New advances in the management of biliary tract cancer

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Abstract
Biliary tract cancers are uncommon malignancies arising from biliary epithelium intrahepatically (peripheral cholangiocarcinoma), in the extrahepatic bile duct, the gall bladder and the ampulla of Vater. Treatment has been challenging because of late presentation, complex surgery, complex biliary obstruction with jaundice and a paucity of high quality data on which to establish standard care. With improvements in imaging, biliary stenting, surgical management and the establishment of a national investigational programme we hope to define the modern management of biliary tract cancers and enable a platform for further research.

Key Words: biliary tract cancer, surgery, photodynamic therapy, chemotherapy, clinical trials

Introduction
Biliary tract malignancy comprises adenocarcinomas of biliary epithelium. These are geographically distinct, arising from biliary epithelium within hepatic substance, known as peripheral cholangiocarcinomas, at the hilum of the biliary tree, where they are known as hilar cholangiocarcinomas, in the distal bile duct and in the gall bladder (gall bladder carcinoma, GBC) (Figure 1). It follows that biliary tract carcinomas are anatomically and aetiologically distinct from pancreatic or small bowel adenocarcinomas, although historically they are often managed similarly.

The management of biliary tract cancer (BTC) has changed dramatically in the last 20 years. The obstacles to progress have been the poor performance status of these patients at the time of presentation and the lack of conclusive histological diagnosis. Improvements in biliary drainage have rendered patients sufficiently fit to allow more sophisticated imaging and histological diagnosis followed by consideration of novel innovative treatments such as photodynamic therapy.

Incidence and aetiology
Biliary tract cancers are uncommon, the incidence being approximately 1500 cases per year [1]. The risk factors fall primarily into two groups: genetic and inflammatory (Table I).

The incidence of BTC in the western world is primarily related to gallstones and primary sclerosing cholangitis (PSC), whereas that in the Far East is related to infective causes. The incidence worldwide is rising and appears to be independent of an associated increase in PSC (Figure 2) [2]. The rise is not associated with any changes in the proportion of patients with unstaged cancer, localized cancer, histological confirmation, tumour size or overall survival. These data suggest that this is a true increase related to an environmental factor as yet unknown.

The presentation of BTC is dependent on the site of the tumour. These symptoms would clearly be guided by predisposing factors such as PSC but in general, intrahepatic tumours present with systemic and advanced features whereas biliary and distal tumours present with obstructive jaundice (Table II) [3].

Pathology
Cholangiocarcinoma is often associated with inactivation of tumour suppressor genes, for example, p53, APC, Smad-4, bcl-2 and p16 [4–6]. Mutations in oncogenes have also been described, for example, K-ras, c-myc, c-erbB-2 and c-neu. These data place
BTC in the family of gastrointestinal carcinomas with a complex molecular profile and malignant development. Molecular profiling may further define the disposition of BTC among gastrointestinal carcinomas and provide insights into aetiology, molecular pathogenesis and potential molecular interventions.

Table I. Risk factors for biliary tract cancer.

- Age (65% greater than 65 years)
- Smoking
- Primary sclerosing cholangitis (PSC)
- Chronic gallstones
- Bile duct adenoma and biliary papillomatosis
- Choledochal cysts (5% will transform)
- Liver flukes
- Chronic typhoid carriers

Table II. Presentation of biliary tract cancer.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intrahepatic (n = 18)</th>
<th>Perihilar (n = 196)</th>
<th>Distal (n = 80)</th>
<th>Total (n = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>0*</td>
<td>91</td>
<td>87</td>
<td>84</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>61†</td>
<td>36</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>Weight loss</td>
<td>11</td>
<td>36</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>Fever</td>
<td>6</td>
<td>14</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

From Nakeeb et al. [3].
* p < 0.01 vs others.
† p < 0.05 vs others.

