REVIEW

Liver transplantation for intrahepatic cholangiocarcinoma: who, when and how

Pablo Achurra[a,b], *Eduardo Fernandes*[d], *Grainne O'Kane*[c], *Robert Grant*[c], *Mark Cattral*[a] *and Gonzalo Sapisochin*[a]

Purpose of review
Using transplant oncology principles, selected patients with intrahepatic cholangiocarcinoma (iCCA) may achieve long-term survival after liver transplantation. Strategies for identifying and managing these patients are discussed in this review.

Recent findings
Unlike initial reports, several modern series have reported positive outcomes after liver transplantation for iCCA. The main challenges are in identifying the appropriate candidates and graft scarcity. Tumor burden and response to neoadjuvant therapies have been successfully used to identify favorable biology in unresectable cases. New molecular biomarkers will probably predict this response in the future. Also, new technologies and better strategies have been used to increase graft availability for these patients without affecting the liver waitlist.

Summary
Liver transplantation for the management of patients with unresectable iCCA is currently a reality under strict research protocols. Who is a candidate for transplantation, when to use neoadjuvant and locoregional therapies, and how to increase graft availability are the main topics of this review.

Keywords
intrahepatic cholangiocarcinoma, liver transplantation, molecular targeted therapies, neoadjuvant systemic therapy

INTRODUCTION

Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary tumor of the liver, and its incidence and mortality have increased in the last decades [1,2]. Average 5-year overall survival is less than 10% since most patients have advanced or disseminated disease at diagnosis.

R0 liver resection with regional lymphadenectomy is the standard of care for resectable disease, but only 12–40% of the patients can undergo resection. Tumor recurrence occurs in 50–70%, resulting in a 5-year overall survival of 25–40% [3▪▪]. The most common site of recurrence after resection is the liver [4]. It is notable that CCA represents a spectrum of diseases with distinct molecular profiles that are often evaluated together in trials given the low prevalence of CCA.

Transplant oncology is a multidisciplinary field that uses liver transplantation to achieve maximum oncological margins and also treat the underlying liver disease in patients with liver cancers (Table 1). It also incorporates strategies to select patients with favorable tumor biology to focus transplant efforts on the patients who will benefit the most. Tumor burden and response to neoadjuvant treatments are some of these strategies. The use of transplant oncology principles has achieved long-term survival in selected patients with hepatocellular carcinoma (HCC), perihilar-CCA, iCCA, metastatic neuroendocrine tumors, and colorectal cancer liver metastases (CRLM) [5,6▪▪,7].

[a]Department of Abdominal Transplant and HPB Surgical Oncology, Toronto General Hospital, University of Toronto, [b]Department of Digestive Surgery, Pontificia Universidad Catolica de Chile, Santiago, Chile, [c]Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada and [d]Department of Surgery and Abdominal Organ Transplantation - São Lucas Hospital Copacabana, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Correspondence to Gonzalo Sapisochin, MD, PhD, MSc, Associate Professor of Surgery, Abdominal Transplant & HPB Surgical Oncology, Toronto General Hospital, University of Toronto, Toronto, ON M5G2C4, Canada.
E-mail: Gonzalo.sapisochin@uhn.ca

Curr Opin Organ Transplant 2024, 29:000–000
DOI:10.1097/MOT.0000000000001136

1087-2418 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

KEY POINTS

- Early studies of liver transplantation in intrahepatic cholangiocarcinoma (iCCA) described very poor outcomes. However, recent series have reported 5-year survivals of 50–70% in selected patients.
- The best outcomes are achieved in cirrhotic patients with very early tumors (<2 cm) and patients with locally advanced tumors with good response to neoadjuvant therapies.
- A wide combination of neoadjuvant systemic therapies, locoregional procedures, and targeted therapies have been used in the reported series.
- Machine perfusion, living donor transplantation, use of marginal grafts, Domino transplantation, and auxiliary liver transplantation are some of the currently developed strategies to increase graft availability for transplant oncology cases.

Graft scarcity continues to be a limitation for the wide development of this field. From a patient's perspective, transplantation may be desirable if it improves survival or quality of life compared to the best alternative treatment available. Conversely, from a population perspective, outcomes for any new indication for transplant must be similar to noncancer indications. In cancer patients, 60% survival at 5 years has been considered the minimal standard after transplant [6▪▪]. However, this ultimately depends on the local waitlist laws and dynamics.

In the field of iCCA, early studies demonstrated very poor outcomes after liver transplantation with a 2-year survival of less than 30%. These studies were difficult to interpret due to heterogeneity; most series included early and advanced cases, iCCA and perihilar-CCA, as well as patients with and without liver cirrhosis (Table 2). Also, the number of patients at risk in most series was small. Based on these studies, most countries consider iCCA a contraindication for liver transplantation. However, in recent years, with better patient selection and the use of neoadjuvant therapies, the results of liver transplantation have improved with a reported 5-year survival of 50–73% [8▪▪]. Indeed, some patients with iCCA can achieve long-term survival after liver transplantation, but determining the best strategy to select these patients remains unclear. Who is a potential liver transplantation candidate? When should selected patients undergo liver transplantation? and how to access liver grafts are currently the main controversies in liver transplantation for iCCA.

Table 1. Principles of transplant oncology

1. LT extends conventional oncologic margins, but disease must be confined to the liver
2. LT efficacy is increased with favorable tumor biology. Response to systemic and locoregional treatments is a good selection tool.
3. Minimal inclusion/exclusion criteria need to be defined *a priori*
4. Transplant appropriateness should be pursued balancing individual vs. community benefit, maximizing graft utility
5. Balance immune regulation to achieve graft tolerance and prevent tumor recurrence.
6. Rule out extrahepatic disease, one of the main risk factors for recurrence.

Who - same diagnosis, different scenarios

Liver transplantation for iCCA has been described in two settings. The first one is in cirrhotic patients with unresectable iCCA, mainly due to liver decompensation. The second one is when the iCCA is technically unresectable, mostly in cases of healthy livers with large or multifocal tumors [9▪▪].

Cirrhotic patients with incidental or 'very early' (≤2 cm) tumors

Most data come from retrospective studies of liver transplantation done for misdiagnosed HCC or from iCCA incidentally found in explanted livers transplanted for other noncancer indications. These cases are usually small tumors without vascular invasion. Since 2000, multiple heterogeneous series have been published and are summarized in Table 2 [10–13]. These retrospective studies helped identify the subgroup of patients that had long-term survival. Patients with 'very early' iCCA, defined as single tumors 2 cm or less, have the best outcomes with a 5-year survival of 65%. Importantly, survival was better in very early iCCA found incidentally on explant compared to when they were identified prior to the liver transplantation (53 vs. 80% 5-year survival) [9▪▪,14]. A recent meta-analysis confirmed that patients with very early iCCA had superior 5-year recurrence-free survival post-liver transplantation compared to advanced iCCA (67 vs. 34%) [11].

