FOUR YEAR EXPERIENCE WITH CHOLANGIOCARCINOMA: A SURVEY OF PATIENTS, CLINICAL PRESENTATION, MANAGEMENT AND PROGNOSIS IN TWO HOSPITALS

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ABSTRACT

Seventeen patients with cholangiocarcinoma diagnosed in Toa Payoh and Tan Tock Seng Hospitals from 1986-90 were studied retrospectively. There was a male preponderance (male:female = 12:5) with a mean age of 58 years (range 28-82 years). All presented with obstructive jaundice. Three had cholangitis. Biliary stones were associated in 3(18%). Two patients (12%) had choledochal cysts. The level of obstruction was identified at the hilum in 12 (70.5%), lower third in 4 (23.5%) and at a choledochojejunostomy anastomosis in 1 (6%). Ultrasound and percutaneous cholangiography (PTC) were the commonest investigations used. Endoscopic retrograde cholangio-pancreatography (ERCP) was performed in 7 (41%) and computer tomography (CT) of abdomen in 6 (35%). Biochemically, a raised alkaline phosphatase (1.5-9 x normal) was typical. Biliary bypass surgery was performed in 7 (41%); Whipple's procedure in 2 (12%) and drainage only in 6 (35%). Nine operated upon survived an average of 6 months (range 2-11 months) and six by drainage survived an average of 62 days (range 13-155 days). Three (of which two declined treatment) were lost to follow up. Cholangiocarcinoma is an uncommon cancer occurring in the older age group. In younger patients, choledochal cyst seems to be an association. Survival is dismal with palliative treatment.

Keywords: Cholangiocarcinoma, Palliative treatment, Surgery, Stenting.

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INTRODUCTION

Cholangiocarcinoma is a rare cause of malignant obstructive jaundice. Presentation tends to be late and definitive diagnosis can be difficult. Prognosis is dismal, the only chance of cure being radical excision

As such, palliation by surgery, external drainage, percutaneous or endoscopic stenting are the usual treatment modalities. We were interested in the clinical presentations of these patients and the response to various palliative measures.

During the period of study, stenting via an endoscopic retrograde approach was not yet a routine procedure in our hospitals and we intend to compare this approach with the other forms of palliation. The patients in this study can then be retrospective controls.

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MATERIALS AND METHODS

Seventeen patients with a diagnosis of cholangiocarcinoma were traced from the case records of Toa Payoh and Tan Tock Seng Hospitals from 1986-90 and retrospectively studied.

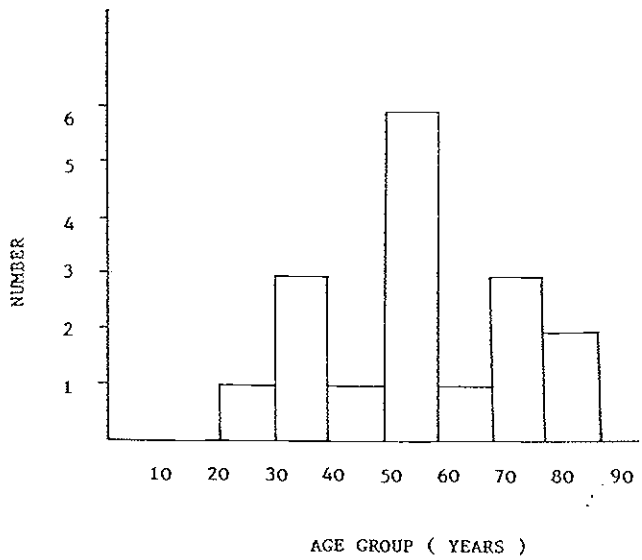
A histological or operative diagnosis was sought whenever possible. If this was not available, a combination of clinical and radiological criteria were used. These were: (1) the presence of a biliary stricture due to a mass lesion in the intrahepatic or extrahepatic bile ducts causing obstructive jaundice and (2) exclusion of carcinoma of the pancreas or gallbladder by ultrasonography or CT scan.

RESULTS

Epidemiology

There was a male preponderance of 12 to 5 females. The peak age distribution was in the 50-60 years group; the youngest being 28 years and the oldest 82 years (Fig 1). The majority were Chinese 14(82%), followed by Malay 2 (12%) and one Thai (6%).

Fig 1 - Age Distribution



Presenting Features

The duration of symptoms ranged from as short as three days to four weeks with a mean of 12.8 days and a median of 12 days. All patients presented with obstructive jaundice. Three also had cholangitis (18%). Right hypochondrial or epigastric pain was a feature in eight (47%). All had palpable hepatomegaly at presentation (Table I). Anaemia (Hb < 10g%) was present in one case.

