

# Cholangiocarcinoma: A 10-Year Experience Of A Single Tertiary Centre In The Multi Ethnicity-Malaysia

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## SUMMARY

Cholangiocarcinoma (CCA) is a rare biliary tract epithelial malignancy. We described the clinical features of CCA patients in our institution. A 10-year retrospective study of patients with cholangiocarcinoma in University Malaya Medical Centre was conducted. Clinical data and outcomes in relation to the three anatomical groups of CCA were collected and analysed. Of the 69 patients that were included 55% were male. Mean age was 61 years. Twelve (17%) had intrahepatic, 38 (55%) perihilar and 19 (28%) distal tumour. Mean age ( $p=0.043$ ), median duration of symptoms ( $p=0.011$ ), jaundice ( $p<0.001$ ), total bilirubin level ( $p=0.003$ ), INR ( $p=0.005$ ) and mean tumour size ( $p=0.048$ ) were significantly related to the site of tumour. Only 12 patients had curative resection with seven R0 resections. Cholangiocarcinoma is increasingly diagnosed in our population. Despite that, the diagnosis is still often late. Age, jaundice and tumour size may predict anatomical location of CCA.

## KEY WORDS:

*Cholangiocarcinoma, Bile duct tumour, Surgery, Malaysia*

## INTRODUCTION

Cholangiocarcinoma (CCA) is a rare malignant tumour of the biliary tract epithelium with a poor prognosis. It accounts for less than 2 % of all human malignancies<sup>1</sup> but is the second most common primary hepatic malignancy after hepatocellular carcinoma<sup>2</sup>. Nonetheless, the worldwide incidence and mortality of CCA have steadily risen over the past three decades<sup>3</sup>.

CCA has high mortality because of its late clinical presentation and a dearth of effective non-surgical treatment options<sup>4</sup>. Typically the tumour occurs in 50 to 70 years of age with a slight male prevalence<sup>5</sup>. The majority will have unresectable disease during diagnosis and usually die within 6 months to a year due to cancer cachexia, liver failure and biliary sepsis<sup>6</sup>. With less than 5% of patients surviving to 5 years this poor long term survival rate is virtually unchanged from past 20 years<sup>5,7</sup>. Surgery remains the only bastion for cure. While radical resection offers an improved outcome it is associated with high perioperative morbidity and mortality rates<sup>8</sup>. Palliative stenting and chemoradiation meanwhile are reserved for advanced, non-resectable patients as well as those with recurrence or decline surgery<sup>3</sup>.

We aim to describe the clinical features of patients with CCA treated in University Malaya Medical Centre (UMMC) with regard to the following; demography, presenting symptoms, risk factors, methods of investigations and therapeutic options.

## PATIENTS AND METHODS

A 10-year retrospective review of all patients' medical records with the diagnosis of CCA treated in our centre between January 1997 and December 2007 was conducted. Our centre is a tertiary medical centre in Malaysia with a specialized hepatobiliary surgery unit and a gastroenterology unit.

All patients with confirmed histological diagnosis by biopsy or without histologically confirmed diagnosis but had strong provisional diagnosis by clinical examination, biochemical results and positive endoscopy or imaging (i.e. ERCP/MRCP and CT of the abdomen) were included in the study. It is not uncommon to make the diagnosis of CCA based on clinical/laboratory/imaging studies without tissue-proven evidence of tumour<sup>7</sup>. Patients with hepatocellular, head of pancreas and gallbladder carcinomas were excluded from the study.

Ultrasonography (USG), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous cholangiography (PTC) were used in combination for diagnosis, staging and assessment of resectability. Metastasis was evaluated by CT thorax, abdomen and pelvis and/or chest radiography (CXR).

Patients were classified according to the anatomic location of the primary lesion into intrahepatic, perihilar and distal type as proposed by the Guidelines for the Diagnosis and Treatment of Cholangiocarcinoma<sup>5</sup>. Intrahepatic tumours were defined as confined to the liver and not involving the extrahepatic biliary tree. Perihilar tumors were those involving or requiring resection of the hepatic duct bifurcation and were typically located in the extrahepatic biliary tree proximal to the origin of the cystic duct. Distal tumors were extrahepatic lesions located in the peripancreatic region<sup>9</sup>.