Noncirrhotic patients with locally advanced disease

Noncirrhotic patients with iCCA who are candidates for liver transplantation are considered unresectable and thus, have locally advanced or multifocal bilobar disease. In general, these patients have a poor prognosis, but there is a subgroup of patients with

Table 2. Recently reported outcomes after liver transplantation for intrahepatic cholangiocarcinoma

Incidental or missdiagnosed as HCC

Study (year of publication)	Patients included	Tumor type	Study design	Patients with cirrhosis	OS for VE tumors	Recurrence rate	RFS for VE tumors	Chemotherapy treatment	LRT
Sapisochin *et al.* (2014) [26]	Eight patients VE 21 patients LA	Incidental or misdiagnosed HCC	Retrospective	100%	3 years: 73% 5 years: 73%	3 years: 0% 5 years: 0%	NA	None	Yes (44.8%)
Sapisochin *et al.* (2016) [20]	15 patients VE 33 patients LA	Incidental or misdiagnosed HCC	Retrospective	100%	3 years: 84% 5 years: 65%	3 years: 18% 5 years: 18%	NA	None	Yes (46%)
Jung (2017) [62]	4 patients VE 12 patients LA	Incidental or misdiagnosed HCC iCCA and mixed type iCCA/HCC	Retrospective	13%	3 years: 52%[a] 5 years: 52%[a]	3 years: 56%[a] 5 years: 78%[a]	NA	None	Yes (93%)
De Martin (2020) [82]	25 patients VE	Incidental or misdiagnosed HCC iCCA and mixed type iCCA/HCC	Retrospective, multicenter	100%	3 years: 87%[a] 5 years: 69%[a]	NA	3 years: 69%[a] 5 years: 55%[a]	NA	NA
Vallin (2013) [83]	10 patients	Incidental or misdiagnosed HCC iCCA and mixed type iCCA/HCC	Retrospective, multicenter	NA	5 years: 24%[a]	3 year: 50%[a]		None	None
Hara (2021) [65]	19 patients	Incidental or misdiagnosed HCC	Retrospective, multicenter	100%	3 years: 63%[a] 5 years: 46%[a]	NA	3 years: 75% 5 years: 75%	NA Yes (8%)	
Lee (2018) [24]	17 patients iCCA (12 VE) 27 iCCA/HCC	Incidental or misdiagnosed HCC iCCA and mixed type iCCA/HCC	Retrospective	NA	5 years: 63.6%[a]	33%[a]		None	Yes (82%)
Huang (2023) [46]	10 patients	Very early and cirrhosis	Retrospective SEER database	100%	5 years: 43.8%	NA	NA	None	NA

Locally advanced with neoadjuvant treatment

Study (year of publication)	Patients included	Tumor type	Study design	pre-LT diagnosis?	OS	RFS	Chemotherapy treatment	Comments
Hong (2011) [45]	38	iCCA and hCCA	Retrospective, single center		3 years: 38% 5 years: 32%		Yes	
Fu (2011) [43]	11	iCCA	Retrospective, single center		3 years: 50%		Yes	
Lunsford *et al.* (2018) [18]	6 patients	>2 cm or multifocal iCCA	Prospective protocol.	Yes	3 years: 83% 5 years: 83%	3 years: 50% 5 years: 50%	Yes, neoadjuvant and adjuvant	MMAJCCC group
Ito *et al.* (2022) [28]	31 patients iCCA 22 patients hCCA	Mixed, 71% had tumors larger than $\geq$ 5cm	Retrospective. Single center.	Yes in 42% of the cases	3 years: 63% 5 years: 49%	5 years: 42%	Yes, neoadjuvant and locoregional therapies. Adjuvant therapy.	UCLA retrospective study.
McMillan *et al.* (2022) [47]	18 patients	>2 cm or multifocal iCCA	Prospective protocol.	Yes	3 years: 71% 5 years: 57%	3 years: 52%	Yes, neoadjuvant and adjuvant	MMAJCCC group
Huang *et al.* (2023) [46]	31 patients with iCCA	Locally advanced + chemotherapy	Retrospective, database	NA	5 years: 61.7%	NA	Yes	SEER database analysis

hCCA, hilar cholangiocarcinoma; iCCA, intrahepatic chonalgiocarcinoma; LA, locally advanced; NA, non available; VE, very early.
[a]Includes mixed data from iCCA/HCC and VE and LA.

1087-2418 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

CE: ; MOT/290207; Total nos of Pages: 11;
MOT 290207

favorable biology and sustained liver-confined disease after neoadjuvant therapy that may benefit from liver transplantation, leading to the development of treatment protocols (Table 2). The largest prospective series is from the Methodist-MD Anderson Joint Cholangiocarcinoma Collaborative Committee (MMAJCCC) that reported a 5-year survival of 57% after liver transplantation in 18 highly selected patients. Tumor burden and response to neoadjuvant therapy are often surrogates of tumor biology in this setting. In addition, some genetic alterations (FGFR and DNA damage repair pathways) have been associated with less aggressive disease, a superior response to first-line chemotherapy, and improved overall survival [15▪▪].

Special considerations

Primary sclerosing cholangitis

PSC is a predisposing factor for the development of CCA with a lifetime risk of 5–20% [14]. Death attributed to PSC is increased nearly four-fold when compared to the general population, and the leading causes of death are cancer and liver failure [16]. Whole-genome sequencing of PSC-associated CCA suggests that specific mutational alterations (TP53) and mutational signatures (substitution base signature 17) occur in the inflamed liver and correlate with short-term survival [17]. Similar to non-PSC patients with iCCA, the literature is limited to reports from incidentally diagnosed tumors on liver explants, very-early (<2 cm) iCCA, and a few case reports of patients with advanced disease [11,18]. PSC patients may have higher MELD due to the underlying liver disease and may access standard criteria deceased donor grafts. Three patients with PSC and advanced iCCA underwent neoadjuvant therapy and transplant in the MMAJCCC series. In our current Toronto prospective study (NCT04195503; https://clinicaltrials.gov/) [19], PSC is not an exclusion criterion and having PSC does not change the neoadjuvant treatment and evaluation strategy.

Multifocal disease

Multifocal disease is seen in nearly 50% of iCCA patients and has been associated to increased risk of recurrence and death. Some authors consider multifocality as metastatic disease [20], a contention supported by phylogenic genomic analyses showing most multifocal nodules within a patient share a common ancestor [21]. Liver resection is not recommended in most cases [3▪▪,22]. However, in strictly selected patients who underwent liver transplantation after neoadjuvant chemotherapy, multifocal disease was not associated with worse survival, suggesting that tumor biology is more important than tumor burden [8▪▪,18]. Recently, a case of urgent re-transplantation after donor transmission of an iCCA was reported. The diagnosis of multifocal iCCA was done during the post reperfusion ultrasound, frozen section biopsies were obtained, and the patient underwent re-transplantation 48 h later [23].

Recurrence after resection

The liver is the most frequent site of recurrence following liver resection, and recurrence is associated with worse survival. Patient outcomes can be improved with repeated surgery if an R0 resection is achievable [9▪▪]. Liver transplantation as salvage therapy after recurrence has also been reported. Three patients in the MMAJCCC series had recurrent disease after anatomic resections and were included in the protocol if they achieved disease stability after 6 months of systemic therapy.

Current prospective studies

Currently, there are three ongoing prospective trials registered in the National Clinical Trial (NCT) database.

The first one is a multicenter trial (NCT02878473) (https://clinicaltrials.gov/). The protocol includes cirrhotic patients with a nonresectable single 2 cm or less iCCA. Patients must not have extrahepatic disease, no vascular invasion, and a CA19–9 of 100 ng/ml or less. Recruitment of patients has been very challenging for a variety of reasons. Indeed, identifying patients with single small tumors is difficult and the need to undergo a tumor biopsy, with the risk of not achieving exception points (if the tumor proves to be iCCA rather than HCC), limits the opportunities to adopt this strategy. The trial remains open at this time.

The second phase 2 study is a single-center trial in UHN, Toronto (NCT04195503; https://clinicaltrials.gov/. Patients with histologically proven iCCA without extrahepatic disease, no vascular invasion, and no lymph node involvement. These patients must demonstrate stable disease after at least 6 months of systemic chemotherapy and/or locoregional treatment. Patients who had previous surgical resection for iCCA are eligible if surgery occurred more than 6 months prior to listing, and patients must have at least 6 months of disease stability or response on systemic therapy. Patients with multifocal disease are also eligible if they comply with the above criteria. Patients receive grafts only from living donors.

