Liver Transplant for Cholangiocarcinoma: A Comeback?

Maximilian Schmeding, Ulf P. Neumann

Abstract
Liver transplant is not a standard therapy for cholangiocarcinoma; complete surgical resection of the tumor is currently the treatment of choice. Palliative options offer only short-term survival.

After initial recurrence rates after liver transplant for cholangiocarcinoma in the 1990s were unacceptably high, cholangiocarcinoma has been regarded widely as a contraindication to liver transplant. Ubiquitous organ shortage further supports this conviction. Careful patient selection and a rigorous perioperative treatment by radiochemotherapy have produced some impressive survival data in specialized transplant centers in recent years. Although the graft shortage is aggravating in the Western world, the issue of liver transplant as a treatment for irresectable cholangiocarcinoma is being discussed.

This review article provides an update and overview on the current status of liver transplant as a potential option for patients with irresectable cholangiocarcinoma.

Key words: CCA, Tumor recurrence

Status quo

Complete surgical resection represents the only potentially curative option for patients with intra- or extrahepatic cholangiocarcinoma (CCA). Despite extensive surgical approaches and perioperative chemotherapeutic treatment, long-term survival of these patients is limited. In many cases, complete surgical resection of the tumor is impossible because of central vascular and biliary tract invasion. For these patients, liver transplant (LT) may be a curative option if extrahepatic tumor dissemination can be ruled out. Alternatively, only palliative treatment options are available such as photodynamic treatment or systemic therapy.

Liver transplant for CCA has been performed in the early era of LT with limited long-term success: Tumor recurrence rates under immunosuppression were unacceptably high. The ubiquitous organ shortage has prompted graft allocation to patients with potentially higher survival chances.

A few highly selected patients with small yet anatomically complicated tumors were further considered for LT. Most of these patients were young and in good general condition compared with the average LT candidate.

Overall, the number of patients receiving LT for CCA in the past 15 years has been extremely small, and no prospective or randomized trials exist concerning the question of acceptable benefit by LT for these patients in the light of worldwide organ shortage. Recently, however, some new data have become available demonstrating acceptable or even excellent results for LT in CCA patients. In all these studies, patients were selected for LT after extensive scrutinizing, yet demonstrating that LT may be an option if we evaluate the potential candidate thoroughly.

In 2014, a study was initiated by the group from Paris, France, to compare the long-term outcome of patients with CCA treated by either surgical resection or LT preceded by radiochemotherapy. To decide upon LT as an option, it is important to distinguish between intra- and extrahepatic cholangiocarcinoma: While the patient with extrahepatic bile duct...
malignancy will likely be a candidate for surgical resection and often presents with lymphatic tumor invasion, the central extrahepatic CCA mostly displays local vascular and biliary invasion rendering surgical resection impossible.

Gall bladder carcinoma as a subtype of extrahepatic CCA should be regarded as a contraindication to LT, as recurrence rates even after curative surgical resection are high. Surgically irresectable tumors would definitely recur after LT and consecutive immunosuppression.

Intrahepatic CCA in the liver periphery should always be approached by (extensive) surgical resection. More radical surgery is often possible for these patients as they do not have parenchymal liver dysfunction such as patients with cirrhosis and hepatocellular carcinoma. Therefore, surgical resection often can be performed; sometimes multimodal approaches (eg, preoperative portal venous embolization and percutaneous bile drainage) may be necessary. In case of anatomic limitations (eg, enormous tumor size or massive vascular invasion), the tumor stage must be regarded as too advanced for an LT. In many cases, extrahepatic tumor spread can be detected in hilar or even retroperitoneal lymph nodes. However, even in this setting a combination of aggressive neoadjuvant treatment followed by LT in cases of good tumor response may be justified in individual cases such as young patients. The universal donor organ shortage in Western countries considerably aggravates this decision. Posttransplant immunosuppressive strategies are being evaluated at the Mayo Clinic, where some excellent data have been published (NCT01888302).

The patients with known primary sclerosing cholangitis (PSC) and an increased risk of CCA development represent a special collective: These patients require close monitoring to detect potentially developing CCA early and in time for transplant before extrahepatic spread. Many patients with PSC are on the waiting list for LT due to PSC-based cirrhosis formation, unbearable jaundice and itching or recurrent cholangitis. However, MELD scores of these patients usually are low, and graft availability may be distant. For this reason the UNOS system in the United States has established an algorithm for CCA patients seeking LT under which except MELD points can be granted to these patients on the waiting list (see Tables 1 and 2).

