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Cholangiocarcinoma in South India: unprecedented, unanticipated and underreported

Priya Nair¹, Harshavardhan Rao B.^{1*}, Anoop K. Koshy¹, Surendran Sudhindran¹, K. Pavithran², Rama P. Venu¹

¹Department of Gastroenterology, ²Department of Medical Oncology, Amrita Institute of Medical Sciences, Kochi, Kerala, India

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*Correspondence:

Dr. Harshavardhan Rao B.,

E-mail: harshavardhanrao1985@gmail.com

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ABSTRACT

Background: The incidence of CCA in India is on the rise especially in Kerala. However, the clinical profile and outcome of these patients has never been reported. The aim of this study was to identify region specific epidemiological trends and natural history of CCA in Kerala.

Methods: This was a single centre, hospital based epidemiology study where incident cases of CCA from January 2014 to August 2016 were studied. Patient demographics and relevant clinical and laboratory data, imaging studies and treatment, were recorded in a predesigned Performa.

Results: A total of 137 patients (mean age 62.92 ± 12.5 years, M:F=1.2) were studied of which 109 patients had Hilar CCA (pCCA), 16 patients had Distal CCA (dCCA) and 12 patients had Intrahepatic CCA (iCCA). A majority of patients were from coastal areas and rubber plantations. Known risk factors were absent in our patients. Bismuth Type IV disease was seen in 55 patients (50.5%). Most intrahepatic CCA (iCCA) (7/12) patients had stage IV disease at presentation. Curative resection was possible in 17/38 patients (44.7%). Patients who underwent treatment with a curative intent were younger with less advanced disease and therefore, had a significant 3 month, 6 month and 1 year survival advantage (p<0.05). The overall 1-year mortality was 66.1% (91/137). The 30-day post-op mortality was 4.3%.

Conclusions: This study highlights a unique epidemiological pattern in our patients characterised by absence of known risk factors and unique geographic clusters. Palliative chemotherapy showed a significant survival benefit in this study which needs further validation.

Keywords: Cholangiocarcinoma, Biliary drainage, Hepatic resection

INTRODUCTION

Cholangiocarcinoma (CCA) is an epithelial cell malignancy arising from different locations within the biliary tree. It represents the second most frequent type of primary liver cancer and ~3% of all gastro-intestinal neoplasias.¹

In general, CCA is considered to be a rare malignancy (incidence <6 cases per 100,000 people.1The epidemiological profile of CCA and its subtypes display enormous geographical variation, perhaps related to exposure to different risk factors.²

CCA tends to be asymptomatic in its early stages and most patients have advanced unresectable disease at the time of diagnosis accounting for it's dismal prognosis. Based on data from SEER 18 (2006-2012), the 5 year survival rate for intrahepatic biliary malignancies is as low as 17.5%. While the 5 year survival rate is about 30% in extrahepatic biliary malignancies. This drops to 24% in case of regional spread and 2% in case of distant metastasis.

Surgical resection is the only curative treatment option. However, different criteria employed for resection coupled with a lack of consensus have lead to heterogeniety in prevalent literature that examines the efficacy and outcome of such treatment.

The exact incidence of CCA is unknown in India owing to a reporting system that groups all hepatobiliary malignancies together. Moreover, there is very little data regarding the risk factors for the development of CCA in India. Our study aims at evaluating the epidemiology of this relatively rare malignancy in our region. In addition, the clinical presentation, management and outcomes of various modalities of therapy employed at our center have been studied.

METHODS

Study population and design

This was a retrospective cohort study conducted at Amrita Institute of medical sciences, Kochi - a large tertiary care referral centre in south India. All patients newly diagnosed with CCA who presented to the centre from January 2014 to August 2016 were included in the study. Patients were diagnosed with CCA using the following criteria:

Histological evidence of cholangiocarcinoma (USG guided/Endoscopic ultrasound guided biopsy). Resected specimen showing cholangiocarcinoma in patients who underwent surgery. Positive endobiliary brush cytology during ERC. Mass lesion/biliary stricture suggestive of malignancy on endoscopic retrograde cholangiography AND persistent serum CA 19-9 level >129 U/mL in the absence of bacterial cholangitis/pancreatic mass.

