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How Grim is Cholangiocarcinoma?

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Abstract Cholangiocarcinoma (bile duct carcinoma) is uncommon (2% of all malignancies). Lymph node involvement at presentation is common and carries a poor prognosis. Haematogenous spread is uncommon and there is currently no established role for chemotherapy or radiotherapy. Liver transplantation should be the best loco-regional treatment but most series report poor long- term survival after transplantation, presumably due to occult metastases. Loco-regional control would be favoured by early diagnosis and accurate preoperative staging but cure (eradication of putative micrometastases) remains grim because of its chemo-resistant nature. New strategies are needed to improve this line of therapy.

Keywords Cholangiocarcinoma, Prognosis

1. Introduction

Hilarcholangiocarcinoma was first described clinically by Altemier et al. in 1957.[1] The apparent increase in incidence in the last two decades particularly in the endemic tropical areas of the world is because of improvements in, and access to diagnostic techniques. Most cholangiocarcinomas are now diagnosed preoperatively.[2] Theusual life expectancy for cholangiocarcinoma is 3-6 months.[3] As bile duct cancer has conventionally been regarded as chemo-resistant the chances of cure from the addition of systemic chemotherapy to loco-regional treatment is limited.[3,4] There are no reported controlled trials which accurately assess whether chemotherapy or radiotherapy improves survival or palliation.[4] The aims of treatment of cholangiocarcinoma is first to relieve biliary obstruction, followed by long-term prevention of cholangitis. The final objective, eradication of the cholangiocarcinoma is less often achieved and occupies third place in this hierarchy of treatments. Stenting can give a useful period of prolonged palliation.[4]

2. Epidemiology and Aetiology

Cholangiocarcinoma is uncommon in the West but more common than hepatocellular carcinomawhich arises from liver cirrhosis mostly due to chronic hepatitis B/C virus infection and chronic alcohol toxicity. 6000 new cases per annum were reported in the USA and around 400 in England and Wales.[2] In North-East Thailand and the Far East the rates were 135.4 and 43.0 per 100 000 for males and females respectively and related to parasitic infestation with the liver fluke(*Clonorchissinensis*).[5] The peak incidence is in the 70 year age group indicating the duration required for the oncogenic process. In the extrahepatic type (90%), two-thirds arise at the hilar confluence (‘Klatskin tumours’ orhilarcholangiocarcinoma) and a third arises in distal bile duct (distal cholangiocarcinoma).[6] The intrahepatic type (10%) is also known as peripheral cholangiocarcinoma.[2] Although the majority are sporadic, a number of factors have been implicated in its aetiology. There is a strong association with inflammatory bowel disease (ulcerative colitis) and primary sclerosing cholangitis (PSC) and the radiological features of the latter may be indistinguishable.[4] The lifetime risk of PSC and cholangiocarcinoma is 5-15%, highest in the first 2 years of diagnosis.[2,4] Other predisposing factors include congenital biliary disease with choledochal anomaly (10-30% risk), 7oriental cholangiohe patitis,[3] aflatoxins,[8] vinyl chloride, thorotrast, nitrosamines,[9] anabolic steroidsand benign biliary tumours (papilloma and adenoma).[4]

3. Pathology and Classification

95% of cholangiocarcinimas are ductal mucus-secreting adenocarcinomas arising from the epithelium of any part of the biliary tract.[10] The rest are squamous cell or small cell carcinomas. Periampullary tumours are generally papillary in form, those in the mid-duct nodular, and tumours of the hepatic duct confluence generally stenosing.[11] Dysplasia is thought to be induced by chronic inflammation from conditions such as PSC or chronic parasitic infection.[10] Theyspread by local infiltration of both adjacent liver tissue and vessels (portal vein and hepatic artery) and produce a dense fibrotic reaction (Fig.1). There is a strong tendency to

