



Review Article on LT and Alternative Treatments in HB Oncology

Liver transplantation as an alternative for the treatment of intrahepatic cholangiocarcinoma: Past, present, and future directions

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ABSTRACT

Intrahepatic cholangiocarcinoma (iCCA) is a rare biliary tract cancer with high mortality rate. Complete resection of the iCCA lesion is the first choice of treatment, with good prognosis after margin-negative resection. Unfortunately, only 12%–40% of patients are eligible for resection at presentation due to cirrhosis, portal hypertension, or large tumor size. Liver transplantation (LT) offers margin-negative iCCA extirpation for patients with unresectable tumors. Initially, iCCA was a contraindication for LT until size-based selection criteria were introduced to identify patients with satisfied post-LT outcomes. Recent studies have shown that tumor biology-based selection can yield high post-LT survival in patients with locally advanced iCCA. Another selection criterion is the tumor response to neoadjuvant therapy. Patients with response to neoadjuvant therapy have better outcomes after LT compared with those without tumor response to neoadjuvant therapy. Another index that helps predict the treatment outcome is the biomarker. Improved survival outcomes have also opened the door for living donor LT for iCCA. Patients undergoing LT for iCCA now have statistically similar survival rates as patients undergoing resection. The combination of surgery and locoregional and systemic therapies improves the prognosis of iCCA patients.

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Introduction

Cholangiocarcinoma (CCA) is a malignancy arising from the bile duct epithelial cells or nearby hepatic progenitor cells [1]. Approximately 90 000 people globally are diagnosed with CCA each year [2], 80%–93% of whom die within 5 years of diagnosis [3]. Most patients present with an advanced stage of disease, leading to poor overall survival (OS) rates [3]. Thus, although the incidence is lower than other cancers, the mortality from CCA is higher [4].

There are two main types of CCA based on anatomic location: intrahepatic (iCCA) and extrahepatic. The iCCA subtype forms in second-order or higher bile ducts within the liver parenchyma, whereas extrahepatic CCA involves bile ducts in the liver hilum

or outside the liver. Extrahepatic tumors are further subclassified anatomically into perihilar and distal CCA (dCCA) (Fig. 1). Perihilar CCA (pCCA, also called Klatskin tumor) occurs in the region of the first-order right and left bile ducts and the common hepatic duct. dCCA occurs in the common bile duct region. iCCA patients comprise around 20% of CCA cases, with pCCA and dCCA encompassing around 55% and 25% of cases, respectively [5]. Reports suggest that the incidence of iCCA is increasing, while the incidence of pCCA and dCCA are decreasing [5,6].

There are multiple risk factors for pathogenesis of iCCA, including cholelithiasis, viral hepatitis, primary sclerosing cholangitis, alcoholic and nonalcoholic steatohepatitis, Caroli's disease, and liver fluke infection [3,6,7]. Lifestyle factors like alcohol overuse and smoking are also risk factors of iCCA [3,7]. These factors initiate carcinogenesis of iCCA through chronic bile duct epithelium inflammation and/or cholestasis, as well as epigenetic and genetic alterations [8,9]. However, a majority of CCA patients do not have a history of these risk factors [6].

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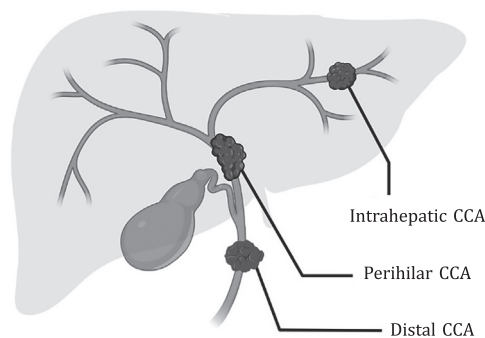


Fig. 1. Diagram of the main subtypes of cholangiocarcinoma (CCA), categorized by anatomical location.

