Current Status of Liver Transplantation for Cholangiocarcinoma

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Cholangiocarcinoma (CCA) is the second most common liver cancer, and it is associated with a poor prognosis. CCA can be divided into intrahepatic, hilar, and distal. Despite the subtype, the median survival is 12-24 months without treatment. Liver transplantation (LT) is recognized worldwide as a curative option for hepatocellular carcinoma. On the other hand, the initial results for LT for CCA were very poor mainly due to a lack of adequate patient selection. In the last 2 decades, improvements have been made in the management of unresectable hilar CCA, and the results of LT after neoadjuvant chemoradiation have been shown to be promising. This has prompted a consideration of hilar CCA as an indication for LT in some centers. Furthermore, some recent research has shown promising results after LT for patients with early stages of intrahepatic CCA. A better understanding of the best tools to prognosticate the outcomes of LT for CCA is still needed. Here, we aimed to review the role of LT for the treatment of patients with perihilar and intrahepatic CCA. Also, we will discuss the most recent advances in the field and the future direction of the management of this disease in an era of transplantation oncology.

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Since the establishment of liver transplantation (LT) as the best treatment option for patients with end-stage liver disease, its indication to treat tumors confined to the liver has grown substantially.\(^1\,^2\)

Hepatocellular carcinoma (HCC) is the most frequent liver cancer, and LT is the best treatment option in selected patients because it removes both the cancer (with the widest possible margins) and the underlying liver disease.\(^3\,^4\) However, as the understanding of tumor biology and multidisciplinary oncological treatments improve, the indication of LT to treat other unresectable tumors confined to the liver (ie, cholangiocarcinoma [CCA], metastatic neuroendocrine tumors) has expanded.\(^6\,^7\) LT has therefore gained momentum as a treatment for patients with cancer. Because of organ shortages, the main concern when offering a transplant to these patients is the impact on other patients on the waiting list.\(^11\) With recent advances in the treatment of hepatitis C virus (HCV), there seems to be a decrease in the number of patients in need of a LT because of HCV, resulting in a potential increase in the organ pool.\(^12\) However, in some regions (such as North America), the increase in the incidence of patients with cirrhosis with nonalcoholic steatohepatitis may result in no change in the organ pool.\(^13\) Furthermore, living donor LT may be another excellent option to provide access to LT to those patients with cancer.

In this regard, the use of LT for the treatment of CCA has become a focus of interest around the
world. This type of tumor arising from the bile duct epithelium is very aggressive, and its prognosis is mainly dependent on its location along the biliary tree and its chance of being completely resected with negative margins.

The role of LT to treat patients with CCA has been explored in some centers for those patients presenting with an unresectable tumor confined to the hepatic hilum (ie, perihilar CCA/Klatskin tumor) and more recently for patients with “very early” (single tumor ≤2 cm) intrahepatic cholangiocarcinomas (iCCAs). So far, only these 2 locations of CCA are the ones where patients can potentially benefit from LT.

Here we aimed to review the role of LT for the treatment of patients with perihilar CCA and iCCA. Also, we will discuss the most recent advances in the field and the future direction of the management of this disease.

CCA Classification

CCA is a malignant tumor of the biliary system that stands as the second most common primary liver cancer after HCC. More than 95% of the time, it consists of an adenocarcinoma that depending on its locations on the biliary tree, can be classified as iCCA or extrahepatic CCA. In turn, the extrahepatic CCA can be subclassified into hilar (Klatskin tumor) or distal CCA (mid third and lower third bile duct lesions; Fig. 1).

Hilar CCA

The incidence of hilar cholangiocarcinoma (hCCA; Klatskin tumor) is approximately 7000 cases per year in North America, representing around two-thirds of all cases of CCA. Unfortunately, the overall survival (OS) for patients suffering from an hCCA is detrimental, ranging between 12 and 24 months.

