

Research Article

Challenges in Surgical Management of Extra-Hepatic Cholangiocarcinoma: A Case Series of 9-Year Experience in Pakistan

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Abstract

Background: Cholangiocarcinoma is rare but with alarmingly increasing incidence worldwide. Managing CCA is still challenging in developed as well as in resource-constraint countries.

Objective: To present single center, 9-year experience with the challenges in surgical management of extra-hepatic cholangiocarcinoma, (ECA) in Pakistan.

Method: Prospective, single-centered case series was conducted in the general surgery department of a tertiary care hospital in Lahore, from November 2005 to May 2014. A total of 34 patients were operated for cholangiocarcinoma (CCA) during the study period and were consecutively enrolled for the study after determining eligibility. Data was analyzed using SPSS version 21.

Results: Male to female ratio was 1.4:1 and mean age of the group was 53 years. Jaundice (100%) was the predominant symptom followed by pruritus in 94%, weight loss in 53%, pain 44% and fever in 32%. All patients had histologically diagnosed CCA. Incidences of hilar, mid and distal common bile duct (CBD) CCA were 53%, 23.5% and 23.5% respectively. Metastatic disease in lymph nodes were found in 41.2% (n=14) of the patients, 8.8% (n=3) patients had intrahepatic abscesses and 35.3% patients had hepatic metastases with ascites. Distal CCA was treated by pancreaticoduodenectomy or local bile duct excision and bilioenteric anastomosis whereas hilar cholangiocarcinoma was managed by Roux-en-Y hepaticojejunostomy subsequent to cholecystectomy and excision of pericholedochal tissues. Free resection margin were achieved in 58.8% (n=20) Overall mortality was 11.7% (n=4) during hospital stay. 50% of the patients were followed up for a mean period of 10.5 months and remained symptom free with better overall quality of life.

Conclusion: Current study described higher incidence of hilar CCA with male preponderance. Presentation is usually late and the best treatment offered can be a surgical palliation either R1 or R2 resection. Preoperative stenting makes dissection difficult and increases the risk of postoperative infections and hence overall morbidity and mortality.

Received | 01-02-2019: **Accepted** | 03-07-2019

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Keywords | Peri-hilar Cholangiocarcinoma, extra-hepatic cholangiocarcinoma, surgical management, case-series.

Introduction

Increasing incidence of cholangiocarcinoma (CCA) is being observed in literature globally.¹⁻³ CCA can emerge at any point of the biliary tree, from the canals of Hering to the main bile duct. Inter and intra tumor biological differences in lesions at various anatomical sites (hilar, perihilar, distal and extrahepatic CCA) can effect prognosis and outcome.^{4,5} Recent advances are moving towards a new classification of CCAs based on multiple cells of origin pointing epidemiological, biological and clinical heterogeneity.⁶ CCAs, taken together, represent the second most frequent type of primary liver cancer and ~3% of all gastrointestinal neoplasias.⁷ It is a rare disease accounting for less than 2% of all human malignancies. Several conditions as primary sclerosing cholangitis, congenital cystic disease and hepatolithiasis (oriental cholangiohepatitis) are associated with increased risk (10-20%).⁴ The tumor originates from epithelial lining of extra hepatic biliary system. Involvement of confluence or right or left hepatic ducts (hilar CCA) is most common and accounts for 40% to 60% of all cases. CCAs remain asymptomatic in early stage, hence are diagnosed late when they have already metastasized. Majority are diagnosed in elderly patients and if left untreated patients will rarely live more than 6 months and that with agonizing symptoms of jaundice, pruritus and debilitating cholangitis.⁷ Unresected cholangiocarcinoma is a rapidly fatal process, though timely and early intervention influences the natural history of the disease and results in better survival.⁸ Nonspecific biomarkers in serum, imaging and/or biopsy samples, are the main diagnostic tools. Direct biliary tract visualization by endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC) or magnetic resonance cholangiopancreatography (MRCP) are considered as diagnostic.⁹

Consensus guidelines for diagnosis and treatment of Cholangiocarcinoma were developed and reformed previously but still debates going on to decide for the optimal treatment modalities.^{7,10} Despite advances in non-surgical treatment, surgical curative and palliative interventions give best long term results. Multidisciplinary approach towards management of hilar cholangiocarcinoma (Klatskin tumor) is associated with better survival.¹¹ Cholangiocarcinoma (CCA) remains a difficult challenge for the surgeons. No

consensus has been reached regarding the optimal treatment modalities so far in literature. Current study was conducted to present the outcomes of our experience with the surgical management of CCA at Department of Surgery, Sheikh Zayed Hospital & Postgraduate Medical Institute, Lahore.

