Low rate of active treatment of patients with hilar cholangiocarcinoma

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ABSTRACT

INTRODUCTION The results of surgical resection and palliative chemotherapy use in hilar cholangiocarcinoma (HC) have been well publicised but the proportion of patients able to undergo these treatments and the comparative outcomes in a population of patients with HC are less well known.

METHODS Patients with HC were identified by review of all patients undergoing percutaneous cholangiography over a nine-year period (2002–2010) in a tertiary facility. The treatment undertaken and outcomes were recorded.

RESULTS Overall, 68 patients were identified (37 female) with a median age of 70 years. Forty-five (66%) were treated solely by insertion of a metal stent (median survival 4.73 months) and nine (13%) also received palliative chemotherapy (median survival 13.7 months). Persisting jaundice after stent insertion was noted in 18 of 35 patients (51%) tested within one month of death. Fourteen patients (21%) underwent surgical resection (median survival 20.2 months).

CONCLUSIONS Patients undergoing surgical resection had significantly longer survival than those receiving only a palliative stent but not compared with those also receiving palliative chemotherapy, with short-term follow-up. Only a third of patients, however, receive active treatment (surgery or chemotherapy) and improvements in long-term biliary palliation are needed.

KEYWORDS

Cholangiocarcinoma – Chemotherapy – Stent – Bile duct neoplasm

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Hilar cholangiocarcinoma (HC) is a rare disease that remains difficult to diagnose and treat effectively. Resection of HC is more dangerous than resection of peripheral hepatic lesions^{1,2} and is suitable for only a minority of patients.^{5,4} Five-year survival rates of 20–35%, however, have been achieved in published series.^{1,5,6} Chemotherapy used in the treatment of inoperable HC includes gemcitabine and cisplatin. A disease control rate of 81% and a median survival of 11.7 months have been reported in the largest published series to date.⁷ Both of these treatment options, however, can only be offered to patients of good performance status and chemotherapy is not used in the presence of jaundice. The benefits of surgery and chemotherapy may therefore be experienced by only a minority of patients with the disease.

Palliation of biliary obstruction in HC can be achieved by either a percutaneous or endoscopic approach. Percutaneous transhepatic cholangiography has become the preferred technique in many centres as it has a higher success rate^{8,9} and fewer complications than the endoscopic approach.¹⁰ In the short term, stent insertion is very effective at restoring bile flow but the longer-term outcomes in terms of survival and relief of jaundice are less satisfactory.^{11,12} The outcome of the selected groups of patients receiving chemotherapy or undergoing surgery are well known but the proportion

that is well enough to receive this treatment has not been described and the relative impact of these treatment options on the population of patients with HC has not been assessed.

Our purpose in undertaking this study was to determine the outcome of curative and palliative treatment of HC in a consecutive series of patients presenting to Derriford Hospital, Plymouth, over a nine-year period. Derriford Hospital serves a local population of approximately 450,000 and has a referral base for tertiary care of 1.7 million. Aspects of the treatment under study included the number of patients receiving chemotherapy or undergoing surgery, the proportion that was jaundiced at the time of death and survival.

Methods

Patients were identified from the register of interventional procedures kept by the interventional radiology suite at Derriford Hospital from January 2002 to December 2010 and from the Peninsula hepatopancreatobiliary unit database, which has been kept since 2005. Follow-up was completed at 31 December 2011. Radiology records were scrutinised for patients with intrinsic hilar lesions, identified by the presence of a new diagnosis of a proximal biliary stricture with malignant features, with or without an associated mass

Table 1 Patient details and treatment outcomes in a consecutive series of patients with hilar cholangiocarcinoma (n=68)			
	Palliative stent only (n=45)	Palliative stent plus chemotherapy (n=9)	Surgical resection (n=14)
Median age (range)	73 (54–95)	61 (47–73)	68 (49–77)
Male-to-female ratio	24:21	2:7	5:9
Biliary reintervention after stent insertion or surgery	3 (7%)	3 (33%)	2 (14%)
Jaundice during follow-up	16/28 (57%)	2/7 (28%)	2/14 (14%)
Median survival	4.7 months	13.7 months	20.2 months

lesion, in the absence of risk for the development of benign stricture. Patients with distal biliary lesions, nodal disease at the hepatic hilum and gallbladder cancer were excluded.

