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• *CLINICAL RESEARCH* •

Management of hilar cholangiocarcinoma in the North of England: Pathology, treatment, and outcome

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Abstract

AIM: To assess the management and outcome of hilar cholangiocarcinoma (Klatskin tumor) in a single tertiary referral center.

METHODS: The notes of all patients with a diagnosis of hilar cholangiocarcinoma referred to our unit for over an 8-year period were identified and retrospectively reviewed. Presentation, management and outcome were assessed.

RESULTS: Seventy-five patients were identified. The median age was 64 years (range 34-84 years). Male to female ratio was 1:1. Eighty-nine percent of patients presented with jaundice. Most patients referred were under Bismuth classification 3a, 3b or 4. Seventy patients required biliary drainage, 65 patients required 152 percutaneous drainage procedures, and 25 had other complications. Forty-one patients had 51 endoscopic drainage procedures performed (15 failed). Of these, 36 subsequently required percutaneous drainage. The median number of drainage procedures for all patients was three, 18 patients underwent resection (24%), nine had major complications and three died post-operatively. The 5-year survival rate was 4.2% for all patients, 21% for resected patients and 0% for those who did not undergo resection (P = 0.0021). The median number of admissions after diagnosis in resected patients was two and three in non-resected patients (P<0.05). Twelve patients had external-beam radiotherapy, seven brachytherapy, and eight chemotherapy. There was no significant benefit in terms of survival (P = 0.46) or hospital admissions.

CONCLUSION: Resection increases survival but carries the risk of significant morbidity and mortality. Percutaneous biliary drainage is almost always necessary and endoscopic drainage should be avoided if possible.

INTRODUCTION

Cholangiocarcinoma is a relatively rare tumor, accounting for approximately 2% of all diagnosed cancers. Its prevalence in England and Wales is approximately 2.0/100 000; however, the mortality rate has risen sharply in the past 30 years[1]. Upper third or perihilar (Klatskin) tumors make up 40-60% of cases[2,3] and are the main subjects of this paper. Klatskin tumors may be categorized as suggested by Bismuth classification into:

- Type I: tumors below the bifurcation of the common hepatic duct;
- Type II: tumors involving the bifurcation, but not extending into the main right or left duct;
- Type III: tumors infiltrating the right (IIIa) or the left (IIIb) hepatic duct;
- Type IV: tumors involving both the right and left hepatic ducts.

Cholangiocarcinoma is a slowly growing tumor and tends to spread longitudinally along the bile ducts with neural, perineural, and subepithelial extensions[4]. Lymph node invasion, particularly to the portal and peripancreatic regions, can be found in 46% of patients at the time of diagnosis[5]. Blood-born metastasis is rare and occurs at later stages of the disease. The prognosis for patients with unresectable tumors is poor and the majority of them die within 6 mo to a year of diagnosis[3].

Most patients present with obstructive jaundice. Preoperative investigations help establish the cause of obstruction, determine the extent of local disease and any evidence of distant metastasis, and evaluate the hepatic vasculature.

Treatment options for Klatskin tumors may be primarily surgical - either curative resection or palliative bypass, or non-surgical using modalities such as chemotherapy,

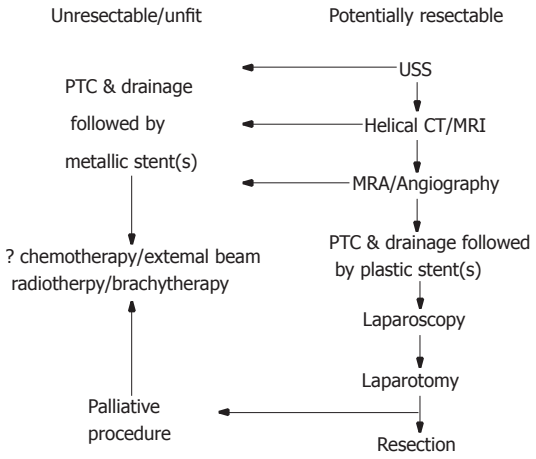

Figure 1 Flow chart demonstrating management options for hilar cholangiocarcinoma. USS, ultrasound scan; CT, computed tomography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; PTC, percutaneous transhepatic cholangiography.

radiotherapy (external or endoluminal), a combination of the two or more recently photodynamic therapy and gene therapy. The use of biliary endoprosthesis is common either as the primary modality in palliation or for relieving jaundice or sepsis prior to more definitive treatment.