Method

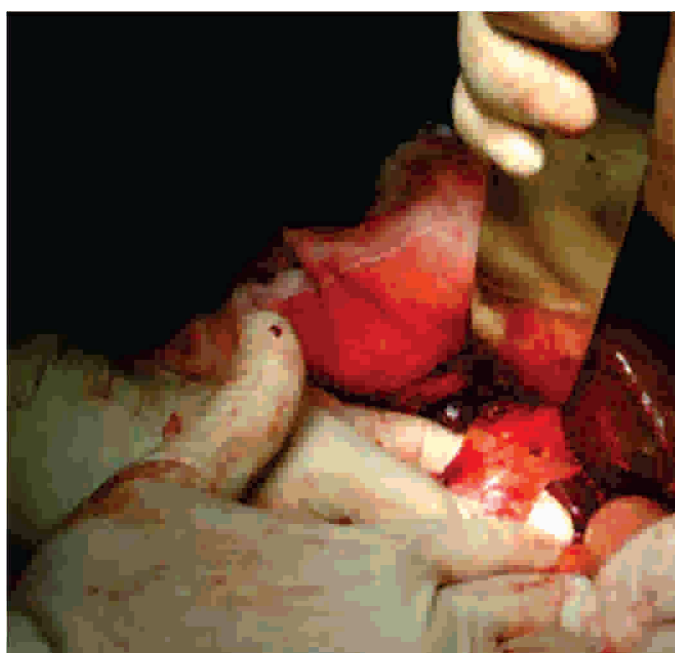
A prospective, single-centered, descriptive case-series was conducted in the department of Surgery at Shaikh Zayed Hospital, Lahore, Pakistan. 34 patients with cholangiocarcinoma underwent surgical resection between November 2005 and May 2014 and were consecutively enrolled for this study. This study described preoperative characteristics, method of surgery and perioperative outcome of surgical care. Written informed consent for procedure and use of patient data for research was obtained and all ethical issues were addressed observing Helsinki's principles of ethics. Data was collected on a pre-designed questionnaire and all compiled data was analyzed on statistical software SPSS version 21, elaborating 9-year experience at our center. Standard diagnostic guidelines were followed in all patients. Algorithm of diagnosis and resectability was followed, including ultra-sonography, CT (computer-tomography), MRI (magnetic resonance imaging), ERCP (endoscopic retrograde cholangiopancreatography) and PTC (percutaneous transhepatic cholangiography). Prior to surgery coagulation status and hypoprothrombinemia were assessed and corrected by parenteral Vitamin K and/or Fresh Frozen Plasma and albumin infusion. Occasionally Patients were admitted in surgical unit through OPD or emergency but 11/34 (32.4%) patients were referred from gastroenterology unit, out of these 36.3% (4/11) were stented for biliary decompression.

A re-sectional strategy was followed in line with Bismuth Corlette classification.¹² Consecutive patients with confirmed and or suspicious of Cholangiocarcinoma surgically managed over a 9-year period and were included in the study.

Operative technique/ procedure and follow up

Our surgical techniques and protocols for CCA management strictly follow the oncological standards.⁷ The abdomen is opened by roof top incision and tumor extent and resectability are assessed. For

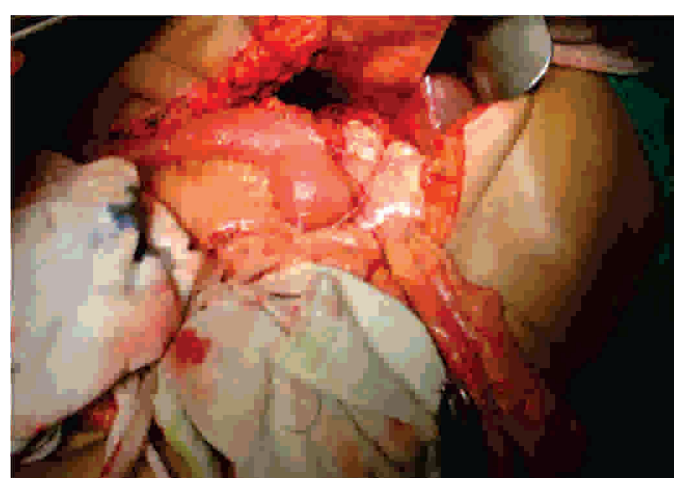
proximal tumors (Hilar), resection of the extra hepatic bile duct is carried out from the retro-duodenal part of the duct up to the hilum or beyond into the right or left ducts along with peri-choledochal tissue with skeletonization of the hepatic artery and the portal vein. No attempt at liver resection and/or vascular resection is made in PHC.¹² In case of invasion of the main vessels the tumor is shaved of the main vessels along with Common Bile Duct (CBD) and CHD (Common Hepatic Duct) and a biliary enteric bypass is carried out usually at or above the confluence more towards the left duct with an aim to construct approximately 2 cm wide anastomosis. Left hepatic duct approach is generally followed by division or lowering of hilar plate. At times, right duct exposure is achieved by incising liver parenchyma in gallbladder fossa. A retrocolic Roux-en-Y hepatic Jejunostomy using a 70cm long jejunal limb is made for the biliary enteric anastomosis. In all cases a sample of bile for culture and sensitivity is taken. For Bismuth Corlette type III tumors a stent (feeding tube size 12Fr) is placed across the anastomosis after dilating the stricture. In case of involvement of left hepatic duct, where viable anastomosis was not possible, external drainage of segment III duct was done as a desperate measure. None of the patients received pre-operative or post-operative chemoradiotherapy. For resectable tumors of distal CBD standard Kaush & Whipple pancreaticoduodenectomy was done. Data was analyzed using SPSS version 21.