It is well-known that the most important prognostic factor is to achieve a complete resection with negative oncological margins, but unfortunately, this is only achieved in 25%-40% of the patients. The current 5-year survival rate after surgery, even in select patients, rarely exceeds 40%. From this low survival after resection derives the concept of treating this patient population with a LT. This concept allows a complete resection with good negative margins in patients who have tumors that are locally unresectable due to the invasion of major vessels, bilobar tumor involvement, or insufficient hepatic reserve. This approach was first attempted in the late 1990s and failed to show any promising results because the 5-year survival rate was reported to be approximately 18% (Table 1). However, this was a retrospective analysis of a small series where patients did not undergo any type of protocolized neoadjuvant or adjuvant treatment.

THE “MAYO CLINIC” PROTOCOL

In the year 2000, the Mayo Clinic group reported their preliminary experience with a protocol of neoadjuvant therapy followed by LT. The neoadjuvant protocol consisted of the combination of external beam and transcatheter radiation with intravenous 5-fluorouracil. A total of 11 out of the initial 19 patients who were found to be eligible for the study completed the protocol and underwent LT, showing encouraging results. In 2004, the previous series was updated and an 82% 5-year survival rate was reported for 24 patients undergoing the “Mayo protocol.” In 2005, the same group published their experience of neoadjuvant chemoradiation followed by LT. In this study, they compared those patients undergoing a resection approach alone against those who underwent neoadjuvant therapy in addition to LT. The LT group with neoadjuvant chemoradiation (38 patients) achieved better OS at 1 year (92% versus 82%), 3 years (82% versus 48%), and 5 years (82% versus 21%) when compared with the resection group (26 patients). Also, the LT group experienced lower posttransplant recurrence (13% versus 27%).
patients who underwent LT were deemed to be unresectable.

On the basis of their experience, the Mayo clinic group described the risk factors for dropout of the LT waiting list due to disease progression. These were found to be as follows: carbohydrate antigen 19-9 (CA19-9) $\geq 500$ U/mL, a mass $\geq 3$ cm, malignant brushing or biopsy, and a Model for End-Stage Liver Disease (MELD) score $\geq 20$. Likewise, factors found to be predictors of recurrence after LT were as follows: an elevated CA19-9, the presence of an encased portal vein, and the evidence of a residual tumor on explant.

Since the establishment of the Mayo protocol, several other groups reported their experience with the same or similar protocols. In 2006, based on the experiences of the Mayo Clinic and the University of Nebraska, Gores et al. proposed that patients with unresectable hilar CCA arising in the setting of primary sclerosing cholangitis (PSC) should receive a MELD score exception points for better allocation of livers. In 2012, a multicenter study of 12 US centers including patients with hCCA who were treated with neoadjuvant therapy followed up by LT reported a 65% 5-year recurrence-free survival and an 11.5% dropout rate after 3.5 months of therapy. This study validated the hypothesis that it is appropriate for selected patients with hCCA to receive the proposed MELD exception points and therefore have a faster access to transplant.

### LIVER RESECTION VERSUS LT FOR hCCA

Other groups have also assessed the role of resection versus transplantation for hCCA. In 2011, Hong et al. found in a 24-year experience that surgical resection was a predictor of worse survival outcome when compared with transplantation. However, data of this study might be misleading because it included iCCA and hCCA as well as patients with and without liver cirrhosis. Also, numbers in the hCCA group were