Imaging

Although the initial imaging investigation for patients with potential BTC is an ultrasound, patients normally proceed to magnetic resonance cholangiopancreatography (MRCP) or endoscopic or percutaneous cholangio-pancreatography (ERCP-PTC). The latter techniques allow for cytological sampling (positive in about 30%), allow stent insertion and in may cases will determine operability. Computed tomography (CT) and magnetic resonance (MR) scanning are often used in parallel to define the intrahepatic extent of the tumour and there is little agreement as to a single optimal imaging investigation [7]. A key aim of any imaging would be to identify appropriate lesions for biopsy and histological confirmation. Endoscopic ultrasound provides a useful guide for fine needle aspiration [8] and positron emission tomography using fluorodeoxyglucose (FDG-PET) can be helpful, particularly in upstaging potentially resectable disease [9].

Hilar cholangiocarcinomas often infiltrate along biliary epithelium, into lymphatics and perineural spaces making staging, particularly preoperative staging, difficult. Endoscopic retrograde cholangio-
pancreatography (ERCP) and percutaneous transhepatic drainage (PTD) are recommended for the added anatomical information they can provide. PTD is better traversing tight malignant strictures [10].

Standard staging algorithms include CT of the chest, abdomen and pelvis to exclude metastatic spread and can be used to calculate remnant tumour-free liver volumes for extended liver resections. MRCP offers a non-invasive method of defining the extent of intrahepatic biliary involvement. Doppler ultrasound can define vascular involvement, although some clinicians still resort to invasive techniques such
as angioportography. CT has a low sensitivity for peritoneal disease and therefore preoperative laparoscopy is usually included (Figure 3c).

## Therapeutic options

The current therapeutic options are biliary stenting, surgery, radiotherapy (RT), photodynamic therapy (PDT) and chemotherapy. This review will not consider biliary stenting.

### Surgery (Table III)

Radical surgical resection offers the only chance of long-term survival in the treatment of BTC but unfortunately <20% of presenting patients are suitable for surgery. The aim of any proposed surgical procedure is to achieve complete tumour removal together with clear resection margins (R0) [11].

Peripheral cholangiocarcinoma can be adequately removed by segmental liver resection and lower third bile duct cholangiocarcinoma (Figure 1) by pancreaticoduodenectomy. Hilar cholangiocarcinoma represents a formidable challenge both in terms of defining preoperatively the extent of tumour extension within the intrahepatic biliary tree and as a technical challenge to achieve adequate surgical clearance. The anatomy of the biliary tract makes this a particular challenge.

Extended right hepatectomy (segments 4–8) with routine caudate lobe resection (segment 1) has been shown to achieve the largest benefit with respect to resectability [12] (Table IV). Most tumours including Bismuth types IIIa/b (extension into right/left hepatic ducts) and IV (both ducts) can be managed with this procedure, as long as adequate segment II/III remnant volumes have been achieved with right portal vein embolization and biliary decompression of the left liver. This represents a major resection with an associated high postoperative morbidity/mortality rate for which patients need to have been assessed to ensure adequate physiological reserve by an experienced anaesthetist and they need to be well counselled on the potential risk. Postoperative liver insufficiency can be avoided by ensuring remnant volumes of at least 25% of the total volume and therefore portal vein embolization is a useful adjunct to cause atrophy of the ipsilateral resection side and hypertrophy of the planned remnant liver.

An understanding of hilar anatomy establishes right-sided resections as preferable to left for two reasons. First, the confluence of the hepatic ducts lies posterior to the right side of the hepatoduodenal ligament, increasing the potential for right hepatic artery involvement. Second, the length of the extrahepatic left hepatic duct proximal to second-order segmental tributaries compared with the relatively short right duct increases the likelihood of an R0 resection if this is the intended anastomotic site. An extended right resection is also a technically easier procedure with a natural transaction line provided by the falciform ligament.