Patients were staged according to tumour-node-metastasis (TNM) system<sup>6,10</sup> and assessed for resectability. Therapeutic options received whether surgical or palliative therapies,

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operative data, morbidity and mortality (first 30 days post-operation) were scrutinized.

Statistical calculations were performed using SPSS version 13.0. Categorical variables were compared using Chi-square tests for association and one-way analysis of variance (ANOVA) to compare continuous variables among the patients with three tumour locations. The results were presented as means  $\pm$  standard deviation (SD), unless otherwise specified. P value  $<0.05$  was considered significant.

## RESULTS

### Demography

Sixty nine patients were included in this study. Of these, 12 (17%) had intrahepatic, 38 (55%) perihilar and 19 (28%) distal tumour. Males were 38 patients (55%) and 31 (45%) were females. Male to female ratio was 1.2:1. Age of patients ranged from 18 to 91 years old with a mean age of 61 (SD  $\pm$  14.2). However, patients with intrahepatic tumour were more likely to be younger ( $P<0.05$ ) compared to perihilar and distal tumours. Among the three major ethnic groups in the country, the majority was Chinese patients, 42 (61%), followed by Malay, 20 (29%) and Indian, 7 (10%) (Table I).

Frequency of admission by year showed increasing patterns. Only one case was reported in 1997 and it increased to 10-folds 5 years later with 10 cases reported in 2002 (Fig 1). More than half of the patients (68%) presented in the latter 5 year study period (2003-2007).

### Risk factors

With regard to predisposing factors, 22 patients (29%) had history of chronic cigarette smoking while diabetes mellitus and regular alcohol intake were found in 13 patients (19%) each. Only five patients (7%) had hepatitis B. Hepatolithiasis and choledochal cyst, were only found in one patient each (1.4%). Table II summarizes the risk factors and location of tumour.

### Clinical evaluation

The most common presenting symptoms of CCA among our patients were jaundice (78%), followed by anorexia (57%), weight loss (52%), abdominal pain (44%), abdominal masses (44%), pruritus (25%), vomiting (9%) and fever (7%). Approximately, 98% extrahepatic CCA were jaundiced (63% perihilar and 35% distal) compared to only one intrahepatic patient ( $P<0.001$ ). No symptoms were found to be significantly related to any three types of CCA. The median duration of complaints prior to medical consultation was 30 days (range 1-365 days). However, patients with intrahepatic lesions tend to present later ( $P<0.05$ ) than perihilar or distal lesions (Table III).

### Investigations

Routine blood samples were taken and the following table shows the mean level of some of the important blood investigations during admission (Table IV).

As evidenced, the level of total bilirubin was significantly higher in those with perihilar lesions as compared to other lesions ( $P=0.003$ ). INR value was also predictive of the site of

the lesion as it was high in patients with distal lesions ( $P=0.005$ ).

CEA, AFP and CA19-9 were not routinely performed for all patients.

### Imaging

Ultrasound was performed in 45 patients (65%) and detected almost 50-76% of obstructed biliary systems. Almost 91% of the patients had CT scan to further elucidate the extent of the pathology. In our observation, about 20% of CCA were not detected by the ultrasound alone as compared to CT scan. Only four patients had MRCP.

Fifty eight patients (84%) had ERCP as the initial invasive investigation. During the procedure, 51 patients (74%) had stricture in the biliary trees at various levels. Of these, 44 (76%) were stented instantaneously to relieve the obstruction while seven (14%) failed stenting. Five of them eventually had PTC drainage. Only 22 patients (38%) with malignant strictures had cytology brushing with only 45% cancer-positive results obtained

### Staging

Preoperative staging was done using information gathered from imaging studies. None had staging laparoscopy because it was not routine in our centre. Staging was based on the American Joint Committee on Cancer TNM staging system. Twenty three patients (33%) had stage 1, 7 (10%) stage 2, 17 (25%) stage 3 and 22 (32%) stage 4 CCA. Stage 3 and 4 were considered unresectable. (Fig. 2)

### Surgical treatment

From the staging, 30 patients (43%) were candidates for surgical resection. However, only 22 patients (32%) underwent laparotomy with curative intent. Three patients (and their relatives) refused surgery citing age as their primary concern (mean age 78 years old) while five patients were later excluded from surgery because of age (mean age 71 years old) and associated comorbidities. At laparotomy, 10 patients had extensive local disease and/or hepatic metastasis that precluded resection leaving only 12 patients to undergo a potentially curative resection (resectability rate of 55%). All planned curative resection patients with biliary obstruction had preoperative biliary drainage either endoscopically or percutaneously (PTBD), except in one.

