Cholangiocarcinoma: Has there been any progress?
Judith Meza-Junco MD1, Aldo J Montano-Loza MD2, Mang Ma MD2, Winnie Wong MD2, Michael B Sawyer MD1, Vincent G Bain MD2

Cholangiocarcinoma is the second most common primary hepatic tumour after hepatocellular carcinoma. Primary sclerosing cholangitis is one of the most commonly recognized risk factors for cholangiocarcinoma; however, approximately 90% of patients have no identifiable risk factors. Extrahepatic type is its most common presentation. Cholangiocarcinoma is considered to be a devastating disease, with low five-year survival rates and few therapeutic options. Although surgical resection has been considered the best treatment option for localized cholangiocarcinoma, local recurrences of this cancer are very common, and imply persistent micrometastatic disease in lymph nodes or at surgical margins, even after extended surgical resection. Consequently, the five-year survival rate after attempted curative resection is only 20% to 40%. Early studies of liver transplantation for cholangiocarcinoma did not show a survival benefit and, currently, this tumour is considered to be an absolute contraindication for liver transplantation in most transplant centres worldwide. Recently, neoadjuvant chemoradiation in combination with liver transplantation for highly selected patients with cholangiocarcinoma has shown impressive results, with five-year survival rates at approximately 76% to 82% — similar to other standard indications for liver transplantation, such as hepatocellular carcinoma or hepatitis C-induced cirrhosis. However, this success of liver transplantation applies only to a subset of patients and most of the data originated from a single centre. Wider application of this strategy, especially for patients with potentially resectable disease, will require validation by other centres.

Key Words: Cholangiocarcinoma; Liver transplant; Neoadjuvant chemoradiation; Primary sclerosing cholangitis

RISK FACTORS FOR CCA
Primary sclerosing cholangitis (PSC) is the major risk factor for CCA in the western world. The lifetime risk of CCA has been reported to be between 5% and 15%, with an annual incidence rate of 0.6% to 1.5%. CCA is usually diagnosed within the first two to three years after the diagnosis of PSC has been established (5-7). Other identified risk factors for CCA development include secondary sclerosing cholangitis due to recurrent pyogenic cholangitis and liver fluke infestation, choledochal cysts and exposure to the x-ray contrast medium thiorotstatr; however, most cases of CCA (approximately 90%) appear to occur sporadically in patients without obvious risk factors (8).

Unfortunately, both intra- and extrahepatic CCAs are most commonly diagnosed at advanced stages because of an absence of specific symptoms, physical examination findings or laboratory abnormalities in early or premalignant stages (9). Currently, diagnostic modalities for CCA include serum tumour markers, radiological and endoscopic imaging, and pathological analysis of biopsies or endoscopic brushings.

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TABLE 1  
Imaging methods for diagnosis of cholangiocarcinoma

<table>
<thead>
<tr>
<th>Imaging method</th>
<th>Author (reference)</th>
<th>Indication</th>
<th>Diagnostic accuracy, %</th>
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<tbody>
<tr>
<td>Computed tomography</td>
<td>Slattery and Sahani (15)</td>
<td>Assessing resectability</td>
<td>60–75</td>
</tr>
<tr>
<td></td>
<td>Kim et al (18)</td>
<td>Detect distant metastases</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Detect regional node metastases</td>
<td>50–61</td>
</tr>
<tr>
<td>Magnetic resonance imaging/magnetic resonance</td>
<td>Slattery and Sahani (15)</td>
<td>Detect bile duct involvement</td>
<td>84</td>
</tr>
<tr>
<td>cholangiopancreatography</td>
<td>Manfredi et al (16)</td>
<td>Detect portal encasement</td>
<td>67</td>
</tr>
<tr>
<td>Endoscopic retrograde cholangiopancreatography</td>
<td>Brugge (17)</td>
<td>Primary tumour detection</td>
<td>70–80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combined with intraductal ultrasound</td>
<td>88–90</td>
</tr>
<tr>
<td>Positron emission tomography and computed tomography</td>
<td>Slattery and Sahani (15)</td>
<td>Detect regional lymph node metastases</td>
<td>76–86</td>
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<tr>
<td></td>
<td>Kim et al (18)</td>
<td>Detect distant metastases</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Change management decision</td>
<td>16–30</td>
</tr>
</tbody>
</table>