The third study is the Oslo University, phase II TESLA Trial (NCT04556214; https://clinicaltrials.gov/). This includes patients with histologically proven iCCA, without extrahepatic disease, no vascular invasion, and no lymph node involvement. Patients must have stable disease after at least 6 months of systemic chemotherapy and/or locoregional treatment.

When: patient selection improves outcomes

Tumor burden, response, and stability after neoadjuvant chemotherapy or locoregional therapies, and the use of biomarkers are currently the main strategies for patient selection.

Tumor burden

In iCCA, the 8th edition of the AJCC staging includes size, number, and vascular invasion as the main prognostic factors for locally advanced tumors and this has been validated in large retrospective studies [24,25▪].

In a multicentric retrospective study of incidental iCCA, patients with very-early (≤2 cm) iCCA who underwent liver transplantation had better outcomes when compared to patients with more advanced disease [26]. Patients with very-early iCCA had a 5-year actuarial survival of 65% compared to 45% in patients with single tumors larger than 2 cm or multifocal disease ($P = 0.02$). Correspondingly, the subgroup analysis of the patients with advanced disease reported that the 5-year survival rate of intermediate-sized tumors (2–3 cm) was 61% compared to 42% for larger tumors (>3 cm) [20]. Several studies around the world reported similar results for liver transplantation on iCCA [24,27]. However, in patients with advanced disease treated with neoadjuvant therapies, the tumor size had no impact on survival outcomes [15▪▪,28]. These results suggest response to neo-adjuvant therapies is a stronger prognostic factor than tumor size or number.

Locoregional therapies

Different loco-regional therapies (LRT) have been developed in recent years. The early arterial enhancement of iCCA on imaging suggests that hepatic artery treatments may improve tumor response to treatment. Hepatic arterial infusion (HAI) chemotherapy, trans-arterial chemoembolization (TACE), and trans-arterial radioembolization (TARE) with yttrium Y-90 have been described. Thermal ablation has also been reported for the treatment of iCCA. The evidence to recommend these treatments is scarce and relies mainly on retrospective studies. Recent reviews offer a comprehensive description of the literature in this field [8▪▪,29,30▪▪].

Thermal ablation is a treatment approach for cirrhotic patients with small (<2 cm), unresectable iCCA. In a recent systematic review and pooled analysis of 645 patients, ablation response rate was 94%, with a mean OS of 30 months [31▪▪]. However, the infiltrative growth pattern, and lack of lymphadenectomy, lead to a disappointing progression-free survival of less than 12 months, and therefore cannot be recommended.

Conventional lipiodol and drug-eluting beads TACE has been reported in iCCA. Studies have also used different chemotherapeutic agents with significant heterogeneity. A pooled analysis of 1145 patients reported a response rate was 26% and OS of 15.9 months [31▪▪]. TARE also represents a treatment option for primary or recurrent unresectable iCCA. A systematic review and meta-analysis of 921 patients with TARE reported an overall disease-control rate of 82% and an OS of 12.7 months. Interestingly, 11% of the cases were downstaged to surgical resection [30▪▪].

The role of external beam radiotherapy (EBRT) in the treatment of iCCA is also uncertain. Most studies include patients treated with multiple modalities. A pooled analysis of 541 patients reported a local control rate of 69% with an OS of 18.9 months [31▪▪].

Ablation, TACE, TARE, and EBRT have all been used for oncological control before liver transplantation [28]. Unfortunately, the significant heterogeneity in the available literature precludes the development of strong recommendations for selecting one LRT over another (Table 2).

In a recent systematic review and meta-analysis of 154 patients with iCCA treated with HAI chemotherapy with floxuridine, the 3-year OS was 39.5%. Interestingly, in one of the included studies from Memorial Sloan Kettering Cancer Center (MSKCC), 8% of the patients were downstaged and resected. Biliary sclerosis is a known complication of HAI therapy, and some patients with ICC have been transplanted for this complication [32,33]. At the University of Toronto, we have transplanted patients with living donor liver grafts who have had a good response to HAI chemotherapy for colorectal liver metastases. The hepatic artery reconstruction can be challenging in this setting because the HAI chemotherapy can damage the intimal layer of the proper hepatic artery and necessitate reconstruction with arterial jump grafts [34▪]. Challenging dissection and atypical arterial anastomosis have also been described when using deceased donor liver grafts [33].

1087-2418 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Neoadjuvant systemic therapies and future molecular targeted therapies

Neoadjuvant chemotherapy has three main theoretical benefits: tumor downstaging to increase resectability and/or increase the R0 resection rate; treatment of micro-metastatic disease; and evaluation of tumor biology to identify patients who would likely not benefit from surgery. These theoretical advantages have been demonstrated in small retrospective case series, but no level 1 evidence exists. Several recent guidelines with review of the evidence and recommendations have been published (Fig. 1) [35–37].

Gemcitabine-based regimens are the current standard of care. The pivotal ABC02 study demonstrated an OS of 11.5 months for gemcitabine-cisplatin when compared to 8.1 months for gemcitabine alone. Recently, combining chemotherapy with immune checkpoint inhibition (ICI) has become the front-line standard of care based on results from the TOPAZ-01 trial (durvalumab, anti-PD-L1) and more recently with KEYNOTE-993 (pembrolizumab, anti-PD-1) [30▪▪,38]. This is noteworthy as the evidence for the safety and timing of ICI pretransplant continues to emerge [39].

Multiple targeted therapies can be used after front-line therapy for up to 40% of patients whose cancers harbor targetable alterations [40▪▪,41], in particular FGFR2 fusions, mutations in IDH1, BRAF, ERBB2, and BRCA1/2. In addition, HER2 amplified CCA and mismatch repair deficient CCA are highly actionable. The role of these treatments earlier in the disease course is still under investigation. Moreover, the presence of an IDH1/2 mutation or FGFR2 fusion may have a prognostic impact dictating favorable disease biology [42].

Neoadjuvant therapy for selection of locally advanced unresectable intrahepatic cholangiocarcinoma

Several small series reported improved survival for patients undergoing liver transplantation after neoadjuvant therapy [43–45]. Based on these reports, more recent retrospective studies demonstrated that neoadjuvant therapy improved survival after liver transplantation in patients with CCA regardless of tumor size [28]. Another recent propensity score-matched analysis of the SEER database reported a 5-year OS of 61.7% in 31 patients with locally advanced disease who had chemotherapy and underwent liver transplantation [46].