All patients who satisfied any one of the above criteria during the study period were included in the study. Patients with hepatocellular cancer/cholangiocellular variant of hepatocellular cancer were excluded from the study.

Patient demographics including age, gender and address of residence were recorded. All known risk factors such as cholelithiasis, alcohol intake, smoking, Type 2 diabetes mellitus, history of parasitic infections, cirrhosis, hepatitis B and C and obesity were meticulously recorded in predesigned proformas. Clinical presentation and other relevant clinical and laboratory data, radiological investigation/procedure reports, endoscopic/surgical procedure reports were obtained during admission in the hospital. Patients were then followed up for a minimum period of 1 year. Overall survival of the study population and mortality at 3 month, 6 month and 1 year were noted to assess the outcome of treatment. Complications

(immediate and delayed) of treatment were also studied at the time of analysis.

Diagnosis and treatment

All patients underwent one or more of the following imaging studies such as Computed tomography (CT), Magnetic Resonance Cholangiopancreatography (MRCP) and Endoscopic Retrograde Cholangiopancreatography (ERCP) for diagnosis and staging of CCA. The image series of each patient was reviewed to assess the type of CCA along with staging and distribution of tumour, by an independent radiologist/endoscopist blinded to the reports and the results were tabulated.

All patients with CCA were further classified into groups according to the anatomic location of their tumor. Intrahepatic CCA was defined as CCA located proximally to the second degree bile ducts (proximal and distal refers to the direction of bile flow such that the intrahepatic bile ducts are proximal to the common bile duct) within the liver. Perihilar CCA was defined as CCA localised to the area between the second degree bile ducts and the insertion of the cystic duct into the common bile duct. Lastly, distal CCA was defined as CCA confined to the area between the origin of the cystic duct and ampulla of Vater.³

Hilar CCA was further classified according to the Bismuth-Corlette Criteria, while TNM staging system was used to stage intrahepatic and distal CCA. The presence and location of lymph node metastasis, distant metastasis and portal vein thrombosis at the time of diagnosis was also assessed and recorded separately.

Patients were selected for surgery based on established criteria (AJCC). Patients with Bismuth IV CCA or with evidence of distance metastasis were offered palliative biliary drainage using the endoscopic technique (ERC) or the percutaneous approach (percutaneous transhepatic biliary drainage - PTBD).

Chemotherapy was offered to all patients with respectable CCA and as a palliative treatment modality for patients with unresectable disease on the understanding that the evidence base is weak and only after risk—benefit assessment. A combination of Gemcitabine and Cisplatin were given as per ESMO (European Society of Medical Oncology) guidelines 2016:

Gemcitabine 1000mg/m2 - Day1 and day 8 once in 3 weeks. Cisplatin 25mg/m2 - Day1 and day 8 once in 3 weeks. If cisplatin was contraindicated it was substituted by carboplatin- AUC 2 on day 1 and day8. A Total 6 cycles were given.

Laboratory tests

Serum alpha fetoprotein (AFP) and Ca19-9 were assessed using chemiluminescentimmuno assay. Anti HCV and

HBsAg were tested using enzyme linked fluroscent assay (Vidas – Biomurex).

Statistical analysis

Quantitative data was summarized as mean (±SD) and categorical data was summarized as (n) and percentage (%). Statistical analysis was carried out using IBM Statistical package for social sciences (SPSS) software version 20.0. Comparison between two groups was done using independent 2-sample T test/Mann Whitney U test and three group comparison was done using ANOVA/Kruskal Wallis for parametric and non-parametric variables respectively. Categorical variables were analysed using Chi-square test/Fisher's exact test for univariate analysis and multivariate analysis was then

carried out using multiple logistic regression analysis. Kaplan Meir curves with log rank estimation for overall survival at 3 months, 6 months at one year and for efficacy of various treatment modalities was carried out as a part of outcome analysis. A p value of less than 0.05 was considered significant.

RESULTS

A total of 137 patients were included in the study. Of these patients, 42 were biopsy proven (resection specimen or intraluminal biopsy), 31 were cytology proved (brush cytology or fine needle aspiration of mass) and the rest of the 64 patients were diagnosed based on imaging studies with an elevated serum Ca 19-9 level.

Table 1: Demographics and clinical characteristics n (%).

