-Original Clinical Research-

Hilar cholangiocarcinoma fifteen-year experience with 243 patients at a single Egyptian center

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Abstract

Background

Hilar cholangiocarcinoma (HCCA) is a challenging problem for surgeons because surgery is the only effective therapy for these patients. In this study, we review 15 years of HCCC cases and treatment at a single Egyptian center.

Methods

From January 1995 to October 2010, 825 patients with HCCC were referred to Gastroenterology Surgical Center, Mansoura University, Egypt. From those 243 underwent potentially curative resection giving respectability rate of 29.4%, and the remaining patients (70.6%) underwent non-surgical treatment because of advanced disease, advanced cirrhosis, poor general condition and distant metastasis and locally advanced diseases. Data were recorded for the 243 cases (subjected to different types of hepatic resection), including demographics, medical history, presenting symptoms, and biochemical, radiological, and pathological parameters.

Results

The overall resectability rate of the patients studied was 29.4% (243/825). Localized resection, right hepatectomy, or left hepatectomy were completed in 30.5%, 22.6%, and 46.9% respectively, and segment one in 58 % R0 status was achieved in 49.8% of patients. The overall complication rate was 35%. Operative mortality was 6.6% with a five-year survival rate of 16%. Recurrence occurred in 92 (37.8%) the site of recurrence was hepatic (24.3%) and local (13.5%). Resection margin (R0) (P<0.001), lymph node status (P<0.001) (negative), degree of differentiation (P<0.001), segment one resection (P<0.001) (positive), and status of liver (P<0.001) (normal or cirrhotic) predicted statistically higher survival (P<0.001). According to multivariate analysis, R0 lymph node status and well differentiated status. Prediction improved survival among all patients.

Conclusion

From these case studies, aggressive surgery with caudate lobe resection with normal liver parenchyma may produce better prognoses in patients with resectable HCCA.

Key words:

Hilar cholangiocarcinoma; Surgery; Egyptian

INTRODUCTION

Hilar cholangiocarcinoma (HCCA) usually has a poor prognosis related to local tumor spread and the effects of biliary obstruction and cholangitis, which can lead to liver cell failure. [1] These tumors are often difficult to manage surgically because of their proximity to and possible infiltration of the portal vein, hepatic artery, and the surrounding liver parenchyma, including the caudate lobe. Resection is currently favored by most experienced hepatobiliary surgeons because it accomplishes both tumor excision and restoration of bilioenteric flow. [2] We report here our fifteen years experience in the surgical treatment of HCCA.

PATIENTS AND METHODS

We reviewed the records of 243 patients with histologically confirmed HCCA who underwent different types of resection at the Gastroenterology Center, Mansoura University, Egypt, from January 1995 until October 2010. Non-surgically managed patients were excluded from the study. Recorded data for the 243 cases included demographics, medical history, presenting symptoms, and biochemical, radiological (US, Spiral CT, MRCP) and pathological information. Of those patients, 15 were referred to our center with history of cholecystectomy and T-tube drainage, and 5 cases with history of exploration without any drainage were treated in other hospitals. Preoperative biliary drainage was completed in our center by ERCP or PTD in 35 and 82 cases, respectively. R0 resection was defined as cases in which no gross or microscopic tumor evidence was left behind, while R1 resections had microscopically positive margins and R2 resections still contained some gross tumor matter. Hospital mortality was calculated as death during the first 30 postoperative days.

Follow-up

Follow-up assessments included clinical and laboratory examinations, tumor marker measurements, ultrasound, and/or CT analysis every three months for the first 2 postoperative years and every six months from the third postoperative year until death. Follow-up examinations were also completed if recurrence was suspected.

Statistical Analysis

Data were analyzed using Microsoft Excel and the Statistical Package for Social Science version 16 (SPSS Inc., Chicago, IL). Quantitative data are represented as mean ± SD, and qualitative data are represented as frequency and proportion. The analysis of the data was performed to test statistical significant difference between groups. For quantitative data, Student's t-test was used to compare two groups, and one-way ANOVA to compare more than two groups. The Chi-square test was used to analyze qualitative data.

Multivariate regression analysis was completed to determine predictable variables for survival, and a Kaplan Meier survival curve was drawn with log rank analysis for the survival function. A P value of ≤ 0.05 at a confidence interval 95% was considered statistically significant.