Table I - Clinical Features

Clinical Feature	No.	%
Jaundice	17	100
Tea Coloured Urine	14	82
Pale Stools	7	41
Pruritus	8	47
Fever	3	18
Right Upper Quadrant/ Epigastric Pain	8	47
Hepatomegaly	17	100

Liver Function tests

An "obstructive" pattern in the liver function tests was typical at presentation. Serum bilirubin ranged from 2 to 27 times normal (mean 10.5mg%). Alkaline phosphatase ranged from 1.5 to 9 times normal (mean 480 IU/L). The alanine transaminase levels (ALT) ranged from 1.5 to 22 times normal (mean 188.4 IU/L). Low albumin (<3.5 g/l) were present in seven patients (mean 3.15 g/l).

Alpha-Feto Protein and HBs Antigen

Alpha-feto protein (AFP) and hepatitis B surface antigen (HBsAg) were done in 13 patients. AFP was negative in all cases. HBsAg was positive in two patients. Due to the retrospective nature of the study, carcinoembryonic antigen (CEA) was not done during the evaluation of the patients.

Radiology

Ultrasound (US) and percutaneous transhepatic cholangiography (PTC) were the commonest investigations. Computer-assisted tomogram (CT) was done in six patients. CT was found to be as useful as US in assessing bile duct dilatation. However the level as well as the aetiology of the obstruction determined by US was poor, being diagnostic of a mass in 2 cases out of 14, giving an accuracy of 14%. CT identified the level and a mass in 4 out 6 cases. PTC and endoscopic retrograde cholangiography (ERCP) were the most useful tests in delineating the level of obstruction and inferring its aetiology (Table II). Biliary tract stones were detected in three cases. Gallbladder stones were present in 3 and common bile duct stones in 2. Liver secondaries were detected radiologically in 2 patients.

Table II - Accuracy of Radiological procedures in determining the level of obstruction

Investigation	No.	Accuracy	%
Ultrasound	14	2	14
PTC	12	11	92
ERCP	7	7	100
CT	6	4	67

Site of Tumour

The commonest site was the hilum of the liver 12/17 (70.5%), followed by the lower third of the bile duct 4/17 (23.5%); in one (6%) the tumour was located at the site of a previous choledochojejunostomy done after resection of a choledochal cyst. There was no intrahepatic duct tumour in this study.

Associated Conditions in the Biliary Tract

Several conditions in the biliary tract were noted to be associated with cholangiocarcinoma. Common bile duct stones (two patients) and gallbladder stones (three patients) were found. A choledochal cyst was found in a 34-year-old male. In this patient, a tumour was found at the bifurcation of the left and right hepatic ducts. In another 28-year-old male, a history of choledochal cyst which was resected eight years previously was obtained. In this patient, a tumour was found at the choledochojejunostomy anastomotic site.

Diagnosis

Histological confirmation of an adenocarcinoma was obtained in six patients (35%) during laparotomy. In another three, a tumour mass was found at operation but not biopsied. In the remaining eight, diagnosis was made on clinical and radiological grounds as they were deemed unfit for surgery. The mode of diagnosis and the distribution of tumour are illustrated in Table III.

Table III - Mode of Diagnosis

Diagnosis Mode	Hilum	Lower Third CBD	Anastomotic Site	No.
Histology	2	3	1	6
Operative	3	0	0	3
Radiologic Features	7	1	0	8
Total	12	4	1	17

Treatment

Surgery was performed on nine patients (53%), mostly with palliation in mind. Whipple's procedure was done in two patients with lower third bile duct tumours. Longmire's operation (hepatico-jejunostomy) was done in four, triple bypass in one. An excision of choledochal cyst with choledochojejunostomy and a revision of a previous choledochojejunostomy were done for the remaining two patients (Table IV A).

Table IVA - Surgical Treatment and Duration of Survival
Mean = 6 months, Median = 5 months

Treatment Modality	No.	Survival (Months)
Surgery		
1. Whipple	2	5, 6
2. Hepaticojejunostomy	4	2, 3, 7*
3. Triple Bypass	1	5
4. Revision of Previous Choledochojejunostomy	1	11
5. Excision of Choledochal Cyst & choledohojejunostomy	1	2
Total	9	

* One patient returned to home country

Percutaneous drainage was used to palliate four patients. Stenting was done percutaneously in one patient and endoscopically in another. Two patients refused treatment. (Table IV B).