Treatment for iCCA may include locoregional therapy, systemic therapy, and/or surgery [10]. Many iCCA patients receive a combination of therapies, for example, systemic therapy combined with local resection. In this review, we focused on a comparison of the two surgical treatments for iCCA: resection and liver transplantation (LT). Consensus guidelines only identify resection with negative margins as potentially curative [11]. However, LT also offers the potential of margin-negative removal of iCCA and can hence be potentially curative. LT is a particularly important option for patients whose iCCA is deemed unresectable.

Resection for iCCA

Surgical resection is the first choice for iCCA treatment if anatomically and physiologically amenable [12]. Removal of the tumor with negative (R0) margins yields good long-term recurrence-free survival (RFS) and OS (Table 1) [13–45]. When R0 resection of liver-limited disease is achieved, resection is considered a potentially curative therapy. Unfortunately, resection with negative margins is not technically feasible for most patients. Additionally, only a minority of patients—an estimated 12%–40%—are candidates for resection at presentation [46]. Even though resection provides a survival advantage, recurrence rates are high without R0 margins, and resection is often limited by the size of the predicted future liver remnant (FLR) [47]. A recent phase II clinical trial has demonstrated the potential for iCCA downstaging to resectability in 9 of 41 patients with locally advanced tumor burden using a combination of systemic therapy (gemcitabine and cisplatin) with locoregional transarterial radioembolization [48].

Patient selection for resection

Several factors are taken into consideration while determining candidacy for resection, and one of the most important factors is FLR size (Fig. 2). Inadequate FLR increases the patient's risk of liver failure postoperatively [46]. Resections that would prohibitively interfere with major vascular or biliary structures of the liver are also generally contraindicated.

Resections can be anatomical or non-anatomical. Anatomical resection involves the removal of the entire section of affected liver, including the associated biliary and vascular pedicles. Proponents argue that anatomic resection reduces the risk of metastasis by removing the blood vessels most likely to carry metastatic tumor cells. Non-anatomical resection aims to maximize liver remnant parenchyma. A study by Si et al. in 2019 compared outcomes of propensity-score matched patients undergoing anatomical and non-anatomical resections [37]. The authors found that patients receiving anatomical resection had significantly better OS and RFS. In

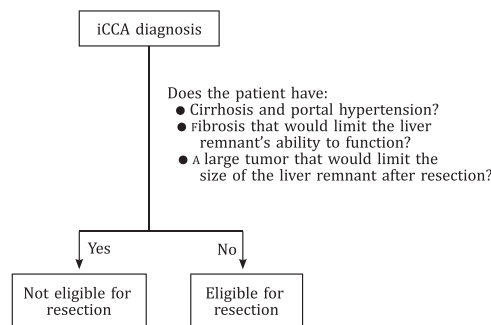


Fig. 2. Criteria for patient with intrahepatic cholangiocarcinoma (iCCA) eligibility for liver resection. Patients with unresectable tumors may be considered for liver transplantation.

addition, multivariate analysis revealed that non-anatomical resection was independently associated with a higher risk of death and recurrence.

Factors affecting recurrence and survival post-resection

Multiple factors are tied to long-term outcomes after hepatic resection. Surgical margins are one of the strongest predictors of tumor recurrence and patient survival after hepatectomy. Patients undergoing margin-negative resection have 5-year RFS rates of 18%–48.3% and 5-year OS rates of 25.3%–44% (Table 1) [24,34,37]. Studies have also identified tumor margin as an independent predictor of OS in multivariable analyses [15,20,26,36]. A recent meta-analysis by Dai and coauthors agreed that wide resection margins (> 10 mm) improves OS and RFS [49].

Tumor characteristics are also associated with RFS and OS after resection. Measures of tumor burden such as largest tumor diameter and tumor number are significantly associated with OS or RFS [15–17,21,24,28,33,35–37,39]. Similarly, higher stage tumors and poorly differentiated tumors also increase the risk of recurrence and death after resection [13,17,33,35,36,40]. Tumor vascular invasion was independently associated with OS [28,40,42] and RFS [33,40,32].

Some studies have proposed a link between biomarkers and post-resection outcomes. Wang and colleagues found that serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) predicted OS after resection [28]. Similarly, Si and colleagues also reported that CEA and CA19-9 were associated with both RFS and OS [37].