RESULTS

Patients and Tumors

Between January 1995 and October 2010, 243 HCCA cases were subjected to different types of hepatic resection. The patient population included 164 men and 99 women with a median age of 53.3 ($\pm$9.9) years (range: 23-75). The main symptoms upon admission were jaundice (99.6%), weight loss (45.6%), fever (35%), and abdominal pain (34.2%). With regards to virology, 42.2% of patients had HCV, and 1.54% had HBV. The liver was normal in 54% of cases and cirrhotic in 46% of cases. Biliary stones, inflammatory bowel disease, and primary sclerosing cholangitis were concomitant diagnoses in 24%, 2%, and 1.1% of patients, respectively (Table 1).

Table 1 Demographic data of 243 resected patients

Data		
Total number		243
Age/year		53.3± 9.97
Sex M/F		149/94(1.58:1)
presentation	Jaundice	242(99.6%)
	Weight loss	111(45.7%)
	Pain	85(35%)
Liver pathology	Cirrhotic	102(42%)
	Non -Cirrhotic	141(58%)
Laboratory Investigation	Alb	3.7±0.44
	Bil	15.2±9.63
	Alk. ph	31.0±39.5
	OT	106.1±137.4
	PT	95.9±105.9
	Ca19.9	381.7±256.2
	alpha-FP	3.2±2.5
	CEA	5.4 ±13.4
	HCV+VE	4(1.6%)
	HBsAg +VE	101(41.6%)
Preoperative drainage	PTD	168(69.1%)
	ERCP	209(86%)

Operative Strategy

Assessment of resectability

Evaluation of patients with HCCC is mainly an assessment of resectability, since resection is the only hope. In the last 20 years the definition of the resectability and standardised opinion has not been agreed upon, especially between Japanese and western authors.[3] Physical status of the patients and liver functions, biliary extend of neoplasm, vascular involvement, presence of lower atrophy, lymph node involvement and presence of distant metastases. All these factors must be taken into consideration before the decision of resection. Our treatment strategy included hepatic resection combined with resection of the extrahepatic bile duct, lymph nodes, connective tissue at the celiac trunk and suprapancreatic areas followed by the hepatoduodenal ligament around the hepatic artery and portal vein in an en bloc fashion. The choice of operative procedure was dependent upon the preoperative evaluation, liver cirrhosis, lobar atrophy and intraoperative findings such as the level of tumor and its intraductal extension.

Localized resection (resection of part of segment 4) was performed in patients with markedly cirrhotic livers, locally advanced tumors and poor general conditions. Left hepatectomy was selected in cases of left lobe atrophy, invasion of the left portal or hepatic branches or extension of the tumor up to the parenchyma of the left lobe. Right hepatectomy was completed in cases of right lobe atrophy, invasion of the right portal or hepatic branches or extension of the tumor up to the secondary branches of the biliary system. Caudate lobe resection was also completed in the majority of cases within the last five years.

Localized resection, right hepatectomy or left hepatectomy were completed in 30.5%, 22.6% and 46.9% of cases, respectively. The criteria of respectability were patients without distant metastasis , peritoneal dissimination , bilateral involvement of biliary system up to the parenchyma of the liver , bilateral vascular involvement. Segment one resection associated with lobar hepatectomy was performed in 58% of cases, and vascular resection was selected in 5 cases (four for the portal vein and one for the hepatic artery). Seventy (28.8%) cases needed more than 3 units of blood for transfusions. One, two, three or four biliary enteric anastomoses were completed in 114 (46.9%), 112 (46.1%), 8 (3.3%), and 3 (1.2%) cases, respectively. Histologic evaluation of the tumors revealed that all were adenocarcinomas. An R0 status was achieved in 49.8% of all resections. Resected lymph nodes were positive for bile duct cancer in 38.3% of patients (Table 2).

Morbidity and Mortality

Of the 243 surgically resected cases, the overall complication rate was 35%. Biliary leak was reported in 53 (22%) cases and biliary fistula in 10 (4%) (two reoperations and eight conservative treatments). Postoperative bleeding was reported in 7 cases (2.8%), and three of these cases were upper GIT hemorrhage (two were due to stress ulcers and were managed conservatively, and one resulted from the enteroenterostomy and was managed by re-exploration). The remaining 4 cases exhibited bleeding from the surface of the liver (2 cases), omental veins (one case) or the stump of the right portal vein (one case). Superficial wound infection occurred in 56 cases (23%), liver cell failure (LCF) in 39 (16%), pneumonia in 10 cases (4%) , left portal vein thrombosis after right hepatectomy in one case leading to death. and renal failure in one case

The operative mortality rate was 16 cases (6.6%). Hepatic cell failure, massive infection, cardiac arrest, hepatorenal syndrome or portal vein thrombosis were the causes of death in 8, 3, 1, 3, and 1 cases, respectively.

