

Outcomes after Surgical Resection of Hilar Cholangiocarcinoma

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ABSTRACT

Objective: To report long term outcomes after surgical resection of hilar cholangiocarcinoma (hCCA).

Study Design: Cohort study.

Place and Duration of Study: Department of Liver Transplant and Hepatopancreaticobiliary Surgery, Shifa International Hospital, Islamabad, Pakistan, from October 2011 to April 2018.

Methodology: A prospective review of maintained database of patients who underwent surgical resection for hCCA was performed. A total of 24 patients were included. Outcome was assessed, based upon 90-day morbidity and mortality, 5-year recurrence-free survival (RFS) and overall survival (OS).

Results: Median age was 49 (23-73) years. Male to female ratio was 1.4:1. Median CA 19-9 level was 113 (2-1200) U/ml. Nine patients (37.5%) underwent right hepatectomy, six had right trisectionectomy (25%), three had central hepatectomy (12.5%) and left hepatectomy (12.5%) each, while three (12.5%) had other surgical procedures. In addition, two (8.3%) patients required portal vein resection and reconstruction. Median blood loss was 1350 (100-2000) ml. Median ICU stay was 4 (2-13) days, while hospital stay was 10 (6-32) days. Sixteen (66.7%) patients experienced at least one morbidity within 90 days, while 90-day mortality was 1/24 (4.1%). The overall recurrence rate was 6/18 (33.4%) and mortality was 9/18 (50%). The actuarial 5-year RFS was 60% and OS was 39%.

Conclusion: hCCA remains a technically challenging surgical problem. Outcomes comparable to international standards can be achieved in experienced centres.

Key Words: *Hepatectomy, Cholangiocarcinoma, Outcomes, Surgery.*

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INTRODUCTION

Hilar cholangiocarcinoma (hCCA) refers to cancer of the extra-hepatic bile ducts involving the right and/or left hepatic ducts and their confluence up to the level of insertion of cystic duct. Cholangiocarcinoma is a rare cancer with a prevalence of <6/100,000 people in majority of the world.¹ Surgery remains the only curative treatment, but majority of patients are not surgical candidates at the time of presentation.² Due to complex anatomy of hilar region, surgery often involves major liver resection along with excision of extra-hepatic biliary tree (EHBT) in hCCA. This increases the complexity of surgical procedure and leads to increased postoperative morbidity (20-66%) and mortality (0-9%).³

Other decisive factors in the management of hCCA include future liver remnant (FLR), involvement of portal vein and/or hepatic artery and excision of caudate lobe.⁴ The role of chemotherapy in neoadjuvant setting is promising, but remains limited.^{5,6} Due to rarity of hCCA and lack of specialized hepatobiliary centres in the

country; outcomes after surgical resection for hCCA have not been reported from Pakistan.

The objective of this study was to report long term outcomes after surgical resection of hCCA.

METHODOLOGY

A prospectively maintained database of patients who underwent surgical resection for hCCA between October 2011 and April 2018 at Department of Hepatopancreaticobiliary Surgery and Liver Transplantation, Shifa International Hospital, Islamabad, was reviewed. A total of 24 patients, age >18 years, who underwent curative surgical resection of hCCA were included. Patients who did not have hCCA on final histopathology were excluded.

Diagnosis of hCCA was based on history, tumor markers (CA 19-9), triple phase CT scan and/or MRI. Assessment of resectability, vascular involvement, nodal disease and future liver remnant (FLR) was based on CT scan and cholangiographic findings. Location was determined based on Bismuth-Corlette classification while staging was performed using American Joint Committee on Cancer, 7th staging manual.^{7,8} For patients with an estimated FLR <30%, preoperative portal vein embolisation (PVE) was considered to induce hypertrophy of the contralateral lobe of the liver and

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prevent liver failure from small FLR after surgery. For patients with total bilirubin >10 mg/dl requiring major liver resection, active cholangitis and/or expected delay in surgery; an ERCP was performed along with stent placement. At this time, cytology and/biopsy was also taken. The main emphasis was to drain the FLR via ERCP or PTC. For those who failed ERCP, PTC was performed for drainage. Otherwise, MRCP was performed on all patients. Surgery was attempted after 4 weeks. All patients were discussed in a multi-disciplinary team meeting and a treatment plan was formulated.

At the time of surgery, a staging laparotomy was performed. After excluding metastatic disease, peri portal lympho-denectomy was performed. For type I BC lesion, excision of extra hepatic bile duct was performed and margins were assessed on frozen section. For type II/III BC tumors, a right or left hepatectomy or trisectionectomy was also performed to ensure adequate margins. Caudatolobe was excised in all patients who had hepatic resection. A *roux-en-Y* hepaticojejunostomy was performed for drainage of remnant liver. For surveillance, a CT scan was performed at 6th month and then annually.