Table IV B - Non-Surgical Palliation and Duration of Survival. Mean = 62 days, Median = 50 Days

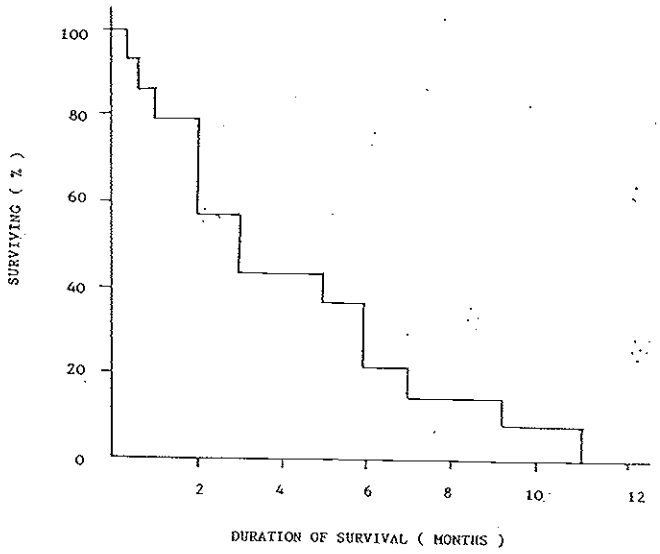
Treatment Modality Non-surgical	No.	Survival (Days)
PTC		
1. External Drainage	4	13, 22, 60, 90
2. Internal Stent	1	30
ERCP Stent	1	155
No Treatment	2	No Follow Up*
Total	8	

* Both returned to home country

Mortality and Morbidity

Fourteen patients were followed up after diagnosis; three patients of whom two refused treatment were lost to follow up after they returned to Malaysia and Thailand. Of the patients who were operated, the mean survival was 6 months (range 2-11 months, median 5 months). Of those treated non-surgically due to poor surgical risks, the mean survival was 62 days (range 13-90 days, median 50 days), (Table IV A & IV B). The overall poor survival is illustrated with the Kaplan-Meier curve (Fig 2).

Fig 2 - Actuarial Survival Curve



Amongst those operated upon, post-operative morbidity was present in the majority. One patient required a second operation 3 months later for duodenal obstruction. Recurrent cholangitis was a common occurrence in six out of nine patients who underwent operation (56%). Other complications included gastrointestinal haemorrhage (two cases), haemobilia (one case), hepatic encephalopathy (one case) and obstruction due to adhesions (one case). The patient who had a previous choledochal cyst excision with choledochojejunostomy 8 years previously underwent an operation to remove intrahepatic stones, initially thought to be the cause of obstructive jaundice. However his jaundice failed to resolve and a biliary fistula developed. At a second laparotomy 4 weeks later a small stricture at the previous choledochojejunostomy anastomosis was identified, resected and cholangiocarcinoma was confirmed by histology.

DISCUSSION

Primary cancer of the liver comprise mainly hepatocellular carcinoma and cholangiocarcinoma. Cholangiocarcinoma is an uncommon cancer in Singapore; there were 121 cases between 1968-82. During the same period, there were 1410 cases of hepatoma and 240 cases of pancreatic adenocarcinoma[1]. Cholangiocarcinoma which has a desmoplastic stroma, is not well vascularized and spreads via lymphatics in the bile duct. It invades locally into the liver, gallbladder, duodenum, and adjacent hepatic and portal vessels. Hematogeneous spread is uncommon compared to hepatocellular carcinoma.

In this series, there was a male preponderance with a peak incidence in the 50-60 year age group. All presented with obstructive jaundice, three also had cholangitis and all patient had hepatomegaly. Liver function tests were nonspecific indicating cholestasis. Anemia (Hb <10g%) was present in one case and hypoalbuminemia was present in 7. The level of obstruction was commonest at the hilum followed by the lower third. In our series we found an association with choledochal cysts in two patients. Both were young, aged 28 and 34 years and we note with interest that excision of a choledochal cyst and choledochojejunostomy 8 years previously in one patient did not prevent the development of cholangiocarcinoma. It is known that the carcinoma can develop even after excision of choledochal cyst and can occur in various parts of the pancreaticobiliary system[2,3]. Other associations that have been described with this tumour include Clonorchis sinensis infestation, primary sclerosing cholangitis and intrahepatic stones[4]. The presence of biliary stones in our series serves as a reminder that this may be a "red herring" diagnosis and emphasize the necessity for a thorough evaluation of the biliary tract before attributing the cause of obstruction to stones. There is no association with hepatitis B infection, nor with alpha-fetoprotein. After diagnosing biliary obstruction, the next step is to determine the extent of involvement in the biliary tree and the etiology, preferably with histology. Various radiologic imaging techniques by ultrasound, CT scan, cholangiography (ERCP or PTC) are used to attain this. A carefully performed, ultrasound scan in experienced hands with high resolution machines can be effective in diagnosing the site and nature of obstruction. This is especially so for extrahepatic bile duct obstruction for which it is superior to CT. Repeated examinations may be necessary due to frequent interference by bowel gas during examination of the common bile duct[5,6]. The relatively low yield in our series is probably due to the early generation ultrasound machine used. Cholangiography usually follows to plan treatment and help in staging. Where expertise is available, the endoscopic approach is preferred to the percutaneous transhepatic method as it is less invasive and risky. It also allows internal biliary drainage while other diagnostic, staging and treatment modalities are planned.