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Table 2 Operative data of 243 resected cases

Item		No	%
Extent of resection	Minor resection	70	28.50
	Major resection	173	71.20
Type of resection	S4	74	30.50
	L	114	46.90
	R	55	22.60
	SR1*	102	42.20
No of biliary ananstomosis	Biliary 1	86	47
	Biliary 2	79	46
	Biliary 3	4	3.30
	Biliary 4	2	1.20
Blood transfusion	Bl T. <3 units	173	71.20
	Bl T. >3 units	70	28.30
LN status	LN +ve	93	38.30
	LN –ve	150	61.70
Tumor differentiation	Diff. well	96	39.50
	Diff. moderate	94	39.50
	Diff. poor	53	21.80

* SR1 = segment one resection in combination with other types of hepatectomy

Recurrence

Of 243 cases, 92 (37.8%) experienced disease recurrence. The site of recurrence was hepatic or local in 59 (24.3%) and 33 (13.6%) patients, respectively. Twenty-five of the patients with local recurrence presented with obstructive jaundice and were treated by percutaneous transhepatic drainage and dilatation of the obstructed anastomotic site. Resection of the recurrence at the anastomotic site and a reconstruction of the anastomosis were performed in 8 cases.

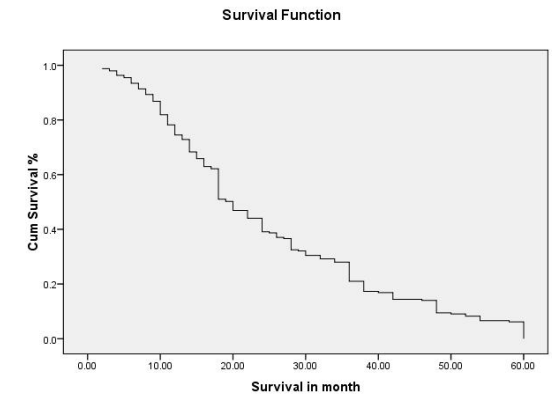
Survival

5 year survival for all patients was 16% with a mean survival of 22.2±15.6 months (range, 0-72 months). Figure 1 and Table 3 show the survival, liver pathology (normal, cirrhotic), type of resection (minor resection, major resection), status of resection margins (R0, R1), lymph node cancer status (positive or negative), degree of differentiation (well, moderate, or poor), and segment I resection (positive or negative) for all patients.

Log-rank analysis showed that normal liver (P<0.001), R0 (P<0.001), negative lymph node status (P<0.001), a well-differentiated tumor (P<0.001), and segment I resection (P<0.001) predicted higher survival. When these prognostic variables were examined according to multivariate analyses, the predictable factors for survival were cut margin negative, segment I resection, a well-differentiated tumor, and negative lymph nodes.

Table 3 Prognostic factors

Prognostic Factors	Types	Mean Survival	SD	Median	*P*
LN	Positive 93(38.3%)	16.2581	12.1645	14	<0.001***
	Negative 150(61.7%)	25.9433	16.4302	24	
Liver	Normal 141(58%)	25.5993	16.6537	24	<0.001***
	Cirrhotic 102(42%)	17.5882	12.8181	16	
S1R	Positive 102(42%)	29.4216	16.9796	27	<0.001***
	Negative 141(58%)	21.4326	13.8323	17	
Diff	DIFF 96(39.5%)	27.0313	16.2127	24	<0.001***
	Moderate 94(38.7%)	22.2234	15.5212	18	
	Poor 53(21.8%)	13.5755	10.4363	12	
Cut margin	Positive 122(50.2%)	15.8074	9.4264	15	<0.001***
	Negative 121(49.8%)	28.7190	17.8751	26	
Resection	Hepatic 173(71.2%)	23.2688	16.0972	22	0.106
	Localized 70(28.8%)	19.6857	14.2509	18	



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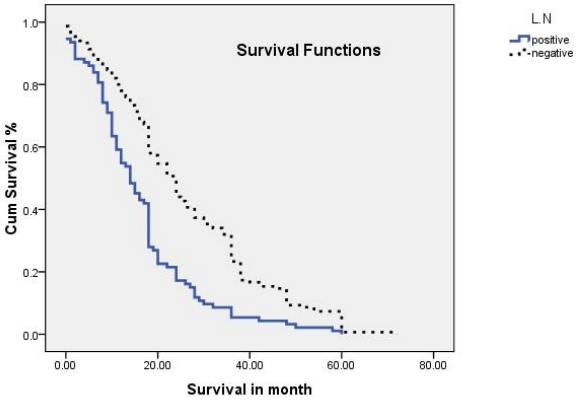