The types of surgery depend on the location of the tumour (Table V). In general, intrahepatic tumours were treated with hepatectomy while perihilar lesions with excision of the extrahepatic biliary tree and lymphadenectomy, with or without hepatectomy. Distal tumours were resected by Whipple pancreaticoduodenectomy. Biliary reconstructions were mostly by Roux-ex-Y hepaticojejunostomy. All surgeries were performed by hepatobiliary-trained surgeons.

The intraoperative and postoperative data by tumour location were shown in Table VI. Median operative time of all tumour types was 480 minutes. None of the surgical operation by tumour location had any significant difference in terms of duration, blood loss, intra operative blood transfusion and convalescence time.

Table I: Patients' characteristics

	Total (n=69)	Intrahepatic (n=12)	Perihilar (n=38)	Distal (n=19)	P §
Mean age in year (SD)	61 (14.2)	52 (3.3)	64 (2.2)	62 (3.4)	0.043#
<b>Sex</b>					0.109
Male (%)	55	16	66	18	
Female (%)	45	20	42	39	
<b>Race</b>					0.325
Chinese (%)	61	14	60	26	
Malay (%)	29	25	55	20	
Indian (%)	10	14	29	57	
<b>Year of presentation</b>					0.480
1997-2002 (%)	32	18	64	18	
2003-2007 (%)	68	17	51	32	

\*P value <0.05 is significant, § Chi-square test unless specified, # ANOVA.

Table II: Associated risk factors and location of tumours

	Total (n=69)	Intrahepatic (n=12)	Perihilar (n=38)	Distal (n=19)	P §
<b>Risk factors</b>					
Smoking	29	15	70	15	0.242
Diabetes mellitus	19	15	54	31	0.950
Alcohol intake	19	15	70	15	0.477
Hepatitis B	7	40	40	20	0.383
Choledochal cyst	1	0	100	0	0.661
Hepatolithiasis	1	100	0	0	0.104

\* values in percentage, P value <0.05 is significant, § Chi-square test

Table III: Presenting symptoms, duration and location of tumours

	Total (n=69)	Intrahepatic (n=12)	Perihilar (n=38)	Distal (n=19)	P §
<b>Presenting symptoms</b>					
Jaundice (%)	78	2	65	33	<0.001#
Anorexia (%)	57	10	62	28	0.190
Weight loss (%)	52	20	58	22	0.570
Abdominal pain (%)	44	27	47	27	0.190
Abdominal mass (%)	44	10	55	35	0.480
Pruritus (%)	25	6	82	12	
Vomiting (%)	9	33	33	33	
Fever (%)	7	20	60	20	
Median duration of symptoms (days)	30	36	21	21	0.011

\*P value <0.05 is significant, # Fisher's Exact test, § Chi-square test

Table IV: Laboratory data on admission and location of tumours

	Total (n=69)	Intrahepatic (n=12)	Perihilar (n=38)	Distal (n=19)	P §
TWC (109)	10.3 (5.7)	10.7(3.8)	9.0 (3.1)	12.6 (9.1)	0.760
Hb (g/dL)	11.8 (2.2)	11.4 (2.6)	11.8 (2.1)	12.2 (1.9)	0.590
Total bilirubin (mmol/L)	178 (158)	45 (109)	216 (163)	188 (131)	0.003
Conjugated bilirubin (mmol/L)	140 (122)	31 (87)	170 (123)	151 (102)	0.002
Albumin (mmol/L)	29 (7)	30 (6)	29 (6)	27 (10)	0.520
ALP (IU/L)	454 (290)	253 (161)	492 (319)	505 (246)	0.280
AST (IU/L)	105 (77)	60 (43)	116 (87)	112 (61)	0.740
ALT (IU/L)	141 (152)	58 (32)	168 (177)	139 (126)	0.870
GGT (IU/L)	608 (453)	425 (404)	672 (474)	593 (429)	0.290
INR 1.2 (0.7)	1.1 (0.1)	1.0 (0.1)	1.6 (1.1)	0.005	

\*values in mean (SD), P values <0.05 is significant, § ANOVA.

