ORIGINAL ARTICLE

# Perihilar and Intrahepatic Cholangiocarcinoma after Resection: Clinicopathological Characteristics, Outcomes, and Implications for Addition of Chemoradiotherapy

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*Received on:* 23 June 2024; *Accepted on*: 29 July 2024; *Published on*: 27 December 2024

## Abstract

**Background:** The purpose of the present study was to evaluate clinicopathological characteristics, patterns of recurrence, survival outcomes, and implications for the addition of chemoradiotherapy for patients with resected perihilar and intrahepatic cholangiocarcinoma (CCA).

**Materials and methods:** For the present retrospective study, we identified 38 and 10 patients with resected perihilar and intrahepatic CCA. In perihilar CCA, adjuvant treatment was given as chemotherapy ($n = 13$) or chemoradiotherapy ($n = 10$). In intrahepatic CCA, neoadjuvant treatment was given with transarterial chemoembolization (TACE, $n = 1$) or chemotherapy plus stereotactic body radiation therapy (SBRT, $n = 1$), and adjuvant treatment was given to 7 patients with chemotherapy or chemoradiotherapy.

**Results:** In perihilar CCA, preoperative biliary drainage procedures were performed in 27 out of 30 patients with jaundice. The adjacent liver showed secondary sclerosing cholangitis ($n = 5$) and fibrosis ($n = 19$). Locoregional recurrence involved the hepaticojejunostomy anastomotic site and lymph nodes. In intrahepatic CCA, the adjacent liver revealed cirrhosis ($n = 1$), secondary sclerosing cholangitis ($n = 1$), and fibrosis ($n = 6$). The sites of recurrence were in the remnant liver and lymph nodes ($n = 6$). In perihilar CCA, the median overall survival (OS) and disease-free survival (DFS) rates were 30.1 months (95% CI: 22.9–37.4) and 15.1 months (95% CI: 9.74–20.5), respectively. The 2-year and 3-year OS were 60.5% and 44.7%, respectively. Multivariate analysis revealed a significant association of no adjuvant treatment with decreased DFS ($p = 0.004$), HR 4.03 (95% CI: 1.57–10.4). Recurrence showed an unfavorable association with OS ($p = 0.056$), HR 2.90 (95% CI: 0.98–8.66). In intrahepatic CCA, the median OS and DFS rates were 41.2 months (95% CI: 13.5–68.9) and 10.8 months (95% CI: 1.98–19.6), respectively. The 2-year and 3-year OS were 66.7% and 53.3%, respectively. The patient with multiple intrahepatic CCA lesions and treated with neoadjuvant chemotherapy and SBRT showed partial pathological necrosis after resection and was disease-free at 3.5 years.

**Conclusions:** The present study showed the effectiveness of the combination of chemoradiotherapy with resection in improving locoregional disease control and survival in patients with perihilar and intrahepatic CCA.

**Keywords:** Biliary tract cancers, Biliary tract neoplasms, Chemoradiation, Chemotherapy, Cholangiocarcinoma, Radiotherapy, Resection, Stereotactic body radiotherapy.

*Euroasian Journal of Hepato-Gastroenterology* (2024): 10.5005/jp-journals-10018-1440

## Introduction

Bile duct cancers have been increasingly being reported as a distinct group with varying characteristics of the different anatomic subsites.[1,2] Surgical resection is the mainstay of treatment for perihilar and intrahepatic cholangiocarcinoma (CCA). However, a limited number of patients present with disease extent suitable for resection.[2] The resected patients remain at risk of recurrent disease during follow-up. The locoregional recurrences entail significant morbidity requiring biliary interventions in patients with resected extrahepatic and intrahepatic CCA.[3] The long-term survival has been reported as 5-year rates of 8–40% after resection from different centers.[4] There is a need for combination treatment approaches with resection in CCA to improve survival. An improvement in survival has been reported with adjuvant chemotherapy in patients with resected perihilar CCA.[5] There is growing evidence on the efficacy of the combination of chemotherapy and radiotherapy with surgery in CCA.[6–9] The purpose of the present study was to evaluate clinicopathological characteristics, patterns of recurrence, survival outcomes, and implications in the addition of chemoradiotherapy for patients with resected perihilar and intrahepatic CCA.

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**How to cite this article:** Sahai P, Rastogi A, Gupta A, *et al*. Perihilar and Intrahepatic Cholangiocarcinoma after Resection: Clinicopathological Characteristics, Outcomes, and Implications for Addition of

## Materials and Methods

### Inclusion Criteria

We identified all patients with the histological diagnosis of perihilar and intrahepatic CCA in surgical resection specimens from 2011 to 2020 from the histopathological and hospital-based cancer registry records of our institute. The patients had given signed informed consent for the procedures and treatments, and for publication of their clinical information in a journal with due efforts to conceal their identity. The patients' records were reviewed retrospectively to obtain demographic features, clinical presentation, risk factors, laboratory investigations, tumor markers, imaging, staging, pathological characteristics, treatment details, and survival outcomes. Tumor staging was performed following the American Joint Committee on Cancer (AJCC) staging system.[10,11] The details of neoadjuvant and adjuvant chemotherapy and radiotherapy were noted.

### Work-up and Treatment

#### *Perihilar Cholangiocarcinoma*

We identified 38 patients with resected perihilar CCA. Imaging was performed with contrast-enhanced computed tomography (CECT) and magnetic resonance cholangiopancreatography (MRCP). Six patients had undergone 18Fluorine-fluorodeoxyglucose positron emission tomography-contrast enhanced computed tomography (18F-FDG PET-CECT) as well for staging. Thirty patients (80%) had presented with obstructive jaundice with serum total bilirubin of >3 mg/dL and preoperative percutaneous transhepatic biliary drainage (PTBD) was performed in 26 and endoscopic retrograde cholangiopancreatography (ERCP) guided stenting in 1 of them. Preoperative portal vein embolization was performed in 4 patients. Surgical resection was performed at 2–8 weeks after the biliary drainage procedure in the majority of patients. In 3 patients, surgery was performed at 12–20 weeks after PTBD. Of 4 patients, the interval between PVE and surgical resection was 4–6 weeks in 3 patients and 11.3 weeks in 1 patient. Thirty-four patients had undergone hepatobiliary resection with hepatectomy plus caudate lobe resection plus extrahepatic bile duct resection plus lymph node dissection plus hepaticojejunostomy. The hepatectomy procedure that was performed was as follows: Right hepatectomy ($n = 13$), right extended hepatectomy ($n = 5$), right modified hepatectomy ($n = 3$), left hepatectomy ($n = 10$), left extended hepatectomy ($n = 2$), and left modified hepatectomy ($n = 1$). The remaining patients had undergone hepatopancreaticoduodenectomy ($n = 2$) and bile duct resection with Roux-en-Y hepaticojejunostomy ($n = 2$). Vascular reconstruction was performed in 7 out of the 34 patients with hepatobiliary resection. The 4 patients who had undergone hepatopancreaticoduodenectomy or bile duct resection did not undergo vascular reconstruction.