	Perihilar CCA (n=109)	Distal CCA (n=16)	Intrahepatic CCA (n=12)
Age (Mean±SD)	63.0±11.9	62.1 ± 17.5	62.67 ± 12.0
Male	60 (55.0)	9 (56.3)	7 (55.5)
Bismuth Stage			
Stage 1	2 (1.8)	NA	NA
Stage 2	6 (5.5)	NA	NA
Stage 3a/b	46 (42.2)	NA	NA
Stage 4	55 (50.5)	NA	NA
Advanced Disease			
Metastasis	18 (16.5)	3 (18.8)	3 (25.0)
Lymph Nodes	18 (16.5)	3 (18.8)	1 (8.3)
PVT *	41 (37.6)	1 (6.3)	7 (58.3)
Clinical Features			
Jaundice	104 (95.4)	16 (100)	11 (91.7)
Pruritus	94 (86.2)	14 (87.5)	5 (41.7)
Weight loss	81 (74.3)	10 (62.5)	9 (73.0)
Anorexia	88 (80.7)	13 (81.3)	11 (91.7)
Fever *	20 (18.3)	7 (43.8)	2 (21.2)
Pain	30 (27.5)	7 (43.8)	6 (50.0)
Risk Factors	•		
Diabetes	46 (42.2)	8 (50.0)	4 (33.3)
Dyslipidemia	20 (18.3)	2 (12.5)	4 (33.3)
Cirrhosis	7 (6.4)	0 (0)	1 (8.3)
Alcohol	28 (25.7)	4 (25.0)	1 (8.3)
Smoking	18 (16.5)	3 (18.8)	2 (16.7)
Surgery	29 (26.6)	7 (43.8)	2 (16.7)
Chemotherapy	27 (24.8)	3 (18.8)	3 (25.0)
Drainage procedure			
ERCP	42 (38.5)	10 (62.5)	3 (25.0)
PTBD	44 (40.4)	2 (12.5)	3 (25.0)
Radiation (EBRT)	4 (3.7)	1 (6.3)	0 (0)

^{*} Denotes a p<0.001. (CCA – Cholangiocarcinoma, PVT – Portal vein thrombosis, ERCP – Endoscopic retrograde cholangio-pancreatography, PTBD – Percutaneous transhepatic biliary drainage, EBRT – External beam radiotherapy)

Table 2: Laboratory characteristics amongst CCA patients = mean (SD).

	Perihilar CCA	Distal CCA	Intrahepatic CCA
Hemoglobin	11.1 (1.6)	10.9 (1.7)	10.4 (2.0)
WBC count	11.1 (4.3)	11.9 (6.0)	10.2 (2.9)
Platelets	306.4 (100.3)	230.4 (103.6)	314.9 (148.2)
Total Bilirubin *	15.0 (10.7)	13.7 (8.2)	8.4 (12.5)
ALP	461.9 (358.3)	541.0 (236.8)	378.7 (226.2)
Albumin	3.09 (0.6)	3.1 (0.7)	3.2 (0.8)
INR	1.2 (0.6)	1.02 (0.1)	1.1 (0.3)
Ca 19-9	33,746.7 (119017.1)	22567.3 (71184.1)	105632.4 (260551.9)

^{*} Denotes a p <0.001. (CCA – Cholangiocarcinoma)

Table 3: TNM stage of CCA in patients who underwent surgery.

TNM Stage n (%)	Perihilar CCA (n=29)	Diatal CCA (n=7)	Intrahepatic CCA (n=2)
Stage I	1 (3.4)	1 (14.3)	0 (0)
Stage II	16 (55.2)	5 (71.4)	1 (50)
Stage III	8 (27.6)	1 (14.3)	1 (50)
Stage IV	4 (13.8)	0 (0)	0 (0)

(CCA – Cholangiocarcinoma)

Table 4: Treatment outcomes based on 3 month, 6 month and 1 year mortality.