#### TABLE 1. Patient Survival and Disease-Free Survival of Patients Transplanted With hCCA

<table>
<thead>
<tr>
<th>References</th>
<th>Center</th>
<th>Study Type</th>
<th>Total Number of Patients</th>
<th>Number of Patients Who Underwent LT (%)</th>
<th>1-Year OS (%)</th>
<th>3-Year OS (%)</th>
<th>5-Year OS (%)</th>
<th>Neoadjuvant Chemotherapy</th>
<th>With or Without Radiation Therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iwatsuki et al.</td>
<td>University of Pittsburgh</td>
<td>Retrospective</td>
<td>72</td>
<td>38 (53)</td>
<td>60</td>
<td>32</td>
<td>25</td>
<td>61% patients</td>
<td>37 (51%) disease-free at 3 years</td>
<td></td>
</tr>
<tr>
<td>Sudan et al.</td>
<td>University of Nebraska</td>
<td>Retrospective</td>
<td>17</td>
<td>11 (65)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Median survival 11 months</td>
<td></td>
</tr>
<tr>
<td>Reo et al.</td>
<td>Mayo Clinic</td>
<td>Retrospective</td>
<td>71</td>
<td>38 (54)</td>
<td>79</td>
<td>61</td>
<td>58</td>
<td>Yes</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Heimbach et al.</td>
<td>Mayo Clinic</td>
<td>Retrospective</td>
<td>106</td>
<td>65 (61)</td>
<td>91</td>
<td>—</td>
<td>76</td>
<td>Yes</td>
<td>Median time to recurrence 22 months</td>
<td></td>
</tr>
<tr>
<td>Rosen et al.</td>
<td>Mayo Clinic</td>
<td>Retrospective</td>
<td>148</td>
<td>90 (61)</td>
<td>82</td>
<td>63</td>
<td>55</td>
<td>Yes</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Kaiser et al.</td>
<td>Germany</td>
<td>Retrospective</td>
<td>47</td>
<td>47 (100)</td>
<td>61</td>
<td>31</td>
<td>22</td>
<td>No</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Darwish et al.</td>
<td>United States</td>
<td>Retrospective</td>
<td>287</td>
<td>216 (75)</td>
<td>—</td>
<td>68 (2 years)</td>
<td>53</td>
<td>Yes</td>
<td>65% 5-year disease-free survival</td>
<td></td>
</tr>
<tr>
<td>Welling et al.</td>
<td>University of Michigan</td>
<td>Retrospective</td>
<td>12</td>
<td>6 (50)</td>
<td>83</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Marchan et al.</td>
<td>Emory</td>
<td>Retrospective</td>
<td>10</td>
<td>8 (80)</td>
<td>80</td>
<td>67% (2 years)</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Mantel et al.</td>
<td>ELITA database</td>
<td>Retrospective</td>
<td>173</td>
<td>28 (16)*</td>
<td>77 (45)</td>
<td>—</td>
<td>59*</td>
<td>Yes</td>
<td>65% 5-year disease-free survival</td>
<td>This article compared patient selection within “Mayo protocol” to beyond that protocol.</td>
</tr>
</tbody>
</table>

*Within Mayo protocol.
|Beyond Mayo protocol.
low (13 patients in the LT group versus 7 in the resection group). It is important to note that this was not a randomized controlled trial and therefore patients in the LT group were unresectable and likely had more advanced disease. Therefore, there is a need for randomized controlled trials that can better compare the outcome of resectable (with similar disease stage) hCCA between LT and resection.

To date, until randomized controlled trials show otherwise, LT after aggressive neoadjuvant therapy including external beam and transluminal radiation, as well as systemic chemotherapy, seems like an adequate treatment for both unresectable hCCA, as well as hCCA arising in the setting of PSC. However, these transplants should be conducted in large academic centers with both a transplant and surgical oncology expertise.

Intrahepatic CCA

Intrahepatic cholangiocarcinoma (iCCA) corresponds to 5%-10% of all CCAs. The incidence of iCCA is 0.6-1.0/100,000 new cases per year in the United States and its incidence is increasing. This increase seems to be greater in groups with risk factors for HCC as cirrhosis, chronic viral hepatitis, and nonalcoholic steatohepatitis.

LT FOR iCCA

Currently, iCCA is a contraindication for LT in most LT centers around the world. This is probably related to the very poor outcomes in the early experience of LT for this disease. The results of initial experiences were difficult to interpret as most series included patients with both iCCA and hCCA as well as patients with and without liver cirrhosis. It is well-known that iCCA and hCCA are different entities that may present with different outcomes, and we also know from the HCC literature that tumors arising from healthy versus cirrhotic livers may also present with different outcomes.