The aim of our study was to assess the management and outcome of hilar cholangiocarcinoma in a single tertiary referral center in the United Kingdom.

MATERIALS AND METHODS

Patients

Our unit is a cancer center recognized for the treatment of hepatobiliary malignancy and covers a population of approximately 3.5 million people across the North of England. The notes of all patients with hilar cholangiocarcinoma presenting to our unit during an 8-year period from June 1995 to June 2003 were identified and assessed retrospectively. Seventy-five patients were identified. Male to female ratio was 1:1 with a median age of 64 years (range 34-84 years). Thirty-seven patients had confirmed histological diagnoses with the remainder being diagnosed on strong radiological evidence. In each case, tumors were categorized using the Bismuth classification. A schematic representation for the treatment of these patients is shown in Figure 1.

Investigations

All patients were assessed using triple phase helical CT or magnetic resonance imaging. Scans performed at referring hospitals were repeated, if deemed to be of insufficient quality. Vascular involvement of hilar vessels by tumors was assessed using magnetic resonance angiography (MRA) or transfemoral angiography if MRA could not be performed or was inadequate for accurate assessment. No percutaneous or endoscopic cholangiography was performed for purely diagnostic reasons. Further imaging and laparoscopic assessment were performed if clinically indicated. Staging procedures were completed, wherever possible, before biliary drainage.

Biliary drainage

It is our policy, to drain all obstructed segments of the bile ducts in all jaundiced patients with hilar cholangiocarcinoma wherever possible. Many patients referred from other units attempted endoscopic stenting of hilar strictures. In our experience, this is often inadequate and therefore staged percutaneous drainage was performed in the majority of cases with the initial placement of internal/external or external biliary catheters being followed by the placement of single or multiple stents. When the possibility of resection was excluded, self-expanding metallic stents were used, otherwise plastic stents were inserted.

Surgical procedures

Tumors were deemed to be unresectable on pre-operative staging in the presence of extra-hepatic metastases, occlusion of main hepatic vessels, or bilateral invasion of secondary biliary radicals into the liver parenchyma. On laparotomy or laparoscopic assessment, evidence of extensive lymph node involvement and peritoneal deposits were also taken to indicate unresectability. Curative resections involved complete removal of all gross and microscopic diseases to achieve negative histological margins with eradication of all metastatic lymph nodes restricted to the scope of dissection (Ro) and restoration of bilio-enteric continuity. Caudate lobectomy was also performed in the majority of cases. For all surgical procedures, duration, blood loss, utilization of critical care beds, and complications were recorded.

Other treatment modalities

Palliative chemotherapy, external beam radiotherapy, and brachytherapy were utilized in selected cases after consultation with clinical oncologists.

Follow-up

For all patients, the last consultation date as well as dates and causes of death were recovered from patient records. For those who lost their follow-up, data were completed by consulting the patients' general practitioners or collected from the local health authority records.

Statistical analysis

Data were analyzed using Minitab statistical software. Numbers of admissions and drainage procedures were compared using the Student's *t*-test and Bismuth classification. Breakdown was made using the χ^2 test. Survival analysis was made using the log-rank test. In all cases, $P<0.05$ was considered statistically significant.

RESULTS

Management for the 75 patients is shown in Figure 2. Of these, 67 (89%) patients presented with obstructive jaundice. Although there was an incidence of type IV tumors in the non-resected group, there was no significant difference in Bismuth classification between resected and

Table 1 Bismuth classification

Bismuth classification	All patients	Resected	Not resected
1	5	0	5
2	14	4	10
3a	12	6	6
3b	13	4	9
4	24	4	20
Not recorded	6	0	6

Table 2 Surgical procedures

Procedure	*n*
Extend right hemihepatectomy and excision of extrahepatic biliary tree	7
Right hemihepatectomy and excision of extrahepatic biliary tree	4
Left hemihepatectomy and excision of extrahepatic biliary tree	6
Segment 4 resection and excision of extrahepatic biliary tree	1
Roux-en-Y segment 2,3,5 bypass	1
Roux-en-Y hepaticojejunostomy and U-tube insertion	1
U-tube insertion	1
Choledochojejunostomy	3
Laparoscopy and lateral segmentectomy (due to hemorrhage)	1
Open/close	2

non-resected groups (χ^2 test, Table 1).