**DIAGNOSIS OF CCA**

Serum carbohydrate antigen (CA) 19-9 is the most commonly used tumour marker for CCA, and in patients with PSC has a sensitivity of 78.6% and a specificity of 98.5% using a cut-off value of greater than 129 U/mL; an increase equal to or greater than 67.3 U/mL over time provided a sensitivity of 90% and specificity of 98% for CCA alone. However, in patients with unexplained biliary obstruction without PSC, the sensitivity of CA 19-9 for detecting malignancy has been reported to be 53% (cut-off value greater than 100 U/mL), whereas true negative rates for patients with nonmalignant liver disease or benign biliary strictures is 76% and 92%, respectively (10,11). Combining tumour markers, such as carcinoembryonic antigen (CEA) and CA 19-9 using the formula: CA 19-9 + (CEA × 40), with a cutoff value of 400 U, gave an accuracy of 86% for the diagnosis of CCA in PSC patients (12). It is important to note that CA 19.9 levels depend on the Lewis phenotype (blood group type). Considering that approximately 7% of the population is Lewis-negative, CA 19-9 levels would, consequently, be undetectable (13).

Currently, magnetic resonance cholangiopancreatography is the most useful imaging method to evaluate CCA, providing information about regional tumour extension, biliary anatomy and intrahepatic metastases (14-17). Recent data showed the usefulness of integrated positron emission tomography and computed tomography over conventional imaging (computed tomography, magnetic resonance imaging and magnetic resonance cholangiopancreatography) in patients with suspected and potentially operable CCA, demonstrating a significantly higher accuracy for diagnosis of regional lymph node metastases and distant metastases. Moreover, integrated positron emission tomography and computed tomography has an important clinical impact on selection of proper treatment because it changed management in 15% to 25% of patients (18,19) (Table 1).

Brush cytology or bile biopsies at endoscopic retrograde cholangiopancreatography are the most useful tools to obtain a histological diagnosis of CCA. Sensitivity for conventional brush cytology varies from 37% to 63%, with specificity ranging from 89% to 100% (20-24).

Digital image analysis (DIA) and fluorescence in situ hybridization (FISH) are new, advanced cytological techniques that have emerged to improve the diagnostic accuracy for CCA and are based on the identification of aneuploidy. DIA is a technique that uses a microscope and camera to quantify the amount of cellular DNA, chromatin distribution and nuclear morphology that are suggestive of malignancy. FISH uses fluorescence-labelled DNA probes to detect chromosomal abnormalities in cells and has been shown to detect malignancy in cytological specimens (25-28) (Table 2).

All of the above diagnostic modalities are complimentary and should be used to diagnose and stage CCA accurately. Without accurate diagnosis and staging, it would be difficult to select the appropriate treatment and study the natural history of disease recurrence after surgical resection or liver transplantation (LT).

**CCA staging**

CCA is usually staged according to the Tumour/Node/Metastasis classification by the American Joint Committee on Cancer, which includes stages I to IV (29). Regarding anatomical location, CCA is classified as intrahepatic and extrahepatic. Extrahepatic CCA can further be subdivided into types I to IV, according to the Bismuth classification (1).

**Biological characteristics of CCA**

To improve the diagnosis and management of CCA, the particular biological features of this cancer should be considered. As recently summarized by Gores et al (30), hepatic resection is frequently impossible, especially because the most common location is perihilar, commonly surrounding but rarely invading the portal vein and hepatic artery. Extension directly into the liver or along the biliary tree is frequent. The affinity of CCA for bile results in radial spread, but usually does not cause a mass lesion that is discernible on imaging studies. Furthermore, CCA has desmoplastic features that make it difficult to obtain high-quality cells for biliary cytology. Finally, CCA mainly recurs regionally, consistent with the notion of micrometastatic disease at resection margins or in lymph nodes. Five-year survival rates following surgical resection with curative intent ranged from 20% to 40% due to CCA recurrence (30).

Therefore, the development of new approaches to achieve more effective control of regional disease in combination with surgical removal should result in improved clinical outcomes.