In 2004, Robles et al. published a retrospective analysis of a multicenter experience with 23 patients who underwent LT for iCCA (Table 2). Notably, in 10 of their patients, the tumor was diagnosed incidentally after LT. The overall 5-year survival was reported to be 42%. Likewise, in 2011, Sapisochin et al. reported a 47% 5-year survival for patients who underwent transplantation with preoperative diagnosis of HCC but had either iCCA or mixed hepato-cholangiocarcinoma (HCC-CCA) in the explant pathology. Moreover, a German series of 10 patients who underwent LT with a preoperative diagnosis of iCCA demonstrated a 5-year survival of 33%. The results of these studies showed a poor and likely unacceptable 5-year survival for LT in the current era of organ shortage.

In 2011, the University of California, Los Angeles (UCLA) group published a series comparing LT and resection using neoadjuvant chemotherapy associating radiotherapy in some patients. In this 24-year experience with a total of 132 CCAs, they performed LT in 38 patients (25 of those were iCCA). The 5-year survival after LT was 32%. Unfortunately, the OS was calculated for both iCCA and hCCA, and the data on each type of cancer were not available. In a subsequent publication, the same group reported a multivariate analysis identifying predictors of tumor recurrence. Multifocal tumors, perineural invasion, infiltrative subtype, and lack of neoadjuvant and adjuvant therapies were found to be associated with a poor prognosis.

On the other hand, tumor size failed to be found as a predictor of tumor recurrence. However, this study was a retrospective analysis where only 13 patients had received neoadjuvant treatment with chemotherapy plus radiation therapy, making the results difficult to interpret.

Several retrospective series were conducted to review the outcomes after LT for patients with incidental iCCA. A Canadian multicenter study found 10 patients who underwent LT for other indications and were found to have CCA features in the explant. The 3-year OS in this series was 30%. Also, Facciuto et al. studied the explanted specimens and found 32 patients with intrahepatic biliary differentiation and cirrhosis. Interestingly, they conducted a matched analysis of this CCA population with HCC control patients. When patients were stratified by Milan criteria, those within Milan had similar OS between groups (78% for CCA versus 79% for only HCC; \( P = 0.61 \)). In the same way, patients outside Milan criteria had a lower 5-year OS compared with those within Milan criteria, but it was not different between CCA and HCC groups (48% for CCA versus 53% for only HCC; \( P = 0.12 \)). In 2016, Vilchez et al. conducted a retrospective analysis using the United Network for Organ Sharing (UNOS) database. They analyzed 4049 patients, of whom 440 had an iCCA diagnosis. The 5-year OS for patients with iCCA in the explant was 47%, but no subgroup analysis according to the size of the tumor was conducted. A population-based study from the United States found a worse OS when
compared with HCC (hazard ratio, 1.1; 95% confidence interval, 1.1-1.2) for patients with iCCA. Unfortunately, only 2.2% of iCCA patients were treated with LT, so it is difficult to extrapolate these worse results to the transplant field.\(^{65}\)

**NEW INSIGHTS**

In the last few years, efforts have been made to analyze homogeneous cohorts (Table 3). A multicenter study of LT centers in Spain published in 2014 their experience with LT for patients found to have iCCA and mixed HCC-CCA in the explant pathology.\(^{67}\) These results were compared with a control group of patients transplanted for HCC. The OS was 50% at 5 years for those patients with exclusively iCCA. Interestingly, this large series found tumor size (>2 cm) and multinodularity as risk factors for tumor recurrence and worse outcomes when compared with similar HCCs. On the other hand, patients with small single tumors had similar results to those of patients with HCC. Following that study, the same Spanish consortium reported a series of 29 patients who were found to have exclusively iCCA in their explant pathology. In this series, patients with “very early” iCCA (≤2 cm) did not present tumor recurrence, and their longterm survival at 5 years was 73%. Instead, patients with tumors >2 cm or with multifocal disease did much worse with a 40% 5-year survival. These promising results suggested that patients with “very early” iCCA should maybe be considered as a formal indication for LT. However, the number of patients on that study was limited, and their conclusions needed validation.\(^{69}\)