The only published prospective study with a clearly defined protocol for patients with locally advanced iCCA is the MMAJCCC. Patients with a solitary tumor at least 2 cm or multifocal disease were included in the protocol. Patients with lymph node or distant metastases and patients with

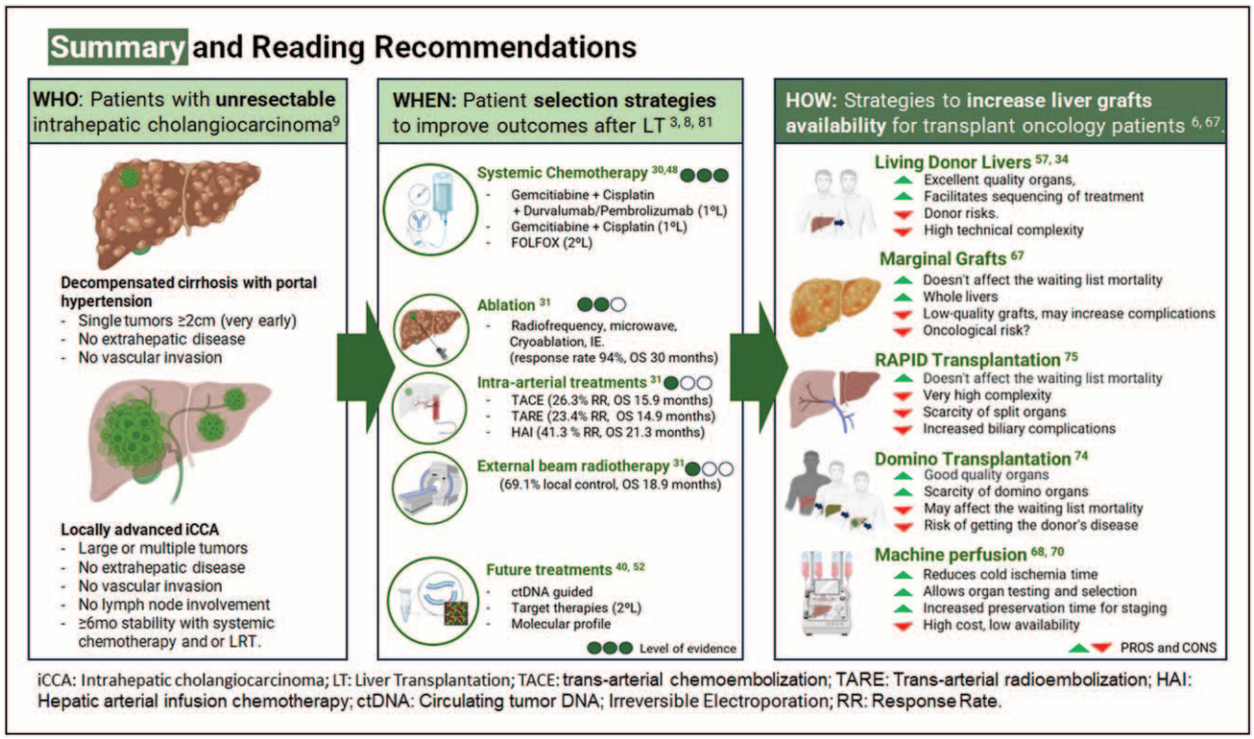


FIGURE 1. Summary and reading recommendations.

involvement of major vascular structures were excluded. The diagnosis was confirmed by percutaneous biopsy. All patients underwent neoadjuvant first-line therapy with Gemcitabine-based chemotherapy. Subsequent lines of therapy, including LRT, EBRT, and target therapies, were employed under the recommendation of a multidisciplinary hepatobiliary tumor board. Overall survival at 1, 3, and 5 years was 100, 71, and 57% in the 18 patients that completed the protocol and underwent liver transplantation. Out of seven patients with recurrence, two patients had extrahepatic disease in the retrospective analysis of pre-liver transplantation imaging; and two patients had positive microscopic margins after resection, highlighting the challenges of patient selection [5,18,47,48▪].

Predictive models and biomarkers

Given the scarcity of liver grafts, liver transplantation should be offered only to patients with the best-predicted outcomes. Better prognostic models, improved knowledge of histopathology, and new biomarkers may help predict biological behavior and guide therapy [49].

Biomarkers like serum carbohydrate antigen 19–9 (Ca 19-9) can be prognostic factors for cholangiocarcinoma and can also be used to measure response to neoadjuvant treatments. New biomarkers are being developed in urine, bile, and serum [50]. Most of these biomarkers have been used to identify de-novo CCA in PSC patients, and their role in the follow-up of cancer treatment, although promising, is still unknown [49].

Molecular differences between tumors, epigenetic alterations, and proteomics have been described recently [40▪▪,51]. Liquid biopsy using circulating tumor DNA (ctDNA) can determine the molecular profile of the tumors, screen for cancer recurrence, and also evaluate response to treatment, guiding the selection of targeted therapies [52▪]. Ultimately, multimodal machine learning systems combining clinical, radiological, pathological, and genomic features may offer the strongest predictions for benefit from liver transplantation [53] (Fig. 2).

How: Strategies to increase graft availability

The shortage of suitable donor organs is still the main barrier to the development and expansion of

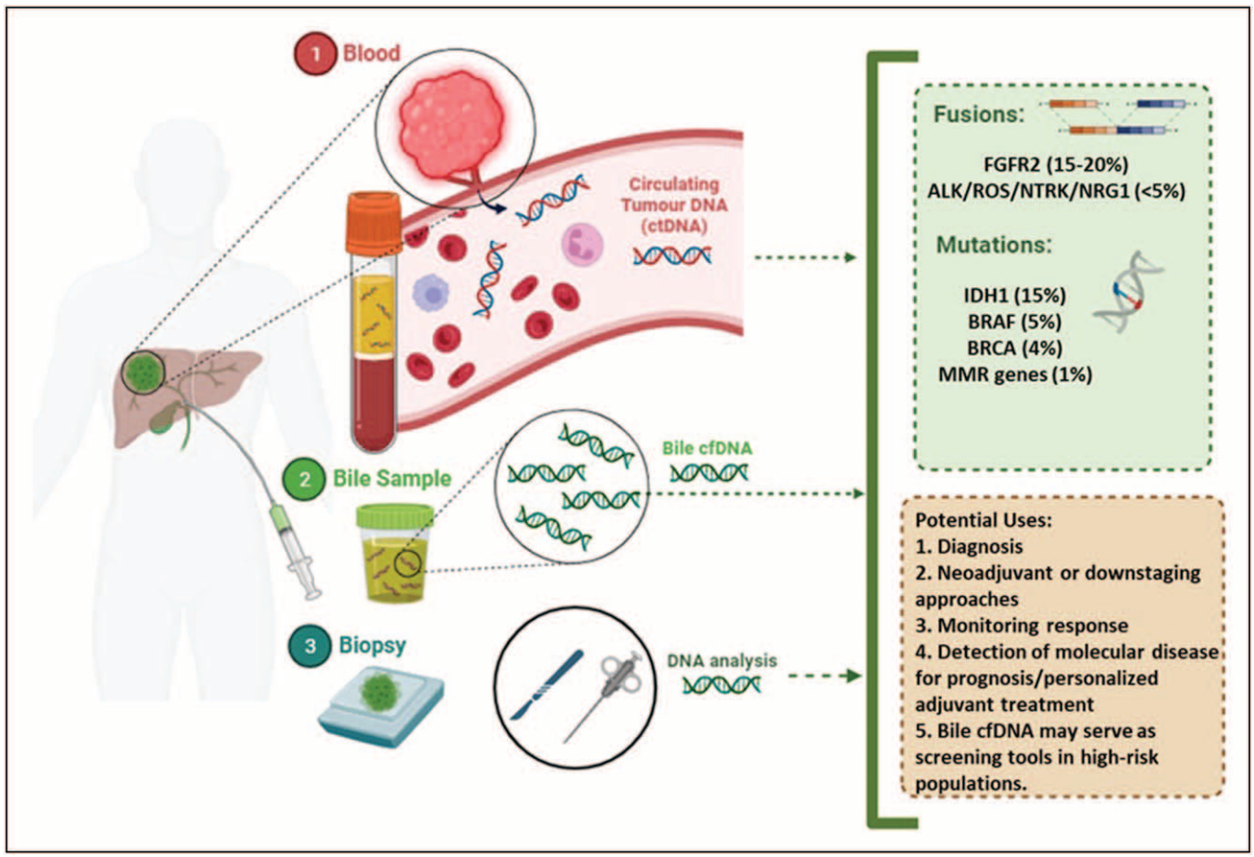


FIGURE 2. The next frontier in biomarkers for intrahepatic chonalgiocarcinoma.