Regarding the above-mentioned limitation, only a select number of patients with CCA are potential candidates for LT. This article evaluates the results of the available data on LT for CCA; based on this information, we try to provide an approach to the question which patient may eventually profit from LT.

In this approach we have analyzed the available data on CCA and liver transplant. Literature research was performed using PubMed (NCBI/NIH) and Cochrane database under employment of the search terms “cholangiocarcinoma,” “bile duct cancer,” “bile duct tumor,” “liver transplant,” “tumor recurrence,” “Klatskin tumor.” Studies currently under way were sought for in “clinicaltrials.gov” and the European EUDRACT register.

The central database “clinicaltrials.gov” displays 4 ongoing trials at the time of data retrieval:
1. Study NCT00301379 is a prospective registry study of neoadjuvant chemoradiation and liver transplant for cholangiocarcinoma patients, initiated at Washington University. While recruiting is estimated until 2015, the primary objectives are to evaluate treatment of patients with unresectable CCA, and determine how many of those patients will receive LT; furthermore, it shall be analyzed how many of these LT patients are alive 2 years after LT (induction treatment with gemcitabine, followed by 3-D conformal radiation with 5-fluorouracil [5-FU] as a radiosensitizer, and maintenance capecitabine [Xeloda] therapy until liver transplant; staging laparotomy is performed before chemoradiation.)