The details of all previous and subsequent interventional biliary procedures undertaken were also retrieved. Details of tumour histology were obtained from the Derriford Hospital pathology department database. Chemotherapy details were obtained by case note review while bilirubin estimations and dates of death were obtained from the hospital patient information system. Decisions relating to patient care were made in a multidisciplinary setting involving surgeons, radiologists and oncologists. Survival times were calculated from the date of diagnosis for all patients. Categorical variables were compared using the chi-squared test and survival times with the logrank (Mantel-Cox) test.

Results

Sixty-eight patients (37 female, 31 male) were identified with a median age of 70 years at the time of diagnosis. Details of the patient population and treatments undertaken are shown in Table 1. Sixteen of thirty-seven women (43%) received active treatment (chemotherapy or surgery) compared with seven of thirty-one men (22%) (*p*>0.05).

Stented group

Of the 54 patients treated percutaneously, 40 patients had insertion of a solitary metallic stent and 14 patients underwent bilateral stent insertion. Fourteen patients (26%) had a histological diagnosis of cholangiocarcinoma. Percutaneous biopsy of solid lesions confirmed malignancy in 11 of 16 patients (69%). Cytological examination of endoluminal brushings confirmed malignancy in two of seven cases (28%). One patient had an operative biopsy. Six patients (11%) underwent reintervention for stent occlusion after the index procedure. Thirty-five patients (65%) had

Figure 1 Survival from diagnosis of a consecutive series of 68 patients with hilar cholangiocarcinoma

a bilirubin estimation performed in the thirty days prior to death. The median bilirubin in this period was 62µmol/l (range: 8–527µmol/l) and was greater than 50µmol/l in 18 patients (51%).

Of the 54 patients receiving biliary stents, 23 (43%) were referred to an oncologist for assessment, after multidisciplinary team discussion. Of these, 14 (61%) were considered not to be good candidates for chemotherapy and 1 patient declined. Nine (17%) of the stented group received chemotherapy. Gemcitabine was used as a single agent in three patients and platinum-based regimes were used in six. The median number of cycles received was five and five patients stopped treatment early owing to worsening performance status or disease progression. Therefore, only four patients in the stented group (7.4%) completed a full course of chemotherapy.

After a median follow-up duration of 4.7 years, the median survival of patients not undergoing surgical resection was 5.6 months. Eighteen patients (33%) survived for more than one year. Patients receiving chemotherapy had a longer median survival than those treated with stenting alone (13.7 vs 4.7 months, *p*=0.025).

Resected group

The characteristics of the resected group are shown in Table 1. One patient was found to be inoperable owing to bilateral vascular invasion and was followed up subsequently in the stented group.

The median interval from the diagnosis of biliary obstruction to surgery was 81 days (range: 28–176 days). Twelve patients (80%) had biliary intervention performed prior to surgery (five patients had endoscopic retrograde cholangiopancreatography and seven had percutaneous transhepatic cholangiography). Of these, eight (66%) required repeat procedures prior to surgery owing to sepsis or inadequate biliary drainage. Five patients required two procedures and three patients required three procedures. All 14 patients undergoing surgical resection required a liver and biliary resection. Ten patients had an extended right hepatectomy and four an extended left hepatectomy. All the

patients had a caudate lobe resection and seven patients required a portal vein resection. Portal vein embolisation to induce hypertrophy of the proposed liver remnant was not undertaken.

The median hospital stay of survivors was 15 days. There were two inpatient deaths (14%) within thirty days of surgery, one due to liver failure and one to small bowel anastomotic leak.

After a median follow-up of 2.55 years, four further patients had died, one of whom had tumour recurrence at the biliary anastomosis, leading to death ten months after surgery. Of the surviving eight patients, one had developed tumour recurrence at the bile duct anastomosis, requiring biliary intervention, two had developed distant recurrence only and five were disease free. The one-year and median actuarial survival was 74% and 20.2 months respectively. Histology of the excised specimens revealed seven T2 and seven T3 lesions, and nine patients (64%) had nodal invasion. Seven patients had resection margin (liver or bile duct) invasion (50%).