Hilar dissection



Obstructed Distal CBD



Bilioenteric Reconstruction at the Hilum

Results

A total of 34 patients with cholangiocarcinoma (CCA) were surgically managed at Surgical Unit 1 Sheikh Zayed Postgraduate Medical Complex Hospital, Lahore over 9-years. 30 patients (88.2%) were resected successfully while 4(11.7%) were unresectable and drained externally. Resections were either R1 or R2 as the disease was advanced. In 20 (58.8%) patients negative histologic margins were achieved. Histological diagnosis was predominantly postoperative due to limitations of endoscopic sampling. Preoperative stenting presented with challenges like, difficult dissection, postoperative wound infection and intra-abdominal collections. Perioperative mortality was 11.7% (n=04).

There were 20 male (58.8%) and 14 female (41.2%) patients with sex ratio of (1.4:1) mean age of the group was 53 years (range 34 years – 79 years). All 34 (100%) patients presented with obstructive jaundice,

94% had pruritus, 53% had weight loss >10 kg while pain and fever were present in 44% and 32% respectively. Predominant presenting symptoms are given in Table-1.

47% (16/34) patients had co-morbid conditions; diabetes mellitus 37.5% (6/16), hypertension 81.2% (13/16) and ischemic heart disease 18.8% (3/16) and chronic obstructive airway disease in 25% (4/16).

In 88% (30/34) patients tumor / strictures were picked up upon ultrasound, 30 % (9/30) at cystic duct level, 46.7 % (14/30) at the hilum and 23.3% (7/30) in distal common bile duct (CBD). Enlarged lymph nodes were seen in 35.2% (12/34) patients and ascites was present in 29.4% (10/34) patients.

CT abdomen was done in 32 patients showing intrahepatic dilatation in 96.8% (31/32) patients and extra hepatic dilatation in 75% (24/32) patients. Tumors were detected in 96.8% (31/32) patients and enlarged lymph nodes were present in 37.5% (12/32) patients. Ascities was positive in 18.7% (6/32) patients. ERCP was performed in 12/34 (35.2%) patients, it showed strictures at cystic duct level in 6/12 (50%) patient and in distal CBD in 4/12 (33.3%) however in 2/12 (16.7%) cases there was failure to cannulate the duct. PTC was performed in 6/34 (11.7%) patients and it showed hilar CCA in 83.3% (5/6) patients and mid CBD stricture in 16.6% (1/6) patient. PTC was usually performed in the morning on the day of surgery. MRCP was done in 5.8% (2/34) patients having hilar CCA.

Operative finding showed hilar CCA in 53% (18/34) patients, distal CBD tumors in 23.5% (8/34) whereas, 23.5% (8/34) patients had tumor at mid CBD level. 41.2% (14/34) patients had metastatic lymph nodes. 8.8% (3/34) patients had intra-hepatic abscesses which were drained and 35.3% (12/34) patients had hepatic metastasis and ascites. On histopathology free resection margins were achieved in 58.8% (20/34) patients. There were 4/34 perioperative deaths making a hospital mortality of 11.7%. Two died from hepatic encephalopathy and one from upper gastrointestinal bleed and fourth patient died of sepsis. Operative findings are summarized in Table-2.