LT for iCCA

Although resection is the preferred local treatment for CCA, some patients are not resectable due to concurrent acute or chronic liver disease, cirrhosis, portal hypertension, or the anatomic features of the iCCA tumor(s) described above [50,51]. These patients may be considered for LT. LT may attain negative oncologic margins and remove intrahepatic micro-metastases [10].

History of LT for hepatic malignancy

Initial attempts to treat primary liver cancer with LT resulted in high recurrence and low OS rates [52,53]. However, a 1996 paper by Mazzaferro and colleagues demonstrated that hepatocellular carcinoma (HCC) patients with relatively low tumor burden can have good post-LT survival [54]. In HCC, we have since learned that these initial limits of HCC tumor size and number could be somewhat expanded while maintaining good outcomes [55–57]. Recent

Table 1
Summary of selected published outcomes after first resection for intrahepatic cholangiocarcinoma.

Studies	Year	n	Median/mean follow-up (mon)	Median overall survival (mon)	Overall survival			Negative margins	Median time to recurrence (mon)	Recurrence	Recurrence-free survival		
					1-yr	3-yr	5-yr				1-yr	3-yr	5-yr
Pichlmayr et al. [13] (T2 tumors)	1995	32		32.4	80%	40%	30%						
Pichlmayr et al. [14]	1996	125		19.9	65%	33.4%	27.1%	72.8%					
Casavilla et al. [15]	1997	34			60%	37%	31%			62%	50%	30%	25%
Roayaie et al. [16]	1998	16	35.7	42.9	87%	66%	44%	31%	20.3	56.3%			
Weimann et al. [17]	2000	95		17.7	64%	31%	21%			10.5%			
Ohtsuka et al. [18]	2003	50		25.5	61%	38%	23%	68%		62%	55%	17%	17%
Morimoto et al. [19]	2003	51			68.2%	44.1%	32.4%	67%		56.9%			
DeOliveira et al. [20]	2007	44		25			40%	45%					
Endo et al. [21]	2008	82	26					85%	21	62.2%			
Konstadoulakis et al. [22]	2008	54		21.8	80%	49%	25%	78%					
Tan et al. [23]	2008	446		23	68%		18%						
Sotiropoulos et al. [24]	2009	41	28		90%	68%	44%	100%	17	61%	75%	35%	25%
Ellis et al. [25]	2011	31	16.2	30.9		40%				52%			
Farges et al. [26]	2011	212		28	77%	43%	28%	76%					
Hong et al. [27]	2011	12						82%				6%	0
Wang et al. [28]	2013	367	39.3	21.0	61.9%	40.8%	35.2%		13.8		48.9%	62.5%	67.3%
Doussot et al. [29]	2015	188	41	48.7	91%	59%	45%			58.5%			
Lindnér et al. [30]	2015	17				29%							
Spolverato et al. [31]	2015	584		27	75%	37%	22%	81.2%	10		44%	18%	11%
Tabrizian et al. [32]	2015	82	27					82%	16	62%	60%	24%	16%
Doussot et al. [33]	2016	189	42.5	47.8				80.4%	23.1	58.2%			
Jung et al. [34]	2017	100			82.0%	58.8%	42.8%	100%		51.7%	71.5%	54.5%	48.3%
Zhang et al. [35]	2017	1142			78%	51%	39%	78%		60%	57%	36%	31%
Bagante et al. [36]	2019	1116	28.8			52.4%	40.5%	87.4%					
Si et al. [37]	2019	46 (Anatomical) 49 (Non-anatomical)			72.9%	45.7%	36.0%	100%			57.7%	35.7%	29.1%
					62.0%	30.8%	25.3%	100%			44.1%	23.9%	18.0%
Spolverato et al. [38]	2019	3670					33.3%			82.6%			
De Martin et al. [39]	2020	20	29							88%			
Hu et al. [40]	2020	1221	38	36.8	79.4%		37.5%	85.3%	15.8	59.4%	54.6%	33.0%	28.2%
Hue et al. [41]	2021	1879		36.1	82.6%	50.2%	33.0%	81.0%					
Rafecas et al. [42]	2021	67	28	31.2	91.0%	49.2%	39.8%	80.6%	24.7		67.2%	32.8%	22.4%
Hamad et al. [43]	2022	1876		41				81.6%					
Kim et al. [44]	2022	461		30.1			34.7%	88.9%					
Lee et al. [45]	2022	464		71.1	89.0%	67.5%	55.9%						