**CCA treatment**

CCA treatment is challenging, particularly due to the propensity of this tumour to disseminate at the time of diagnosis.
In primary sclerosing cholangitis 47 (negative cytology, 20) 100 (negative cytology, 100) Moreno-Luna and Gores (27)

Fluorescence in situ hybridization

Without primary sclerosing cholangitis 37–75 84–100

In primary sclerosing cholangitis (brush cytology) 60–100 100 Ponsioen et al (20)

Cytology

In primary sclerosing cholangitis 43 (negative cytology, 14) 87 (negative cytology, 88) Baron et al (25)

Digital image analysis

In primary sclerosing cholangitis (>129 U/mL) 78.6 98.50 Nehls et al (10)

Carbohydrate antigen 19-9

Table 2

<table>
<thead>
<tr>
<th>Marker/method</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Author (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate antigen 19-9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In primary sclerosing cholangitis (&gt;129 U/mL)</td>
<td>78.6</td>
<td>98.50</td>
<td>Nehls et al (10)</td>
</tr>
<tr>
<td>Without primary sclerosing cholangitis (&gt;100 U/mL)</td>
<td>53</td>
<td>&gt;90</td>
<td>Levy et al (11)</td>
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<tr>
<td>Cytology</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>In primary sclerosing cholangitis (brush cytology)</td>
<td>60–100</td>
<td>100</td>
<td>Ponsioen et al (20)</td>
</tr>
<tr>
<td>Without primary sclerosing cholangitis</td>
<td>37–75</td>
<td>84–100</td>
<td>Boberg et (22)</td>
</tr>
</tbody>
</table>

Fluorescence in situ hybridization

In primary sclerosing cholangitis | 43 (negative cytology, 14) | 87 (negative cytology, 88) | Baron et al (25) |

Without primary sclerosing cholangitis | 39 (versus 18 by cytology) | 77 (versus 98 by cytology) | Moreno-Luna et al (26) |

Digital image analysis

In primary sclerosing cholangitis | 47 (negative cytology, 20) | 100 (negative cytology, 100) | Moreno-Luna and Gores (27) |

Without primary sclerosing cholangitis | 34 (versus 15 by cytology) | 91 (versus 98 by cytology) | Kipp et al (28) |

Therefore, it is considered to be a devastating cancer, usually with an ominous prognosis. In 1974, Launois et al (31,32) were the first to propose radical surgical resection as a potentially curative option for CCA, suggesting an improvement of survival. Patient survival after surgery is directly related to the ability to attain negative resection margins and the absence of spread to regional lymph nodes. Resectability rates may be as high as 65%; however, curative resection or margin-free resection rates are usually less than 50% (33). Moreover, surgical resection has been associated with five-year survival rates of 9% to 63% (34-36). Overall five-year survival rates have been reported to be 30% to 41% for hilar tumours, 31% to 63% for intrahepatic tumours and 20% to 37% for extrahepatic CCA when margin-free resection is achieved (37-39) (Table 3). This neoplasm mainly recurs regionally, which implies persistent micrometastatic nodal disease or disease at resection margins despite extended surgical resection. This regional recurrence is frequent and devastating. Mortality rates of surgical resection are 5% to 10%, with most deaths resulting from infection. The perioperative morbidity rates vary between 31% and 85% (40).

Otherwise, there are no standard treatments for metastatic CCA. Several small studies of single-agent or combined chemotherapy regimens for unresectable CCA using drugs such as 5-fluorouracil (5-FU) (administered by bolus or infusion), capecitabine, cisplatin, mitomycin C, paclitaxel, oxaliplatin and gemcitabine have been reported. In general, these trials have demonstrated little efficacy, with partial response rates ranging from 0% to 30% and median survivals of between two and 12 months (41). Gemcitabine alone or in combination with 5-FU or capecitabine may be a reasonable option for patients not considered candidates for surgery but able to tolerate chemotherapy, although this conclusion has not been confirmed in a randomized controlled trial (42).