Overall postoperative morbidity/ complications during hospital stay were 41%. Major Post operative complications included surgical site infection (SSI)

24% (8/34), intrabdominal collection 21% (7/34) and these were managed conservatively by opening the wounds and US guided aspiration respectively. 17.6% (6/34) had preoperative biliary stenting 4 were stented in our institution while 2 were referred from outside. One out of 34 patients (2.9%) had stress ulceration of stomach and was managed conservatively. 8.8% (3/34) patients had postoperative pulmonary complications and 11.7% (4/34) developed cholangitis. The postoperative hospital stay ranged from 16 to 28 days with a mean period of 19 days.

Overall mortality was 11.7% (4/34). Total 88% (30/34) patients left the hospital in a satisfactory state with decrease in bilirubin levels, relief of pruritus and anorexia, hence improved quality of life.

Follow Up

We lost half (50%) of our patients in follow up beyond 6 to 8 postoperative weeks. However, 50% remained in follow up with range of 3.5 months to 18 months and mean follow up of 10.5 months. During follow up patients remained free from jaundice and pruritus and were satisfied with improved quality of life. Their subsequent morbidity was due to malignant ascites and/or metastatic diseases or co-existing morbidities.

Table 1: Presenting Symptoms of CCA

Symptoms	Percentage (n = 34)
Jaundice	100% (n=34) duration : 15 days to 3.5 months Mean 18.1mg / dl (9mg/dl to 34mg/dl)
Pruritus	94% (32/34)
Weight loss	53% (> 10 kg) (18/34)
Pain Abdomen	44% (15/34)
Fever	32% (11/34)

Table 2: Operative Findings of CCA

Anatomical Location / Operative Findings	Percentage	No. of Patients
Hilar CCA	53%	(18/34)
Distal CBD	23.5%	(8/34)
Middle CBD	23.5%	(8/34)
Operative Findings	Percentage	No. of Patients
Lymph Nodes	41.2%	(14/34)
Hepatic Metastasis	35.3%	(12/34)
Intrahepatic abscess	8.8%	(3/34)

Discussion

To the best of our knowledge this data represents one of the largest published reports so far, on the surgical treatment of cholangiocarcinoma from Pakistan. A

study from Pakistan published in 2009 on presentations and outcome of cholangiocarcinoma highlighted the delayed presentation of CCA in Karachi.¹³

Predominantly, in our study patients were males (59%) and mean age was 53 years (range 34–79 years) which is almost similar to a single center experience of Vladov¹⁴ and a systematic review and meta analysis of fifty-seven studies (4756 patients) in which patient age ranged from 49 to 67 years with 57% males⁽¹⁵⁾. This shows that the incidence of CCA is more in males than females globally and involving middle age predominantly.

In our study, pre-operative diagnosis and assessment was based on history, physical examination, laboratory investigations and imaging, including CT, US, ERCP, PTC and in two cases by MRCP. Diagnostic modalities help in localizing and staging tumors. Diagnostic algorithm based on currently available, highly sensitive and specific modalities can be used to diagnose CCA in suspects.⁹ One of the challenges we encountered in our experience was the under estimation of the extend of the disease by imaging. We found that tumors were more advanced than what they appeared to be on CT scans and or other modalities.

Approximately 80–90% of CCA are extra hepatic, with 50–70% originating in peri-hilar area and 20–30% involving the distal bile ducts.¹⁶ We had similar distribution, 53% hilar CCA, 24% distal CBD tumors whereas 24% at mid CBD level. It was similar to findings reported in a study.¹⁴

Preoperative biliary stenting remains a challenge since it leads to pericholedochal fibrosis and makes dissection difficult. We had 17.6% patients with preoperative biliary stenting. These patients were difficult to dissect because of cholangitis and pericholedochal adhesions. In literature, preoperative biliary drainage remains a controversial issue in such situations as it also increases rate of bacterial colonization of the biliary tree and perioperative infectious complications.^{7,17} This leads to yet another challenge of postoperative wound infection, most of our patients with this complication were those who had preoperative stenting. Conversely, many recent studies indicate a reduced incidence of liver failure when preoperative biliary drainage was used. Recent series dealing with cholangiocarcinoma especially

proximal carcinoma recommend transhepatic bile drainage to reduce serum bilirubin level to 2-3mg/dl prior to surgery.^{5,18} This is especially important when liver resection is added to the procedure as it significantly reduces postoperative fulminant liver failure. Acceptable recovery of the hepatic function after bile drainage takes about 4 weeks – 6 weeks.⁸ It is believed that bile drainage beyond 4-6 weeks will be associated with higher septic complications increasing morbidity. However, in our study we have operated upon patients with high bilirubin levels >15mg/dl and they had reasonably acceptable postoperative course. We have observed in current study that after surgical enterobiliary drainage, bilirubin level falls to 50% in approximately 7-10 days with significant relief from pruritus. Early referral to the surgical department and the decision of pre-operative biliary drainage should be taken in consultation with the operating surgeon. Hence to date, various studies on preoperative biliary drainage have failed to develop consensus and debate goes on.^{16,18}