	Total Number	3 month mortality	6 month mortality	1 year mortality
Surgery		•	•	•
Perihilar	29	3 (10.3)	8 (27.6)	14 (48.3)
Distal	7	1 (14.3)	2 (28.6)	5 (71.4)
Intrahepatic	2	1 (50)	1 (50)	2 (100)
Palliative Chemotherapy				
Perihilar	14	2 (14.3)	4 (28.6)	8 (57.1)
Distal	1	1 (100)	1 (100)	1 (100)
Intrahepatic	2	0 (0)	0 (0)	1 (50)
Palliative biliary drainage		•	•	•
Perihilar	56	23 (41)	33 (58.9)	41 (73.2)
Distal	8	2 (25)	2 (25)	5 (62.5)
Intrahepatic	4	3 (75)	3 (75)	3 (75)
No treatment				
Perihilar	10	8 (80)	9 (90)	9 (90)
Intrahepatic	4	2 (50)	3 (75)	3 (75)

The baseline characteristics of the patients are provided in Table 1. The mean age at presentation was 62 ± 12 years (Range 29-97 years) with a peak incidence in the 60-65 year age group. Males were more commonly affected with a male to female ratio of 1.8:1. Sixteen patients (11.7%) had distal CCA, 109 patients (79.6%) had perihilar CCA and 12 patients (8.8%) had intrahepatic CCA. The geographic distribution of patients through the region is depicted in Figure 1.

Risk factors (Table 1)

Five patients (3.6%) had cholelithiasis and 8 (5.8%) patients had alcohol related cirrhosis of the liver. Four patients a past history of Typhoid. One patient had choledochal cyst. Type 2 Diabetes Mellitus and Dyslipidemia were seen in 58 (42.3%) and 26 (18.9%) patients respectively. History of alcohol abuse was noted in 33(24%) patients and 23 (16.7%) patients were smokers. Known risk factors for CCA showed no significant correlation in this study.

Table 5: Tumor histology, degree of differentiation, diameter, margin, per neural and lymph node involvements by tumor location. (%).

	Total (n=38)	Perihilar (n=29)	Distal (n=7)	Intrahepatic (n=2)
Tumor histology				
Adenocarcinoma	27 (71.0)	20 (68.9)	5 (71.4)	2 (100)
Other	11 (29.0)	9 (31.1)	2 (28.6)	0
Other	11 (29.0)	9 (31.1)	2 (28.6)	0
Degree of differentiation				
Well	19 (50.0)	17 (58.6)	2 (28.6)	0
Moderate	16 (42.1)	12 (41.4)	4 (57.1)	0
Poor	3 (7.9)	0	1 (14.3)	2 (100)
Margin				
Negative	17 (44.7)	13 (44.8)	4 (57.1)	0
Positive	21 (55.3)	16 (55.2)	3 (42.9)	2 (100)
Lymph node involvement				
Negative	27 (71.0)	22 (75.7)	4 (57.1)	1 (50)
Positive	11 (29.0)	7 (24.3)	3 (42.9)	1 (50)
Perineural involvement				
Negative	9 (23.7)	6 (20.6)	2 (28.6)	1 (50)
Positive	29 (76.3)	23 (79.3)	5 (71.4)	1 (50)
Lymphovascular invasion				
Negative	23 (60.5)	20 (68.9)	3 (42.9)	0
Positive	15 (39.5)	9 (31.1)	4 (57.1)	2 (100)

^{*} Denotes a p value < 0.001

Clinical presentation (Table 1)

The common clinical symptoms at presentation were jaundice (95.6%), pruritus (82.5%), anorexia (81.8%) and weight loss (73%). Pain abdomen was reported in a third of the patients (31.4%) and fever (21.2%) was seen in a minority. On stratification, pruritus as a symptom was more commonly see in pCCA and dCCA; while iCCA presented more commonly with fever (p<0.001). Ascites was noted in 12 patients (8.8%) and was equally common among all types of CCA.

Laboratory tests

Relevant laboratory variables have been detailed in Table 2. The mean total and direct bilirubin was found to be higher in those patients who had a background of alcoholism (p=<0.001). The tumor markers carcinoembryonic antigen, alphafetoprotein and carbohydrate antigen 19-9 were available for only half the patients and did not show any correlation with tumor location or stage.

Diagnosis and staging

Bismuth staging in pCCA patients

A total of 109 patients (79.6%) had pCCA of which, 46 patients (42.2%) had Bismuth III disease, 55 patients

(50.5%) had Bismuth IV disease and 8 patients (7.3%) has Bismuth I/II disease. CCA affected predominantly the left ductal system in 49 patients (44.9%) and 33 patients (30.2%) had predominantly right sided disease, while 26 patients (23.8%) had equal involvement of both sides.