Twenty-three out of the 38 patients (60.5%) had received adjuvant treatment. Adjuvant treatment was administered with chemotherapy ($n = 13$, 56.5%) or chemoradiotherapy ($n = 10$, 43.5%). Two patients were advised chemoradiotherapy which they did not receive. Adjuvant treatment was started at 4–6 weeks after the surgery. If required for postoperative healing, adjuvant treatment was started by 8–12 weeks. The patients with R1 resection were given adjuvant concurrent chemoradiation (CCRT) preferably before chemotherapy. The protocol for adjuvant chemotherapy was 4–6 cycles of gemcitabine with cisplatin (GemCis, $n = 5$), gemcitabine with capecitabine (GemCap, $n = 3$), gemcitabine with oxaliplatin (GemOx, $n = 2$) or gemcitabine alone ($n = 3$). GemCis regimen was administered as gemcitabine 1000 mg/m$^2$ body surface area (BSA) and cisplatin 25 mg/m$^2$ intravenously both on day 1 and day 8 every 21 days. GemCap regimen was given as gemcitabine 1000 mg/m$^2$ intravenously on day 1 and day 8 with capecitabine 750 mg/m$^2$ given twice daily orally from day 1 to day 14 every 21 days. GemOx regimen was given as gemcitabine 1000 mg/m$^2$ and oxaliplatin 100 mg/m$^2$ intravenously both on day 1 and day 8 every 21 days. Gemcitabine alone was administered at 1000 mg/m$^2$ intravenously on days 1, 8, and 15, and cycles were repeated every 28 days. The modifications in chemotherapy dose and delays were allowed as per the patients' tolerance and adverse effects.

The patients treated with adjuvant chemoradiotherapy were given 4–6 cycles of chemotherapy before or after CCRT. The chemotherapy regimen was gemcitabine with capecitabine given before ($n = 1$) and after CCRT ($n = 2$). GemCis regimen was given before ($n = 3$) and after ($n = 1$) CCRT. One patient had received gemcitabine alone chemotherapy after CCRT. One patient had received adjuvant CCRT alone. The patient with squamous cell carcinoma (SCC) histology had received 4 cycles of paclitaxel and carboplatin-based chemotherapy after CCRT. Capecitabine 625 mg/m$^2$ twice a day orally was given as the concurrent chemotherapeutic drug with radiotherapy except in the patient with SCC histology who was treated with cisplatin. The patient with SCC histology was given CCRT 50 Gy/25 fractions/5 weeks with weekly cisplatin 40 mg/m$^2$ intravenously followed by 4 cycles of paclitaxel 175 mg/m$^2$ day 1 and carboplatin AUC 5 day 1 intravenously every 21 days adjuvant chemotherapy.

Radiotherapy dose fractionation was 45–50.4 Gy/25–28 fractions/5–5.5 weeks with 5 fractions per week. Radiation target volumes covered the tumor bed with the hepaticojejunostomy anastomotic site and nodal volumes, that is, portal, coeliac, and superior mesenteric artery with or without paraaortic regions (Fig. 1). The nodal volumes were delineated as defined under the Radiation Therapy Oncology Group (RTOG) guidelines. The planning was performed with volumetric modulated arc therapy (VMAT) or intensity modulated radiation therapy (IMRT) techniques.

#### *Intrahepatic Cholangiocarcinoma*

We identified 10 patients with resected intrahepatic CCA. The patients had undergone CECT for diagnostic imaging. Imaging was also performed with MRCP ($n = 4$) or contrast-enhanced magnetic resonance imaging (CEMRI) ($n = 2$). Five patients had undergone PET-CECT as well for staging. For the diagnosis of disease before resection, patients had undergone fine needle aspiration (FNA) ($n = 3$) or biopsy ($n = 3$) from the lesion which revealed adenocarcinoma ($n = 5$) or malignant cells ($n = 1$).

Of the 10 patients, 2 were treated with neoadjuvant therapy. In 1 out of the 2 patients, a preoperative clinical diagnosis of hepatocellular carcinoma (HCC) with non-alcoholic steato-hepatitis (NASH) related chronic liver disease with Child Pugh

Chemoradiotherapy. Euroasian J Hepato-Gastroenterol 2024;14(2): 134–144.

**Source of support:** Nil

**Conflict of interest:** None

**Patient consent statement:** The author(s) have obtained written informed consent from the patients for publication of case details and related images.

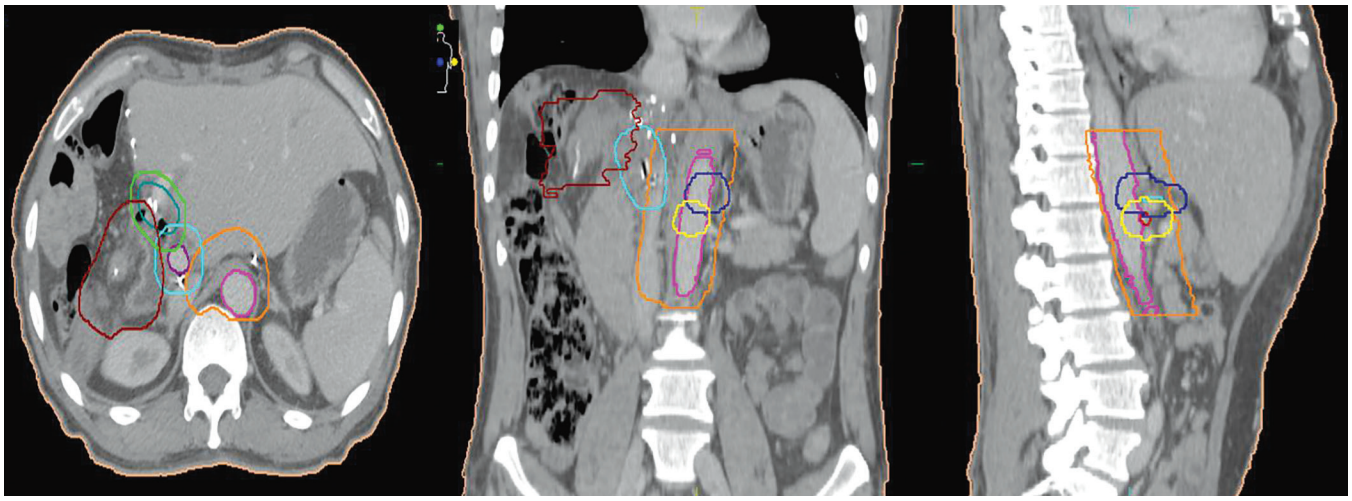


**Fig. 1:** Adjuvant radiotherapy target volume contours i.e., tumor bed (red), hepaticojejunostomy anastomosis expansion (green), portal vein expansion (light blue), aortic expansion (orange), coeliac artery expansion (dark blue), superior mesenteric artery expansion (yellow) for a patient with perihilar cholangiocarcinoma on axial, coronal, and sagittal images of CECT abdomen