studies indicate that tumor biology is another predictor of post-transplant outcomes: patients with more aggressive HCC have decreased survival [58–60]. Carefully selected patients demonstrating radiologic and biologic (e.g., biomarker) tumor stability or response to neoadjuvant locoregional or chemotherapy can have excellent outcomes, even when tumor burden exceeds traditional cutoffs [58]. Combining tumor size with biomarkers such as alpha-fetoprotein and des- γ -carboxy prothrombin can predict post-LT recurrence and OS more accurately [61,62].

History of LT for CCA

Like HCC, CCA was once a contraindication for LT. As treatments for CCA improved, some centers began to report successful cases with combined neoadjuvant therapy and LT for pCCA [63,64]. Following these successes, researchers at the Mayo Clinic set out to identify selection criteria for patients expected to have good outcomes after LT for pCCA [65]. Heimbach and colleagues reported on 28 patients receiving neoadjuvant radiotherapy combined with 5-fluorouracil and subsequent LT. The patients had excellent 1- and 5-year post-LT OS rates of 88% and 82%, respectively. Patients with unresectable pCCA \leq 3 cm with elevated CA19-9 ($>$ 100 U/mL) and/or biopsy proven pCCA are eligible for exception points if they have neither intra- nor extrahepatic metastases nor regional lymph nodes metastases.

History of LT for iCCA

Initial attempts at LT for iCCA also yielded poor results, with dismal 1-year OS rates between 13.9% and 53% prior to 1996 (Table 2) [13-15,17,27,30,34,38,39,41,44,45,52,66-90]. Between 1990 and 2010, 5-year survival rates ranged between 0 and 40%, with 1 report of 83% survival in a cohort of 10 patients [69]. These early studies did not restrict LT based on tumor burden; their selection protocols only excluded patients with resectable tumors. Papers that did report 5-year OS rates over 50% only included patients with incidentally diagnosed iCCA [69]. Outcomes published in the early 2010s (2010–2013) included slightly improved 1-year OS rates ranging between 51% and 84.2%, but with low 5-year OS rates between 21.8% and 45% [27,76-78].

LT gained greater acceptance after the suggestion of size-based selection criteria for iCCA, as with HCC and pCCA. In 2014, Sapisochin and colleagues published a retrospective study examining the outcomes of patients undergoing LT for iCCA [79]. They identified a subgroup of patients with “very early” iCCA, defined as a single iCCA tumor \leq 2 cm in diameter. Post-LT OS rates for “very early” patients were 100%, 73%, and 73% at 1, 3, and 5 years, respectively. A subsequent multicenter study reported 1-, 3-, and 5-year OS rates of 93%, 84%, and 65% for similarly stratified patients [81]. LT recipients with “advanced” iCCA, defined as multiple tumors or a single tumor $>$ 2 cm in diameter, had OS rates of 79% at 1 year, 50% at 3 years, and 45% at 5 years post-LT [81]. Importantly, the authors noted that tumor size was not a significant predictor of RFS in their multivariate analysis, suggesting that size did not fully reflect biological aggressiveness in their cohort.

In addition to size-based selection, evidence of the benefits of neoadjuvant therapy and LT for iCCA continued to grow. Hong and colleagues reported higher post-LT recurrence rates in iCCA patients who did not receive neoadjuvant therapy [91]. Similarly, a study by Hu et al. found that receiving neoadjuvant therapy reduced the risk of death [risk ratio (RR) = 0.050; P = 0.005] and recurrence (RR = 0.233; P = 0.042) in univariate analysis [77].