Discussion

The main findings of the study relate to the poor outcome of palliative treatment options of hilar cholangiocarcinoma, the low rate of histological diagnosis of malignancy and the low proportion of patients in whom active treatment is possible. Two-thirds of the cohort did not receive active treatment other than stent insertion and the median survival for this group was 4.7 months. In only nine patients was palliative chemotherapy considered a suitable option and over half of these did not complete a full course. Only 26% of the whole group had histologically confirmed cholangiocarcinoma. In the remainder, the diagnosis was made by radiological criteria alone. The very poor survival of this group supports the accuracy of a radiological diagnosis of cholangiocarcinoma in these patients. Patients undergoing surgery have better survival than those having stent insertion alone but not better survival than those who also receive chemotherapy.

In the selected patients who are well enough to undergo surgery or receive chemotherapy, surgery has little advantage in the short term, with similar survival at one year. Death following surgery, however, was rare after 500 days in our series whereas the group receiving palliative chemotherapy suffered continued attrition, reaching a mortality rate of 100% at three years. It is probable with further follow-up that surgery would confer a significantly better outcome than palliative chemotherapy.

The strength of this study lies in the capture of all data in 68 consecutive patients undergoing treatment for proximal malignant biliary obstruction over a 9-year period. The percutaneous approach is the standard biliary intervention technique used in our hospital in patients with proximal obstruction and it is unlikely any patients were treated solely by endoscopic techniques in this period. The cohort may not, however, have contained all patients presenting with the disease as some patients may have received only supportive care if they were felt to be too unwell to undergo

interventional procedures. The group that received palliative treatment is likely to have included patients with more advanced disease or of worse performance status than the group undergoing surgery although staging and assessment data are not available to confirm this.

The low rate of biliary reintervention (7%) may have been a significant factor in the poor outcome of the palliated group. Although metal stents are useful in the palliation of malignant biliary obstruction, they inevitably fail after a period owing to tumour ingrowth or occlusion with debris.¹⁵ Due to the rigid nature of these stents and associated inflammation, they can be difficult to recatheterise successfully, which may lead to a view that insertion of a wall stent is a permanent and final procedure. Possible causes of death include the effects of disseminated malignancy or the complications of biliary obstruction and intervention. The high rate of jaundice in the month prior to death supports the latter possibility.

The results of the ABC-02 study published in 2010 showed a survival benefit of combination treatment with gemcitabine and cisplatin in the palliative treatment of cholangiocarcinoma, reporting a median survival of 11.7 months,⁷ and this regime is likely to become standard treatment. Our results suggest, however, that only a very small minority of patients tolerate chemotherapy successfully, due either to poor general health or recurrent jaundice, and that improvements in biliary drainage are necessary to increase the proportion of patients able to receive active treatment.

Analysis from the time of initial presentation in the group undergoing surgery revealed similar difficulties to the palliated group in achieving adequate biliary drainage. Two-thirds of the patients in this group required repeat biliary intervention before undergoing surgery, which is reflected in the long time interval from presentation to resection (median 81 days).

A randomised trial of preoperative biliary drainage in pancreatic head tumours did not show any advantage to preoperative stenting¹⁴ and an 'early surgery' policy may also be beneficial in hilar cholangiocarcinoma. The perioperative mortality rate of our group (14%) is difficult to compare with that of other series owing to the low sample size. Studies have shown that resection of hilar cholangiocarcinoma has a higher mortality than liver resection not involving the biliary tree.^{1,4} The rate of resection margin involvement in our resected patients (50%) is similar to that of other published series where R0 rates of 40–60% have been reported.^{1,6,15,16}

Conclusions

Our results reveal the major difficulties in achieving effective and lasting biliary drainage either for definitive palliation or as a prelude to surgery. These difficulties are often overlooked in series describing the effect of active treatments, which are only possible after biliary drainage has been achieved. Improvements in achieving biliary drainage are likely to have a greater impact on the overall survival of patients with the disease than marginal increases of survival in the minority of patients who receive chemotherapy.

The very poor outcome of the palliative option must also be considered when assessing the risks of surgery.

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