1087-2418 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Transplant Oncology. The significant mortality on the waiting list worldwide limits patient selection, reserving liver transplantation for the patients who will benefit the most and leaving behind many patients with potentially high survival outcomes. In this scenario, some have argued that iCCA should still be a contraindication for liver transplantation, mainly because of organ scarcity [54▪].

New strategies to increase the number of liver grafts are essential to expand liver transplantation indications. Living donor liver transplant (LDLT), the use of marginal grafts, normothermic machine perfusion, domino livers, and the RAPID procedure are the main strategies to obtain liver grafts to transplant patients with extended oncological criteria.

Living donor liver transplantation

In North America, one out of six patients die on the waiting list every year. Living-donor liver transplantation provides an alternative without affecting the organ-scarce waiting list and thus reducing mortality. Outcomes after living donor liver transplant are comparable, if not better, to those after a deceased donor liver transplant. For some transplant oncology indications (CRLM, hCCA, and iCCA), LDLT also facilitates coordination with oncology, timing of chemotherapy, and completing the study of the recipient [55]. For example, in Toronto, selected patients with CRLM discontinue neoadjuvant therapy 6 weeks before transplant and also undergo a staging laparotomy 1 week before the scheduled transplant day [56,57▪].

LDLT offers a unique source of liver grafts different from the deceased donor pool that are not available to the general waiting list. In Europe and in most centers of North America, living donor grafts have a marginal role, representing fewer than 10% of all transplants [58]. On the other hand, living donors are the main source of liver grafts in Asian centers, and they have expanded the criteria for the treatment of HCC. However, the donor risk is a crucial part in decision making and should be balanced against the predicted benefit of the recipient, a concept known as double equipoise [6▪▪,59].

Most studies report similar or better outcomes with LDLT when compared to DDLT, and there is a clear waitlist survival advantage [60,61]. Most series with LDLT for iCCA were incidental findings on pathology [62–65]. Hafeez Bhatti *et al.* [62] recently published a series of 16 patients who underwent a LDLT and had incidental iCCA. Seven patients had bridging therapy with LRT (the disease was misdiagnosed as HCC), and overall 3-year recurrence-free survival was 47%. The subgroup of patients with well moderately differentiated tumors had 64% 3-year recurrence-free survival [63].

LDLT can sometimes be very challenging. The main technical caveats of this approach are related to the extension of the liver resection to achieve R0 margins. The IVC commonly needs resection, and the hepatic artery and portal vein are sometimes short for the reconstruction of right lobe living donor grafts. If a jump graft is needed, we recommend to use deceased donor vessels when available (infrarenal IVC, iliac arteries, and veins; Fig. 3).

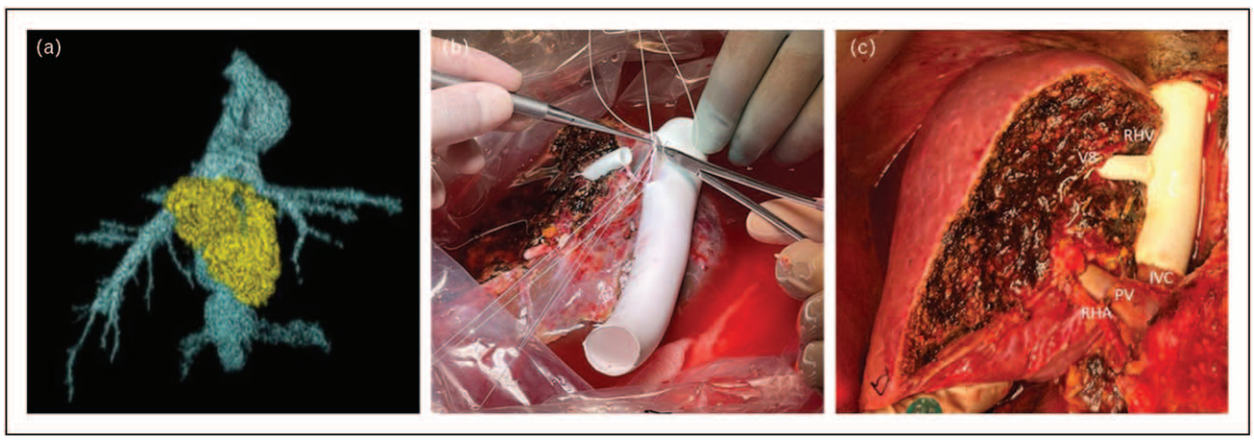


FIGURE 3. Technical challenges in living donor liver transplant for intrahepatic cholangiocarcinoma. A 54-year-old woman, presented with a 10 cm iCCA with vena cava involvement, unresectable due to important vascular involvement and small future liver remnant. After eight cycles of neoadjuvant chemotherapy with Gemcitabine-Cisplatin and Durvalumab, she underwent a LDLT with cava replacement. (a) 3D reconstruction of the tumor invasion of the IVC. (b) Reconstruction of the IVC with PTFE in the backtable. (c) Final liver implant. IVC, inferior vena cava; PV, Portal vein; RHA, Right hepatic artery; RHV, right hepatic vein; v8, segment 8 vein.

CE: ; MOT/290207; Total nos of Pages: 11;
MOT 290207

Marginal grafts

More than 20% of liver allografts from deceased donors intended to be transplanted are discarded. These marginal allografts historically demonstrated worse allograft and patient outcomes compared with nonmarginal allografts. However, selective use of marginal allografts in high-volume centers bolsters donor supply and reduces waitlist mortality [66].

Marginal livers are mainly composed of older donor livers (70 years or older); donation after circulatory death (DCD) grafts, and steatotic livers [67▪]. Many times, we consider that patients are oncologically too stable to receive a high-risk organ, but for extended oncological indications, this may be their only option. Marginal grafts are very sensitive to cold ischemia. One large UNOS database study found that outcomes for marginal allografts could approach those from benchmark allografts when cold ischemia time was minimized [66].

The use of marginal donors ('livers that nobody wants') is one of the main strategies to provide grafts for extended oncological indications without negatively impacting the patients on the current waiting list. In the MMAJCCC prospective experience of liver transplantation in ICCA, marginal grafts were the main source of livers with 100% survival at 1 year [15▪▪] Many patients with iCCA do not have portal hypertension and other comorbidities and may be able tolerate better the early graft dysfunction (EGD) that can occur with marginal grafts. Notably, 'marginal' livers are increasingly being used for standard liver transplantation indications to reduce waitlist mortality; thus, currently discarded grafts likely pose the highest risk of EGD [15▪▪,68▪,69].

Machine perfusion

Normothermic machine perfusion (NMP) increases preservation time, reduces cold ischemia, and also allows for assessing the viability of organs in ex-vivo conditions [68▪]. The use of normothermic machine perfusion in marginal grafts resulted in a 50% lower discard rate in a recent randomized control trial [69]. The increase in preservation time is very important for high-risk recipients like transplant oncology cases [68▪,70▪]. NMP increases preservation time for the staging laparotomy, frozen section sampling, dissection of adhesions, and preparation for complex vascular reconstructions. Up to one-third of the patients with resectable disease on imaging will have occult metastatic or locally advanced disease during diagnostic laparotomy [70▪,71]. In the MMAJCCC series, two patients were aborted during transplant due to extrahepatic disease, and two had positive microscopic margins. The use of NMP enhances transplant logistics without compromising the liver graft and gives time to reallocate the graft to a backup recipient. There is also growing evidence that ischemia-reperfusion injury after liver transplantation can trigger a series of inflammatory cascades and microvascular dysfunction that may promote cancer recurrence [72,73]. Liver perfusion technology may help rescue and reduce ischemia-reperfusion injury of marginal livers.