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longitudinal subepithelial growth along the biliary tree with perineural invasion being a negative prognostic feature. [12] Lymphatic spread is via the periductal nodes to the coeliac nodes and carries a poor prognosis.[2,4] In one series lymph node or visceral metastases were present at diagnosis in 83% of those with extrahepatic biliary tumours.[13] Multicentricity is frequently described as being due to retrograde seeding since haematogenous spread is uncommon.[10] It is not easy to ascertain the limits of tumour invasion on gross inspection but many express the tumour marker carcinoembryonic antigen (CEA) on histochemical staining.[14] This may help to identify foci of malignancy in small biopsy specimens.[10,14] Formal pathological staging is by the Tumour size, Node and Metastases (TNM) system but such complete staging can only be made after surgery and pathological examination of the resected specimen. (Table 1)[15] A preoperative clinical staging system must take account of both biliary and vascular involvement. The scheme proposed by Bismuth describes Type 1 tumours, entirely below the confluence, Type II tumours, affecting the confluence, and Type III tumours extending to the first order right or left intrahepatic ducts (Table 2).[16] However, this classification does not describe the origin and mode of spread of cholangiocarcinoma, as many originate eccentrically in the right or left hepatic duct and subsequently involve the confluence. This has an impact on surgical management.

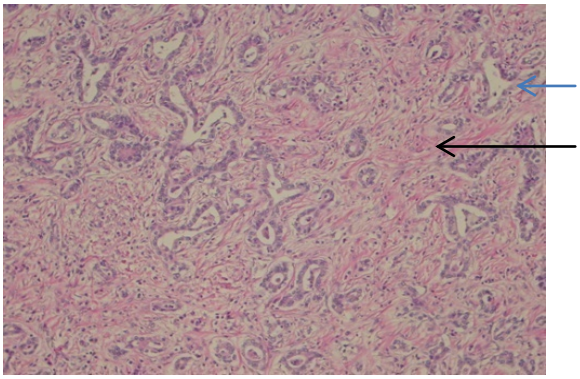

Figure 1. Intrahepaticcholangiocarcinoma: *well-differentiated tubular adenocarcinoma (blue arrow) with a variable fibrous stroma (black arrow)*

Table 1. TNM staging

***T1* – confined to mucosa**
***T2* - invading muscle**
***T3* - invading adjacent organs (liver, gallbladder, stomach)**
***N1* - hilar lymph nodes**
***N2* - regional lymph nodes**
***M1* - distant metastases**

T= tumour, N=node, M= metastases

Table 2. Bismuth classification

Type I - below the hilar confluence
Type II - at the confluence
Type III - extending into first order right (IIIa) or left(IIIb)ducts
Type IV - bilateral second order duct involvement

4. Clinical Features

Obstructive jaundice is the primary clinical finding and the disease may be extensive before jaundice develops clinically. The extrahepatic type presents earlier with obstructive jaundice and early pruritus. If the cholangiocarcinoma is located distal to the cystic duct, patients may present with a distended gallbladder (Courvoisier's sign). [2-4] The intrahepatic (peripheral) type present late with no jaundice or could simply be an incidental finding on ultrasound or computed tomography(CT).[4] Non-specific symptoms include ill-defined abdominal pain for some time before diagnosis. Fever may occur due to cholangitis in obstructed biliary segments, especially if there has been radiological or other intervention. Hepatomegaly may be noted in up to 25% of patients andweight loss as a systemic effect of malignancy is common[3]. A history of previous parasitic infestation, occupational exposure to aflatoxins, inflammatory bowel disease especially ulcerative colitis and hepatitis should be sought.[4]

5. Investigative Techniques

Liver function tests are useful in defining the degree of obstructive jaundice and as a baseline for follow-up. Elevated alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) may be an early isolated abnormality in an asymptomatic but icteric patient.[3,4] Tumour markers are of limited value. The carbohydrate antigen CA-19.9 and CEA are raised but these are not specific or sufficiently reliable in isolation. [18] CA 19-9 may be elevated greater than 100U/ml and has been found to be useful in detecting cholangiocarcinoma in patients with PSC awaiting liver transplantation,and as follow-up surveillance for tumour recurrence in patients.[3,4] Many patients are chronically anaemic on presentation, and leucocytosis indicative of cholangitis may be a significant adverse prognostic factor in obstructive jaundice.[3,4] Nutritional status has a major impact on surgical risk. Low haemoglobin may also be regarded as a nutritional index but the most significant parameters are low serum albumin and history of recent weight loss.[19] Haematological tests should include measurement of coagulation status.