Table 1. Characteristics of All Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>1-Year Survival (%)</th>
<th>3-Year Survival (%)</th>
<th>5-Year Survival (%)</th>
<th>Additional Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>European transplant no registry</td>
<td>1987</td>
<td>38</td>
<td>40</td>
<td>16</td>
<td>0</td>
<td>no</td>
</tr>
<tr>
<td>Pichlmayr</td>
<td>1996</td>
<td>25</td>
<td>60</td>
<td>21</td>
<td>17</td>
<td>no</td>
</tr>
<tr>
<td>Casavilla</td>
<td>1997</td>
<td>20</td>
<td>64</td>
<td>34</td>
<td>26</td>
<td>no</td>
</tr>
<tr>
<td>Iwatsuki</td>
<td>1998</td>
<td>38</td>
<td>60</td>
<td>32</td>
<td>25</td>
<td>no</td>
</tr>
<tr>
<td>Shimoda</td>
<td>2001</td>
<td>25</td>
<td>67/71</td>
<td>32/35</td>
<td>32/35</td>
<td>no</td>
</tr>
<tr>
<td>Meyer</td>
<td>2000</td>
<td>207</td>
<td>72</td>
<td>48</td>
<td>23</td>
<td>no</td>
</tr>
<tr>
<td>Sudan</td>
<td>2002</td>
<td>11</td>
<td>45</td>
<td>45</td>
<td>no</td>
<td>radiochemotherapy</td>
</tr>
</tbody>
</table>
Table 2. Liver Transplant for Cholangiocarcinoma: Recent Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of Patients</th>
<th>1-Year Survival (%</th>
<th>3-Year Survival (%</th>
<th>5-Year Survival (%</th>
<th>Additional Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robles14</td>
<td>2004</td>
<td>36 (2+pp)</td>
<td>82</td>
<td>53</td>
<td>30</td>
<td>None</td>
</tr>
<tr>
<td>Ghali15</td>
<td>2005</td>
<td>10</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>None</td>
</tr>
<tr>
<td>Rea16</td>
<td>2005</td>
<td>38</td>
<td>92</td>
<td>82</td>
<td>82</td>
<td>Chemoradiation (Mayo)</td>
</tr>
<tr>
<td>Heimbach17</td>
<td>2006</td>
<td>65</td>
<td>91</td>
<td>82</td>
<td>76</td>
<td>Chemoradiation (Mayo)</td>
</tr>
<tr>
<td>Kaiser18</td>
<td>2008</td>
<td>47</td>
<td>62</td>
<td>31</td>
<td>21</td>
<td>None</td>
</tr>
<tr>
<td>LT after 1998</td>
<td></td>
<td>15</td>
<td>57</td>
<td>48</td>
<td>-</td>
<td>None</td>
</tr>
<tr>
<td>Rosen19</td>
<td>2008</td>
<td>90</td>
<td>90</td>
<td>80</td>
<td>71</td>
<td>Chemoradiation (Mayo)</td>
</tr>
<tr>
<td>Becker (UNOS)20</td>
<td>2008</td>
<td>280</td>
<td>74</td>
<td>-</td>
<td>-</td>
<td>None</td>
</tr>
<tr>
<td>Seehofer21</td>
<td>2009</td>
<td>16</td>
<td>63</td>
<td>38</td>
<td>38</td>
<td>None</td>
</tr>
<tr>
<td>Friman22</td>
<td>2011</td>
<td>53</td>
<td>25</td>
<td>38</td>
<td>58</td>
<td>None</td>
</tr>
<tr>
<td>LT after 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LT after 1995 + TNM &lt;2</td>
<td>2011</td>
<td>20</td>
<td>84</td>
<td>33</td>
<td>22</td>
<td>None</td>
</tr>
<tr>
<td>Hu23</td>
<td>2011</td>
<td>22</td>
<td>90</td>
<td>63</td>
<td>-</td>
<td>Chemoradiation</td>
</tr>
<tr>
<td>Panjala24</td>
<td>2011</td>
<td>7</td>
<td>100</td>
<td>67</td>
<td>-</td>
<td>None</td>
</tr>
<tr>
<td>AIS25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong26</td>
<td>2011</td>
<td>38</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>33 % tumor- recurrence-free survival Patients with and without perioperative chemotherapy</td>
</tr>
<tr>
<td>Gu (metaanalysis)27</td>
<td>2012</td>
<td>605</td>
<td>73</td>
<td>42</td>
<td>39</td>
<td>With radio chemotherapy. V/o radio chemotherapy.</td>
</tr>
<tr>
<td>Friman et al40</td>
<td>2011</td>
<td>53</td>
<td>83</td>
<td>57</td>
<td>65</td>
<td>None</td>
</tr>
<tr>
<td>Darwish et al42</td>
<td>2012</td>
<td>216</td>
<td>78 (recurrence- free 2-year survival)</td>
<td>65 (recurrence-free survival)</td>
<td>-</td>
<td>Radio-(chemo-) therapy</td>
</tr>
<tr>
<td>Duignan et al43</td>
<td>2014</td>
<td>20 (out of 27)</td>
<td>94 (of all patients initially evaluated discharged)</td>
<td>61 (4-year surv; of all patients discharged)</td>
<td>-</td>
<td>Radiochemotherapy 20% perioperative mortality</td>
</tr>
<tr>
<td>Welling8</td>
<td>2014</td>
<td>6 (of 17 initially evaluated)</td>
<td>83</td>
<td>-</td>
<td>-</td>
<td>Stereotactic-body-radiation + capcitabine</td>
</tr>
</tbody>
</table>

Abbreviations: incidental CCA, all cases occurred in known primary sclerosing cholangitis; IHCC, intrahepatic cholangiocarcinoma; pp, simultaneous pancreatic resection

2. Study NCT01549795 from Padua, Italy, began recruiting in 2012. Irresectable CCA patients are considered for LT after pretreatment with external beam radiation (45 Gray) and endoluminal bile duct brachytherapy (20 Gray) combined with capecitabine. Before LT a laparoscopic hand-assisted evaluation of the abdominal cavity is performed. This is a single-arm trial without control group.

3. Study NCT02178280 from Nanjing University Medical School, China, was started in June 2014. This nonrandomized single-arm study also combines neoadjuvant brachytherapy with external beam radiation and capecitabine before LT.

4. Study NCT02232932 from Paris, France, was initiated in 2014 and aims to include 60 individuals until 2021. This prospective, open-label, randomized, multicenter comparative study compares LT for CCA preceded by neoadjuvant radiochemotherapy to conventional hepatic and bile duct resection. Treatment in the LT group consists of external beam radiation and capecitabine.

5. Study NCT01151761 from Stanford University was started in 2011 and is currently not recruiting. Results have not been published yet. It is a nonrandomized phase II study of stereotactic body radiotherapy and chemotherapy for unresectable cholangiocarcinoma followed by liver transplant. The primary endpoint is 12 month’s progression-free survival, secondary endpoint is LT rate of all subjects included (substances used: gemcitabine, carboplatin, capecitabine, 5-FU).