class A was made and was treated with neoadjuvant drug-eluting beads transarterial chemoembolization (DEB-TACE) with doxorubicin. The other patient with clinical presentation of two intrahepatic lesions measuring 8.3 × 8.9 × 8.5 cm and 4.6 × 3.7 cm with serum CA19.9 of 89.2 U/mL had undergone portal vein embolization and then modified gemcitabine and oxaliplatin (mGEMOX)-based NACT followed by stereotactic body radiation therapy (SBRT). The mGEMOX regimen consisted of gemcitabine 900 mg/m$^2$ and oxaliplatin 80 mg/m$^2$ both given on day 1 and day 8 every 21 days. Dose modifications were done with clinical evaluation and monitoring of blood investigations, that is, complete blood count, and liver and kidney function tests. The gross tumor volumes (GTV) were delineated on a CECT abdomen (venous phase) and a 4-D CT was acquired for planning via the Anzai respiratory gating system (AZ-733VI, Anzai Medical Co. Ltd., Tokyo, Japan) along with an abdominal compression belt on the patient. The internal target volume (ITV) margins around the GTV were derived from the 4-D CT. The planning was performed with the VMAT technique for SBRT on computerized treatment planning system (Monaco version 5.11.03). The dose schedule for SBRT was 25 Gy in 5 daily fractions over 1 week given to PTV of both the lesions simultaneously with cone-beam computed tomography (CBCT) image guidance. The dose constraint was aimed at <15 Gy to ≥700 cc to the liver and a maximum point dose of <54 Gy EQD2 to the gastrointestinal luminal organs. Stereotactic body radiation therapy was performed with a linear accelerator (Versa HD, Elekta Oncology Systems, Crawley, UK). The target and dose volumes for the SBRT plan are illustrated in Figure 2. After SBRT, further chemotherapy was given with gemcitabine plus capecitabine; and irinotecan, 5-fluorouracil plus leucovorin-based regimens until surgery at 1 year from diagnosis and start of NACT and at 8 months after SBRT. All 10 patients had undergone partial hepatectomy. The surgical procedure performed in the patients was as follows: right hepatectomy ($n = 2$), right extended hepatectomy ($n = 1$), left hepatectomy ($n = 2$), left extended hepatectomy ($n = 2$), left modified hepatectomy ($n = 1$), central hepatectomy ($n = 1$), and extended cholecystectomy ($n = 1$).

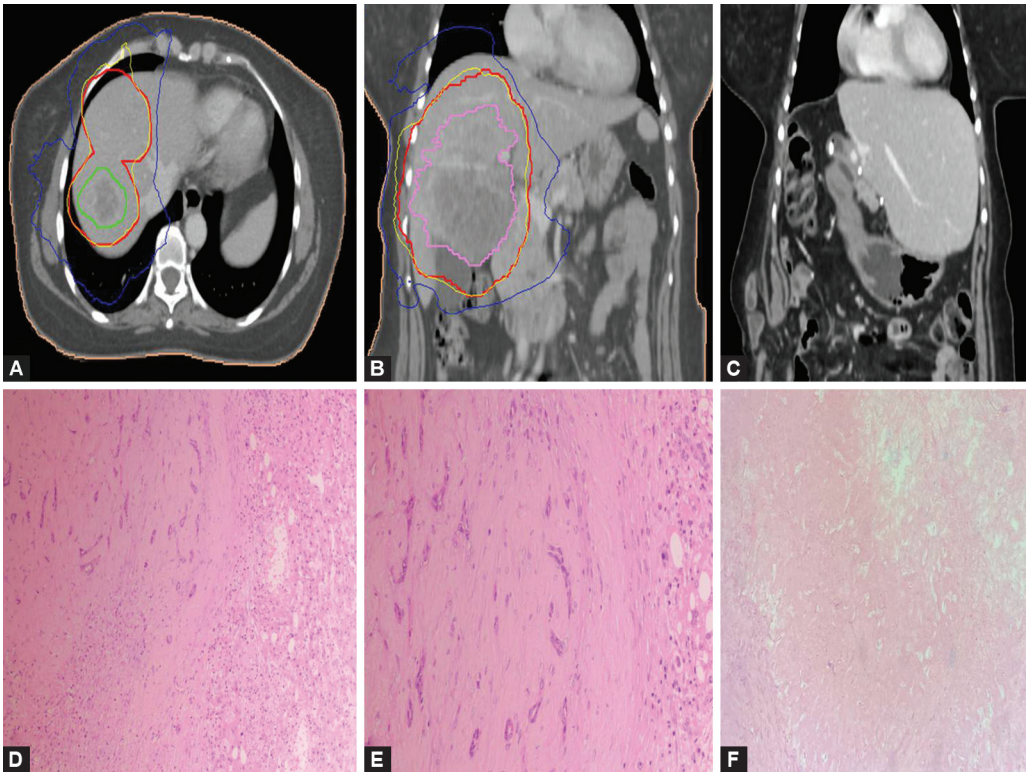
Of 7 patients who had received adjuvant treatment, 5 had received chemotherapy while 2 had received chemoradiotherapy. Gemcitabine-based chemotherapy as a single agent or in combination with cisplatin or capecitabine for 4–6 cycles was used in an adjuvant setting in 4 patients. One of the 7 patients who had received NACT and SBRT followed by resection received adjuvant chemotherapy with capecitabine for 4 cycles. The adjuvant CCRT protocol was with 45 Gy/25 fractions/5 weeks with concurrent capecitabine which was followed by gemcitabine chemotherapy in one of the 2 patients.

## Follow-up

The patients were followed up after surgery with clinical evaluation, blood investigations, tumor markers, and imaging. The patients were advised to follow-up every 3 months for 2 years and 4–6 monthly thereafter. The data cut-off of the present study was 31 December 2023. The dates of disease recurrence and last follow-up or death were recorded. The patterns of recurrence after surgery were noted as observed in the imaging with CECT, CEMRI, and/or positron emission tomography-contrast enhanced computed tomography (PET-CECT) with or without pathological confirmation. The treatment given for recurrence was noted.

## Statistical Analysis

Descriptive statistics were presented as median (range) or mean ± SD. Overall survival (OS) was calculated from the day of diagnosis to the date of last follow-up or the date of death. Disease-free survival (DFS) was calculated from the date of the surgery to the date that recurrent disease, death, or last follow-up was recorded. Survival was estimated as per the Kaplan–Meier method followed by a log-rank test. All patients were included in the intention-to-treat analysis. The factors associated with recurrence and survival after resection were analyzed using Cox proportional hazards regression to calculate the hazard ratio (HR) and its 95% CI: for survival or DFS. In univariate analysis, the variables with a $p$-value of $< 0.20$ were analyzed in multivariate analysis in which a $p$-value of $< 0.05$ was considered statistically significant. The analysis was carried out using SPSS version 28, IBM Corp. Ltd., Armonk, NY, USA.




**Figs 2A to F:** Stereotactic body radiation therapy target volumes in a patient with intrahepatic cholangiocarcinoma. (A and B) On axial and Coronal images of CECT abdomen with GTV segment VIII/VII (green), GTV segment IV/V (pink), PTV (red) with 100% dose isoline 25 Gy (yellow), 50% dose isoline (blue); (C) Coronal image of CECT abdomen at 2 years after surgical resection shows remnant left lobe of liver; Photomicrographs from the surgical specimen show irregular glands lined by malignant cells surrounded by desmoplastic stroma with features of residual adenocarcinoma along with adjacent liver parenchyma on right side of the images show mild macrovesicular steatosis [(D) HE, 100×; (E) HE, 200×]; Photomicrograph shows post-neoadjuvant chemoradiotherapy coagulative necrosis of malignant glands with surrounding desmoplastic stroma [(F) HE, 400×]

## Results

### Patient and Disease Characteristics

#### *Perihilar Cholangiocarcinoma*

We identified 38 patients with resected perihilar CCA. The clinical presentation of the patients is listed in Table 1. Out of the 26 patients who had undergone preoperative PTBD, 24 had decreased serum bilirubin levels before surgery. The patient who had undergone ERCP with stenting also had decreased serum bilirubin levels before surgery. Of 24 patients, the level of serum bilirubin before surgery was <3 mg/dL in 3, 3–5 mg/dL in 15, 5–7 mg/dL in 3, and 10.2–12.8 mg/dL in 3 patients.