TNM staging in iCCA and dCCA

Out of the 12 patients (8.8%) with iCCA, 8 patients (66.7%) had stage IV disease with distant metastasis. None of the patients presented with Stage I disease. In contrast, more than half the patients with dCCA (9/16 patients [56.2%]) had stage I/II disease.

Portal vein thrombosis and distant metastasis

Portal vein thrombosis (PVT) was seen in 49 patients (35.8%) at the time of diagnosis. Among these patients, a larger proportion of patients with iCCA(8/12 patients(66.7%)) had PVT as compared to the other types of CCA(37.6% and 6.2% in pCCA and dCCA respectively)(p=0.005). Bismuth type IIIb patients were found to present more commonly with PVT as compared to Bismuth IIIa disease among patients with pCCA. Metastatic disease (Liver, lung, peritoneal and bone) was seen in 24 patients(17.5%) and 22 patients (16.1%) had lymph nodal involvement with periportal nodes being the most common finding followed by para-aortic and peripancreatic nodes.

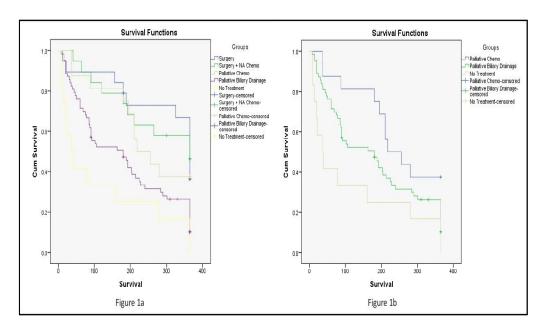


Figure 1: (a) Comparison of survival in patients who underwent surgery, palliative chemotherapy and other palliative treatment. (p \leq 0.001). (b) Comparison of survival in patients who underwent palliative chemotherapy, only palliative biliary drainage and no treatment at all. (p \leq 0.001).

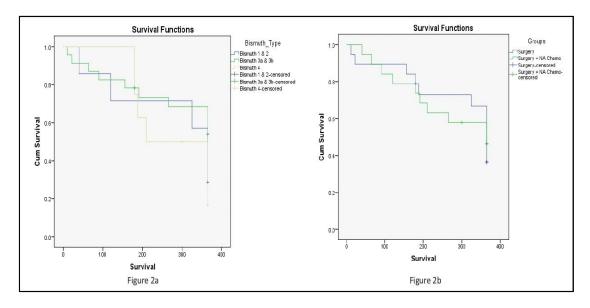


Figure 2: (a) Comparison of survival in patients with pCCA who underwent surgery based on their Bismuth classification. (b) Comparison of survival in patients who underwent surgery alone versus surgery with adjuvant chemotherapy.

Treatment outcomes

The overall survival of the patient cohort during the study period was 210 days with a 3-month mortality of 33.6%; 6 month mortality of 48.4% and a 1 year mortality of 75%. The outcomes of various treatment and palliative modalities utilized for therapy in our cohort of patients in terms of 3 month, 6 month and 1 year mortality is given in Table 3.

Factors which had a statistically significant correlation with mortality were PVT at diagnosis, diabetes mellitus and post procedure (ERCP / PTBD) cholangitis (p=0.05).

Treatment with a curative intent

Surgery with a curative intent was offered to 38/137 patients (27.7%) of which, 29 patients had pCCA, 7 patients had dCCA and 2 patients had iCCA. The TNM stage of all patients who underwent surgery is given in Table 3. Majority of the dCCA patients who underwent surgery had TNM Stage I/II disease (6/7 patients (85.7%)).

Among patients with pCCA, 21/29 patients (72.4%) and 8/29 patients (27.5%) had Bismuth III and IV disease respectively. Both patients with intrahepatic CCA who underwent surgery had TNM stage II disease. Twenty one patients underwent left hepatectomy, 10 patients underwent right hepatectomy and the patients with dCCA underwent Whipple's procedure (n=6).