6. Study NCT00708877 from the University of Utah has recruited 5 patients from 2007 until July 2011
when recruitment was terminated for preliminary analysis. The study recruited T3 and N1 patients to evaluate the successful (Mayo) neoadjuvant radiochemotherapy protocol for this subgroup of more advanced cancer stage.

7. A multicenter study was conducted in Germany in 2012, led by the Berlin group, investigating the feasibility of LT for CCA patients incorporating pretransplant staging laparotomy (details to be released). However, this study currently has been stopped.

8. Study NCT01888302 from the Mayo Clinic is evaluating the immunosuppressive and adjuvant treatment for patients having undergone LT for CCA.

Critical analysis of the current data and future perspectives
Liver transplant for intra- and extrahepatic bile duct carcinoma does not represent a standard procedure. After dismal survival results in the 90s, CCA has been seen as a contraindication to LT. The aggravation of the virtually ubiquitous organ shortage has limited the consideration of CCA patients for LT in European and North American transplant centers. However, because of the discouraging results from the early years are based on a liberal patient selection, a reevaluation of CCA patients for LT under specified pre- and perioperative circumstances seems worthwhile. Recently, several studies have demonstrated that careful patient selection combined with perioperative (radio) chemotherapy may generate survival results that can compare to those of classic standard indications.8-10

While many authors advocate extended surgical resection for extrahepatic bile duct malignancy, others favor LT accompanied by intensive perioperative radiochemotherapy.9,11 Some groups favor complete surgical avoidance of the liver hilus with standard aortic interposition of donor iliac artery.12 This procedure is relevant in the light of elevated vascular complication rates after a LT after neoadjuvant radiochemotherapy.13

Unresectable cholangiocarcinoma is progressively shifting into the focus as an indication for LT. However, the diagnosis of resectability is defined heterogeneously in different centers. Extensive hepatic resection including vascular resection and reconstruction must be considered as an organ-sparing alternative with comparable long-term outcome in specialized departments.11,14,15 This is important because of the scarcity of donor grafts. The advantage of LT compared with hepatic resection for CCA is shown by a study by the Paris group to compare the long-term outcome of patients with CCA treated by surgical resection or LT preceded by radiochemotherapy (NCT02232932). However, recruitment is scheduled until the year 2021; therefore, results will not be available for some time. Further, selection bias based on surgical irresectability cannot be completely ruled out. To clarify the picture LT, candidates with CCA should be looked on in 2 different collectives: patients with PSC and associated CCA, and patients without PSC.

For patients with PSC, CCA diagnosis usually is established at an early tumor stage as most of these patients are under constant medical surveillance. Cholangiographic detection of malignant bile duct stenosis, small intrahepatic mass, positive brush cytology, and CA 19-9 elevation are all early markers of CCA development in PSC.16-18 As liver function often is limited for patients with long-standing PSC with consecutive cirrhosis, extensive hepatic resection does not represent an option. Additionally, PSC patients run an elevated risk of biliary leakage after partial hepatectomy. A clear definition of CCA can be difficult in PSC patients. In many cases of suspected CCA after a transplant, pathology is unable to detect a malignancy.19 Detecting specific biomarkers in peripheral blood samples may help clarify the diagnosis.20

For patients with PSC, LT should be discussed as the more potent and definite solution than resection. Until now, studies demonstrate encouraging long-term survival results if careful patient selection is performed.21-23

Patients without primary sclerosing cholangitis presenting with extrahepatic cholangiocarcinoma-/Klatskin tumor
For resectable extrahepatic bile duct tumors in patients without parenchymal disease, surgical resection is the criterion standard. Impressive long-term survival rates have been shown by various authors.11,14,24,25 Extended surgical resection with complete hilar clearance including resection of the right hepatic artery and the portal venous bifurcation has been advocated. Even for patients with positive lymph node status or incomplete surgical resection, modern adjuvant protocols offer a chance of
improved long-term survival.\textsuperscript{26} Especially in these cases, LT does not represent an option as recurrence rates under immunosuppression have shown to be unacceptably high.\textsuperscript{27-29} If extended extrahepatic bile duct resection, including pancreatic head resection in combination with LT, leads to improved survival in extrahepatic CCA patients; however, partly because of increased perioperative mortality, most centers do not have improved results with this patient collective.\textsuperscript{14-30}