#### *Intrahepatic Cholangiocarcinoma*

We identified 10 patients with resected intrahepatic CCA. The characteristics of the patients are listed in Table 2. All patients had normal serum total bilirubin and albumin levels at the time of diagnosis. Of the 8 patients who had serum CA19.9 level tested at diagnosis, 5 had raised while 3 had normal values. The level of CA19.9 was raised ranging from 89.2 to 2598.4 with a median of 174 U/mL. In 1 patient, serum alfa-fetoprotein was also raised (168.1 ng/mL) along with the CA19.9 level. The patient treated with DEB-TACE had decreased serum alfa-fetoprotein (AFP) level and radiological partial response before surgery. The patient treated with NACT and SBRT had decreased serum CA19.9 of 41.2 U/mL before surgery and 23.5 U/mL at 3 weeks after surgery.

### Pathological Examination

#### *Perihilar Cholangiocarcinoma*

The pathological characteristics of the 38 patients are listed in Table 1. Frozen section was performed in 21 patients from the bile duct margin and/or peritoneal or liver nodule, aortocaval/intraaortic lymph node, hilar tissue, or hepatoduodenal ligament (HDL) tissue. The frozen section was reported as positive for malignant cells on the bile duct margin ($n = 3$) and HDL tissue ($n = 1$). One out of the 3 patients with positive margin on the bile duct had positive malignancy on periductal tissue too. The suspected nodules in the liver, peritoneum, and lymph nodes in the aortocaval region were reported as negative for malignant cells.

The histological diagnosis was as follows: adenocarcinoma ($n = 35$), adenosquamous carcinoma with signet ring cell formation ($n = 1$), intraductal tubulo-papillary neoplasm with invasive carcinoma ($n = 1$), and keratinizing squamous cell carcinoma ($n = 1$). Among the 35 patients with adenocarcinoma, 1 had focal sarcomatous change, 1 had infiltrating-sclerosing differentiation, 1 had mucin-secreting adenocarcinoma, 1 had foci of squamoid differentiation, and 1 had an associated papillary tumor.

The following groups of lymph nodes were resected: hilar in 19, hepatoduodenal ligament in 13, cystic in 6, periportal/retroportal in 5, pericholedochal/peripancreatic/retropancreatic in 4, common hepatic artery in 3, and aortocaval in 10 patients. The number of positive resected lymph nodes was as follows: 1

**Table 1:** Clinical presentation of patients with resected perihilar cholangiocarcinoma

| *Characteristic* | *Number of patients (%)* |
|---|---|
| Patients | 38 |
| Age (years) | |
| Median (range) | 54.5 (33–78) |
| Gender | |
| Male | 28 (73.7) |
| Female | 10 (26.3) |
| Serum total bilirubin at presentation (mg/dL) | |
| ≤3 | 8 (21.1) |
| 3–10 | 6 (15.8) |
| 10–20 | 20 (52.6) |
| >20 | 4 (10.5) |
| Serum albumin at presentation <3.5 gm/dL | 30 (79) |
| Serum CA19.9 at presentation (U/mL) | |
| >37 | 16 (42.1) |
| ≤37 | 12 (31.6) |
| Bismuth classification | |
| II | 4 (10.5) |
| IIIa | 20 (52.6) |
| IIIb | 11 (29) |
| IV | 3 (7.89) |
| Preoperative PTBD | 26 (68.4) |
| pT classification | |
| pT1 | 5 (13.2) |
| pT2 | 26 (68.4) |
| pT3 | 7 (18.4) |
| pN classification | |
| pN0 | 18 (47.4) |
| pN1 | 17 (44.7) |
| pNx | 3 (7.90) |
| Pathological stage | |
| I | 3 (7.89) |
| II | 17 (44.7) |
| III | 18 (47.4) |
| Resection margin | |
| R0 | 25 (65.8) |
| R1 | 13 (34.2) |
| Tumor size | |
| ≤2 cm | 12 (31.6) |
| >2 cm | 26 (68.4) |
| Total lymph nodes dissected | |
| Median (range) | 6 (1–22) |
| Total lymph nodes dissected | |
| <5 | 17 (44.7) |
| ≥6 | 18 (47.4) |
| Not dissected | 3 (7.89) |
| Positive resected lymph nodes | |
| Median (range) | 2 (1–18) |
| Number of positive resected nodes | |
| 1 | 7 (18.4) |
| 2 | 4 (10.5) |
| 3 | 3 (7.90) |
| 4 | 2 (5.26) |
| 18 | 1 (2.63) |
| Positive resected nodal groups | |
| Hilar | 4 (10.5) |
| Hepatoduodenal | 4 (10.5) |
| Pericholedochal/Peripancreatic/Retropancreatic | 4 (10.5) |
| Periportal/Retroportal | 3 (7.90) |
| Cystic | 2 (5.26) |
| Common hepatic artery | 0 |
| Liver infiltration present | 28 (73.7) |
| No liver infiltration | 10 (26.3) |
| Perihilar tissue infiltration | 22 (57.9) |
| Perineural invasion present | 35 (92.1) |
| Intraneural invasion present | 11 (29) |
| Lymphovascular invasion present | 18 (47.4) |

*(Contd...)*

**Table 1:** *(Contd...)*

**Table 2:** Characteristics of patients with resected intrahepatic cholangiocarcinoma

| *Characteristic* | *Number of patients* |
|---|---|
| Patients | 10 |
| Gender | |
| Male | 4 |
| Female | 6 |
| Serum CA19.9 at presentation (U/mL) | |
| >37 | 5 |
| ≤37 | 3 |
| Not documented | 2 |
| pT classification | |
| pT1 | 2 |
| pT2 | 6 |
| pT3 | 2 |
| pN classification | |
| pN0 | 5 |
| pN1 | 2 |
| Not dissected | 3 |
| Resection margin | |
| R0 | 7 |
| R1 | 3 |
| Histology | |
| Adenocarcinoma | 9 |
| Adenosquamous carcinoma | 1 |
| Perineural invasion present | 7 |
| Lymphovascular invasion present | 6 |
| Adjuvant treatment given | 7 |
| Adjuvant treatment not given | 3 |
| Recurrence not detected | 4 |
| Recurrence detected | 6 |

($n = 7$), 2 ($n = 4$), 3 ($n = 3$), 4 ($n = 2$), and 18 ($n = 1$). In patients with R0 resection, the closest margin ranged from 0.2 to 1.5 cm. Of the 25 patients with R0 resection (65.8%), 8 had a margin of <0.5 cm while for the 17 remaining patients, it was >0.5 cm. Mucin was present on microscopic examination in 18 patients. Of the 36 patients with information on tumor differentiation, 4 were well, 30 were moderately, and 2 were poorly differentiated.

Immunohistochemistry (IHC) was performed in 11 out of the 38 patients. Immunohistochemistry showed positivity for CK7 and MUC1 in the 9 tested specimens. In the 9 specimens with positive CK7 and MUC1, additional stains were seen as CK19 positive in 1, CK20 positive and CDX2 negative in 1, CK20 positive and CDX2 positive in 1, CDX2 positive in 1, and CK20 negative in 1 specimen. IHC positive expression for CK7, CK20, and CK19 was seen in 1 specimen. Immunohistochemistry showed negative expression for CK7 and CK19 in 1 specimen. Immunohistochemistry on sections from the paraffin blocks of the surgical specimen in 1 patient which was performed when recurrence was detected showed the tumor cells were positive for Her2 (3+), negative for PDL1 and PD1, retained nuclear expression of MSH2 and MSH6 while nuclear expression was not retained for MLH1 and PMS2, hence showing mismatch repair (MMR) deficiency. In another patient, IHC on the cytology specimen from the recurrent liver lesion showed negative expression for PD1 and PDL1.