Hence, in 2016, Sapisochin et al. conducted a multicenter international study with the aim of validating the previous findings. A total of 48 (59%) out of 81 patients with iCCA features at the explant pathology were found have only iCCA. Among them, 31% (15 patients) constituted the “very early” iCCA group. This group of patients was then compared with 33 (69%) patients with “advanced” disease (single tumor >2 cm or multifocal disease). The 5-year actuarial survival rates were 65% in the “very early” iCCA group versus 45% in the advanced group. The cumulative risk of recurrence at 5 years was 18% versus 61%, respectively. These data support the previous findings that “very early” iCCA (≤2 cm) should formally be considered as candidates for LT.\(^{8}\) Notably, all of these

<table>
<thead>
<tr>
<th>References</th>
<th>Center</th>
<th>Study Type</th>
<th>Total Number of Patients</th>
<th>1-Year OS (%)</th>
<th>3-Year OS (%)</th>
<th>5-Year OS (%)</th>
<th>Neoadjuvant Chemotherapy With or Without Radiation Therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Grady et al.(^{(52)})(1988) King’s College</td>
<td>Retrospective</td>
<td>13 hCCA 13 iCCA</td>
<td>38 10 10</td>
<td>No</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yokoyama et al.(^{(57)})(1990) University of Pittsburgh</td>
<td>Retrospective</td>
<td>19 hCCA 2 iCCA</td>
<td>24 24 0</td>
<td>No</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meyer et al.(^{(56)})(2000) Cincinnati Transplant Tumor Registry</td>
<td>Retrospective</td>
<td>207 72</td>
<td>48 23</td>
<td>No</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shimoda et al.(^{(59)})(2001) UCLA</td>
<td>Retrospective</td>
<td>9 hCCA 16 iCCA</td>
<td>86 39</td>
<td>—</td>
<td>4 patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robles et al.(^{(56)})(2004) Spain</td>
<td>Retrospective</td>
<td>36 hCCA 23 iCCA</td>
<td>82 65 42</td>
<td>No</td>
<td>2-year disease-free survival 52% for hCCA and 35% for iCCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghali et al.(^{(60)})(2005) Canada</td>
<td>Retrospective</td>
<td>10</td>
<td>30</td>
<td>No</td>
<td>1 patient had iCCA-HCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong et al.(^{(9)})(2011) UCLA</td>
<td>Retrospective comparing resection × LT</td>
<td>132</td>
<td>38 32</td>
<td>Yes</td>
<td>LT for 25 iCCA LT for 13 hCCA 29% patients underwent LT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panjala et al.(^{(61)})(2012) Mayo</td>
<td>Retrospective</td>
<td>22 90 63</td>
<td>—</td>
<td>Yes</td>
<td>74% patients underwent LT Median time to recurrence 37 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dugnian et al.(^{(59)})(2014) Dublin</td>
<td>Retrospective</td>
<td>27 73</td>
<td>73 61 (4 years)</td>
<td>Yes</td>
<td></td>
<td>74% patients underwent LT Median time to recurrence 37 months</td>
<td></td>
<td></td>
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</tbody>
</table>
studies were conducted in patients who were either transplanted with the suspicion of HCC and were found to have iCCA in the explant (misdiagnosis) or underwent transplantation due to decompensated cirrhosis and were incidentally diagnosed with an iCCA. Certainly, this is the main caveat of these encouraging results, and the outcomes of patients with known iCCA before transplant is still to be investigated and will need to be evaluated prospectively. Also, it is important to mention that the first treatment option for patients with iCCA should be liver resection if possible.\(^{(51)}\) As with HCC, LT for early stages of iCCA should be reserved for patients where liver resection is not an option (ie, portal hypertension). All patients evaluated in previous studies analyzing LT for “very early” iCCA only included patients who were not candidates for liver resection.\(^{(8,56,69)}\)