Table V: Types of surgical resection

Types of surgery	Patients(n=12)
Left hemihepatectomy	2
Right hemihepatectomy	1
Segmental hepatic resections	2
Extrahepatic bile duct resection	5
Whipple's procedure	2

Table VI: Intraoperative and postoperative data by tumour location

	Total (n=12)	Intrahepatic (n=3)	Perihilar (n=6)	Distal (n=3)	P §
Duration of operation (min)	480	480	460	540	0.666
Blood loss (ml)	2150	2800	1700	2000	0.525
Intraoperative blood transfusion (ml)	800	800	800	1200	0.900
Duration of ICU stay (days)	3	4	3	3	0.675
Duration hospital stay post-operative (days)	12	8	17	12	0.139

\*values are median, P value <0.05 is significant, § Chi-square test

Table VII: Postoperative complications and operative mortality by tumour location

	Total (n=12)	Intrahepatic (n=3)	Perihilar (n=6)	Distal (n=3)	P §
Post-operative complications	8 (67%)	2 (25%)	5 (63%)	1 (13%)	0.350
Ileus	3 (25%)	2 (67%)	1 (33%)	0	0.135
Bleeding	2 (17%)	0	1 (50%)	1 (50%)	0.549
Intraabdominal abscess	3 (25%)	0	3 (100%)	0	0.135
Surgical site infection	2 (17%)	0	2 (100%)	0	0.301
Deep venous thrombosis	1 (8%)	0	1 (100%)	0	0.580
Anastomotic stenosis	1 (8%)	1 (100%)	0	0	0.195
Bile leak	1 (8%)	0	1 (100%)	0	0.580
Operative mortality	1 (8%)	0	0	1 (100%)	

\*P value<0.05 is significant, § Chi-square test

Table VIII : Tumour histology, degree of differentiation, diameter, margin, perineural and lymph node involvements by tumour location

	Total (n=12)	Intrahepatic (n=3)	Perihilar (n=6)	Distal (n=3)	P §
<b>Tumour histology</b>					
Adenocarcinoma	11 (92%)	2 (18%)	6 (55%)	3 (27%)	
Other	1 (8%)	1 (100%)	0	0	
<b>Degree of differentiation</b>					
Well	5 (42%)	2 (40%)	2 (40%)	1 (20%)	
Moderate	6 (50%)	1 (17%)	3 (50%)	2 (34%)	
Poor	1 (8%)	0	1 (100%)	0	
<b>Tumour diameter</b>					
Mean size in cm (SD)	9.6 (±15.2)	27.1 (±24.3)	2.8 (±2.2)	5.7 (±15.2)	0.048#
<b>Margin</b>					
negative	7 (58%)	3 (43%)	3 (43%)	1 (14%)	
positive	5 (42%)	0	3 (60%)	2 (40%)	
<b>Lymph node involvement</b>					
negative	8 (67%)	2 (25%)	4 (50%)	2 (25%)	
positive	4 (33%)	1 (25%)	2 (50%)	1 (25%)	
<b>Perineural involvement</b>					
negative	5 (42%)	3 (60%)	2 (40%)	0	
positive	7 (58%)	0	4 (57%)	3 (43%)	
<b>Lymphovascular invasion</b>					
negative	7 (58%)	2 (29%)	4 (57%)	1 (14%)	
positive	5 (42%)	1 (20%)	2 (40%)	2 (40%)	

\*P value <0.05 is significant, #ANOVA

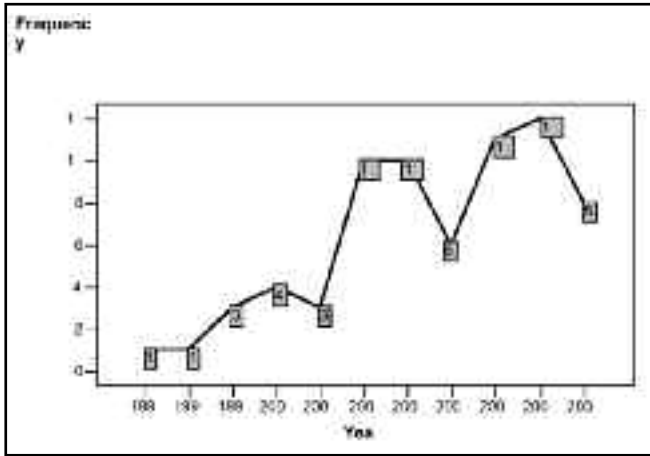


Fig. 1: Number of cases per annum.