Radiologically, ultrasound can identifydilated biliary tree to the level of tumour. Masses within the liver may indicate secondaries, or microabscesses secondary to biliary obstruction.The presence of gallbladder stones is readily identified, and abnormalities of the gall bladder wall may raise suspicion of gall bladder cancer. Duplex scanning may differentiate between compression and portal venous invasion.[3,4] A dynamic or triple- phase computed tomography (CT) have some advantages over ultrasound in detecting hilar mass, lymph node involvement, liver metastases (intrahepatic spread), vascular involvement, portal vein occlusion and lobar atrophy due to biliary obstruction (Fig.2).[20] Magnetic resonance imaging (MRI)/

magnetic resonance cholalangiography (MRCP) defines the anatomical location of the tumour and combined with magnetic resonance angiography assesses contralateral vascular involvement.[3,4] Positron emission tomography (PET) would detect unsuspected distant or intrahepatic metastases in up to 30% of patients with cholangiocarcinoma. [3] Endoscopic retrograde cholangiopancreatography (ERCP) may assess the extent of distal cholangiocarcinoma and achieve biliary stenting. Percutaneous transhepatic cholangiography (PTC) is necessary for hilarcholangiocarci nomas to delineate anatomy and achieve external drainage. [3,4] Bilateral drains are required if right and left ducts are disconnected. Although routine preoperative biliary drainage increase risk of postoperative infective complications, it is performed prior to extended liver resection, or if there is cholangitis or renal failure.[4,21]

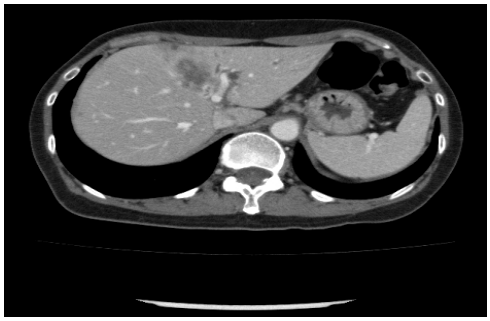

Figure 2. Intrahepatic cholangiogram CT image: The quadrate lobe contains a mass. Peripheral enhancement of the tumour and peripheral bile duct dilatation are shown

A *preoperative tissue diagnosis* may often be obtained by biopsy orcytological brushings at ERCP or PTC, but the diagnostic value relies heavily on accurate targeting of the biopsy and an experienced cytopathologist.[22] Ascholangiocarcinoma is readily diagnosed by imaging, preoperative biopsy is not routinely indicated unless considering palliative systemic chemotherapy. In a poor-resourced area, fine-needle aspiration cytology (FNAC) may confirm the diagnosis but has the small risk of converting an operable cancer to a non-operable one through peritoneal seeding.[4] There is also the risk of bleeding if clotting factors had not been corrected by priorintramuscular vitamin k injections.

*Staging laparoscopy +/- laparoscopic US:*The combination of laparoscopy and laparoscopic ultrasound may improve the accuracy of pre-operative staging and assessment of resectability. By detecting peritoneal disease or intra-abdominal metastases reported in up to 30% of patients missed on ultrasound and CT, it eliminates an unnecessary laparotomy.[23] Otherwise when patients are found to be unresectable at laparotomy, a biopsy should be taken to confirm the diagnosis and an operative biliary-enteric bypass considered.[4]

6. Assessment of Resectability

Surgical resection is the only therapy which offers a chance of cure, although only 10% of patients present at a stage where resection is possible.[3,4]. The following criteria would suggest an irresectable tumour: (1) involvement of bilateral second order intrahepatic ducts or multifocal tumour on cholangiography; (2) extensive involvement of the portal vein; (3) involvement of major vessels or ducts on opposite sides of the liver; (4) liver atrophy or infection inconsistent with a viable liver remnant after resection.[3,4,23] A poor prognosis of less than 6 months is expected for patients with irresectable disease. [3,4]

7. Management Options

Surgical resection follows an accurate preoperative staging, treatment of sepsis and renal failure, and a preoperative drainage of the future liver remnant (FLR). [4,24] As some lesions may require major hepatic resection for their eradication, an adequately functioning liver remnant tissue, and not an atrophic and possibly infected lobe must be ascertained.[16,17]