The effects of combined LT and neoadjuvant therapy led some centers to consider response to therapy when selecting LT candidates. Authors from Houston Methodist Hospital have shown that patients with locally advanced, unresectable iCCA receiving neoadjuvant therapy can have good OS after LT [85,89]. Per center protocol, patients were eligible for LT if their tumors were radiologically regressing or stable for \geq 6 months on neoadjuvant systemic therapy. Patients (n = 18) with locally advanced iCCA had OS rates of 100% at 1 year, 71% at 3 years, and 57% at 5 years post-LT [89]. Thus, selecting patients based on tumor biology and measured by response to neoadjuvant therapy can lead to good post-LT survival rates.

Recent papers have continued to emphasize the importance of combination neoadjuvant therapy. Ito and colleagues from the University of California, Los Angeles reported that patients receiving combination neoadjuvant systemic and locoregional therapy had improved outcomes post-LT relative to use of either single therapy [88]. Tumor size did not affect OS or RFS after LT. An analysis of National Cancer Database iCCA data revealed that LT recipients were more likely to receive neoadjuvant and/or adjuvant therapies than patients undergoing resection, emphasizing the importance of combination therapies [44].

Patient selection for LT

As detailed above, initial reports of positive outcomes after LT for iCCA involved either very small or incidentally discovered tumors, with a diameter of 2 cm or less (Table 2) [79,81]. Combined with the success of patient selection based on tumor burden for HCC and pCCA, most centers only performed LT for patients with a very small iCCA tumor burden. Additional reports by teams from Mount Sinai Medical Center and Sun Yat-sen University have also supported the efficacy of size-based cutoffs and outcomes [80,92]. A recent meta-analysis by Ziogas and others agreed that smaller tumor size was associated with improved survival [93].

However, limiting LT to patients with very small iCCA tumors disqualifies most patients from receiving this potentially lifesaving therapy, including some who may have non-aggressive tumors. Additionally, the landmark study by Sapisochin and colleagues noted that tumor size was not an independent predictor of tumor recurrence [81]. Recent studies have also shown that tumor burden is not an accurate predictor of outcomes after transplantation for iCCA [88,94].

Protocols that select patients based on tumor biology have shown promise. For example, reports from Houston Methodist Hospital have shown that tumor response to neoadjuvant therapy is a better predictor of OS than tumor size [85,89]. Patients with locally advanced iCCA who respond to neoadjuvant treatment (most frequently gemcitabine/cisplatin chemotherapy) achieved good long-term survival post-LT. Other studies have shown a strong association between post-LT OS and RFS and variables such as microvascular invasion and poor differentiation [39,77,82]. Patient selection based on tumor biology may allow for treatment of advanced tumors with excellent, potentially curative outcomes.

Tumor genetic mutations and expression patterns show great promise in identifying iCCA patients amenable to LT. Pre-LT identification of mutations through technologies such as next-generation sequencing of solid tumor biopsies and cell-free DNA, RNA, and/or protein expression could help clinicians select appropriate neoadjuvant therapies and prognosticate patient outcomes [10,95,96]. In addition, sequencing explanted tumors may help transplant oncology teams tailor surveillance and select effective therapies to treat recurrence. Studies of LT recipients with iCCA have se-

Table 2
Summary of published outcomes after liver transplantation for intrahepatic cholangiocarcinoma.

