the surgical management of patient with evidence of metastatic lymph nodes, especially patients with involvement of N2 nodes (para-aortic, superior mesenteric artery, and celiac artery nodes). A recent study suggests routinary sampling of the highest peripancreatic lymph node, considered as a sentinel node for N2 disease, in order to identify patients with biliary tract malignancy who may not benefit from standard surgical resection [18]. This surgical approach could be useful especially in association with the staging laparoscopy, that is a practical and accurate method to establish which patients are candidates for moderate, extreme, or palliative treatment [20]. To date the surgical approach is the best therapeutic strategy to achieve a realistic chance of cure for cholangiocarcinoma [21]. Unfortunately at the time of diagnosis, patients with cholangiocarcinoma are frequently found to have disease beyond the limits of surgical therapy. The resectability rate is still low, varying from 19% to 85% in the literature [22-27]. In our study the overall resectability rate is 60.5%, and a rate of surgical resectability with curative intent, free-margins (R0), around 55%. Extra-hepatic cholangiocarcinoma develops through the lymphatic ways that are numerous along the extra-hepatic biliary channels. The value of hilar lymphadenectomy is only diagnostic. Besides, it is usually admitted that a radical resection must have at least 1 cm of free margin of resection. The improvements in the quality of preoperative non-invasive imaging, as CT scan, MR imaging, and CT-PET scan, in association with explorative/diagnostic laparoscopy can significantly improve the results of surgery and reduce the incidence of unnecessary explorative laparotomy procedures. The small quantity of patients affected by this rare pathology and the late diagnosis, also in high-volume hepatobiliary centers, are the main problems for studying and evaluating quantitatively new methods and techniques in terms of diagnosis, therapy and surgical procedures. This represents a great incentive to increase and improve the collaboration between hepato-biliary centers, also located in different country, to amplify the knowledge and find a better diagnostic and therapeutic approach, in this highly specialist and technically difficult field. The prognosis for the patients affected by cholangiocarcinoma is unfortunately still unsatisfactory. In fact, in literature, the 5 years survival rate after resection varies from 8 to 89% [28-34]. In our study the overall 5 years survival rate was 19.6%, and in the subgroup of patients who underwent R0 resection the 5 years survival rate was 32.6%. The radical resection (R0) is one of the most important prognostic factors after surgical resection, and this study confirms the leading role of tumor free margins in the improvement of the survival rate. In conclusion our experience confirms the main role of surgical R0 resections with curative intent, since them represent the lonely therapy, actually for achieving a long term survival. These data are widely confirmed in literature [35,36]. Complete resection of the neoplasia is also confirmed in this study as one of the most important prognostic factors in the surgical treatment of the cholangiocarcinoma; so this should be the main target for the surgeon together with the reduction of the postoperative morbidity and mortality. The patients afflicted by this devastating cancer must be correctly studied preoperatively, accurately prepared for the surgical procedure, and in every case the possibility of a different therapeutic approach should be evaluated, for example chemotherapy and/or radiotherapy as adjuvant or neoadjuvant treatment [35,37]. The adequate clinical evaluation, the correct surgical procedure, the opportune adiuvant/neoadiuvant therapy, and a careful management of the patients pre and postoperatively can improve the results. On the basis of all these considerations colangiocarcinoma should be treated, preferably, in high specialization centers for hepato-biliary diseases, where a dedicated medical staff, with a good experience, surgical practise and modern facilities can obtain the most important results to decrease mortality and increase long-term survival: Early diagnosis and adequate treatment.

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