Investigations

All patients received transcutaneous ultrasonography, of them 72 patients (96%) underwent assessment with CT scanning, 42 (56%) had MRI scans, and 18 (24%) received transfemoral angiography.

Biliary drainage

Biliary drainage was necessary in 70 patients, of them 65 (93%) required percutaneous drainage. A total of 51 endoscopic biliary drainages were performed in 41 patients, of which 15 (29%) failed. Percutaneous drainage was subsequently required in 36 of the 41 patients who underwent ERCP, due to failure or inadequate drainage or stent occlusion. Of the 199 drainage procedures performed, 49 (24.6%) had complications including 20 failures, 20 episodes of biliary sepsis, and 3 cases of pancreatitis. The median number of drainage procedures for all patients was three.

Surgical procedures and complications

A total of 27 surgical procedures were performed in 26 patients (Table 2). Eighteen patients underwent resection (24%) and three underwent portal vein resection. Major complications occurred in nine (50%) including three post-operative deaths (16.7%). The breakdown of complications is shown in Table 3. The median blood loss (range) in resected cases was 2.4 L (range 1-12 L), the median duration of procedure was 8 h (6-18) and the median critical care stay was 6 d (range 2-40d).

Follow-up

The median follow-up time was 9 mo. The 5-year survival rate was 4.2% for all patients, 21% for resected patients and 0% for those who did not undergo resection (P = 0.0021, log-rank test, Figure 2). The number of admissions after diagnosis was significantly lower (P<0.05, Student's t-test) in resected patients (median = 2) than in non-resected patients (median = 3).

Table 3 Complications of resection

Complication	*n*
Death	3 (17%)
Sepsis	9 (50%)
Bile leak	6 (33%)
Collection	6 (33%)
Chest infection	5 (28%)
Liver failure	5 (28%)
Wound infection	4 (22%)
Bleeding	3 (17%)
ARDS	1 (6%)
Hepatic artery thrombosis	1 (6%)
GI obstruction	1 (6%)
Pleural effusion	1 (6%)
Renal failure	1 (6%)
Respiratory arrest	1 (6%)
Wound dehiscence	1 (6%)

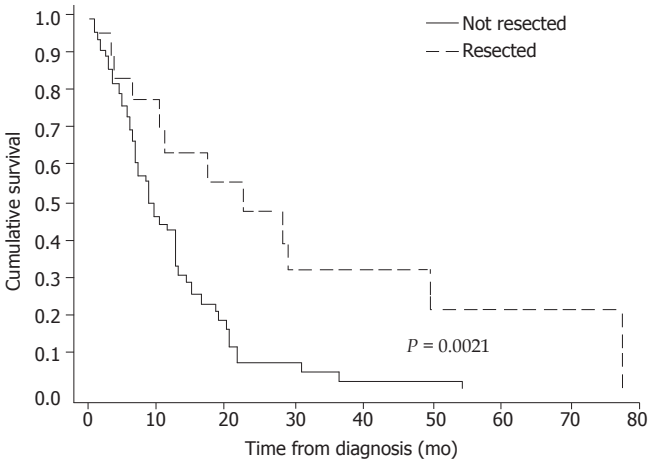

Figure 3 Kaplan–Meier survival plots for all patients with breakdown in resected and non-resected groups.

Other treatment modalities

In 23 patients who did not undergo resection, radiotherapy or chemotherapy was employed (Figure 3). These conferred no significant benefit in terms of survival (P = 0.46, log-rank test) (Figure 4), number of drainage procedures, or total hospital admissions.