For patients with anatomically unresectable Klatskin tumors or considerable parenchymal damage, extended liver resection is not a choice. For these patients, LT is the only chance for a potential cure. However, several parameters have been identified to negatively affect survival after LT for this collective: Elevated CA 19-9 levels (most authors name values > 1000 IU/mL), visible tumor mass of > 3 cm on computed tomography scan, and tumor-positive lymph node status significantly affects individual tumor recurrence and survival. Therefore, exploratory laparotomy is suggested for CCA patients who are potential candidates for LT, to rule out lymphatic tumor spread.\textsuperscript{9,31} Klatskin tumors often present with early spread in the perineural sheath layers; therefore, extensive lymphadenectomy and complete clearance of the vascular structures is of critical importance for both resection and transplant.\textsuperscript{32-34} Several transplant protocols including perioperative radiochemotherapy incorporate staging laparotomy before listing for transplant because of this reason.\textsuperscript{9,12,34,35}

Patients presenting with intrahepatic cholangiocarcinoma

Cases of intrahepatic CCA as a potential indication for LT should be divided into 2 categories:

1. Patients with CCA without parenchymal liver disease and normal liver function: For these patients, surgical resection is the gold-standard treatment. If the tumor is large or involves extrahepatic structures, prohibiting primary resection LT must be ruled out because microscopic extrahepatic spread is almost universal in these cases, and tumor recurrence after LT would be likely.\textsuperscript{3,6,36} However, in some selected cases (eg, young patients) an aggressive (radio) chemotherapeutic induction treatment may be followed by LT if the tumor response is proven nonsurgically.

2. Patients with CCA in the presence of PSC, consecutive parenchymal damage, and impaired liver function: Most of these patients are already considered candidates for LT because of PSC or are under close surveillance of their physician. Therefore, CCA occurring in these patients is likely to be detected early, leaving LT as a curative option.\textsuperscript{37} However, several risk factors for tumor recurrence after LT have been identified.\textsuperscript{22,19} Therefore, careful patient selection is important to successful long-term survival after LT in these patients.

In these patients, treatment protocols including perioperative radiochemotherapy have demonstrated successful long-term survival results. The most frequently used and best-evaluated protocol is the one from the Mayo Clinic, Rochester: It incorporates external beam radiation with 45 Gray in 30 fractions over a 3-week period accompanied by 5-FU infusion (500 mg/m²), endoluminal Iridium192 brachytherapy (20-30 Gray) 2 weeks after the end of an external beam radiation. Until transplant capecitabine is given orally until transplant only paused for staging laparotomy.\textsuperscript{9,31,38,39}

Strict patient selection and consecutively positive results have led to criteria for CCA patients eligible to except MELD points in a number of UNOS areas in the United States. This is important because wait time until transplant after being listed is a risk factor for tumor recurrence.\textsuperscript{28} A catalogue of criteria (except MELD status) to be granted has been proposed by Gores and associates\textsuperscript{40} (Table 3).

### Table 3. Criteria for Cholangiocarcinoma as a Justified Indication for Liver Transplant Under Except Model of End-Stage Liver Disease Conditions

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neoadjuvant radiochemotherapy</td>
</tr>
<tr>
<td>• Staging laparotomy and lymph node dissection after neoadjuvant therapy and before LT listing</td>
</tr>
<tr>
<td>• Tumor diagnosis by: CA 19-9 &gt; 100 IU/mL, malignant-appearing stricture in endoscopy or malignant biopsy or cytology or aneuploidy</td>
</tr>
<tr>
<td>• Unresectable tumor because of an anatomic position or underlying disease (eg, primary sclerosing cholangitis)</td>
</tr>
<tr>
<td>• If CT or MRI show a detectable mass, this should be &lt; 3 cm in diameter</td>
</tr>
<tr>
<td>• Staging for intra- or extrahepatic metastases by CT/MRI every 3 months</td>
</tr>
</tbody>
</table>