The 5-year survival varies between 29% and 100% for those patients with completely resected disease, suggesting that there is significant variability both in surgical technique and methodology of reporting (Figures 4 and 5, Table V). Neuhaus and colleagues [13] have achieved R0 5-year survival rates of 65%, advocating more radical resections to increase the

<table>
<thead>
<tr>
<th>Extent of resection</th>
<th>1989–98 (n=19)</th>
<th>1999–2004 (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central resection only</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Right hepatectomy</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Right hepatectomy with extension to segment 4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Right trisectionectomy</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Left hepatectomy</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Left hepatectomy with extension to segment 4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Left trisectionectomy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Left lateral sectionectomy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Concomitant complete caudate lobectomy</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>Concomitant portal vein resection</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

From Liu et al. [12].
likelihood of complete tumour excision and negative margins. In certain circumstances therefore they have included removal of the portal vein confluence and reconstruction of the left portal vein branch together with an extended right resection. This enables the surgeon to employ a ‘no touch technique’, avoiding the tumour and its immediate surrounding tissue. This has been achieved with acceptable perioperative mortality figures (8% 60-day death rate). Other factors that independently affected outcome and were significant on multivariate analysis included perineural sheath infiltration, lymphangiosis carcinomatosa and histopathological grading.

Transplantation

Outcomes are poorer after transplantation for cholangiocarcinoma than for any other diagnosis [10]. Single-centre reports demonstrate that careful patient selection of patients with early stage disease with the use of neoadjuvant therapies including chemoradiotherapy may produce outcomes approaching those of other diagnoses for which transplantation is used [15].

Gall Bladder Carcinoma

Surgery for GBC is guided by similar strategies. As for cholangiocarcinoma, lymph node involvement is common at approximately 50% and there is peritoneal and distant metastasis of 10-20% at presentation. Peritoneal and distant metastasis increases to 50% with serosal involvement of the gall bladder, thus careful preoperative evaluation of the extent of gall bladder involvement is critical. Those tumours limited to the mucosa of the gall bladder (T1–2 tumours) should be treated with cholecystectomy. Any more advanced tumours should be treated with aggressive lymphatic and nodule resection, although there are few randomized data to suggest this improves survival. There are only two major surgical series of GBC (Table VI).

There is a single adjuvant study reporting an improvement in survival for GBC patients receiving a postoperative regimen of mitomycin C and fluorouracil; however, the numbers are small and the data need confirmation with a more commonly accepted regimen [26]. The value of adjuvant therapy will be examined in a UK National Cancer Research Institute study randomizing patients between surveillance and adjuvant chemotherapy.

Radiation therapy

All therapeutic modalities are hampered by poor data supporting their use and RT is no exception. The published data describe series of patients (<40 in number) treated with adjuvant [27] and palliative [28] radiation. The evidence would not support standard use of either modality. There are similarly limited datasets describing the use of brachytherapy [29,30], intraoperative radiation [31] and chemoradiation [32,33]. The conclusion is that RT should only be considered in the context of a clinical trial.

Photodynamic therapy

Photodynamic therapy (PDT) is a two-stage treatment. A photosensitizer is given systemically and taken up preferentially by tumour. The exact mechanism of this preferential uptake is not completely understood. Most photosensitizers are modified hematoporphyrins that absorb light at a specified wavelength following tumour localization. Normal tissue is unaffected as it does not take up photosensitizer nor is it subsequently exposed to light. The differential in terms of treatment effect is therefore both biological and anatomical. There has been increasing use of PDT concurrent with improved photosensitizers. The technology required to deliver PDT is not sophisticated, requiring only standard ERCP equipment and a relatively cheap light source.

Table V. 5-year survival following surgery for cholangiocarcinoma.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No.</th>
<th>5-year survival (%)</th>
<th>R0 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartlett et al. 1996 [19]</td>
<td>23</td>
<td>58</td>
<td>100</td>
</tr>
<tr>
<td>Jarnagin et al. 2001 [21]</td>
<td>160</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Huang et al. 2004 [22]</td>
<td>31</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Rea et al. 2004 [23]</td>
<td>46</td>
<td>26</td>
<td>80</td>
</tr>
</tbody>
</table>

Table VI. Outcome following surgery for GBC.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>5-year survival (%)</th>
<th>R0 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsukada et al. 1996 [24]</td>
<td>106</td>
<td>33</td>
<td>70</td>
</tr>
<tr>
<td>Puhalla et al. 2002 [25]</td>
<td>60</td>
<td>18</td>
<td>75</td>
</tr>
</tbody>
</table>
There is a thermal cytotoxic effect resulting in tissue necrosis, the extent of which depends on the type of photosensitizer used [34].