Studies	Year	n	Median/mean follow-up (mon)	Median overall survival (mon)	Overall survival			Negative margins	Median time to recurrence (mon)	Recurrence	Recurrence-free survival		
					1-yr	3-yr	5-yr				1-yr	3-yr	5-yr
O'Grady et al. [66]	1988	13		7.8	38%	10%	10%			64.9%			
Ringe et al [67]	1989	10								100%			
Yokoyama et al. [52]	1990	2			50%	0				39.1%			
Goldstein et al. [68]	1993	17		11.1	53%				14.3	64.7%	40%		
Pichlmayr et al. [13]	1995	18		5.0	13.9%								
Pichlmayr et al. [14]	1996	24		15.5	60%	21.4%	17.1%						
Casavilla et al. [15]	1997	20			70%	29%	18%			55%	67%	31%	31%
Goss et al. [69]	1997	10			100%		83%						
Weimann et al. [17]	2000	24		5.5	21%	4%	0			4.2%			
Meyer et al. [70]	2000	307		11.7	72%		23%		9.7	51%			
Shimoda et al. [71]	2001	16			62%	39%		100%	10.6	53.8%	70%	35%	
Pascher et al. [72]	2003	186			58%	38%	29%						
Robles et al. [73]	2004	59		66	77%	65%	42%		22	35%	68%	45%	27%
Ghali et al. [74]	2005	10	28	30		30%			26	80%			
Sotiropoulos et al. [75]	2008	10		25.3	70%	50%	33%						
Hong et al. [27]	2011	25					34%	65%		41%		39%	33%
Fu et al. [76]	2011	11	10	9	51%	51%			3.8	45.5%	51.9%	51.9%	
Hu et al. [77]	2011	20	15.0	17.0	84.2%	32.7%	21.8%		12.5		55.6%	28.8%	18.8%
Vallin et al. [78]	2013	10	33		80%	60%	45%		10	50%			
Sapisochin et al. [79]	2014	29	36.4		79%	61%	45%		14.6	24%			
		8 (Very early)			100%	73%	73%			0			
		21 (Not very early)			71%	43%	34%			33%	89%	71%	71%
Lindnér et al. [30]	2015	5					60%						
Facciuto et al. [80]	2015	7								31%			58%
Sapisochin et al. [81]	2016	48	35				67%						
		15 (Very early)		57.3	93%	84%	65%			13.3%	93%	82%	82%
		33 (Advanced)		10.5	79%	50%	45%			51.5%	70%	53%	39%
Takahashi et al. [82]	2016	13	18.8							53.8%	67%	42%	
Vilchez et al. [83]	2016	440			79%	58%	47%			-			
Jung et al. [34]	2017	16	39.1		62.5%	62.5%		100%		78.1%	50.0%	50.0%	
Lee et al. [84]	2018	9		35.5	81.3%	51.9%				29.4%			
Lunsford et al. [85]	2018	6		36	100%	83.3%	83.3%		7.6	50%	50%	50%	50%
Spolverato et al. [38]	2019	385					41.3%						
De Martin et al. [39]	2020	24	42										
Krasnodębski et al. [86]	2020	8		18	75%	37.5%	25%				71.4%	28.6%	28.6%
Hue et al. [41]	2021	74		36.1	89.4%	53%	40.8%	91.9%					
Hara et al. [87]	2021	19	46	49	79%	63%	46%		31	53%	79%	45%	45%
Kim et al. [44]	2022	66		24.2			36.1%	93.9%					
Lee et al. [45]	2022	62			88.9%	72.9%	67.9%						
Ito et al. [88]	2022	31		28.8	74%	54%	43%				71%	44%	37%
McMillan et al. [89]	2022	18	26		100%	71%	57%	88.9%	11	38.9%	70%	52%	
Safdar et al. [90]	2022	95	26.2	52.8	82.1%	68.7%	57.1%						

Table 3

Gene mutations identified in liver transplantation recipients (reported as percent of the total study population) with intrahepatic cholangiocarcinoma that have approved targeted therapies.

Gene & alteration	Gruttadauria et al. 2021 [97]	McMillan et al. 2022 [89]	Therapy
<i>FGFR2</i> fusions	0	27%	Pemigatinib
<i>IDH1</i> p. R132H/C/G/L/S/I	60%	35%	Ivosidenib
<i>BRAF</i> p. V600E	25%	19%	Dabrafenib + Trametinib
<i>NTRK</i> fusions	NR	6%	Entrectinib, Larotrectinib
<i>RET</i> fusions	NR	NR	Selpercatinib
High microsatellite instability	NR	NR	Pembrolizumab
High tumor mutational burden	NR	NR	Pembrolizumab

FGFR: fibroblast growth factor receptor; *IDH1*: isocitrate dehydrogenase 1; *KRAS*: Kirsten rat sarcoma viral oncogene homolog; *NTRK*: neurotrophic tyrosine receptor kinase; NR: not reported, *RET*: rearranged during transfection.

quenced explanted tumors and identified mutations in genes such as fibroblast growth factor receptor (*FGFR*) and isocitrate dehydrogenase 1 (*IDH1*), which have approved targeted therapies (Table 3) [89,97]. Intratumoral heterogeneity has been observed in iCCA [98–100] and has been linked to overall prognosis in iCCA patients [101]. Additional research is needed to learn whether such heterogeneity has significant role in prognosticating outcomes in LT candidates and recipients.