Incidental CCA in LT

Incidental CCA in patients who underwent LT have shown poor results. In a multicentre study from Canada, Ghali et al (43) reported outcomes after LT in 10 recipients found to have incidental CCA in their explanted native liver. The median duration of follow-up was 28 months, eight of 10 patients had PSC, and all tumours were stage I or II (no invasion beyond the bile duct and negative lymph nodes). The three-year survival rate was 30%, with a median time to recurrence of 26 months and a median time to death of 30 months. These results showed that intermediate- and long-term survival rates were no better than those for individuals transplanted with an established diagnosis of CCA and emphasizes the importance of screening PSC patients for CCA before LT.

Goss et al (44) reported their experience with 127 PSC patients who underwent LT. A total of 113 patients (89%) were transplanted without evidence of CCA, and had one-, two- and five-year survival rates of 90%, 88% and 87%, respectively. On the other hand, four patients (3%) with known CCA at the time of LT had tumour recurrence within six months of follow-up. The one-, two- and five-year survival rates were 33%, 32% and 0%, respectively, and were significantly worse than in patients without known CCA.

Other studies have reported somewhat better survival rates for patients with incidental CCA after LT. Becker et al (45) evaluated a multi-institutional experience of LT for CCA in 280 patients who were identified from the United Network for Organ Sharing database. Patients were stratified into three groups: CCA patients transplanted before 1994 (n=101), CCA patients transplanted after 1994 (n=102) and incidental CCA patients (n=77). Interestingly, patients with an incidental diagnosis of CCA at the time of LT had five-year survival rates of...
were similar to those transplanted for CCA before 1994 (20% versus 30%, respectively), and poorer survival rates than patients with CCA transplanted after 1994 (20% versus 63%, respectively; P<0.01).

A group at the University of Pittsburgh (Pittsburgh, Pennsylvania, USA) showed slightly better results in a cohort of 27 patients who underwent LT, with a five-year survival rate of 36%. The six surviving patients had T1 or T2 tumours, and four had received preoperative radiotherapy (46).

Taken together, all of these results imply that LT in patients with incidental CCA confers poor outcomes, because overall survival rates at five years vary from 0% to 36%; therefore, it is important to rule out this malignancy, particularly in patients at high risk (ie, PSC) waiting for LT. It may be helpful to try external beam irradiation in these incidental CCA cases in an attempt to neutralize what is believed to be nodal micrometastatic disease; however, this therapeutic strategy has not been evaluated in clinical trials.

**LT for CCA**

There is a subgroup of patients with CCA in whom surgical resection is not possible even when there are no known metastases. These patients have bilateral involvement of hepatic ducts or underlying cirrhosis. For these patients, LT appears to be a potential treatment.

Early reports of LT for CCA demonstrated five-year survival rates of 0% to 20%; these series included patients with metastatic nodes, bilobar CCA, and multiple or large-size solitary CCA (38,47). In addition, other authors reported five-year survival rates of 23% to 26%, and recurrence rates of 51% to 84% after LT for unresectable extrahepatic CCA (48-50). Liver transplant centres in Spain reported similar results, with a three-year survival rate of 30% (51).

Unfortunately, due to historical data that have shown unacceptable results for CCA, this therapeutic option is discouraged and most transplant centres worldwide have considered CCA an absolute contraindication for LT.

**Neoadjuvant chemoradiation for CCA**

In recent years, a few centres have applied rigorous selection criteria and pretransplant neoadjuvant chemoradiation in CCA patients. The results were significantly better and have renewed debate over LT feasibility for CCA. Because the combination of neoadjuvant chemoradiation and LT has achieved promising results, this new approach has been proposed to attempt to control tumour growth during the potentially long wait time for LT and decrease recurrence after LT.

In 2002, a group (Sudan et al [52]) from the University of Nebraska (Lincoln, Nebraska, USA) evaluated the effects of neoadjuvant chemoradiation combined with LT in a selected group of patients with hilar CCA. The neoadjuvant protocol included 6000 cGy biliary brachytherapy and intravenous infusion of 5-FU (300 mg/m²/day) until transplantation. Five of 17 patients progressed before LT, and one died because of sepsis. Of 11 patients who underwent LT, five (45%) were alive and without evidence of tumour recurrence during a median follow-up of eight years. The results of LT for CCA are summarized in Table 4. These widely disparate results showed that the patient groups were heterogeneous and the effectiveness of neoadjuvant treatment varied. It also emphasizes the importance of accurate tumour staging.