The microscopic examination of the adjacent liver showed secondary sclerosing cholangitis with cholestasis, steatosis, and portal fibrosis ($n = 5$); chronic biliary pathology with bridging fibrosis with cholestasis ($n = 5$) with three of those showing steatosis as well; portal fibrosis with cholestasis ($n = 14$) with four of those showing steatosis as well; hepatocyte cholestasis with steatosis ($n = 6$); hepatocyte cholestasis ($n = 2$) and with multiacinar necrosis (n=1). There was no steatosis, necrosis, cholestasis, or fibrosis in 1 patient. Information on the adjacent liver was not available for 3 patients and in the remaining 1 patient with bile duct resection, the adjacent liver was not examined.

Of the 30 patients in whom gallbladder was resected, 17 were reported with chronic cholecystitis out of which 4 were along with cholesterolosis on pathological examination. Two out of the 30 specimens were reported with cholesterolosis, 1 with chronic cholecystitis with intestinal and pyloric metaplasia, and 1 with high-grade dysplasia. Tumor invasion in the mucosa of the gallbladder was seen in 1 patient. No specific pathology was observed in the gallbladder in 8 patients.

### *Intrahepatic Cholangiocarcinoma*

On gross examination, satellite nodules were observed in 3 patients. There was a tumor thrombus in a vein in the gross specimens of 3 patients. The largest tumor dimension ranged from 5 to 14 cm with a median of 6 cm. Eight patients had adenocarcinoma as a histological diagnosis, 1 patient had adenocarcinoma with cholangiocellular dedifferentiation, and 1 patient had adenosquamous carcinoma. The adjacent liver on microscopic examination showed cirrhosis ($n = 1$), bridging fibrosis ($n = 1$), portal fibrosis ($n = 5$), and secondary sclerosing cholangitis with periductal fibrosis ($n = 1$). Hepatocyte steatosis was noted in 9 of 10 patients. All patients had tumor infiltration into the liver. Two patients had tumor infiltration into hilar soft tissue. The tumor was perforating the visceral peritoneum and infiltrating into gallbladder muscularis propria in 1 patient. Micro- and macrovascular invasion was noted in 3 patients. Mucin in tumor cells was noted in 2 patients. Seven patients had R0 and 3 had R1 resection. The patient with adenocarcinoma histology treated with NACT followed by SBRT showed residual tumors with sizes of $7 \times 6 \times 5$ cm and $3.5 \times 3 \times 2.5$ cm, with few tumor nodules measuring 0.5–1 cm, staged as ypT2N0M0 with 50–60% posttreatment coagulative necrosis on microscopic examination (Fig. 2). The closest resection margin was 0.1 cm from liver parenchyma. The tumor cells were negative for ER, PR, Her2, and PDL1 and showed loss of nuclear expression for MSH6 and PMS2 revealing deficient MMR. The patient treated with DEB-TACE showed coagulative necrosis with residual tumor on microscopic examination in the resected specimen with cirrhotic adjacent liver. Of the 7 patients whose gallbladder was resected, three had chronic cholecystitis on microscopic examination.

## Adjuvant Treatment

### *Perihilar Cholangiocarcinoma*

Of the 38 resected patients, 7 had post-hepatectomy liver failure (PHLF) out of whom 6 (15.8%) had mortality because of multiorgan dysfunction syndrome (MODS). Three out of 6 patients had sepsis with MODS. The patients had died at 9, 12, 14, 18, 31, and 139 days after the surgery. The patient who died at 139 days had postoperative non-occlusive portal vein thrombosis and sepsis with liver failure. The surgical procedure which was performed in the 6 patients with PHLF was hepatobiliary resection with right hepatectomy ($n = 2$), right extended hepatectomy ($n = 1$), left modified hepatectomy ($n = 1$), left hepatectomy ($n = 1$) and hepatopancreaticoduodenectomy ($n = 1$). One out of 7 patients who had recovered after PHLF had undergone left hepatectomy and had received adjuvant chemoradiotherapy afterward. Three out of the 13 patients had received 1–3 cycles and could not complete the planned cycles of adjuvant chemotherapy due to toxicity. One out of the 3 patients had died of chemotherapy related toxicity. The remaining 10 patients had completed adjuvant chemotherapy. All patients for whom CCRT ($n = 10$) was planned had completed the treatment. Two out of the 10 patients had died of treatment related toxicity after CCRT.

### *Intrahepatic Cholangiocarcinoma*

Six patients had completed adjuvant treatment. The remaining 1 patient who had received neoadjuvant DEB-TACE had developed decompensation with ascites after day 1 dose of first cycle of GemCis chemotherapy and hence could not receive further cycles.

## Patterns of Recurrence

### *Perihilar Cholangiocarcinoma*

Recurrence was detected in 21 out of the 38 patients (55.3%). In 11 patients, serum CA19.9 was done at the time of recurrence and it was raised in 9 and was normal in 2 patients. The median time to recurrence from the surgery was 14.6 months (range, 4.57–62.4). Of the 21 patients, 18 had recurrence within 2 years with 5 out of 18 recurred within 1 year after surgery. Three out of the 21 patients had recurrence after 2 years at 24.3, 51, and 62.4 months. The patterns of documented recurrence were as follows: local plus nodal ($n = 9$), distant ($n = 4$), local ($n = 2$), local, nodal plus distant ($n = 2$), nodal ($n = 1$), local plus distant ($n = 1$). Of the 19 patients with documented recurrence, 15 (80%) had local and nodal disease.

The sites of local recurrence were as follows: hepaticojejunostomy anastomosis ($n = 11$), porta soft tissue ($n = 2$), and deposit at the cut edge of the liver ($n = 1$). The nodal sites of recurrence were periportal, portocaval, peripancreatic, perigastric, coeliac,

subphrenic, epiphrenic, anterior diaphragmatic, preaortic, paraaortic, aortocaval, and mesenteric regions. The distant sites were peritoneal nodules, liver lesions, subhepatic lesion, subcapsular lesion spleen, perirenal lesion, and brain lesions. Out of the 10 patients treated with adjuvant chemoradiotherapy, 5 did not have a recurrence, 1 had recurrence in hepaticojejunostomy with paraaortic, mesenteric lymph nodes, and subhepatic metastasis, 1 had suspected hyperenhancement on hepaticojejunostomy anastomosis with nodule in coeliac region on CECT of abdomen, 2 had recurrence in distant sites, and the details of recurrence were not available in the remaining 1 patient. 7 out of the 21 patients had histopathological or cytological proven recurrence showing adenocarcinoma ($n = 5$), malignant cells ($n = 1$), or atypical cells ($n = 1$).

### *Intrahepatic Cholangiocarcinoma*

Recurrence was noted on CT imaging in 6 patients. Of the 6 patients, 2 had undergone PET-CT as well for restaging. The median time to recurrence from the surgery was 7.8 months (range, 3.2–14.1). Out of the 6 patients, 5 had recurrence within 1 year. The sites of recurrence were as follows: Intrahepatic lesions in the remnant liver ($n = 2$), intrahepatic lesions in the remnant liver and nodes ($n = 2$), and nodal ($n = 2$). The sites of nodal recurrence were as follows: periportal, peripancreatic, portocaval, paraesophageal, coeliac, and retroperitoneal. Five of the 6 patients with recurrence had cytological ($n = 4$) or histological ($n = 1$) evidence of adenocarcinoma. Of the 4 patients who had undergone serum CA19.9 level at recurrence, 2 had raised values without jaundice (402 and 1303.5 IU/mL) while 2 had normal level.