Domino liver transplantation

Domino liver transplantation involves transplanting the liver from a patient with metabolic disease into a patient with end-stage liver disease with the expectation that the recipient will develop minimal metabolic symptoms due to extrahepatic compensation. The metabolic disease patient can get a deceased or living donor graft and will donate his whole liver to a potential recipient. These higher-risk grafts have been used in oncological patients with positive long-term outcomes [74].

Auxiliary partial orthotopic liver transplantation and RAPID procedure

Auxiliary liver transplantation techniques have been proposed as an option for increasing the number of grafts [75▪]. The RAPID concept is a fusion of the APOLT (Auxiliary partial orthotopic liver transplantation) and the ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) [76]. The RAPID procedure consists of a two-step procedure: in step 1, a left hepatectomy is followed by a partial liver segment 2-3 (left lateral segment) transplantation and right portal vein ligation in the recipient's liver. As soon as the transplanted graft has reached sufficient volume and function, the second step of the procedure is performed, resecting the residual diseased right liver lobe [77]. It has been described with left lateral segment grafts from split deceased donor livers or from living donors [78]. This strategy reduces the risk of small-for-size syndrome when using small grafts in adult recipients.

The main drawbacks of RAPID livers are the scarcity of deceased donor grafts that can be split, the increased risk of biliary complications, and the high complexity of the procedure. There is also a possible risk of tumor dissemination and increased growth of the malignant disease secondary to immunosuppressive therapy during the 2–4 weeks of the liver regeneration phase [79,80]. Also, most recipients reported so far had CRLM, were not cirrhotic, and had good liver function prior to transplantation.

1087-2418 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

CE: ; MOT/290207; Total nos of Pages: 11;
MOT 290207

CONCLUSION

It is a clear that some patients with iCCA may achieve long-term survival after liver transplantation [81]. The main limitations are the challenges in identifying appropriate candidates and graft scarcity. Future growth will depend on better selection tools and strategies to increase the availability of grafts. Until then, liver transplantation for iCCA should be performed under strict research protocols with stringent inclusion criteria.

Acknowledgements

None.

Financial support and sponsorship

This project received no funding.

Conflicts of interest

Gonzalo Sapisochin is a Consultant for Integra, AstraZeneca, Roche, and Heparegenix. Pablo Achurra has nothing to declare.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Von Hahn T, Ciesek S, Wegener G, *et al.* Epidemiological trends in incidence and mortality of hepatobiliary cancers in Germany. Scand J Gastroenterol 2011; 46:1092–1098.
2. Van Dyke AL, Shiels MS, Jones GS, *et al.* Biliary tract cancer incidence and trends in the United States by demographic group, 1999-2013. Cancer 2019; 125:1489–1498.
3. ■■ Alvaro D, Gores GJ, Walicki J, *et al.* EASL-ILCA Clinical Practice Guidelines on the management of intrahepatic cholangiocarcinoma. J Hepatol 2023; 79:181–208.

EASL-ILCA most recent evidence-based guidelines on the management of intrahepatic cholangiocarcinoma. Includes recommendations for diagnosis, prognosis, surgical, and medical management of iCCA.

4. Choi WJ, Williams PJ, Claasen MPAW, *et al.* Systematic review and meta-analysis of prognostic factors for early recurrence in intrahepatic cholangiocarcinoma after curative-intent resection. Ann Surg Oncol 2022; 29:4337–4353.
5. Ivanics T, Toso C, Ilyas SI, Sapisochin G. Transplant oncology in locally advanced intrahepatic cholangiocarcinoma: one more step on a long road. Am J Transplant 2022; 22:685–686.
6. ■■ Sapisochin G, Hibi T, Toso C, *et al.* Transplant oncology in primary and metastatic liver tumors: principles, evidence, and opportunities. Ann Surg 2021; 273: 483–493.

Principles, evidence, and opportunities of transplant oncology. This study describes the field, its main objectives, challenges and provides the framework of the main topics of future discussion in this new field of transplantation.

7. Liver and Intestinal Organ Transplantation Committee. Briefing to the OPTN Board of Directors on updating national liver review board guidance and policy clarification. Organ Procurement and Transplantation Network. Washington, DC: US Department of Health & Human Services; 2021.
8. ■■ Sapisochin G, Ivanics T, Heimbach J. Liver Transplantation for intrahepatic cholangiocarcinoma: ready for prime time? Hepatology 2022; 75:455–472.

A comprehensive review that describes the most common scenarios to offer LT for iCCA. Focuses on alternative treatment options such as liver directed therapies, liver resection, and systemic therapy.

9. ■■ Mazzaferro V, Gorgen A, Roayaie S, *et al.* Liver resection and transplantation for intrahepatic cholangiocarcinoma. J Hepatol 2020; 72:364–377.

Surgical review focused on the treatment of iCCA. It includes a description and comments about surgical strategies for resection, recurrence management, downstaging strategies, and liver transplantation.

10. Goldaracena N, Gorgen A, Sapisochin G. Current status of liver transplantation for cholangiocarcinoma. Liver Transpl 2018; 24:294–303.
11. Ziogas IA, Giannis D, Economopoulos KP, *et al.* Liver transplantation for intrahepatic cholangiocarcinoma: a meta-analysis and meta-regression of survival rates. Transplantation 2021; 105:2263–2271.
12. Schaefer B, Zoller H, Schneeberger S. Con: liver transplantation for expanded criteria malignant diseases. Liver Transpl 2018; 24:104–111.
13. Sun D, Lv G, Dong J. Liver transplantation for intrahepatic cholangiocarcinoma: what are new insights and what should we follow? Front Oncol 2022; 11:841694.
14. Takakura WR, Tabibian JH, Bowlus CL. The evolution of natural history of primary sclerosing cholangitis. Curr Opin Gastroenterol 2017; 33:71–77.
15. ■■ McMillan RR, Javle M, Kodali S, *et al.* Survival following liver transplantation for locally advanced, unresectable intrahepatic cholangiocarcinoma. Am J Transplant 2022; 22:823–832.

Largest single-center experience of liver transplantation in patients with iCCA after neoadjuvant therapy.

16. Boonstra K, Weersma RK, van Erpecum KJ, *et al.* Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. Hepatology 2013; 58:2045–2055.
17. Holzapfel N, Zhang A, Choi WJ, *et al.* Whole-genome sequencing of 20 cholangiocarcinoma cases reveals unique profiles in patients with cirrhosis and primary sclerosing cholangitis. J Gastrointest Oncol 2023; 14:379–389.
18. Lunsford KE, Javle M, Heyne K, *et al.* Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. Lancet Gastroenterol Hepatol 2018; 3:337–348.
19. https://clinicaltrials.gov/.
20. Sapisochin G, Facciuto M, Rubbia-Brandt L, *et al.* Liver transplantation for 'very early' intrahepatic cholangiocarcinoma: international retrospective study supporting a prospective assessment. Hepatology 2016; 64:1178–1188.
21. Chen S, Xie Y, Cai Y, *et al.* Multiomic analysis reveals comprehensive tumor heterogeneity and distinct immune subtypes in multifocal intrahepatic cholangiocarcinoma. Clin Cancer Res 2022; 28:1896–1910.
22. Lamarca A, Santos-Laso A, Utpatel K, *et al.* Liver metastases of intrahepatic cholangiocarcinoma: implications for an updated staging system. Hepatology 2020; 73:2311–2325.
23. Fernandes E. de SM, Almeida TRR de, Correa RR, *et al.* Urgent liver retransplantation due to transmission of intrahepatic cholangiocarcinoma by donor: the first report in the literature. Arq Bras Cir Dig 2023; 36:e1740.
24. Lee AJ, Chun YS. Intrahepatic cholangiocarcinoma: the AJCC/UICC 8th edition updates. Chin Clin Oncol 2018; 7:52.
25. ■ Buettner S, Van Vugt JLA, IJzermans JNM, Koerkamp BG. Intrahepatic cholangiocarcinoma: current perspectives. In: OncoTargets and therapy. Vol. 10. Dove Medical Press Ltd; 2017:; 1131–1142.