Resected specimen pathology and staging

R0 resections were reported in 13 of 18 resected cases (72%). The pathological breakdown of resected cases by

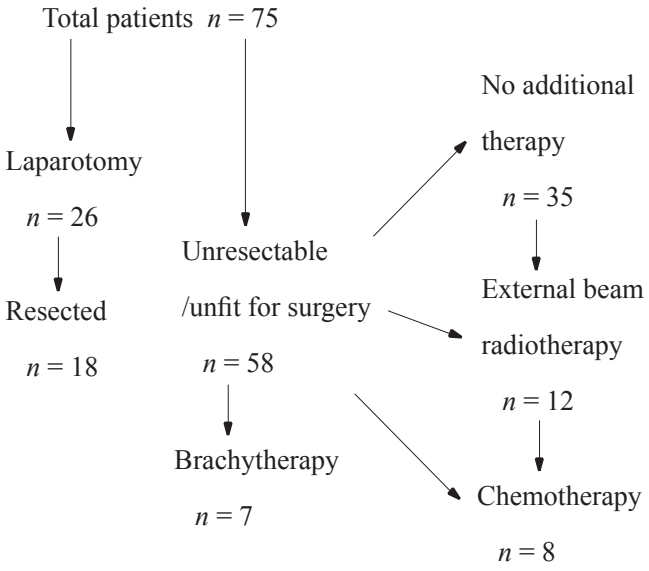

Figure 2 Flow chart showing management outcomes.

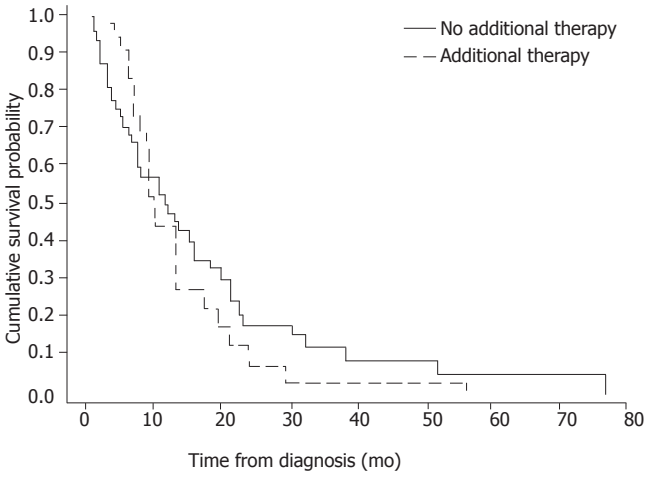

Figure 4 Kaplan-Meier survival plots for non-surgical therapeutic modalities in non-resected patients.

TNM classification is shown in Table 4. Vascular invasion was present in 9 cases (50%), perineural invasion in 13 cases (72%) and lymphatic invasion in 7 cases (39%). Patients who had node-negative resections tended to have a better survival than those who had node-positive resections (Figure 5) but this did not reach statistical significance ($P = 0.1$, log-rank test).

DISCUSSION

Our study is one of the few UK studies, documenting experienc-es in the management of hilar cholangiocarcinoma. The disease generally has a dismal prognosis; however, our findings demonstrate that an aggressive approach to the resection of these tumors results in prolonged survival. Resection is the only potentially curative treatment, and many patients do develop recurrence; however, these still benefit in terms of survival, fewer hospital admissions and decreased necessity for

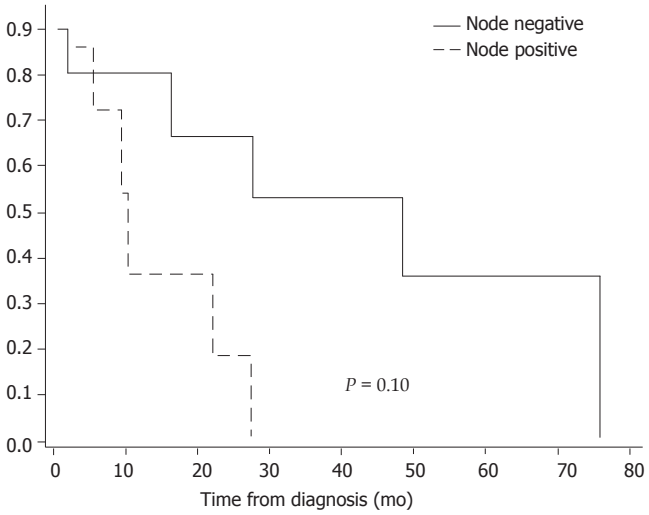

Figure 5 Kaplan-Meier survival plots for node positive and node negative resections.