The defining study on PDT in CCA was performed by Marian Ortner and colleagues [35]. Thirty-nine patients were randomized to receive stenting or stenting with PDT. Many patients had advanced disease and a poor performance status that precluded standard palliation with chemotherapy. The study which originally planned to recruit 200 patients was terminated early by the data monitoring committee, as there was a dramatic difference in the observed survival. PDT conferred a survival advantage of 10 months (493 vs 98 days). In addition, there was a group of 20 patients who received PDT despite being ineligible who had a similar survival to those treated with PDT, suggesting that this PDT effect was real.

The data have been criticized for the small numbers as well as the poor survival of the control group (most were jaundiced and did not receive palliative treatments) and it is unlikely that clinical practice will be changed by 20 patients. However, these are stimulating data with impressive survival benefit achieved with minimum toxicity (mild photosensitivity in 10%). In addition, the patients have an improvement in their bilirubin, an improvement in their quality of life and reduction in subsequent life-threatening events, particularly cholangitis. The potential of PDT will be examined in a UK National Cancer Research Institute study randomizing patients between stenting alone and PDT with stenting.

Table VII. Randomized studies using palliative chemotherapy in BTC.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Survival (months)</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glimelius et al. [37]</td>
<td>37</td>
<td>6 vs 2.5</td>
<td>5FU/Etop vs BSC</td>
</tr>
<tr>
<td>Takada et al. [38]</td>
<td>31</td>
<td>6 vs 3</td>
<td>5FU/Dox/MMC vs BSC</td>
</tr>
<tr>
<td>Kornek et al. [39]</td>
<td>51</td>
<td>0.7 vs 9.3</td>
<td>MMC/Gem vs MMC/Capcitabine</td>
</tr>
<tr>
<td>Ducruex et al. [40]</td>
<td>58</td>
<td>5 vs 8</td>
<td>5FU vs Cis/5FU</td>
</tr>
<tr>
<td>Rao et al. [35]</td>
<td>50</td>
<td>12 vs 9</td>
<td>FELV vs ECF</td>
</tr>
<tr>
<td>Valle et al. [41]</td>
<td>86</td>
<td>–</td>
<td>Gemcitabine vs Gemcitabine-Cis</td>
</tr>
</tbody>
</table>

BSC, best supportive care; Cis, cisplatin; Dox, doxorubicin; Etop, etoposide; 5-FU, 5-fluorouracil; MMC, mitomycin C.

Palliative chemotherapy

There is no standard palliative chemotherapy for BTC as the data derive from small, mostly unrandomized series treating mixed populations and reported in inconsistent formats. Many agents have been tried and are reported extensively elsewhere [36] but most studies have used fluoropyrimidine- or gemcitabine-based schedules. In a malignancy for which estimates of change in tumour size are challenging, overall survival in a randomized context is likely to be the most reliable endpoint to estimate efficacy. The low incidence of BTC means that such trials are difficult to establish and to date studies have not been designed to reliably report survival differences (Table VII).

All studies have accrued <60 patients and none were powered for survival. In addition, the two earlier studies by Glimelius et al. [37] and Takada et al. [38] included patients with pancreas cancer. These data cannot recommend a standard palliative treatment for BTC. There are a plethora of non-randomized phase II studies that are difficult to interpret. This is highlighted by a dramatic difference between the response rates (9–57%) yet a relatively small difference in median survival (7–9 months) [42]. However, it is clear that there is activity with fluoropyrimidine- and gemcitabine-based regimes and the confirmation of their comparative benefit rather than the demonstration of the benefit of palliative chemotherapy over best supportive care should be the aim of current research programmes.

Table VIII. Some recent studies in BTC.