Preoperative tissue diagnosis is desirable, especially if non-operative management is considered , but is often difficult due to the inaccessible site of the tumour. Fine needle aspiration has not been useful due to the focal and sclerotic nature of the tumour. The yield of brush cytology of the bile duct via ERCP or PTC varies from 18% to 70%[7-9] depending on the technique used. Occasionally, hilar secondaries, lymphoma, gallbladder cancer invading the hilum, primary sclerosing cholangitis and even benign stricture can mimic the tumour[8,10].

In the absence of a tissue diagnosis, the overall clinical picture with a combination of cholangiographic (ERCP or PTC), ultrasonographic or CT criteria becomes important in establishing the diagnosis[5,6].

Complete excision offers the only chance of a cure[11-13]. Once the diagnosis is made and "curative" surgery is a possibility , adequate staging to determine resectability should be done. Metastases can be detected pre-operatively by ultrasound

or CT. Cholangiography is required to determine the extent of intrahepatic bile duct involvement. Recently, endoscopic ultrasound has been used to provide detailed information on the size and local extent of the tumour[14]. Doppler ultrasound is a useful method for assessment of major vessel involvement. Angiography is needed when major liver resection is planned. Unfortunately, overall surgical resectability is usually low, about 21% in one series[15], due mainly to late presentation and results are often poor. Results are best for lower third tumours (after Whipple's procedure) but poor for hilar (Klatskin) tumours[13]. Two patients subjected to "curative" Whipple's procedure in our study survived only 5 and 6 months (Table IV A).

Klatskin tumours deserve special mention as they comprise a significant proportion (70%) of our patients. In one series from the Netherlands[16], "curative" resection with hepatectomy for hilar tumours resulted in increased postoperative mortality (40% compared to 9% for local resection) but did not increase the number of curative resections nor significantly influence survival (local resection alone, mean survival 25 months; local and hepatic resection, mean survival 27 months). Major hepatic resection in another series from Sweden[12] resulted in a six month median survival, 32% one year survival, and a few patients (3 out of 22) were "cured" surviving more than ten years. However there was significant mortality (27%) and morbidity (57%). In our study, none were subjected to surgery with "curative" intent.

Palliation by surgical bilio-enteric anastomosis[16,17], percutaneous[18] or endoscopic[19-21] insertion of drains and stents are therefore the usual means of treatment. Provided the expertise is available, there is increasing evidence that the endoscopic approach is effective and accompanied by lower procedure related mortality and fewer complications[20]. In our study (Table IV A), 7 patients were subjected to palliative surgery: 4 hepaticojejunostomies, one triple bypass, 2 choledochojejunostomies (of which one was a revision) with a median survival of 5 months. In the group treated by non-surgical palliation (Table IV B), the median survival was 50 days. It is noted that the two groups are not comparable as the less ill patients were subjected to surgery and those at high risk for surgery were treated "conservatively". Most low lying bile duct tumours can be managed endoscopically but the high location of Klatskin tumours can pose technical problems and require the percutaneous approach. If the stricture is very tight and cannot be traversed with a stent, the patient often ends up with an external tube drain. This was the case for 5 of our patients who had a median survival of 30 days. Technological advances in the form of expandable metal "Wallstents"[22] and cholangioscopic laser treatment may be common in the future[23,24].

The median survival after palliative surgery in this study was 5 months (Table IV A). This bleak prognosis can lead to a nihilistic attitude, but it also highlights the need for a team of skilled biliary surgeons, radiologists and endoscopists in the joint management of this cancer. The current approach would be to identify fit patients with resectable tumours for radical surgery (about 20%) and endoscopic or radiological (percutaneous) palliation for poor risk patients or unresectable tumours.

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