Preoperative contralateral portal vein embolisation (PVE) is done to stimulate FLR hypertrophy. Prior bilateral bilobar biliary drainage is done. A repeat CT scan in 4-6 weeks would assess response (volume of FLR) prior to surgery.[25] An extended right or left hepatectomyis performed depending on preoperative imaging which demonstrates involvement of second order ducts in the right or left liver. This is combined with routine caudate lobe (segment 1) resection because of the risk of leaving residual tumour i.e. oncological clearance. [26] Resection of the nodes and lymphatics along the hepatoduodenal ligament may also be important for survival.[27] The portal vein is resected and reconstructed if indicated to achieve R0 (complete)resection but there is no evidence that more extended resections and vascular reconstructions confer any survival benefit.[28] The proximal and distal bile duct margins are sent for frozen section analysis. If the distal margin is positive for tumour a simultaneous Whipple's pancreatico- duodenectomy is performed. If negative, a retrocolic Roux-en-Y hepatico-jejunostomy is performed.[29,30] The operative mortality is 5-10% in specialized centres.[31,32] Distal cholangiocarcinoma is treated by pancreatico-duodenectomy and peripheral (intrahepatic) cholangiocarcinoma is treated by anatomical liver resection.[21,31] Local ductal resections carry a very low mortality and morbidity, but the addition of major hepatectomy raises mortality considerably to 10-30%. [32] Postoperative complications include liver failure (small-for-size syndrome), sepsis and bile leak. Few authors quote five-year survival rates following radical treatment, and the reported mean survivals vary from nine months to 3.6 years and the median from 7 to 15 months.[33,34] Following appropriate selection of patients and if complete R0 surgical resection is achieved the patients may experience a 5-year survival rate as high as 40%.[29] Some authorsbelieve that resection should be confined to patients

in whom cure is a realistic goal, anddebulking of tumour with a good internal biliary-enteric bypass provides best palliation.[2-4]

Adjuvant therapy

Neoadjuvant and adjuvant therapies have for the most part not improved survival in patients with this tumour. The benefits of adjuvant therapy for biliary tract cancer is unclear with conflicting results from non-randomised studies.[35-37] There is little evidence from controlled studies for the value of chemotherapy for tumours of the bile duct although there have been some promising responses to continuous infusional 5-FU with intermittent epirubicin and cisplatin reported by some groups.[38,39] A systematic review and meta-analysis supports adjuvant therapy for cholangiocarcinoma but prospective randomized trials involving 2 active comparators among patients with positive lymph nodes or R1 disease rather than against a non-treatment arm is suggested.[40] Postoperative radiotherapy overall does not improve survival.[41-46] The location and not staging seem to determine the role for adjuvant chemoradiation therapy in individual cases.[47-50] Intraoperative radiotherapy has been reported with low morbidity and mortality but the effects on survival are unidentified.[51] There is also an untested possibility of hormone manipulation in biliary cancer as demonstrated by tumour growth retardation by cholecystokinin in a metastatic cholangiocarcinoma cell line in nude mice.[52]

Table 3. Summary of Adjuvant therapy trials

Adjuvant Chemotherapies

Trials	Outcome
Oberfield et al.[35] *The role of chemotherapy in the treatment of bile duct cancer. World J Surg 1988;12:105-8*	conflicting
Todorok et al.[36] *Chemotherapy for bile duct carcinoma in the light of adjuvant chemotherapy to surgery. Hepatogastroenterology 2000;47:644-649.*	conflicting
Ducreux et al.[37] *Effective treatment of advanced biliary tract carcinoma using 5-FU continuous infusion with cisplatin. Ann Oncol 1998;9:653-656*	promising
Choi et al.[38] *Effects of 5-fluorouracil and leucovorin in the treatment of pancreatic-biliary tract adenocarcinomas. Am J ClinOncol 2000; 23:425-428*	promising
Murakani et al.[39] *Adjuvant gemcitibine plus S-1 Chemotherapy improves survival after aggressive surgical resection for advanced biliary carcinoma. Ann Surg 2009;250:950-956*	promising
Horgan et al.[40] *Adjuvant therapy in the treatment of biliary tract cancer: A systematic review and meta-analysis. J. Clin Oncology 2012;30:1934-1940*	promising