## Salvage Treatment

### *Perihilar Cholangiocarcinoma*

11 patients were treated with palliative chemotherapy with 2 of them undergoing PTBD as well for recurrent disease. The chemotherapy regimens used were as follows: GemCis ($n = 4$), capecitabine with oxaliplatin (CapOx, $n = 4$), GemCap ($n = 2$), and capecitabine ($n = 1$). One out of the 4 patients treated with GemCis had received CapOx as the second line regimen after 8 cycles of GemCis. After chemotherapy, 3 out of the 11 patients underwent salvage CCRT 50–52.5 Gy/25 fractions/5 weeks with VMAT technique with concurrent capecitabine. One out of the 3 patients treated with chemotherapy followed by CCRT had stable disease as per RECIST 1.1 at the last follow-up. Ten out of the 11 patients had progressive disease, 9 of whom had died. Percutaneous transhepatic biliary drainage alone was performed in 2 patients who died after 1.5 and 2.5 years after the procedure, respectively. Eight patients were advised best supportive care and had died of cancer. One patient did not have recurrence on follow-up and had died of age-related causes. Of 38 patients, 7 were alive with no evidence of cancer and 2 patients with cancer.

### *Intrahepatic Cholangiocarcinoma*

1 patient had a clinical presentation with jaundice and was treated with PTBD. Palliative chemotherapy was given to 1 patient with CapOx regimen. One patient was treated with CCRT with 52.5 Gy/25 fractions/5 weeks with concurrent weekly gemcitabine. One patient had received radiofrequency ablation (RFA) for the liver metastatic lesions followed by chemotherapy. The 4 patients had progressive disease out of whom 3 had died. At the last follow-up, out of the 10 patients, 4 were alive with no evidence of disease, 1 was alive with disease, and 5 had died of cancer.

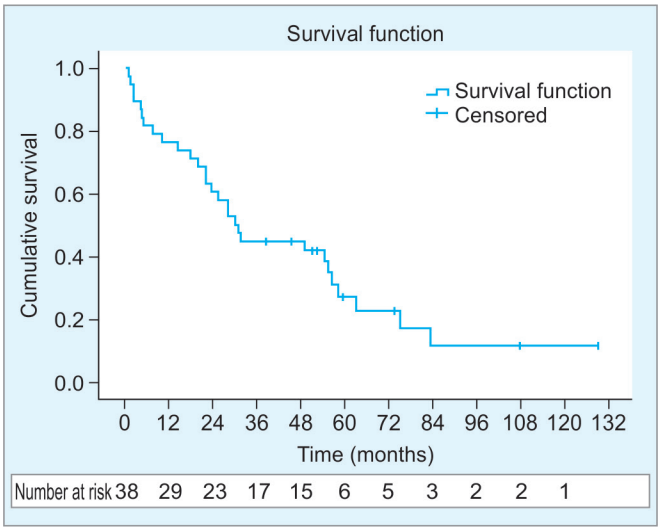



**Fig. 3:** Kaplan–Meier graph depicting overall survival for patients with resected perihilar cholangiocarcinoma

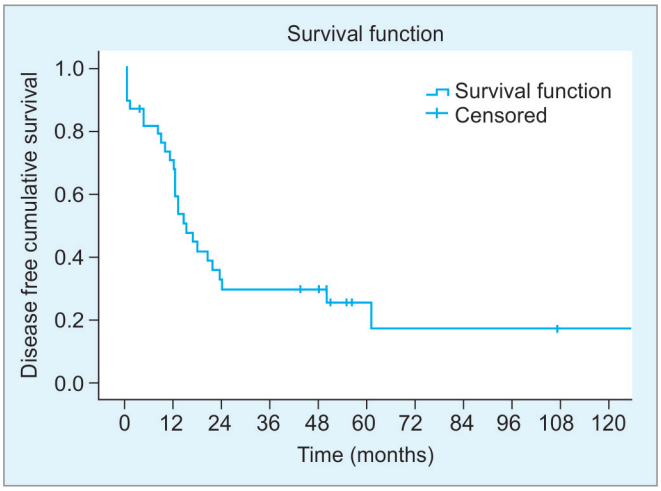



**Fig. 4:** Kaplan–Meier graph depicting disease-free survival for patients with resected perihilar cholangiocarcinoma

## Survival

### *Perihilar Cholangiocarcinoma*

The median follow-up of the patients with resected perihilar CCA was 29.2 (range, 0.89–130.2). The median OS was 30.1 months (95% CI: 22.9–37.4) with 1-year, 2-year, 3-year, and 5-year rates of 76.3, 60.5, 44.7, and 27.1%, respectively (Fig. 3). The median DFS was 15.1 months (95% CI: 9.74–20.5) with 1-year, 2-year, 3-year, and 5-year rates of 67.5, 32.7, 29.7, and 25.5%, respectively (Fig. 4). The survival estimates concerning the variables are listed in Table 3. For the analysis of the association of adjuvant treatment and recurrence with survival, the 6 patients with perihilar CCA who had mortality after surgery were excluded. Cox regression univariate analysis for survival of patients with resected perihilar CCA is shown in Table 4.

The following variables showed association with DFS on univariate analysis: T classification, resection margin, and adjuvant treatment (Table 4). The following variables showed association with OS on univariate analysis: N classification, stage, adjuvant treatment,