<table>
<thead>
<tr>
<th>Author (reference)</th>
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<th>Five-year survival rate</th>
<th>Recurrence, %</th>
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<tr>
<td>Liver transplantation not including neoadjuvant chemoradiation</td>
<td></td>
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<tr>
<td>Pichlmayr et al (38)</td>
<td>25</td>
<td>17%</td>
<td>NR</td>
</tr>
<tr>
<td>Pichlmayr et al (47)</td>
<td>18</td>
<td>14% at 1 year</td>
<td>NR</td>
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<tr>
<td>Casavilla et al (48)</td>
<td>20</td>
<td>18%</td>
<td>55</td>
</tr>
<tr>
<td>Shimoda et al (49)</td>
<td>25</td>
<td>35% at 3 years</td>
<td>41</td>
</tr>
<tr>
<td>Robles et al (51)*</td>
<td>59</td>
<td>30% and 42%</td>
<td>53 and 35</td>
</tr>
<tr>
<td>18% and 23% at 10 years</td>
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<td></td>
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<tr>
<td>Becker et al (45)*</td>
<td>102</td>
<td>63%</td>
<td>NR</td>
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<tr>
<td>101</td>
<td>30%</td>
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<tr>
<td>Liver transplantation including incidental cholangiocarcinoma</td>
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<td>Ghali et al (43)</td>
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<td>30% at 3 years</td>
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<td>Becker et al (45)</td>
<td>77</td>
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<td>NR</td>
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<td>Neoadjuvant chemoradiation and liver transplantation for cholangiocarcinoma</td>
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<td>Iwatsuki et al (46)‡</td>
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<td>55</td>
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<td>Sudan et al (52)</td>
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<td>45% at 7 years</td>
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<td>38</td>
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<td>13</td>
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<td>Heimbach et al (56)</td>
<td>65</td>
<td>76%</td>
<td>17</td>
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</table>

*Results are presented for hilar (n=36) and peripheral (n=23) cholangiocarcinoma respectively. †Patients transplanted before 1994 (n=101), and patients transplanted after 1994 (n=102). ‡Sixty per cent of patients received external radiotherapy with or without 5-fluorouracil sensitization before or after liver transplantation. Six of eight patients who survived more than five years received radiotherapy (four preoperatively and two postoperatively). NR Not reported

**MAYO CLINIC PROTOCOL OF LT FOR CCA**

By applying strategies of more rigorous selection criteria and intensive neoadjuvant chemoradiotherapy regimens, the Mayo Clinic (Rochester, Minnesota, USA) has been able to obtain significantly improved outcomes after LT in unresectable extrahepatic CCA. Of 71 patients who were enrolled in the treatment protocol, 54 were evaluated for surgical resection and 38 underwent LT. Patients treated with LT received neoadjuvant therapy, including external beam radiotherapy, with a target dose of 4500 cGy in 30 fractions and a transluminal boost of radiation using a transcatheter iridium-192 brachytherapy wire, with a target dose of 2000 cGy to 3000 cGy. Concomitantly, 5-FU was administered at 500 mg/m² as a daily intravenous bolus for the first three days of radiation. Patients continued to receive oral capecitabine (2000 mg/m²/day in two divided doses, two out of every three weeks) as tolerated until LT. All patients underwent a staging operation before transplantation; extrahepatic metastases, lymphatic node metastases, and local extension of disease to adjacent organs or tissues precluded LT. Thus, only patients with operatively confirmed stage I to II disease underwent LT.

Of 54 patients in the surgical group, 26 (48%) underwent surgical resection, and 28 (52%) had unresectable disease. One-, three- and five-year patient survival rates were 82%, 48% and 21%, respectively, after surgical resection, and 92%, 82% and 81%, respectively after LT (P<0.02). There were fewer tumour recurrences in transplanted patients than in surgical patients (13% versus 27%). Eight patients in the LT group did not have tissue or cytology diagnoses of CCA in
the explanted livers; however, they had suspicious cytology, malignant-appearing strictures, high CA 19-9 levels without acute biliary obstruction, and positive DIA and FISH tests for aneuploidy at the time of evaluation for LT. Moreover, when excluding these eight patients from the survival analysis, the five-year survival rate only changed from 82% to 80% (53). An update of this protocol was presented at the Third Annual Canadian Liver Transplant Forum in November 2007. Up to October 2007, 148 patients, of which 124 underwent a staging operation, have been included, with 90 undergoing LT. The mean (± SD) five-year survival rate after the start of therapy in 148 patients was 55±6% and five-year survival after LT in the 90 patients was 71±7% (personal communication).