Table 4 Pathological breakdown for resected cases

TNM classification	*n*
T1 N0	0
T1 N1	1
T2 N0	7
T2 N1	3
T3 N0	3
T3 N1	2
T3 N2	1
T4 N1	1

biliary drainage. Our results are comparable with several reported series of surgical resections for Klatskin tumors, with 5-year survival of 8-56%, in-hospital mortality of 6-17% and morbidity of 30-50%[2,3,6-11]. Negative resection margins have been shown to be important in prolonging survival although this could not be independently assessed in our study due to small numbers[3,8,12-14].

Major resection of a cholestatic liver is associated with an increased risk of serious complications due to impairment of liver function, including reticuloendothelial cells, mitochondrial and microsomal functions, impaired protein synthesis, wound healing and cell medicated immunity. All obstructed segments of the bile ducts in all patients undergoing preoperative assessment for surgical resection are therefore drained in our center. This facilitates not only the relief of jaundice, but also provides valuable information regarding the proximal extent of the tumor. In addition, it identifies the most common organisms isolated from the bile cultures to formulate the most appropriate perioperative antibiotic regimen.

In our study, endoscopic biliary drainage of hilar lesions had a high failure rate and almost all patients had to have subsequent percutaneous procedures in order to achieve adequate drainage. This is comparable with previously published data. Success rates for adequate endoscopic

biliary drainage for hilar tumors has been reported to be between 55% and 81%[15-18]. Even in studies supporting this modality, stent occlusion requiring further drainage procedures has been reported between 33% and 94% with morbidity of 22% and 44%[15,20]. Rerknimitr[15] describes an 81% rate for successful endoscopic drainage for Bismuth type II, III or IV tumors; however, 54% developed cholangitis and 30 of the 32 who did not undergo resection required further procedures within a mean of 47 d from initial drainage. Liu[18]describes a cohort of 55 patients undergoing endoscopic biliary drainage. Of these, only 73% had successful prosthesis insertion (16% required multiple procedures) with only 20 having satisfactory drainage. Of the 16 patients treated with palliative intent only, only 3 were successfully palliated by endoscopic means with the remainder requiring percutaneous drainage. Finally, Nomura[20]describes a significantly higher risk of cholangitis in patients treated endoscopically when compared to percutaneous drainage. Biliary obstruction due to hilar cholangiocarcinoma should therefore be ideally managed with percutaneous biliary drainage. Plastic internal-external catheters are placed initially and are then internalized. The majority of patients present with unresectable disease and in these cases, effective and reliable relief of the primary symptom - usually obstructive jaundice is paramount. For these patients also, percutaneous drainage is the method of choice. Self-expanding metallic Wallstents are preferred over plastic stents that have been shown to have longer duration of patency (6-8 mo), are more cost-effective, and are associated with a shorter hospital stay[21-23].

The use of palliative non-surgical treatment modalities conferred no benefit in our study. To date, there is no chemotherapeutic regimen that markedly improves survival in patients with advanced Klatskin tumors. Almost all phase II trials using single agents failed to demonstrate any beneficial effects with partial response rate of less than 10%[24-27]. Using combination therapy, however, the overall response rate has generally been shown to be slightly better at around 27%[28-32]. Radiotherapy may be delivered as an external beam irradiation using linear accelerator or by intraluminal brachytherapy. Trials assessing the palliative radiotherapy have generally been disappointing although a few have shown promising results. Shinchi *et al*[33]. have shown in a retrospective review of 51 patients that external radiotherapy combined with metallic stents can offer a mean survival rate of 10.6% mo, which was significantly longer than stenting alone (4-6 mo), with a much improved quality of life. Kuvshinoff *et al*[34]. also reported similar encouraging results in 12 patients managed with intra-ductal brachytherapy and external beam radiation; the mean survival being 14.5 mo.

In conclusion, resection of hilar cholangiocarcinoma, when possible, increases survival although it carries the risk of significant morbidity and mortality. Percutaneous biliary drainage is almost always necessary and ERCP should be avoided. There is no evidence of benefit from chemotherapy or radiotherapy in non-resected patients, although there is data from other studies suggesting some beneficial effects.

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