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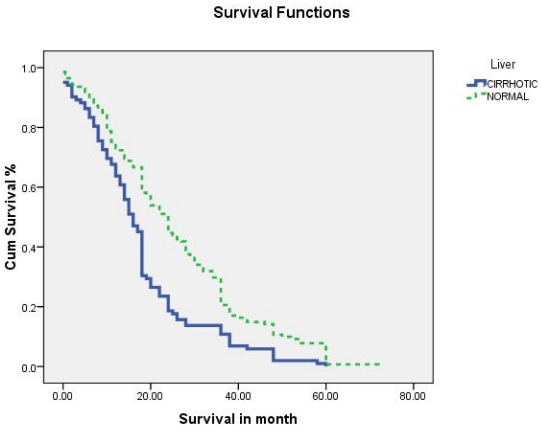

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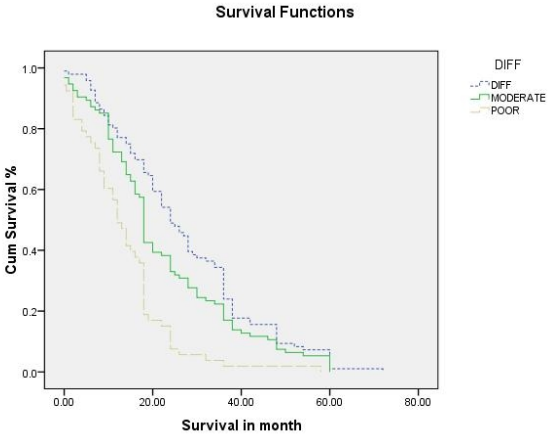

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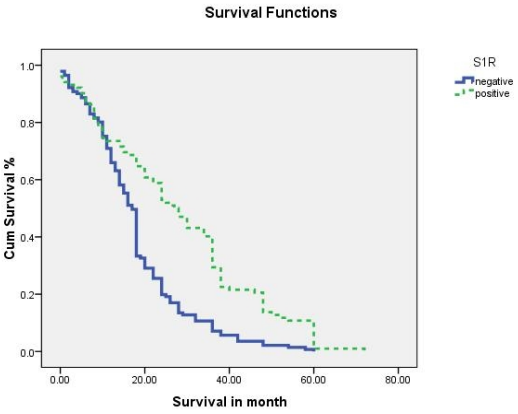

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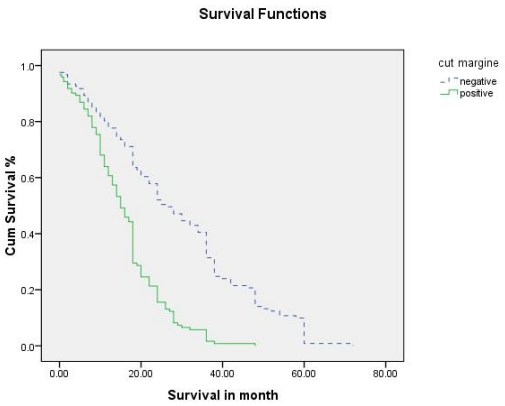

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Figure 1 Overview of the patient survival analysis.(A)Overall patient survival**.** (B) Lymph node (dashed line represents negative lymph node status)**.** (C) Liver status (dashed line represents normal liver). (D) Tumor differentiation (dashed line represents normal liver). (E) Segment I resection (dashed line represents positive resection). (F) Cut margin (dashed line represents the free cut margin).

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DISCUSSION

Surgery is the only effective therapy for HCCA and is aimed at complete resection of the tumor with negative histological margin, relief of symptoms related to biliary obstruction and restoration of bile drainage to the bowel. Patients who are found to have irresectable disease should be offer palliative therapy to relieve jaundice and pruritis. [4-6] In all cases considered unresectable, palliation must be obtained by the easiest, most comfortable method, [1] such as endoscopic stenting, percutaneous stenting or surgical bypass. However, surgical palliation should be considered if curative resection has been excluded during laparotomy for a planned curative resection. [7] We have reported our 15-year experience with 243 patients subjected to surgery for HCCA at a single medical center with resectability rate 29% in comparison to other centers (36-56%).[8,9] this low resectability can be explained by : first the high incidence of high liver cirrhosis (42%), second most of our patients were referred from rural areas with a long history of jaundice. In these areas people believe that jaundice means hepatitis and subconsciously attributed their symptoms to simple benign disorders, consequently a significant number of patient's delay is usually needed.