**LT for intrahepatic CCA**

Contrary to the favourable outcomes with LT for extrahepatic perihilar CCA reported by a single centre (Mayo Clinic), intrahepatic CCA treated with LT conforms high rates of disease recurrence and poor survival and, thus, cannot be advocated. Median survival of these patients has been reported to be just five months. Overall survival at one year ranges from 14% to 70%, from 34% to 50% at three years, and from 0% to 33% at five years in series with few patients with intrahepatic CCA treated with LT (54,55).

**Predictors of disease recurrence after LT**

The same group has also reported their experience regarding clinicopathological predictors for disease recurrence (56). Up to January 2006, 106 patients had been enrolled in this protocol. Eleven patients had died or had evidence of disease spread before neoadjuvant treatment was completed, and 18 patients experienced disease progression diagnosed at laparotomy and were therefore, excluded from the study. Of the remaining 87 patients, 65 transplants have been reported to date. For these 65 patients, one- and five-year survival rates were 91% and 76%, respectively; 11 patients (17%) developed recurrence between seven and 64 months after LT (median 22 months); and eight patients died from recurrent disease within a median follow-up of 18 months. The predictors of recurrence were older age, pretransplant CA 19-9 level greater than 100 U/mL, previous cholecystectomy, mass detected on cross-sectional imaging, residual tumour in explant greater than 2 cm in size, tumour grade and perineural invasion in explant. PSC, percutaneous biliary intubation and sex were not associated with recurrence.

**Should LT for CCA be performed in other centres?**

It may be difficult to generalize the Mayo Clinic protocol to all transplant centres. Given the chronic organ shortage, it is important that the favourable results reported by the Mayo Clinic be reproduced if the protocol is to be applied more widely. This is a complex protocol for highly selected patients, in which patients are declined participation if they do not fulfill rigorous criteria. A dedicated team of oncologists, hepatologists, radiotherapists, endoscopists and transplant surgeons will be needed to manage these patients. Only centres with such a multidisciplinary team may wish to incorporate this protocol into their transplant indications and attempt to gain experience to achieve similar or better results. Further refinements to the protocol may be possible. Currently, the protocol is a ‘package deal’, but are each of the different components critical to its success? What is the relative importance of debulking the primary tumour versus treatment of microscopic tumour deposits in regional lymph nodes?

It will be important to clarify which CCA patients should undergo LT. It appears that PSC patients with localized extrahepatic CCA may benefit from LT because surgical resection in this setting is a temporizing measure at best and may complicate future LT. However, surgical resection outcomes are improving with the recognition that the caudate lobe requires removal in hilar cancers and vascular reconstruction can be performed safely (57). In these cases, surgical resection avoids the laborious process of chemoradiation and the necessity of lifelong post-transplant immunosuppression.

For patients with unresectable extrahepatic CCA meeting the Mayo Clinic criteria for LT, this approach offers the only chance for cure.

**SUMMARY**

CCA is a devastating disease with a poor survival rate and few therapeutic options. Although surgical resection has been considered to be the best treatment option for localized CCA, local recurrences are very common, which implies persistent micrometastatic disease in the regional lymph nodes or at surgical margins. Early studies of LT for CCA did not show a survival benefit and currently, this tumour is considered to be an absolute contraindication for LT in most transplant centres worldwide. Recently, neoadjuvant chemoradiation in combination with LT for highly selected patients with extrahepatic CCA has shown impressive results, albeit at a single centre, five-year survival is approximately 76% to 82%, thereby approximating results for other standard indications for LT. It qualifies as an important advance in the battle to cure hilar CCA. Wider application of this strategy for CCA treatment, especially for patients with potentially resectable disease, will require validation by other centres.

**REFERENCES**

Cholangiocarcinoma