Living donor LT for iCCA

Recent studies have begun to examine whether iCCA patients are good living donor liver transplantation (LDLT) candidates. Traditionally, iCCA patients were excluded from LDLT because the benefit to the recipient (OS, RFS) was not large enough to offset the risk to the donor [102]. Many reports of outcomes in LDLT recipients with iCCA come from patients with an incidental iCCA diagnosis [87,103]. Fortunately, the recent improvements in post-LT outcomes described above have renewed the possibility of LDLT for these patients as double equipoise becomes more achievable.

In 2005 a case series by Jonas and colleagues reported outcomes in 2 iCCA patients undergoing LDLT [104]. Both patients had experienced recurrence at 31 months but were alive at 46 and 35 months post-LDLT, respectively. Hafeez Bhatti et al. identified a combined cohort of 16 incidentally diagnosed iCCA and pCCA patients undergoing LDLT for presumed diagnosis of HCC in a large retrospective review of their center's data [103]. They reported an overall 3-year RFS of 47%. Importantly, patients with well- or moderately-differentiated tumors had a 3-year RFS of 64%, suggesting that outcomes may improve with careful patient selection. A multicenter study from Japan by Hara et al. yielded RFS rates of 79%, 45%, and 45% at 1, 3, and 5 years post-LDLT in patients incidentally diagnosed with iCCA in explant pathology [87]. Post-LDLT OS rates were 79%, 63%, and 46% at 1, 3, and 5 years, respectively. A recent systematic review by Rauchfuß et al. identified 6 patients undergoing LDLT for iCCA; 3 LDLT recipients recurred. Patients who were still alive had a median follow-up of 30.5 months [102].

Transplantation vs. resection: direct comparisons

Comparisons between resection and LT for iCCA are difficult to make since there has not been a trial directly comparing them in similar patient cohorts. For example, in 1995 Pichlmayr et al. [13] reported a 1-year OS rate of 13.9% in LT recipients, versus 80% in patients with stage II tumors undergoing resection [32]. However, in this study, patients with advanced tumors were not excluded from LT: 72% (13/18) of LT recipients had stage IV iCCA, compared to 41% (13/32) of resected patients. It is therefore unsurprising that such papers have reported worse survival in LT recipients relative to those undergoing resection [17,34,42].

Some authors have assessed outcomes after resection and LT in patients treated under a single protocol (Table 4). A subset of these papers matched LT recipients to patients undergoing resection. For example, Jung et al. compared the outcomes of 16 LT iCCA recipients to 100 propensity-matched patients undergoing resection [34]. The OS ($P = 0.082$) or RFS ($P = 0.121$) were similar between the two groups of patients. Hue and colleagues also compared iCCA patients undergoing LT or resection using data from the United States National Cancer Database (NCDB) [41]. OS rates were similar for LT recipients and both unmatched ($P = 0.34$) and matched ($P = 0.57$) resection patients. Similarly, an NCDB analysis by Kim et al. found that propensity-matched resection recipients had similar OS to LT recipients ($P = 0.53$) [44]. Lee et al. also conducted a multivariate analysis of NCDB data; LT recipients were at a significantly reduced risk of dying relative to matched resected patients (adjusted hazard ratio = 0.33, 95% CI: 0.16–0.68; $P = 0.04$) [45].

As described above, patients who are good candidates for resection are clinically different from good candidates for LT. LT is a more aggressive approach, generally for sicker patients with locally advanced iCCA and underlying liver disease. Resection is often for patients with early, localized iCCA lesions. However, there is a growing body of evidence showing that LT has similar or improved outcomes compared to resection for iCCA, despite these differences in the patient populations. These data support the efficacy and importance of LT for iCCA, affirming the continued utilization of donor grafts in these patients.