Hong and associates analyzed their collective of 40 patients concerning risk factors for tumor recurrence and identified multifocal tumor growth, lymphovascular invasion, perineural infiltration, infiltrative growth character, PSC, hilar position, and lack of neoadjuvant treatment as risk factors for recurrence. However, this small collective is heterogeneous and has been collected over a long time
(15 y), suggesting biases like a lack of perioperative treatment and various operative strategies during the study.29

Despite impressive results of LT for CCA in some studies, care must be taken when interpreting the results: In the most important series to date from the Mayo Clinic, only 38 of 71 enrolled patients received LT. For these 38 patients, a vital tumor was detectable in only 22 of the 38 liver explants on pathological examination. If tumor absence in the other 16 cases was due to previous neo-adjuvant treatment or if diagnosis of malignancy had been false in the first place remains unclear.9,12

A Scandinavian study of 53 patients demonstrated 58% 5-year survival for patients with stage T1 and T2 tumors and CA 19-9 values < 100 IU/mL. The authors did not detect differences between hilar and intrahepatic tumors.41

A meta-analysis of 14 studies incorporating 605 LT patients for CCA demonstrated 42% 3-year survival and 39% 5-year survival. For patients treated with perioperative radiochemotherapy survival figures improved to 65% three-year survival and 57% five-year survival.42

Pooled data from 12 US transplant centers demonstrates 5-year recurrence-free survival of 65%.43 A small collective treated by a similar protocol in Ireland, and published in 2014, displayed a 61% four-year survival rate for patients who left the hospital after undergoing an LT. However, perioperative mortality was high at 20% in this collective of 20 patients.44

Gemcitabine plus cisplatin has been shown to improve patient survival in the R1- or palliative situation of CCA.2,26 Therefore, one may speculate that perioperative protocols including these substances may improve long-term survival of CCA LT patients further.

Moreover, molecular and genetic analysis followed by specific targeting may contribute to improve selection criteria for CCA patients eligible for LT or not. Next generation sequencing displays promising results to identify specific subsets of CCA.45 The hedgehog pathway as well as notch-expression and potential curcumin-treatment have recently been defined as candidates.46,47 Zhu and associates demonstrated that the IL-6/Stat3-miR-17-92 cluster-PTEN signaling axis plays a decisive role in CCA tumor development and progression.48 Fibroblast growth factor receptor 2 fusions and ERRFI gene mutations as well as up-regulation of HER-2 signaling have been identified as relevant genomic targets in some patients.49,50 These findings, however, will have to be translated from the laboratory into clinical practice.

Posttransplant immunosuppression is likely to play a decisive role regarding the risk of CCA recurrence after an LT. The mammalian target of rapamycin (mTOR) inhibitors have been discussed to express potentially antineoplastic effects in the setting of an LT for hepatocellular carcinoma.51 The mTOR complex-1 activation by growth factor-mediated EPH receptor-2 has been proved essential for CCA growth and metastasis, thereby opening a window for potential mTOR-inhibitor treatment.52 However, currently, no reliable long-term data exist. Based on the potential antineoplastic potential of mTOR inhibitors, a study currently going on at the Mayo Clinic is examining the effects of mTOR inhibitor-based immunosuppression on survival after LT for CCA (NCT01888302).

Regarding the currently available data, it becomes quite clear that an LT for CCA is justified both for intrahepatic and hilar tumors in well-selected cases. However, considering the problem of universal organ shortage, surgical resection should be performed wherever possible. Protocols of extended en bloc resection have demonstrated impressive long-term survival.11 This is especially important because definite tumor diagnosis and staging can be difficult: This factor may lead to organ allocation to patients who should not be eligible for an LT, either because their suspected malign tumor proves to be nonmalignant, or already has produced metastatic spread.

Careful patient selection is critical for allocating the scarce resource of liver grafts to patients. Algorithms have been developed to identify these patients53; however, accuracy of diagnostic tools and wait time between diagnosis and LT combine to make this a complex challenge.

Current multicenter studies are underway, which will further clarify which perioperative regimen is most effective. Until this time, it is difficult for the transplant community to draw the line between yes and no to liver transplants for CCA patients.

Intensive patient recruitment is crucial to shed more light on this issue. However, this is a difficult task, as the slow recruitment of the German “product” trial underscores. (The study currently is on
Considering the limited number of eligible patients, it may require more time before a clearer picture is obtained.

References

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