<table>
<thead>
<tr>
<th>Trial identifier</th>
<th>Compounds</th>
<th>Phase</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG-S0202</td>
<td>Gemcitabine and capecitabine</td>
<td>II</td>
<td>57 patients Median survival 7 months</td>
</tr>
<tr>
<td>CWRU-2299</td>
<td>Rebeccamycin analogue</td>
<td>II</td>
<td>6–37 patients Indolocarbazole compounds Recruitment completed</td>
</tr>
<tr>
<td>UCCCRC-11045</td>
<td>BMS-247550 (Ixabepilone)</td>
<td>II</td>
<td>21–30 patients Novel epothilone Recruitment completed</td>
</tr>
<tr>
<td>FCCC-03042</td>
<td>Bortezomib</td>
<td>II</td>
<td>35 patients Proteasome inhibitor</td>
</tr>
<tr>
<td>NYWCCC-NCI-6254</td>
<td>Triapine and gemcitabine</td>
<td>II</td>
<td>78 patients Ribonucleotide reductase inhibitor</td>
</tr>
<tr>
<td>SWS-SAKK-44/02</td>
<td>Capcitabine and gemcitabine</td>
<td>II</td>
<td>19–44 patients Recruitment completed</td>
</tr>
<tr>
<td>NCCTG-N9943</td>
<td>Gemcitabine and pemetrexed</td>
<td>II</td>
<td>85 patients</td>
</tr>
<tr>
<td>OSI-904-202</td>
<td>OSI7904L versus 5-FU/LV</td>
<td>RII</td>
<td>58 patients Liposome encapsulated Thymidylate synthase inhibitor Recruitment completed</td>
</tr>
<tr>
<td>NCT00090025</td>
<td>XL119 (becatecarin) versus 5-fluorouracil (5-FU)</td>
<td>RIII</td>
<td>600 patients Topoisomerase II inhibitor Terminated early because of 5-FU advantage</td>
</tr>
</tbody>
</table>
Table IX. The portfolio of National Cancer Research Institute (UK) trials now available.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Acronym</th>
<th>Numbers</th>
<th>Phase</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant chemotherapy</td>
<td>BILCAP</td>
<td>300</td>
<td>3</td>
<td>Survival</td>
</tr>
<tr>
<td>Photodynamic therapy</td>
<td>PHOTOSTENT2</td>
<td>300</td>
<td>3</td>
<td>Survival</td>
</tr>
<tr>
<td>Palliative chemotherapy</td>
<td>ABC-02</td>
<td>400</td>
<td>3</td>
<td>Survival</td>
</tr>
</tbody>
</table>

The largest study reported in abstract form in 2006 is that of Valle and colleagues [42]. Although there appeared to be an improvement in 6 month DFS (57% vs 48%) in favour of the combination of gemcitabine and cisplatin vs gemcitabine, the study was not powered to provide a statistically meaningful result and this benefit may be offset by a significant increase in fatigue (29% vs 9%). Patients received more treatment on the combination arm (23.1 vs 15.0 weeks), suggesting that there were fewer disease-related treatment delays and reasons for stopping on the combination arm. The UK National Cancer Research Institute has expanded this study to provide a statistically meaningful survival endpoint with quality of life assessments. This will provide the largest dataset in BTC research and define the palliative chemotherapy for BTC.

Current studies in advanced BTC
Table VIII details some recent studies in BTC. Increasingly BTC are being recognized as a tumour type in which novel agents may be used.

Key questions in the management of BTC
The key questions for the management of BTC are as follows:

1. Is more aggressive surgery justified? The non-randomized data suggest that some patients are cured by more extensive hepatic and nodal resection but this needs to be formally tested.
2. Does adjuvant chemotherapy improve survival following surgery? The data from Takada et al. [38] suggest a benefit and benefits have been demonstrated in all major tumour types.
3. Does improved biliary drainage with PDT improve survival? The early data from Ortner need to be validated [35]. The feasibility of conducting PDT has been confirmed in a phase II NCRI study [43].
4. What is the optimum chemotherapy schedule? There is consensus among oncologists that palliative chemotherapy is of benefit but the optimum schedule needs to be formally identified.
5. Is radiation of value?

Table IX describes the portfolio of National Cancer Research Institute (UK) trials now available. All studies are powered for survival and this portfolio is accompanied by a tissue collection module. It is hoped that the studies will help define the twenty-first century management of BTC.

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