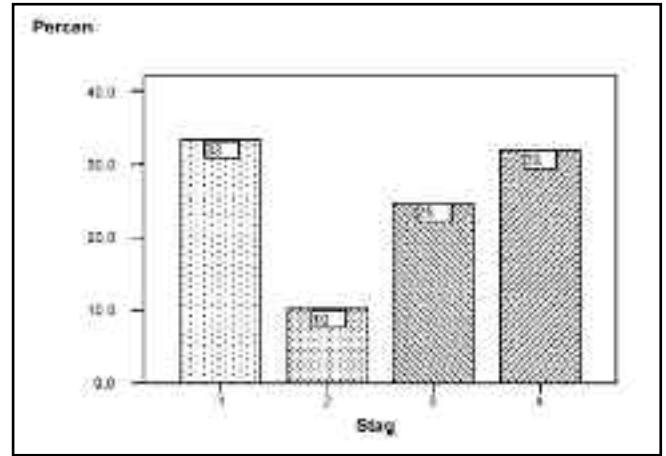


Fig. 2: Preoperative staging of all patients.

Out of 10 patients (45%) who were deemed to have advanced inoperable disease at laparotomy, three of them underwent palliative hepaticojejunostomy and gastrojejunostomy while four had gastrojejunostomy alone. Two patients just had cholecystectomy and biliary stent insertion while one patient had only laparotomy and biopsy.

*Surgical morbidity and mortality*

Post-operative complications after curative resection were observed in eight patients (67%). Some patients had more than just one complication. They occurred in all three tumour types but these were not statistically significant. Table VII summarized all postoperative complications and operative mortality by tumour location. Only one patient died of complications within 30 post-operative days and hence brings our perioperative mortality rate to 8%.

*Tumour characteristics*

Of the 12 curatively resected patients, 11 (92%) had adenocarcinoma on histology while one patient had papillary adenocarcinoma. The mean tumour diameter was 9.6cm (SD± 15.2) and ranged from 0.5 cm to 55 cm. Intrahepatic tumour size was larger compared to perihilar and distal tumours (P <0.05). Five patients (42%) had well-differentiated adenocarcinoma and the remaining was moderate or poorly differentiated. Perineural involvement and lymphovascular invasion occurred in 58% and 42% of the resected tumour respectively. Regional lymph node metastasis occurred in 33% of tumours. Resection with negative margins (R0 resection) was achieved in seven patients (58%) while the rest was microscopically positive. Table VIII summarized the tumour characteristics.

*Palliation*

About 47 patients (68%) were not operated and hence palliated. Thirty one patients (66%) had palliative endoscopic stenting and 23 patients (49%) by PTBD with or without concurrent stenting while 13 patients had both. Sixteen patients live long enough to have their stent changed on follow up in which nine had metal stents. Three patients (6%) received palliative chemotherapy alone, which included a variety of chemotherapeutic agents (5-fluorouracil, cisplatin,

gemcitabine). Three patients (6%) were too ill and hence received best supportive care.

**DISCUSSION**

This study represents the largest published retrospective cohort series of CCA from Malaysia. We believe that this tumour is increasingly diagnosed in our population although the exact incidence is still undetermined. In an older series from similar institution, 24 patients with biliary tract carcinoma were seen in the 5-year period from 1981 to 1985. Chinese patients were again the majority compared to Malay and Indian<sup>29</sup>.

CCA is best classified anatomically into intrahepatic, perihilar and distal tumours<sup>9, 11, 12</sup>. Perihilar CCA or Klatskin tumour represents the majority which accounts for almost 40-60% of cases while distal and intrahepatic tumours account for approximately 20-30% and 10% respectively. The tumour locations in our series were 17 % intrahepatic, 54% perihilar and 29% distal in tandem with the figures from the literature<sup>9, 13</sup>.

The demography of our patients seems to be comparable to the other larger series. A review of 294 patients with CCA by Nakeeb *et al.*<sup>9</sup> reported a mean age of 62.2 years old and De Oliveira *et al.*<sup>13</sup> showed a median age of 65 whilst our mean patient's age of 61 years. However, patients with intrahepatic tumour presented at a significantly younger age as compared to perihilar or distal tumour (P<0.05). Male has a slightly higher preponderance in this study with male to female ratio of 1.2:1 which again similar to the findings by both Nakeeb *et al.* (1.2:1)<sup>9</sup> and DeOliveira *et al.*(1.38:1)<sup>13</sup>.