**Table 3:** Survival estimates with respect to variables for patients with resected perihilar cholangiocarcinoma

| | *Overall survival* | | | | *Disease free survival* | | | |
|---|---|---|---|---|---|---|---|---|
| *Variable* | *1-yr (%)* | *2-yr (%)* | *3-yr (%)* | *Median (months) (95% CI)* | *1-yr (%)* | *2-yr (%)* | *3-yr (%)* | *Median (months) (95% CI)* |
| T1 | 60 | 60 | 60 | 55.9 (0.00–159.6) | 40 | 40 | 40 | 7.92 (0.58–15.3) |
| T2 | 80.8 | 65.4 | 50 | 31.1 (2.57–59.7) | 80.1 | 40.6 | 40.6 | 16.8 (9.96–23.6) |
| T3 | 71.4 | 42.9 | 14.3 | 21.9 (17.1–26.7) | 42.9 | 14.3 | 14.3 | 12 (6.76–17.2) |
| N0 | 88.9 | 72.2 | 61.1 | 54.8 (27.5–82.1) | 76.7 | 35.4 | 35.4 | 16.8 (6.88–26.7) |
| N1 | 58.8 | 41.2 | 17.6 | 18 (2.36–33.7) | 51.8 | 51.8 | 22.6 | 12.5 (6.40–18.6) |
| Stage | | | | | | | | |
| I | 100 | 100 | 100 | 56.8 (55.4–58.1) | 66.7 | 66.7 | 66.7 | 21.7 (0.00–43.6) |
| II | 88.2 | 76.5 | 64.7 | 54.8 (41.8–67.8) | 81.6 | 43.9 | 43.9 | 20.5 (8.68–32.3) |
| III | 61.1 | 38.9 | 16.7 | 18 (6.63–29.4) | 54.5 | 21.2 | 21.2 | 12.5 (8.63–16.4) |
| R0 | 84 | 60 | 48 | 31.1 (0.00–64.5) | 87.3 | 37.4 | 37.4 | 18 (8.29–27.7) |
| R1 | 61.5 | 61.5 | 38.5 | 28.2 (0.00–60.1) | 30.8 | 15.4 | 15.4 | 8.84 (0.00–20.7) |
| Tumor ≤2 cm | 66.7 | 58.3 | 50 | 30.1 (0.00–76.2) | 64.8 | 18.5 | 18.5 | 16.8 (7.11–26.5) |
| Tumor >2 cm | 80.8 | 61.5 | 42.3 | 28.2 (20.6–35.7) | 68.7 | 35.2 | 35.2 | 13.1 (9.16–17) |
| Total nodes resected 5 or less | 75 | 60 | 45 | 28.2 (17.9-38.4) | 52.9 | 26.5 | 26.5 | 14.4 (9.39–19.4) |
| Nodes resected 6 or more | 77.8 | 61.1 | 44.4 | 31.1 (24.3-38) | 76.3 | 31.8 | 31.8 | 18 (8.33–27.6) |
| Histology adenocarcinoma | 77.1 | 60 | 42.9 | 30.1 (23.2–37.1) | 67.6 | 26.1 | 26.1 | 14.4 (9.28–19.5) |
| Histology other | 66.7 | 66.7 | 66.7 | Not reached | | | | |
| Adjuvant treatment not given | 88.9 | 66.7 | 44.4 | 31.1 (22.4–39.9) | 66.7 | 66.7 | 66.7 | 12.5 (12.1–12.9) |
| Adjuvant treatment given | 87 | 73.9 | 56.5 | 54.8 (23.4–86.2) | 86.1 | 51 | 51 | 50.3 (0.00–105.5) |
| Recurrence not detected | 81.8 | 72.7 | 72.7 | Not reached | NA | NA | NA | NA |
| Recurrence detected | 95.2 | 71.4 | 42.9 | 31.1 (26.2–36.1) | | | | |
| Local recurrence not detected | 81.3 | 62.5 | 56.3 | 49.2 (14.3–84.1) | NA | NA | NA | NA |
| Local recurrence detected | 100 | 78.6 | 50 | 31.1 (0.00–72.9) | | | | |
| Nodal recurrence not detected | 83.3 | 66.7 | 55.6 | 49.2 (11.3–87) | NA | NA | NA | NA |
| Nodal recurrence detected | 100 | 75 | 50 | 31.1 (0.00–70.9) | | | | |
| Distant recurrence not detected | 91.3 | 73.9 | 56.5 | 54.8 (10.5–99.1) | NA | NA | NA | NA |
| Distant recurrence detected | 85.7 | 57.1 | 42.9 | 31.5 (11.3–51.6) | | | | |

NA, not applicable

and recurrence (Table 4). On Multivariate analysis, adjuvant treatment after surgery showed a statistically significant association with DFS ($p = 0.004$). No adjuvant treatment showed HR 4.03, (95% CI: 1.57–10.4). Recurrence after surgery showed an unfavorable association with OS ($p = 0.056$) with HR 2.90 (95% CI: 0.98–8.66). An increased risk of recurrence was observed with stage II, $p = 0.16$, HR 2.14 (95% CI: 0.74–6.21) and stage III ($p = 0.004$), HR 4.97 (95% CI: 1.69–14.6) as compared with stage I.

### *Intrahepatic Cholangiocarcinoma*

The median follow-up of the patients with resected intrahepatic CCA was 25.1 months (range, 2.5–67.8). The median OS was 41.2 months (95% CI: 13.5–68.9) with 1-year, 2-year, and 3-year, and 5-year rates of 88.9, 66.7, and 53.3, and 40%, respectively. The median DFS was 10.8 months (95% CI: 1.98–19.6) with 6-month, 1-year, 2-year, 3-year, 88.9, 44.4, 33.3, 33.3%, respectively. The patient treated with NACT, SBRT, and resection was disease-free at a follow-up period of 42.6 months.

## Discussion

The present study showed local and nodal recurrences after resection in perihilar and intrahepatic CCA. Hepaticojejunostomy anastomotic site was a commonly involved site of recurrence after resection of perihilar CCA. Recurrence showed an unfavorable association with OS. The 3-year OS was 42.9% with recurrence vs 72.7% with no recurrence. A statistically significant association of adjuvant treatment was seen with DFS.

The risk factors that have been linked to the development of intrahepatic CCA are primary sclerosing cholangitis, parasitic infections, congenital abnormalities of bile ducts, viral infections, and metabolic abnormalities.[12] In the present study, steatosis, fibrosis, and secondary sclerosing cholangitis were identified in the adjacent liver of resected specimens of both intrahepatic and perihilar CCA. The patients with extrahepatic CCA are mostly diagnosed with jaundice.[1,2] In the present study, 80% of the patients with perihilar CCA had presented with jaundice with 71.1% (27 of 38) undergoing biliary drainage prior to resection. The patients with intrahepatic CCA had presented with normal serum bilirubin levels at the diagnosis.

Risk factors have been identified for recurrence and poor survival after resection of CCA.[13] A meta-analysis identified vascular invasion, lymph node metastases, and R1 resection to be the factors associated with recurrence within 12 months after surgery for perihilar CCA.[4] Lymph node metastasis status determines the prognosis in patients with resected perihilar CCA with a reported

**Table 4:** Cox regression univariate analysis for survival of patients with resected perihilar cholangiocarcinoma

| | *Overall survival* | | | *Disease free survival* | | |
|---|---|---|---|---|---|---|
| *Variable* | *p-value* | *HR* | *95% CI* | *p-value* | *HR* | *95% CI* |
| T1 | | 1.0 | | | 1.0 | |
| T2 | 0.84 | 0.90 | 0.30–2.67 | 0.08 | 0.41 | 0.15–1.13 |
| T3 | 0.61 | 1.4 | 0.38–5.09 | 0.63 | 0.74 | 0.22–2.48 |
| N0 | | 1.0 | | | 1.0 | |
| N1 | 0.05 | 2.15 | 1.00–4.63 | 0.30 | 1.52 | 0.69–3.36 |
| Nx | 0.49 | 0.59 | 0.13–2.65 | 0.80 | 0.82 | 0.18–3.68 |
| Stage I | | 1.0 | | | 1.0 | |
| Stage II | 0.76 | 1.27 | 0.28–5.81 | 0.37 | 0.55 | 0.15–2.04 |
| Stage III | 0.13 | 3.16 | 0.71–14.0 | 0.97 | 1.03 | 0.29–3.64 |
| R0 | | 1.0 | | | 1.0 | |
| R1 | 0.43 | 1.37 | 0.63–2.96 | 0.06 | 2.09 | 0.96–4.53 |
| Tumor ≤2 cm | | 1.0 | | | 1.0 | |
| Tumor >2 cm | 0.37 | 0.71 | 0.33–1.51 | 0.25 | 0.58 | 0.23–1.47 |
| Adjuvant treatment given | | 1.0 | | | 1.0 | |
| Adjuvant treatment not given | 0.07 | 0.50 | 0.24–1.05 | 0.004 | 4.03 | 1.57–10.4 |
| Recurrence not detected | | 1.0 | | | | |
| Recurrence detected | 0.06 | 2.90 | 0.98–8.66 | NA | NA | NA |
| Local recurrence not detected | | 1.0 | | | | |
| Local recurrence detected | 0.46 | 1.39 | 0.58–3.32 | NA | NA | NA |
| Nodal recurrence not detected | | 1.0 | | | | |
| Nodal recurrence detected | 0.65 | 1.22 | 0.52–2.88 | NA | NA | NA |
| Distant recurrence not detected | | 1.0 | | | | |
| Distant recurrence detected | 0.45 | 1.42 | 0.57–3.58 | NA | NA | NA |