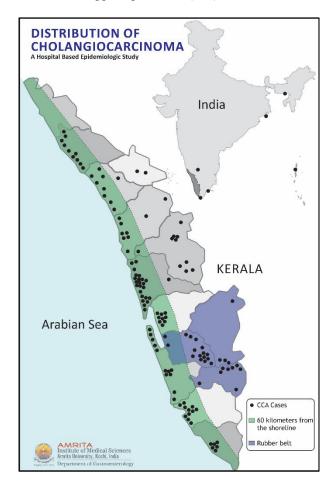


Figure 3: Geographic distribution of CCA cases..

A total of 15 patients required pre-op biliary drainage. Only one patient with dCCA and 6 patients with pCCA underwent pre-op biliary drainage with ERC. Nine patients underwent pre-op biliary drainage with PTBD; of which one patient underwent PTBD followed by ERCP. Four patients developed Cholangitis prior to surgery as a result of biliary drainage, but this did not correlate with an increased 3-month mortality.

Of the 38 patients who underwent surgery, 19 patients (50%) had adjuvant chemotherapy with Gemcitabine and Cisplatin of which 15/19 patients (78.9%) had pCCA. The three month, six month and one year mortality for the patients of pCCA and dCCA who underwent surgery is given in Table 4. Both patients of iCCA who underwent surgery died within 6 months due to progressive disease.

The six month and one-year mortality for patients who underwent surgery alone was 21.1% and 63.6%

respectively versus 26.3% and 53.7% in the patients that underwent surgery along with adjuvant chemotherapy. The overall mortality at one year for patients with Bismuth stage 3a and 3b pCCA who underwent surgery was 42.9% and 48.7% respectively as compared to 83.6% in patients with Bismuth Type4 pCCA who underwent surgery (p=<0.001). The Kaplan Meir curves show a significant survival advantage for surgery as compared to other modalities of management. (See figure2 and 3) It is worthwhile to note however, that surgical patients were significantly younger and had higher bilirubin levels than patients who underwent palliative drainage. (p≤0.001).

Eight patients (21%) had postoperative complications (sepsis (75%) and bleeding (25%)). The 30-day mortality rate was 4.3% and the cause for mortality was sepsis. The post-operative resected specimens were evaluated for tumor histology, degree of differentiation, diameter, margin positivity, perineural and lymph node involvement, details of which are furnished in Table 5. Tumor histology finding of poorly differentiated adenocarcinoma significantly correlated with poor survival (p \leq 0.05). Among the patients who had tumor free margins, 4 had disease recurrence after 3 months. Of the 16 patients who died at 1 year (%), 11 died due to disease progression, 3 patients died due to sepsis during chemotherapy and 2 patients died due to unrelated causes.

Palliative treatment

Ninety nine patients could not undergo any treatment with a curative intent. Palliative treatment was offered to 85 patients (63.5%) and 14 patients (10.2%) decided not to undergo any form of treatment. 63/99 (63.6%) of these patient's presented with inoperable disease and 10/99 (10.1%) were over eighty years old or could not undergo surgery due to a poor general condition. Eight patients had been planned for surgery but they died prior to the procedure due to disease progression (6 patients) and sepsis (2 patients) secondary to pre-op biliary stenting.

Of those who underwent palliative therapies, only 17/85 patients (20%) underwent palliative chemotherapy with Cisplatin and Gemcitabine with biliary drainage. Biliary drainage procedures (ERCP/PTBD) were performed in 68/85 patients (80%). The three month, six month and one year mortality for the 17 patients who underwent palliative chemotherapy was 18.7%, 31.2% and 62.5% versus 42.9%, 52.7% and 89.9% for patients who underwent palliative biliary drainage alone (p≤0.001).

Biliary drainage

Including pre-op drainage, a total of 83 patients underwent biliary drainage. Of these, 48/83 (57.8%) patients underwent ERCP, of which five patients underwent PTBD followed by ERC. PTBD was the sole biliary drainage modality used in 35/83 (42.1%) patients. Of the 35 who underwent PTBD, 19 (54.2%) had post procedure complications, (cholangitis, bleeding and biliary leak) as

compared to 8/48 patients (16.6%) patients who developed post ERCP complications, mainly cholangitis (p<0.001). None of the patients who underwent ERCP developed post ERCP pancreatitis.