For the purpose of this study, patient demographics, CA 19-9 levels, type of surgical procedure, and operative as well as histopathological variables were assessed. Outcomes were assessed based on 90-day morbidity and mortality and 5-year recurrence-free and overall survival. Recurrence-free survival was calculated by subtracting date of recurrence from date of surgery. Overall survival was calculated by subtracting date of last follow-up / death from date of surgery. For determination of survival, Kaplan Meier curves were used. Significance between categorical variables was determined using Fisher's exact test. A p-value of <0.05 was considered statistically significant. The Statistical Package for Social Sciences (SPSS) version 20 was used for statistical analysis. The Hospital Ethics Committee granted approval for the study.

RESULTS

Median age was 49 (23-73) years. Median duration of symptoms was (0.2-36) months. Male to female ratio was 1.4:1. Median Ca 19-9 level was 113 (2-1200) U/ml. Preoperative biliary drainage was performed in 17 (70.8%) patients as shown in Table I. The positive bile culture rate in patients who had a PBD *versus* those who did not was 17/17 (100%) *versus* 2/7 (28.5%) (p <0.001).

Details of surgical procedures are shown in Table I. Two (8.3%) patients required portal vein resection and reconstruction, while no arterial resection was performed. In addition, one (4.1%) patient required Whipple's procedure along with a major hepatectomy due to peri ductal infiltrating tumor type. A total of seven (29.1%) patients underwent a trisectionectomy. Median blood loss was

1,350 ml (100-2000). Median ICU stay was 4 days (2-13), while hospital stay was 10 days (6-32).

On histopathological analysis, 10 (41.7%) patients had pT3 tumors and lymph node metastasis was seen in 6 (25%) patients as shown in Table II. Seven (29.1%) patients had positive margins. Median number of lymph nodes removed was 13.3 (6-39); while median number of positive lymph nodes was 0.5 (0-6). Thirteen (54.1%) patients received adjuvant chemotherapy or chemoradiation.

Sixteen (66.7%) patients experienced at least one morbidity within 90 days, while 90-day mortality was 1/24 (4.1%). The mortality was attributable to posthepatectomy liver

Table I: Patient characteristics and management.

Patient characteristics	Number	Percent
Gender (Male)	14	58.4
Endoscopic retrograde cholangiopancreatography	16	66.7
Percutaneous transhepatic biliary drainage	1	4.1
Surgical procedure		
Resection of bile duct	2	8.4
Resection of bile duct + Rt hepatectomy	6	25
Resection of bile duct + Rt hepatectomy + Portal vein resection	2	8.4
Resection of bile duct + Rt trisectionectomy	6	25
Resection of bile duct + Rt hepatectomy + Pancreaticoduodenectomy	1	4.1
Resection of bile duct + Lt hepatectomy	3	12.5
Resection of bile duct + Lt trisectionectomy	1	4.1
Resection of bile duct + Central hepatectomy	3	12.5
Adjuvant treatment		
Adjuvant chemotherapy or radiation	13	54.1

Table II: Histopathological variables.

	Number	Percent
Tumor size		
T1	5	20.8
T2	4	16.6
T3	10	41.6
T4	3	12.5
Grade		
Well	4	16.7
Moderate	17	70.8
Poor	3	12.5
Lymphovascular invasion	10	41.7
Perineural invasion	18	75
Nodal Involvement		
N1	5	20.8
N2	1	4.1
Positive margins	7	29.1

Table III: Total postoperative complications along with Clavien Dindo grading.

	Number	Percent
Wound infection (3A)	12	50
Sepsis (4)	6	25
Bile leak (3A)	1	4.1
Re-exploration for bleeding(3B)	1	4.1
Liver failure (5)	1	4.1

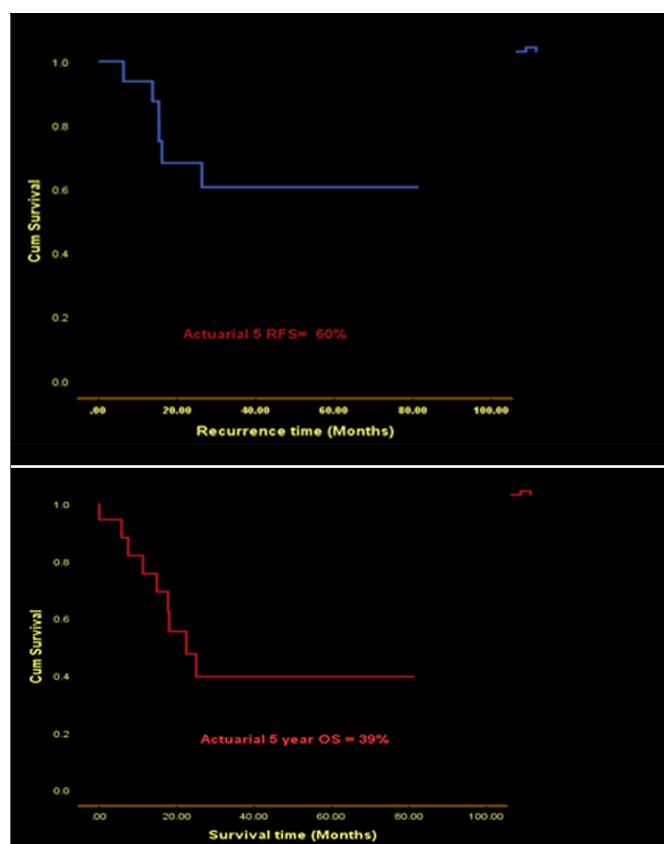


Figure 1: Actuarial 5-year recurrence-free survival and overall survival.