NA, not applicable

1-year, 3-year, and 5-year survival rates of 87.7, 37, and 26.4% vs 69.5, 13.9, and 9.3% in patients with node-negative vs positive disease, respectively.[14] The patients with perihilar CCA had 3-year OS 61.1 and 17.6% with node-negative and node-positive disease, respectively in the present study. Resection margin width determines survival and a value of 2.5 mm or more, preferably 310 mm needs to be aimed for patients with intrahepatic CCA.[15,16] A study on resected perihilar CCA reported the proportion of patients with R1 resection as 31.7%.[17] The 3-year DFS for R0 and R1 resection was 37.4 and 15.4%, respectively in the present study. Tumor size, poor tumor differentiation, and perineural invasion are the factors that also have been linked to early recurrence after resection in perihilar CCA.[4] In an analysis of patients treated over two decades, 26 patients were able to undergo repeat surgical resection for recurrent CCA out of whom 5 did not experience further recurrence on follow-up.[18] Hence, prevention of recurrence needs to be the aim in resected CCA since a limited number of patients can undergo repeat surgery or receive other salvage treatments with curative intent. Tumor biology in combination with the patient and disease characteristics plays a role in influencing the survival outcomes in CCA.[16] In patients with resected intrahepatic CCA, TP53, and KRASG12 mutations have shown significant association with OS.[19]

Adjuvant or neoadjuvant chemotherapy showed significant survival benefit especially in patients with positive margins and tumor size >5 cm in an analysis of patients with CCA treated with resection over 20 years.[20] Furthermore, patients with margin- and node-negative perihilar CCA have also shown improved survival with adjuvant chemotherapy.[5] In all patients, a statistically different median survival of 28.2 vs 19.9 months with adjuvant chemotherapy vs without adjuvant chemotherapy was reported.[5] The STAMP randomized trial evaluated the effectiveness of adjuvant chemotherapy with GemCis vs capecitabine in node-positive extrahepatic CCA.[17] There was no statistically significant difference in survival outcomes (2-year DFS 38.5 vs 25.1%; median DFS 14.3 vs 11.1 months) between the two arms. The 2-year local recurrence rate was 36.3% with adjuvant capecitabine for 8 cycles in the STAMP trial. With adjuvant radiotherapy, an improved survival has been reported as compared to without radiotherapy in patients with biliary tract carcinoma with a median 28.9 vs 14.5 months, 1-year 82.4 vs 55%, and 2-year 58.8 vs 25%.[21] The median OS observed in the present study was 30.1 months and 41.2 months in perihilar and intrahepatic CCA, respectively. The median DFS was 50.3 vs 12.5 months with and without adjuvant treatment in perihilar CCA. The SWOG S0809 phase II trial reported a 2-year OS of 68% with adjuvant CCRT followed by 4 cycles of GemCap in resected extrahepatic CCA.[22] The phase III BILCAP study reported median OS 53 months vs 36 months with adjuvant capecitabine as compared with observation (adjusted HR 0.75 95% CI: 0.58–0.97, $p = 0.028$) after resection in CCA and gallbladder cancer on a per-protocol analysis.[23] In the adjuvant setting, newer approaches like chemoimmunotherapy have been evaluated in resected perihilar CCA.[24]

Neoadjuvant chemotherapy with radiotherapy protocols has been used in patients with CCA for liver transplantation. There is growing evidence on the efficacy of liver transplantation in perihilar and intrahepatic CCA when integrated with chemotherapy and/

or radiotherapy in selected patients.[25] Stereotactic body radiation therapy has been used to treat patients with CCA. Most of the patients with CCA suitable for resection undergo upfront hepatectomy. Whether NACT in resectable CCA leads to lesser recurrence rates and improved survival has been studied by various centers. An analysis of patients from the National Cancer Database revealed an increased OS with NACT in intrahepatic, perihilar, and distal CCA even in patients with margin- and node-negative disease.[26] No differences were observed between patients treated with NACT or adjuvant chemotherapy. Another study has reported improved survival with NACT compared with upfront surgery in intrahepatic CCA warranting prospective studies.[27] A study evaluated the associations of survival with pathologic responses after NACT in high-risk intrahepatic CCA.[28] Although the pathologic response was not found to be associated with improved survival, NACT may help patients undergo extensive resections for disease control. With gemcitabine and cisplatin-based NACT, an improved OS (median 49 months) has been reported in patients with intrahepatic CCA undergoing resection.[29] The sequencing of adjuvant chemotherapy and chemoradiotherapy needs to be explored further on whether concurrent chemoradiotherapy followed by chemotherapy should be preferred in case of R1 resection.

Patients with multiple tumors have been reported to show worse survival as compared with those with solitary tumors in intrahepatic CCA after surgical resection.[13] In the present study, the patient with intrahepatic CCA with multiple tumors had a pathologic response after multimodality therapy with NACT, SBRT, and partial hepatectomy showing a favorable outcome and was disease-free at a follow-up period of 3.5 years. A phase II trial evaluated a combination of gemcitabine, cisplatin, and nab-paclitaxel (GAP) in patients with resectable, high-risk intrahepatic CCA with tumor size >5 cm, radiographic major vascular invasion, multiple tumors, or lymph node involvement.[30] The combination of GAP chemotherapy with surgery was found feasible and resulted in a median OS of 24 months. In a meta-analysis of patients with intrahepatic CCA treated with NACT, no increase in postoperative complications were observed.[31] In patients with resectable perihilar CCA with lymph node metastases, tumor size responses have been observed with NACT resulting in curative intent surgery.[32] With SBRT, radiological responses and disease control rates have been reported in intrahepatic CCA.[33,34]

The nodal metastases in perihilar CCA have been noted in hepatoduodenal ligament, common hepatic artery, and posterior superior pancreaticoduodenal regions.[35] The tumors in a central location in intrahepatic CCA are more prone to the involvement of lymph nodes in hepatoduodenal and other regions.[36] Recurrent paraaortic or aortocaval lymph nodes were seen on follow-up in patients with resected perihilar CCA in the present study. Although the periaortic lymph node involvement is considered a distant metastasis in perihilar CCA, the inclusion of aortic nodal volume may be considered while planning adjuvant radiotherapy to decrease the risk of nodal recurrences.

The recurrence rates seen after surgical resection in patients with CCA underscores the aggressive nature of the disease necessitating multimodality treatment. The present study showed effectiveness of combination of chemoradiotherapy with resection in improving locoregional disease control and survival in patients with perihilar and intrahepatic CCA. The different regimens and sequencing of chemotherapy and radiotherapy with resection need to be further explored for CCA.

## Declaration

### Availability of Data and Material

The data analyzed for the study is available in the article.

## Authors' contributions

The manuscript has been read and approved by all the authors. The requirements for authorship have been met and each author believes that the manuscript represents honest work.

### Ethics Approval

It was not obtained as the study is a retrospective analysis of data from medical records.

## Acknowledgments

The authors would like to acknowledge Dr Nuneno Nakhro, Junior Resident for her contribution in data extraction.

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