Short summary covering incidence factors, peroperative workup, surgical and medical management strategies for iCCA.

26. Sapisochin G, Rodríguez De Lope C, Gastaca M, *et al.* very early' intrahepatic cholangiocarcinoma in cirrhotic patients: should liver transplantation be reconsidered in these patients? Am J Transplant 2014; 14:660–667.
27. Sakamoto Y, Kokudo N, Matsuyama Y, *et al.* Proposal of a new staging system for intrahepatic cholangiocarcinoma: analysis of surgical patients from a nationwide survey of the Liver Cancer Study Group of Japan. Cancer 2016; 122:61–70.
28. Ito T, Butler JR, Noguchi D, *et al.* A 3-decade, single-center experience of liver transplantation for cholangiocarcinoma: impact of era, tumor size, location, and neoadjuvant therapy. Liver Transplant 2022; 28:386–396.
29. Owen M, Makary MS, Beal EW. Locoregional therapy for intrahepatic cholangiocarcinoma. Cancers (Basel) 2023; 15:2384.
30. ■■ Mauro E, Ferrer-Fàbrega J, Sauri T, *et al.* New challenges in the management of cholangiocarcinoma: the role of liver transplantation, locoregional therapies, and systemic therapy. Cancers. Vol. 15, MDPI; 2023.

Recent review about the new challenges in the management of cholangiocarcinoma. The discussion includes hCCA and iCCA. Includes a well done summary of locoregional therapies and systemic therapies providing summary tables and grades of recommendation.

31. ■■ Edeline J, Lamarca A, McNamara MG, *et al.* Locoregional therapies in patients with intrahepatic cholangiocarcinoma: A systematic review and pooled analysis. Cancer Treat Rev 2021; 99:102258.

This systematic review provides a pooled analysis of locoregional-directed therapies for iCCA. Includes a narrative discussion, graphs of the main pooled results and evidence-based proposed recommendations.

32. He J, Cameron AM. Is hepatic artery infusion pump therapy a new bridging strategy to liver transplant for advanced liver malignancy? Ann Surg Oncol 2023.
33. Hill AL, Cullinan DR, Ahmed O, *et al.* Liver transplantation after hepatic artery infusion pump therapy: single-center experience and technical considerations. Ann Surg Oncol 2023; 30:4775–4780.
34. ■ Rajendran L, Claasen MP, McGilvray ID, *et al.* Toronto management of initially unresectable liver metastasis from colorectal cancer in a living donor liver transplant program. J Am Coll Surg 2023; 237:231–242.

Toronto experience in transplant oncology for CRLM using living donor grafts.

35. Kubo S, Shinkawa H, Asaoka Y, *et al.* Liver Cancer Study Group of Japan Clinical Practice Guidelines for Intrahepatic Cholangiocarcinoma. Liver Cancer 2022; 11:290–314.
36. Choi WJ, Sapisochin G. Pushing the limits for the surgical treatment of intrahepatic cholangiocarcinoma. Hepatobiliary Surg Nutr 2023; 12:99–104.

CE: ; MOT/290207; Total nos of Pages: 11;
MOT 290207

37. Le Roy B, Gelli M, Pittau G, *et al.* Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. Br J Surg 2018; 105:839–847.

38. Kelley RK, Ueno M, Yoo C, *et al.* Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023; 401:1853–1865.

39. Aby ES, Lake JR. Immune checkpoint inhibitor therapy before liver transplantation: case and literature review. Transplant Direct 2022; 8:E1304.

40. ■■ Ilyas SI, Affo S, Goyal L, *et al.* Cholangiocarcinoma — novel biological insights and therapeutic strategies. Nat Rev Clin Oncol 2023; 20:470–486.
Recent nature review of molecular profiles of iCCA, potential target therapies, and description of the tumor microenvironment that helps understand and imagine the future therapeutic strategies and selection of patients for liver transplantation.

41. Kendre G, Murugesan K, Brummer T, *et al.* Charting co-mutation patterns associated with actionable drivers in intrahepatic cholangiocarcinoma. J Hepatol 2023; 78:614–626.

42. Farshidfar F, Zheng S, Gingras MC, *et al.* Integrative genomic analysis of cholangiocarcinoma identifies distinct IDH-mutant molecular profiles. Cell Rep 2017; 18:2780–2794.

43. Fu BS, Zhang T, Li H, *et al.* The role of liver transplantation for intrahepatic cholangiocarcinoma: a single-center experience. Eur Surg Res 2011; 47:218–221.

44. Rana A, Hong JC. Orthotopic liver transplantation in combination with neoadjuvant therapy: a new paradigm in the treatment of unresectable intrahepatic cholangiocarcinoma. Curr Opin Gastroenterol 2012; 28:258–265.

45. Hong JC, Jones CM, Duffy JP, *et al.* Comparative analysis of resection and liver transplantation for intrahepatic and hilar cholangiocarcinoma: a 24-year experience in a single center. Arch Surg 2011; 146:683–689.

46. Huang G, Song W, Zhang Y, *et al.* Liver transplantation for intrahepatic cholangiocarcinoma: a propensity score-matched analysis. Sci Rep 2023; 13:10630.

47. McMillan RR, Javle M, Kodali S, *et al.* Survival following liver transplantation for locally advanced, unresectable intrahepatic cholangiocarcinoma. Am J Transplant 2022; 22:823–832.

48. ■ Abdelrahim M, Al-Rawi H, Esmail A, *et al.* Gemcitabine and cisplatin as neoadjuvant for cholangiocarcinoma patients prior to liver transplantation: case-series. Curr Oncol 2022; 29:3585–3594.
This study describes the neoadjuvant therapies used in the MMAJCCC experience, that is the largest experience of liver transplantation after response to neoadjuvant treatment.

49. Chen X, Du J, Huang J, *et al.* Neoadjuvant and adjuvant therapy in intrahepatic cholangiocarcinoma. J Clin Transl Hepatol 2022; 10:553–563.

50. Fung BM, Tabibian JH. Primary sclerosing cholangitis-associated cholangiocarcinoma: special considerations and best practices. Expert Rev Gastroenterol Hepatol 2021; 15:487–496.

51. Safarpour AR, Askari H, Ejtehadi F, *et al.* Cholangiocarcinoma and liver transplantation: what we know so far? World J Gastrointest Pathophysiol 2021; 12:84–105.

52. ■ Choi WJ, Ivanics T, Gravely A, *et al.* Optimizing circulating tumour DNA use in the perioperative setting for intrahepatic cholangiocarcinoma: diagnosis, screening, minimal residual disease detection and treatment response monitoring. Ann Surg Oncol 2023; 30:3849–3863.
Recent review about the evidence and future perspectives of using circulating tumor DNA in the diagnosis, management, and prognosis of iCCA.