Future directions

Although research and clinical advances have improved outcomes after LT for iCCA, additional studies are still needed. Early work has shown that biomarkers have the potential to identify patients likely to survive after LT and respond to neoadjuvant treatment, leading to better post-surgical outcomes. Additional research is needed to identify non-invasive predictors of post-LT outcomes that can be measured prior to evaluation for transplantation. These biomarkers would allow clinicians to identify aggressive tumors, regardless of size, and prioritize LT in patients with the lowest risk of recurrence.

Similarly, advances in adjunctive therapies have the potential to further improve transplant outcomes for iCCA. Neoadjuvant and adjuvant targeted therapies tailored to a patient's tumor genetic profile can work in concert with LT to increase post-transplant survival even further. Drug development is an area of active basic and translational research to create new therapies for iCCA tumors that do not respond to current therapies [105]. Effective neoadjuvant therapies are particularly important given the effectiveness of LT candidate selection strategies based on response to neoadjuvant therapy.

Table 4
Summary of direct comparisons of outcomes of patients undergoing resection or liver transplantation in the literature.

Studies	Year	<i>n</i>		Overall survival						Recurrence-free survival					
		Resection	LT	Resection			LT			Resection			LT		
				1-yr	3-yr	5-yr	1-yr	3-yr	5-yr	1-yr	3-yr	5-yr	1-yr	3-yr	5-yr
Pichlmayr et al. [13]	1995	32	18				13.9%								
Stage II		10	3	80%	40%	30%									
Stage III		9	2	62%											
Stage IVA		13	11	52%											
Stage IVB		0	2												
Casavilla et al. [15]	1997	34	20	60%	37%	31%	70%	29%	18%	50%	30%	25%	67%	31%	31%
Weimann et al. [17]	2000	95	24	64%	43%	21%	21%	8%	0						
Hong et al. [27]	2011	12	25							34%	6%	0			
Lindnér et al. [30]	2015	17	5		29%			60%							
Jung et al. [34]	2017	16	100	82.0%	58.8%	42.8%	62.5%	62.5%		71.5%	54.5%	48.3%	43.8%	43.8%	21.9%
De Martin et al. ¹ [39]	2020	20	24	92%	59%	40%	90%	76%	67%	69%	45%	36%	87%	79%	75%
Hue et al. [41]	2021	1879	74	82.6%	50.2%	33.0%	89.4%	53.0%	40.8%						
Kim et al. [44]	2022	198	66												
Lee et al. [45]	2022	464	62	89.0%	67.5%	55.9%	88.9%	72.9%	67.9%						

¹ Paper reports survival outcomes for combined cohort of patients with intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma. LT: liver transplantation.

Conclusions

iCCA patients have a poor prognosis without treatment but may be cured with combinations of surgery and systemic and/or locoregional therapy. Resection is the preferred surgical treatment when feasible, but LT can yield excellent long-term outcomes in well-selected patients with unresectable tumors. Post-LT outcomes depend on patient selection, which can be either size-based and/or tumor biology-based. Selection based on tumor aggressiveness has the potential to expand lifesaving treatment to patients with large but indolent tumors. Post-LT survival rates are anticipated to increase with the development of non-invasive biomarkers and better selection criteria. Improvements in post-LT outcomes will also depend on the introduction of further neoadjuvant and adjuvant therapies for iCCA.

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Fig. 1 was created using BioRender software (BioRender.com).

CRediT authorship contribution statement

Sudha Kodali: Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Ashton A Connor:** Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Souhail Thabet:** Conceptualization, Data curation, Writing – original draft. **Elizabeth W Brombosz:** Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Visualization, Writing – original draft, Writing – review & editing. **R Mark Ghobrial:** Conceptualization, Investigation, Supervision, Resources, Validation, Writing – review & editing.

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R Mark Ghobrial is a member of the advisory board for TransMedics and has received stock in the company. For the rest authors, no benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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