DISCUSSION

Cholangiocarcinoma is the most common primary malignancy of the liver after HCC, representing 10–25% of primary hepatic malignancies worldwide.⁴ A heterogenic mode of presentation coupled with a dramatic geographic variation in incidence portends the possibility of region-specific risk factors, tumor behaviour and epidemiology.⁵⁻⁹ According to existing data, CCA rarely presents before the age of 40, with a peak prevalence in the seventh decade of life.^{6,7} The peak prevalence in our region was noted to be in the early sixth decade. Our study also showed a higher male preponderance of 1:1.8 as compared to other parts of the world.^{6,8,10,11}

Overall, extrahepatic CCA is more prevalent as compared to intrahepatic CCA barring a few areas in east Asia where iCCA is more common. However, a rising incidence of iCCA has been noted in multiple recent reports from United States of America and United Kingdom. 6,12-16

There is a paucity of data from India regarding the epidemiology, risk factors or incidence of CCA. Owing to the lack of a uniform reporting system for CCA in the country, which includes gall bladder cancer and hepatocellular carcinoma with CCA, the incidence trends for CCA over specified time periods is unknown. To that end, we have studied incident cases of CCA over a 2 year period for relevant demographics, diagnostic and therapeutic options employed; as a starting point to sensitise the need for a systematic reporting of the disease as a public health concern in the country. This is the first hospital based epidemiology survey of CCA in India which demonstrates an extremely high incidence (137 cases) of CCA over a two year period. The mean age at presentation was 62±12 years (Range 29 - 97 years) with a peak incidence in the 60-65 year age group which is similar to patient cohorts in other geographical areas.⁵⁻⁷ The male preponderance as mentioned earlier, however, is more pronounced with a ratio of 1:1.8. An overwhelming majority of our patients presented with pCCA (109/138 patients) as compared to the other subtypes of patients. More than half of our patients presented at an advanced stage of disease precluding curative surgical options of therapy.

Most cholangiocarcinomas arise de novo and no definite risk factors are identified. However, several conditions associated with the development of CCA have been described. These include biliary tract stones, viral hepatitis B and C, liver cirrhosis, obesity, congenital hepatic fibrosis, Caroli's disease, diabetes mellitus inflammatory bowel disease and primary sclerosing cholangitis. 3,10,17 Most CCA studies do not distinguish site (example- ductal, hilar, peripheral) or histology and in reports which

considered intrahepatic and extrahepatic CCA separately, some potential risk factors seem to have a differential effect on CCA depending on site. Texposure to the toxic agents dioxin and thorotrast, 10 as well as infections with liver parasites-Opisthorchisviverrini and Clonorchissinensis, have also been linked to an increased risk of cholangiocarcinoma. The pathogenic role of hepatitis C and hepatitis B in CCA differs in western countries, where hepatitis C is more prevalent, as opposed to Asian countries, where hepatitis B is a major risk factor. P.21-24

Our patient cohort exhibited a unique risk factor profile with chronic cigarette smoking, regular alcohol intake and diabetes mellitus identified to have a bearing on the development of CCA. These factors however, did not predispose to any specific anatomical subtype. None of our patients had previously described risk factors like chronic hepatitis B/C, hepatolithiasis, and inflammatory bowel disease or choledochal cyst. Liver flukes are not endemic to this region and are not anticipated to have a major role in CCA from India. In this study, the incidence of CCA is higher in areas of rubber plantation. Exposure to potential carcinogens like tannins may have a role in pathogenesis. Similarly, a significant number of patients came from coastal belts. Exposure to toxins used for freezing and storage of sea food may have a role in carcinogenesis in these patients. (Figure 3)

The clinical presentation of cholangiocarcinoma can be nonspecific, even in late stages of the disease, making the diagnosis of this malignancy challenging for both primary clinicians and specialists.²⁵ A majority of our patients presented with jaundice, pruritus and weight loss. Clinical presentation varied across subtypes with dCCA presenting at an earlier stage with jaundice and pruritus whereas, iCCA presented mainly at an advanced stage (8/12 patients (66%)). Total Bilirubin, Hemoglobin and albumin were found to significantly impact post-treatment outcome in our patients.