In our study, 23.5% patients with distal CBD tumors were managed by proximal pancreaticoduodenectomy whereas patients with tumor of mid CBD 23.5%, and hilum 53% were managed by CBD excision cholecystectomy and excision of pericholedochal tissues followed by biliary enteric anastomosis at or above the confluence. Dissection and reconstruction at hilum is challenging of shorter extrahepatic course of right hepatic duct compared to the left duct. No liver resections were done. Studies from centers of excellence in managing CCA indicate that roughly one third of all hilar CCA patients will be candidates for curative resection and of these only patients in which negative histological margins were achieved were expected to have meaningful long term survival. The median survival time of patients with non-resectable hilar cholangiocarcinoma is about 3 months without intervention.¹¹ Even palliative resection with histologically positive margin have survival benefit over palliative endoprostatic treatment. Approximately 1/3rd of the hilar CCA are amenable to surgical resection (R0 or R1) with or without liver resection.¹⁹ Major hepatic resection (Segment I & IV) have shown 5 year survival varying from 8% to 45%. This needs to be reassessed in future because of short study period, variable extent of the disease and experience

of the surgeons. Use of hepatectomy improves survival and offers chance of cure in patients with more advanced diseases. It is challenging that rarity of the disease has limited our knowledge of variable prognostic factor such as histological.^{7,19,20} Papillary tumor morphology is an important prognostic factor and aggressive resectional approach warrant prolonged survival compared to, more common nodular sclerosing morphology. For Bismath type I and II hilar cholangiocarcinoma, the surgical approach should be aggressive and based on tumor histology. For nodular and infiltrating type, right hepatectomy offers best long term survival.²⁰

Although most of our patients presented late, overall in 55.8% patients, negative resection margins were achieved which is lower than a recent study reporting 73.9% Ro.²¹

Our long term survival remained low and it is probably due to advanced metastatic disease as 41.2% patients had metastasis to lymph nodes and 35.3% had hepatic metastasis and malignant ascites though a slightly higher abdominal lymph nodes involvement was found in 58.9% ECA in a study.²² Mean follow up was 8.5 months with a range of 3.5 to 18 months. We lost approximately 50% of our patients in follow up those who remained in follow up were Jaundice and pruritus free, and had good quality of life. Poor follow up remains challenging and onus lies on lack of awareness and understanding on part of the patients and scarcity of dedicated cancer centers in the country, Overall perioperative mortality was 11.7% which is comparable to 10.1% mortality in surgical management of hilar CCA.²³

Major post operative complications rate was around 51.5%¹⁴ and 43%²⁴ in few studies, while our rate was 41%. SSI (Surgical Site Infection) being the most common 24% patients, Intra-abdominal collection was found in 21%, pulmonary complications in 9% and these complication rates were lower than the experience of Vladov¹⁴ and were managed conservatively. Our complication rate was slightly lower than these studies, however, on the other hand, while looking at the rates of wound infection and abdominal abscesses we found slightly lower rates in another study.^{25,24}

Extra-hepatic CCA is, still a, challenging disease and

results are not very encouraging for the patient and the physician. Cure is a rarity in advanced disease and possible only if early diagnosis and treatment is done. Though standard treatment modality for CCA is debatable, still stage of presentation, extra hepatic metastasis and histologically negative resection margins determines prognosis.¹² Aggressive surgical management remains a best option.

Limitations of our study are small sample size, advanced disease at presentation and limited follow-up,

Conclusion

Cholangiocarcinoma is an uncommon malignancy and uniformly presents with obstructive jaundice. Early diagnosis and management is a key to long term survival. However, this is attainable in only a minority <30% of the patients. Distal CCA is treated by pancreaticoduodenectomy or local bile duct excision and bilioenteric anastomosis whereas hilar CCA is managed by hepaticojejunostomy. Main challenges faced are underestimation of the disease extent by preoperative imaging, difficult dissection and more postoperative complications with preoperative stenting, difficult hilar dissection, poor follow up, and rarity and late presentation of the disease. On account of our limited experience we can say that local resection (R0/R1) without major liver resection can achieve worthwhile palliation as regards relief of jaundice, itching and quality of life. Besides chemo radiotherapy has not shown significant survival benefit in adjuvant settings hence it is appropriate to hypothesize that surgical resection and bilioenteric bypass can provide desirable palliation in these unfortunate patients.

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