failure (PHLF). Details of postoperative morbidity are shown in Table III. Long term follow-up data was available for 18 patients. The recurrence rate was 6/18 (33.4%) and mortality was 9/18 (50%). The actuarial 5-year RFS was 60% and OS was 39% as shown in Figure 1. Recurrence rate in patients with negative and positive margins was 3/13 (23%) *versus* 3/5 (60%) ($p=0.2$). Recurrence rate in patients with negative and positive lymph nodes was 4/15 (26.7%) *versus* 2/3 (66.7%) ($p=0.2$).

DISCUSSION

The current study reports long term recurrence-free and overall survival in patients with hCCA who underwent surgical resection with curative intent. The results of the current study are comparable to previously published literature both in terms of distribution of histopathological variables and postoperative outcomes.^{3,9-11} The five-year reported survival for microscopic negative (R0) resection varies between 25%-45%, while for microscopic positive (R1) resection, it was only 0-23%. The postoperative morbidity ranged between 20-66%.

The positive margin rate, recurrence rate and long term survival in the current study was comparable to previously published reports on outcomes after surgical resection for hCCA.⁹⁻¹⁴ The low postoperative mortality in the current study can be attributed to a high volume

living donor liver transplant and hepatobiliary surgery experience.^{15,16} It has been shown that site-specific specialisation leads to improvement in outcomes.³ Majority of patients were referred for surgical intervention after a biliary drainage. All patients had positive cultures on peroperative bile fluid and stents sent for microbiological assessment, which is comparable to 87% positive bile culture rate in PBD group *versus* 17% in non PBD group reported previously.¹⁷ Although it is becoming increasingly clear that all patients with hCCA do not mandate preoperative stenting; which group would benefit most, remains a subject of debate. Nevertheless, whenever drainage was performed, FLR drainage was a must. The purpose of preoperative drainage was not to bring the bilirubin down but to ensure a sepsis-free FLR. Infection and cholestasis in remnant liver can hamper regenerative ability and have a prognostic value in patients with low FLR. It has been shown that preoperative cholangitis increases the risk of postoperative hepatic insufficiency by three-folds and risk of death by seven-folds.¹⁸

Role of vascular resection and reconstruction also remains debatable in the setting hCCA. It has been shown that postoperative outcomes with portal vein resection are acceptable and comparable to patients without portal vein resection.¹⁹ Outcomes after arterial resection and reconstruction in hCCA remain poor with 400% increase in mortality.²⁰ Thus, specialised / experienced centres can embark upon venous resections with little increase in morbidity and mortality. The authors experienced no post-op mortality in patients who underwent portal venous resection.

Majority of patients in the current study had a right-sided major liver resection. Short extra-hepatic length of RHD *versus* LHD, close proximity of the right hepatic artery to the common hepatic duct (CHD), and early take off of left hepatic artery from common hepatic artery in most patients make left-side less vulnerable to involvement. We perform excision of caudate as a routine in all patients undergoing liver resection for hCCA. This is due to tendency of hCCA to spread longitudinally along bile ducts and thus leaving caudate behind risks incomplete radical resection. A few patients underwent central hepatectomy (Taj Mahal operation) in the current study. This is a less practised, but useful technique in patients with low FLR who are not candidates for PVE. Adjuvant chemotherapy was used in patients with nodal disease or positive margins as practised worldwide.²¹

The limitations of the current study include its retrospective design and the potential to have missed significant events. In addition, a relatively smaller sample size makes comparison between various prognostic groups difficult. Considering the rarity of hCCA, the current study represents a significant patient number with long term follow-up.

The current study reports on outcomes after surgical resection for hCCA. To the best of the authors' knowledge,

this is the first report from Pakistan on long term outcomes and results appear to be comparable to international reports. Previously, results for patients who underwent palliative management for cholangio-carcinoma have been published but no single centre experience on curative surgical management of hCCA has been reported.²² There is a need to refer these patients to specialised/ experienced centres. Moreover, multicentre collaboration needs to be developed to have a better understanding and precise picture of this malignancy in Pakistani population.

CONCLUSION

hCCA remains a technically challenging surgical problem. Outcomes comparable to international standards can be achieved in specialised / experienced centres.

ETHICAL APPROVAL:

Hospital Ethics Committee granted approval for the study.

CONFLICT OF INTEREST:

Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

FSD, AR, ABHB: Made substantial contributions to the conception or design of the work; acquisition, analysis, or interpretation of data for the work; drafted the work and revised it critically; approved the final version to be published; agreed to be accountable for all aspects of the work. MA, NS, SKA: Made contributions to acquisition, analysis, or interpretation of data for the work; approved the final version to be published; agreed to be accountable for all aspects of the work.

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