The first important step in a correct therapeutic approach to HCCA is a precise preoperative evaluation, which aims to provide the most accurate information possible about the stage of the tumor. Better prognoses have been shown to be associated with resection rather than with palliative treatment. [10-14] In our study, in those patients who underwent laparotomy and had tumors that were underestimated at the preoperative evaluation, such as those exhibiting peritoneal and or metastatic spread, palliative treatment in the form of biliary decompression was obtained by different methods (transmural drainage and surgical endoprothesis). Infiltration of the portal vein (main trunk or bifurcation without vascular thrombosis) or involvement of the local or locoregional lymph nodes and/or the adjacent liver are not absolute contraindications for resection.

The prognosis after HCCA resection is still unsatisfactory with 5-year overall survival rates varying from 9-35% in the majority of case studies. [2,15,16] In the present study, we observed a 16% 5-year survival rate.These poor results could be due to late diagnoses and presences of liver cirrhosis in 46% of our patients

Since the first successful liver and bile duct resection for the treatment of HCCA, there has been a debate about the extent of resection (localized or extensive). [11,17-19] In our experience, skeletonization resection of the extrahepatic biliary system is rarely sufficient to ensure radical treatment of the tumor because it must be combined with liver resection and even with caudate resection and biliary anastomosis in the first and second order ducts of the residual liver. In this study, 30.5% of patients underwent localized resection and 69.5% underwent major resection with median survival rates of 18 and 22 months, respectively, with no significant differences between the two groups (P<0.106) these results are similar to those observed in some studies[20] and contrary to those in other reports. [21]

The free safety margin (R0) is defined as the macroscopic and microscopic tumor-free areas at the resected specimen margin. However, an earlier belief at our center and others[2, 21-24] was that increased morbidity and mortality associated with aggressive liver resection for HCCA potentially outweighed the benefits derived from obtaining negative surgical margins. It is now widely recognized, according to our study and others, that margin status is one of the strongest predictors of long-term survival. This model indicates that more aggressive surgery to achieve negative margins, including hepatic resection, is needed and has recently improved the 5-year survival rate for HCCA. At our center, the R0 rate of negative margins was 50.2% vs. the positive margin rate of 49.8% with median survival rates of 15 and 26 months, respectively (P≤0.001). These results are comparable with those reported in other studies. [3,25]

The concept of the importance of caudate lobe resection in association with hepatectomy in HCCA patients was adopted in recent years as it usually infiltrated with the tumors varying from 48% to 96%.[11,27] The value of this resection is now accepted, with a 5-year survival rate of 46% in those patients who underwent caudate lobe resection in comparison with 12% in patients without caudate lobe resection. [27] In our study, 42% of patients underwent segment I resection in addition to hepatectomy and had a median survival of 27 months that was significantly higher than patients who did not undergo the procedure (58% with a median survival of 17 months; P=0.001). Therefore, removal of the caudate lobe should be completed in every resectable case because many authors have appreciated the importance of this procedure.

Lymph node involvement is an important prognostic factor in HCCC and is present in 30-50% of patients who have undergone surgical resection. [20, 28] Most publications advise lymph node dissection at the porta hepatis and around the hepatic artery for staging and disease control. [3, 2, 29] Our policy was to start with lymph node dissection at the celiac trunk, common hepatic artery, retero-duodenal and porta hepatis. In the literature, different studies have shown that the 5-year survival rate in patients with lymph node metastasis does not exceed 25%.[31-34] We observed similar results in our study as negative lymph nodes were present in 61% of patients with a median survival of 24 months, which was statistically

significant as compared to the 38% of patients with positive lymph nodes and a median survival time of 14 months (P= 0.001).

In Egypt, Hepatocellular carcinoma developed in addition to cirrhosis due to HCV in more than 80% of cases,[34] and cholangiocarcinoma has been known to occur with cirrhosis in 42% of patients. This high incidence of cirrhosis in those patiets can be attributed to high incidence of HCV , majourity of the patients live in rural areas and near different sources of pollution. Despite numerous reports concerning the prognostic factors of HCCA, to our knowledge, no studies have evaluated liver cirrhosis and HCV infection as prognostic factors. The present study showed that higher survival was predicted for patients with normal livers as compared to those with cirrhotic livers (P<0.001). In addition to all studied risk factors, the histologic type of HCCA has been reported to be an important prognostic factor, and patients with well-differentiated tumors were found to have a better prognosis than those with the moderately differentiated and undifferentiated types. [16, 31] We found similar results in the present study.

CONCLUSION

HCCA now is not uncommon disease in Egypt and develops on top of cirrhotic liver. In 43% of patients, aggressive surgery with caudate lobe resection in normal liver parenchyma may produce better prognoses in patients with resectable HCCC.

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