There was a dramatic increase in the number of CCA treated in the latter 5-year period of this study, which was 32% in 1997-2002 versus 68% in 2003-2007. While the number of referred patients had doubled across the study period, similar trend was also noted from patients who came directly to us. This could be due to improve detection and diagnosis or rather due to increase awareness of local surgical expertise hence referrals<sup>30</sup>.

Only a few CCA in our series had strong risk factors such as hepatitis B, hepatolithiasis and choledochal cyst<sup>14,16</sup>. None had history of primary sclerosing cholangitis<sup>14</sup> or liver fluke infestation<sup>17</sup> which is not endemic in Malaysia. Chronic cigarette smoking, regular alcohol intake and diabetes mellitus were other observed associated risk factors<sup>18, 19</sup>. Nevertheless, none of these were found to show predilection for any particular site of tumour.

The most common symptom attributable to CCA was jaundice. We found that most extrahepatic CCA patients (perihilar and distal tumours) will have jaundice in comparison to intrahepatic CCA ( $P < 0.001$ ). This is further confirmed by the level of bilirubin, which was exceptionally higher in perihilar tumour (extrahepatic) than intrahepatic tumour ( $P = 0.002$ ). Similar observations were also noted by DeOliveira *et al.*<sup>13</sup> and Alexopoulou *et al.*<sup>20</sup>. Other blood parameter that could possibly signify the location of tumour is the International Normalized Ratio (INR) as it was higher in the distal tumour patient ( $P = 0.005$ ). The possible explanation to this is vitamin K-dependent coagulation factors will be decreased in the presence of obstructive jaundice leading to deranged coagulation profile<sup>5</sup>. However, the rest of other symptoms and blood parameters were not significantly related to a certain type of CCA.

A large proportion of our patients had ERCP as opposed to MRCP. ERCP is advantageous over MRCP as being diagnostic and cytology-enabled as well as therapeutic to decompress the obstructed biliary system<sup>6</sup>. Although the success rate of internal stent placement is high, the role of PTBD should not be undermined especially where endoscopic drainage has failed. PTBD is also helpful at visualization of proximal biliary tumour and its anatomy<sup>5</sup>. Failure of biliary decompression will result in cholangitis and risks of liver failure and sepsis<sup>21</sup>. Decompressing an obstructed biliary system for potentially resectable CCA is our preferred preoperative measure to prevent those risks even though a series by Figueras *et al.*<sup>22</sup> had demonstrated no significant differences in morbidity or mortality with or without preoperative biliary drainage. None of our patients who underwent hepatic resection developed liver failure post-operatively.

Despite improved diagnostic methods and a relatively early presentation, only a third of our patients (32%) underwent surgery with merely 12 of them had curative resection. More than half (58%) of them were unresectable and the remaining were inoperable because of comorbidity and/or advanced age. This was not surprising because a similar figure was also quoted from the literature<sup>7</sup>. Nevertheless, our resectability rate of 55% (12/22) was comparable to other larger series, where it was reported to be at 18-70%<sup>23</sup>. With regard to the postoperative complications, our surgical morbidity based on types of CCA was not significant. In high volume centres with vast experience, the operative mortality and morbidity rates vary from 6-14% and 32-65% respectively<sup>24-26</sup>. Our 30-day operative mortality and morbidity rates were 8% and 67% respectively in keeping with most other centres.

For the majority of patients who are not for curative resection, palliative treatment to relieve jaundice and cholangitis to avoid liver failure can be achieved surgically via biliary-enteric bypass or stent placement via PTBD or ERCP<sup>27</sup>.

The major limitation of our study was that it only involved a single centre and may not represent the entire population of this country. The number of the study cohort was small and this may reduce the impact of various statistical analyses.

## CONCLUSION

Cholangiocarcinoma is increasingly diagnosed in our population as evidenced by the number of patients seen per year throughout our study period. Despite that, diagnosis of the disease is still often late with only 32% of the cases being operable. In our experience, younger age at presentation, absence of jaundice and larger tumour size may suggest intrahepatic nature of cholangiocarcinoma.

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