Table 4. Adjuvant radiotherapy

Trial	Outcome
Pitt et al.[41] Perihilarcholangiocarcinoma: *Postoperative radiotherapy does not improve survival. Ann Surg 1995; 221: 788-798*	No improvement on survival
Gerhard et al.[45] *Benefits of adjuvant radiotherapy after radical resection of locally advanced main hepatic duct carcinoma. Int J RadiatOncolBiolPhys 2000; 46:581-587*	No improvement on survival
Kim et al.[43] *Role of postoperative radiotherapy in the management of extrahepatic bile duct cancer. Int J RadiatOncolBiolPhys 2002;54:44-49*	No improvement on survival
Sagawa et al.[42] *Effectiveness of radiation therapy after surgery for hilarcholangiocarcinoma. Surg Today 2005, 35: 548-552*	No improvement on survival
Vern-Gross et al.[44] *Survival outcomes in resected extrahepaticcholangiocarcinoma: effect of adjuvant radiotherapy in surveillance. Epidemiology and end results analysis.*Int J RadiatOncolBiolPhys 2011;81:189-198	No improvement on survival

Table 5. Adjuvant chemoradiotherapy and intraoperative radiotherapy

Trial	Outcome
Nakeeb et al.[48] *Radiation therapy, chemotherapy and chemoradiation in hilarcholangiocarcinoma. Hepato-pancreaticobiliary (Oxford) 2005; 7: 278-282*	dependent on location of tumour
Hughes et al.[49] *Adjuvant concurrent chemoradiation for adenocarcinoma of the distal common bile duct. Int J RadiatOncolBiolPhys 2007,68:178-182.*	dependent on location of tumour
Itoh et al. [50] *Magnitude of combination therapy with radical resection and external beam radiotherapy for patients with carcinoma of the extrahepatic bile duct and gallbladder. Dig Dis Sci 2005; 50:2231-2242*	promising
Busse et al.[51] *Intraoperative radiation therapy for biliary tract carcinoma: results of a 5-year experience. Surgery 1989; 105: 724-33*	low morbidity and mortality, no effect on survival

Liver transplantation

Provided regional nodal metastases and other sites of extrahepatic tumour can be excluded, then total hepatectomy with transplantation may be possible for these patients.[53] Otherwise most developed tumour recurrence, and the longest survival in the Hanover series was 27 months.[54] Few of those patients whose tumours have transgressed the boundaries of local respectability will be suitable for transplantation. Liver transplantation may be an option in those patients with locally advanced *hilarcholangiocarcinoma* with vascular involvement precluding R0 resection.[55] However, 5-year survival figures must be comparable with those for other indications for liver transplant, given the ongoing cadaveric organ shortage. Most series report poor long –term survival after liver transplantation for cholangiocarcinoma, presumably due to occult metastases at the time of the procedure.[56] There are also concerns that pre-transplant radiotherapy significantly increases post-transplant morbidity. Cholangiocarcinoma is thus at present not an indication for liver transplantation in UK or Europe.[3,4]

Palliative treatment

Stents may be inserted either endoscopically or percutaneously.[57] Self-expanding metallic stents have superior results toplastic stents for relief of jaundice in unresctable cases.[58,59] It is well –worthwhile for local recurrence and can give a useful period of prolonged palliation.[60] Stent-related complications include cholangitis, tumour in-growth and bleeding. Biliary-enteric bypass for proximal biliary cancer is more difficult than for distally placed tumours, but it is often possible to carry out a hepaticojejunostomy to the left duct. A palliative segment III bypass accessed by splitting the liver just to the left of the umbilical fissure, with an operative mortality of 7% gives an excellent duration of palliation. It may be indicated if stenting fails or in patients with longer life expectancy.[61] Photodynamic therapy using an intravenous injection of a photosensitiser (e.g. photofrin) followed by laser application (via ERCP or PTC) causes release of free radicals leading to tumour cell lysis. It is undertaken after metallic stent insertion.[62] Patients who are unresectable due to locally advanced diseases but have no evidence of distant metastases may be candidates for palliative radiotherapy using a combination of external beam radiation and intraluminal Ir-192 brachytherapy.[63]

8. Conclusions

The prognosis of patients with cholangiocarcinoma remains grim.As surgical resection offers the only chance of cure, early diagnosis and theroutine use of more aggressive resections inorder to achieve margin-negative resections would result in longer survival times for these patients. New strategies are needed to improve adjuvant therapy. As cure is less often achieved, the first priority is to relieve jaundice followed by long-term prevention of cholangitis.Attention to the multidisciplinary approach in management will confer a significant survival advantageeven when curative resection is not possible.

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