53. Lipkova J, Chen RJ, Chen B, *et al.* Artificial intelligence for multimodal data integration in oncology. Cancer Cell 2022; 40:1095–1110.

54. ■ Wegermann K, Henson JB, King LY. CON: intrahepatic cholangiocarcinoma should be a contraindication to liver transplantation. Clin Liver Dis (Hoboken) 2023; 21:52–55.
This short review addresses the main arguments against liver transplantation as a therapy for iCCA. After reviewing the available evidence, highlights the inferior survival for iCCA when compared to other indications. The authors support that given that liver allografts are a scarce resource, from a population standpoint, indications with better survival should be prioritized.

55. Hernandez-Alejandro R, Ruffolo LI, Sasaki K, *et al.* Recipient and donor outcomes after living-donor liver transplant for unresectable colorectal liver metastases. JAMA Surg 2022; 157:524–530.

56. Goto T, Ivanics T, Cattral MS, *et al.* Superior long-term outcomes of adult living donor liver transplantation: a cumulative single-center cohort study with 20 years of follow-up. Liver Transplant 2022; 28:834–842.

57. ■ Li Z, Rammohan A, Gunasekaran V, *et al.* Novel benchmark for adult-to-adult living-donor liver transplantation: integrating Eastern and Western experiences. Ann Surg 2023; 278:798–806.
Description of the results and postoperative outcomes of benchmark living donor liver transplants across 15 high-volume centers.

58. Cotter TG, Minhem M, Wang J, *et al.* Living donor liver transplantation in the United States: evolution of frequency, outcomes, center volumes, and factors associated with outcomes. Liver Transplant 2021; 27:1019–1031.

59. Pomfret EA, Lodge JPA, Villamil FG, Siegler M. Should we use living donor grafts for patients with hepatocellular carcinoma? Ethical considerations. Liver Transplant 2011; 17:S128–S132.

60. Heinemann M, Liwinski T, Adam R, *et al.* Long-term outcome after living donor liver transplantation compared to donation after brain death in autoimmune liver diseases: experience from the European Liver Transplant Registry. Am J Transplant 2022; 22:626–633.

61. Sierra L, Barba R, Ferrigno B, *et al.* Living-donor liver transplant and improved post-transplant survival in patients with primary sclerosing cholangitis. J Clin Med 2023; 12:2807.

62. Jung DH, Hwang S, Song GW, *et al.* Clinicopathological features and prognosis of intrahepatic cholangiocarcinoma after liver transplantation and resection. Ann Transplant 2017; 22:42–52.

63. Hafeez Bhatti AB, Tahir R, Qureshi NR, *et al.* Living donor liver transplantation for intra hepatic cholangiocarcinoma. Ann Med Surg 2020; 57:82–84.

64. Sotiropoulos GC, Kaiser GM, Lang H, *et al.* Liver transplantation as a primary indication for intrahepatic cholangiocarcinoma: a single-center experience. Transplant Proc 2008; 40:3194–3195.

65. Hara T, Eguchi S, Yoshizumi T, *et al.* Incidental intrahepatic cholangiocarcinoma in patients undergoing liver transplantation: a multicenter study in Japan. J Hepatobiliary Pancreat Sci 2021; 28:346–352.

66. Zhang T, Dunson J, Kanwal F, *et al.* Trends in outcomes for marginal allografts in liver transplant. JAMA Surg 2020; 155:926–932.

67. ■ Goldaracena N, Cullen JM, Kim DS, *et al.* Expanding the donor pool for liver transplantation with marginal donors. Int J Surg 2020; 82:30–35.
This interesting study discusses the current status of liver transplantation using marginal donor grafts and efforts to optimize recipient outcomes. Attention is focused on elderly donors, steatotic livers, DCDs, and split liver grafts.

68. ■ Mergental H, Laing RW, Kirkham AJ, *et al.* Transplantation of discarded livers following viability testing with normothermic machine perfusion. Nat Commun 2020; 11:2939.
This article reports the outcomes of the recent VITTAL clinical trial in machine perfusion for liver transplantation. It highlights how machine perfusion can be used for viability testing, enabling the successful transplantation of 71% of discarded livers. It also improves transplant logistics allowing to increase preservation time.

69. Nasralla D, Coussios CC, Mergental H, *et al.* A randomized trial of normothermic preservation in liver transplantation. Nature 2018; 557:50–56.

70. ■ Hann A, Nutu A, Clarke G, *et al.* Normothermic machine perfusion—improving the supply of transplantable livers for high-risk recipients. Transplant Int 2022; 35:10460.
This recent review describes the benefits of normothermic machine perfusion for liver transplantation using suboptimal grafts and in surgically challenging recipients. The benefits of NMP are maximized in this population justifying the elevated costs of the technology.

71. Patrono D, Colli F, Colangelo M, *et al.* How can machine perfusion change the paradigm of liver transplantation for patients with perihilar cholangiocarcinoma? J Clin Med 2023; 12:2026.

72. Dueland S, Smedman TM, Syversveen T, *et al.* Long-term survival, prognostic factors, and selection of patients with colorectal cancer for liver transplant: a nonrandomized controlled trial. JAMA Surg 2023; 158:e232932.

73. Li CX, Man K, Lo CM. The impact of liver graft injury on cancer recurrence posttransplantation. Transplantation 2017; 101:2665–2670.

74. Celik N, Squires JE, Soltys K, *et al.* Domino liver transplantation for select metabolic disorders: expanding the living donor pool. JIMD Rep 2019; 48:83–89.

75. ■ Lim C, Turco C, Balci D, *et al.* Auxiliary liver transplantation for cirrhosis: from APOLT to RAPID: a scoping review. Ann Surg 2022; 275:551–559.
This manuscript reviews the auxiliary liver transplantation techniques for cirrhotic patients. It describes the surgical technique, outcomes and risks of the heterotopic auxiliary liver transplantation, auxiliary partial orthotopic liver transplantation, the two-stage partial liver transplantation, and the RAPID procedures.

76. Line PD, Hagness M, Berstad AE, *et al.* A novel concept for partial liver transplantation in nonresectable colorectal liver metastases: the RAPID concept. Ann Surg 2015; 262:e5–e9.

77. Ravaioli M, Fallani G, Cescon M, *et al.* Heterotopic auxiliary segment 2-3 liver transplantation with delayed total hepatectomy: new strategies for nonresectable colorectal liver metastases. Surgery 2018; 164:601–603.

78. Nadalin S, Konigsrainer A, Capobianco I, *et al.* Auxiliary living donor liver transplantation combined with two-stage hepatectomy for unresectable colorectal liver metastases. Curr Opin Organ Transplant 2019; 24:651–658.

79. Nadalin S, Genedy L, Konigsrainer A, *et al.* Living donor liver transplantation for colorectal liver metastasis: a narrative review. Dig Med Res 2020; 3:31–131.

80. Ge J, Lai JC. Split-liver allocation: an underused opportunity to expand access to liver transplantation. Liver Transpl 2019; 25:690–691.

81. Abreu P, Gorgen A, Oldani G, *et al.* Recent advances in liver transplantation for cancer: the future of transplant oncology. JHEP Rep 2019; 1:377–391.

82. De Martin E, Rayar M, Golse N, *et al.* Analysis of liver resection versus liver transplantation on outcome of small intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma in the setting of cirrhosis. Liver Transpl 2020; 26:785–798.

83. Vallin M, Sturm N, Lamblin G, *et al.* Unrecognized intrahepatic cholangiocarcinoma: an analysis of 993 adult cirrhotic liver explants. Clin Transplant 2013; 27:403–409.

1087-2418 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.