### Future Perspectives

Prospective trials should allow the identification of hCCA patients who would benefit from either LT or surgical resection. To answer this question, there is currently 1 prospective, randomized, multicenter study (Liver Resection Versus Radio-Chemotherapy-Transplantation for Hilar Cholangiocarcinoma [TRANSPHILL] study NCT02232932) comparing LT preceded by neoadjuvant radiochemotherapy versus standard of care liver and bile duct resection. The primary outcome for this study is OS.\(^{(70)}\) Hopefully in the future, we will have some insights if LT is a better treatment than LR in resectable patients. On the other hand, due to encouraging results from some Asian centers, arterial resection and reconstruction in some cases of bilateral arterial involvement may be considered as an alternative to LT, and this treatment strategy should be further investigated in the future.\(^{(71)}\)

For iCCA, the encouraging results from retrospective studies opens a new door when considering LT for patients with “very early” iCCA. Indeed, given that the radiological features of iCCA (especially in cirrhosis) have yet to be established, a tumor biopsy in patients considered for LT with a nodule without typical HCC features will need to be performed. In this regard, a prospective trial (NCT02878473)\(^{(72)}\) aiming to transplant patients with “very early” iCCA will be recruiting in the near future to prospectively confirm that these patients can benefit from this treatment and to open a new indication for LT. The main caveat for such a protocol will be the difficulty of precisely diagnosing these tumors in patients where a tumor biopsy cannot be performed. One of the unanswered questions is if as with hCCA and the Mayo protocol, these patients will require neoadjuvant chemoradiation. Also, it is unclear if by using chemoradiation protocols LT could be offered to patients with a >2 cm iCCA. These unanswered questions will need to be studied in the near future to better understand and improve the management of patients with cirrhosis diagnosed with CCA.

To date, available data on systemic therapy for CCA have demonstrated limited therapeutic efficacy. Data from the Adjuvant capecitabine for biliary tract cancer (BILCAP) randomized trial, presented recently at the American Society of Clinical Oncology, showed encouraging results of capecitabine as adjuvant therapy.

### TABLE 3. Survival and Disease-Free Survival of Patients Transplanted With iCCA

<table>
<thead>
<tr>
<th>References Center Study Type</th>
<th>Total Number of Patients</th>
<th>1-Year OS (%)</th>
<th>3-Year OS (%)</th>
<th>5-Year OS (%)</th>
<th>5-Year Disease-Free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotiropoulos et al.(^{(63)}) (2008) Mainz Retrospective</td>
<td>10</td>
<td>70</td>
<td>50</td>
<td>33</td>
<td>—</td>
</tr>
<tr>
<td>Vallin et al.(^{(66)}) (2013) France Retrospective Multicenter</td>
<td>10</td>
<td>80</td>
<td>60</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>Sapisochin et al.(^{(67)}) (2014) Spain Retrospective Multicenter</td>
<td>27</td>
<td>78</td>
<td>66</td>
<td>51</td>
<td>36</td>
</tr>
<tr>
<td>Facciuto et al.(^{(64)}) (2015) Mont Sion Medical Center Retrospective</td>
<td>7 iCCA</td>
<td>71</td>
<td>—</td>
<td>57</td>
<td>44</td>
</tr>
<tr>
<td>Vilchez et al.(^{(68)}) (2016) UNOS database Retrospective Multicenter</td>
<td>440</td>
<td>79</td>
<td>58</td>
<td>47</td>
<td>—</td>
</tr>
<tr>
<td>Sapisochin et al.(^{(8)}) (2016) Canada Retrospective Multicenter</td>
<td>15 iCCA single ≤ 2 cm</td>
<td>93</td>
<td>84</td>
<td>65</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>33 iCCA multiple or &gt; 2 cm</td>
<td>79</td>
<td>50</td>
<td>45</td>
<td>61</td>
</tr>
</tbody>
</table>

NOTE: All articles included patients without neoadjuvant chemoradiation.
after resection of biliary cancers. The OS in the capicitabine group was 15 months longer compared with observation.\(^{(73)}\) The applicability of this in the transplant setting is unknown and probably difficult to extrapolate, but it should be explored in the future under research protocols aiming to increase the survival of transplant recipients with CCA.