Diagnostic modalities and staging of the disease using cross-sectional imaging like (MRI-MRCP, Contrast enhanced Computerised tomography) and/or endoscopic ultrasonography gives little information regarding tumor behaviour and lack sensitivity in assessing extent of disease.26 However, they are useful to assess vascular involvement, lymph nodal and distant metastasis which aid in pre-operative decision making.²⁷ Peri hilar CCA patients were classified using Bismuth-Corlette system which is based on the anatomic location of the CCA within the biliary tree and is meant to helpful for operative decision making.²⁸ Patients with pCCA type IV accounted for 50% of the patients and type III accounted for 46%. Left sided disease (Bismuth Type IIIb) was more common in our population and these patients presented more often with portal vein thrombosis and advanced disease. Therefore, the spatial distribution of the disease may have a bearing on the prognosis, a finding that merits further study.

The only curative options for pCCA are surgical resection and neo-adjuvant chemo radiation followed by liver transplantation. Surgical resection entails lobar hepatic and bile duct resection, regional lymphadenectomy, and Rouxen-Y hepaticojejunostomy. Potential contraindications to curative surgical resection include contralateral or bilateral vascular encasement and pCCA extension bilaterally to the level of the secondary biliary branches.²⁸ It is worthwhile to note that only one-third of our patients (31%) with pCCA underwent surgery, of which only 11 underwent curative resection. A majority of our patients with pCCA were managed with palliative measures like biliary drainage procedures and palliative chemotherapy. As a corollary to this observation, it would be reasonable to conclude aggressive disease behaviour of pCCA in our region necessitating public health reforms for better screening programmes. Distal CCA usually presented earlier in the disease and a larger proportion were amenable to surgical therapy. Intrahepatic CCA in our patient cohort had a dismal prognosis owing to advanced stage at presentation and limited therapeutic options.

In general, CCA is associated with poor long-term survival and surgically unresectable disease is currently incurable.²⁹ Even with optimal surgery for iCCA, the 5-year overall survival (OS) and recurrence rates are 15-40% and 50-60% respectively, with a median disease free interval of 26 months necessitating the need for chemotherapy and radiation. 30,31 This relative therapeutic resistance can be attributed to the desmoplastic nature of the tumour, a rich conducive tumour microenvironment and a profound genetic heterogeneity.¹⁷ In this study, patients who underwent surgery had a significant survival advantage as compared to patients who underwent only palliative biliary drainage. However palliative treatment was offered exclusively to patients with advanced unresectable CCA. It is worthwhile to note that, palliative chemotherapy with gemcitabine based regimens did provide a significant survival benefit which was equivalent to surgery with adjuvant chemotherapy over a period of 1 year. Traditionally considered to be resistant chemotherapeutic agents, CCA has shown some promising results in recent data with Gemcitabine and Cisplatin.³² Our study is the first report on CCA from the Indian subcontinent highlighting a hitherto unknown high incidence in the region. Scope for extrapolation of these results is limited owing to the restriction of patient population to a single centre. However, a strong case can be made for a structured reporting system that can potentially identify CCA as a public health concern in this part of the country. The concentration of cases in coastal areas and rubber plantation regions, can provide future directions for prospective studies in the area to confirm this distribution and additionally, efforts to identify novel etiopathogenic determinants specific to these regions. Heterogeneity in the case selection for each therapeutic modality can be explained due to the lack of a management protocol and the retrospective design of the study. Further prospective trials with a standard management protocol may shed light on key survival observations made in this study. The relative resistance to chemotherapy traditionally described for CCA needs to be re-examined in the Indian context, in light of the findings of this study which indicate a good response in the small number of patients who did receive chemotherapy. Well-designed prospective randomised controlled trials are warranted for further validation of these observations.

CONCLUSION

In conclusion, CCA patients in this study exhibit some unique epidemiologic features with a conspicuous absence of known risk factors. Geographical patterns of disease incidence were noted in coastal and rubber plantation areas, highlighting the potential role of environmental factors that facilitate carcinogenesis in these patients. This however, requires large scale community studies in these regions which can define disease clusters and allow further characterisation of unique risk factors for CCA. In addition, treatment with a curative intent was not possible in a majority of patients owing to an advanced stage at presentation. This reiterates the need to identify novel avenues for early diagnosis of the disease in the future.

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