Certainly, target therapies in the context of LT for CCA will also need to be better assessed. Genetic aberrations such as KRAS mutation, fibroblast growth factor receptor 2 gene fusions, and somatic mutations in IDH1/2 are common in CAA and potentially candidates to targeted therapies.\(^{(74,75)}\) In the same way, vascular endothelial growth factor (VEGF) expression is reported in up to 40% of CCA.\(^{(76)}\) However, the results with VEGF blockers in CCA are disappointing. Although sorafenib failed to prove beneficial in phase 2 studies, bevacizumab associated with gemcitabine and oxaliplatin has shown a median progression-free survival of 7 months in a single-arm phase 2 study.\(^{(77,78)}\) Immune checkpoints have also been proven to be dysregulated in CCA resected tissue.\(^{(79)}\) However, the clinical experience in immunotherapy for CCA is incipient with 2 phase 2 trials that are ongoing (NCT02628067 and NCT02268825).\(^{(80,81)}\) The results of these trials will hopefully provide a better understanding of the role of these new therapies in patients with CCA.

Another possible consideration is if genomic features can play a role in identifying adequate candidates with iCCA for LT. Recent studies have identified messenger RNA and noncoding RNA expression associated with iCCA outcomes. Sia et al. analyzed the gene expression profile using samples of 149 patients and identified 2 main biological classes of iCCA:

1. The inflammation class, characterized by activation of inflammatory signaling pathways, overexpression of cytokines, and signal transducer and activator of transcription 3 (STAT3) oncogene activation.
2. The proliferation class characterized by activation of oncogenic signaling pathways (including RAS, mitogen-activated protein kinase, and MET), DNA amplifications at 11q13.2, deletions at 14q22.1, mutations in KRAS and BRAF, and gene expression signatures previously associated with poor outcomes for patients with HCC.\(^{(82)}\)

Unfortunately, there is still limited understanding of genomics abnormalities in iCCA, and it is unclear if these genomic classes will predict the outcomes of iCCA after LT.

**Conclusion**

The era of “Transplant Oncology”\(^{(6)}\) is happening now and is likely to advance further in the next decade. Selected patients with CCA can benefit from a radical treatment such as LT to achieve a cure. However, further research to better define inclusion criteria and neoadjuvant and adjuvant treatments is needed. The hCCA should be an indication for LT under a strict neoadjuvant chemoradiation protocol, and patients must be carefully followed while listed to identify tumor progression and avoid posttransplant recurrence. Posttransplant analysis suggests patients with cirrhosis with very early iCCA may achieve excellent OS. In this regard, it is possible that patients diagnosed preoperatively of a “very early” iCCA may achieve the same results after LT. Further prospective research is needed to confirm these encouraging results.

**REFERENCES**


1. Patients with CCA that are likely to have a poor prognosis include
   a. CA19-9 > 500 U/mL
   b. Mass >2cm
   c. MELD >20
   d. Malignancy found on brushing or biopsy

True or False

2. Patients with PSC and hilar cholangiocarcinoma are not eligible for liver transplantation

3. Intrahepatic CCA has a better prognosis after resection than HCC

4. Sorafenib, an effective treatment for HCC appears promising in iCCA

5. Very early iCCA (<2cm) seems to have similar prognosis after LT than HCC

6. Hilar CCA can be considered for liver transplantation after aggressive neoadjuvant therapy including radiation and chemotherapy

7. iCCA is currently a contraindication to liver transplantation

8. Intrahepatic CCA >2cm in diameter and multinodularity are risk factors for poor prognosis after transplant

9. The first choice of therapy for patients with iCCA should be resection

10. The prevalence of iCAA is increasing due to an increase in PSC cases