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INVITED REVIEW

Liver Transplantation for Intrahepatic Cholangiocarcinoma: Ready for Prime Time?

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Abstract

Cholangiocarcinoma (CCA) represents the second-most common primary liver malignancy after HCC and has risen in incidence globally in the past decades. Intrahepatic cholangiocarcinoma (iCCA) comprises 20% of all CCAs, with the rest being extrahepatic (including perihilar [pCCA] and distal CCA). Though long representing an absolute contraindication for liver transplantation (LT), recent analyses of outcomes of LT for iCCA have suggested that iCCA may be a potentially feasible option for highly selected patients. This has been motivated both by successes noted in outcomes of LT for other malignancies, such as HCC and pCCA, and by several retrospective reviews demonstrating favorable results with LT for a selected group of iCCA patients with small lesions. LT for iCCA is primarily relevant within two clinical scenarios. The first includes patients with very early disease (single tumor, ≤2 cm) with cirrhosis and are not candidates for liver resection (LR). The second scenario is patients with locally advanced iCCA, but where the extent of LR would be too extensive to be feasible. Preliminary single-center reports have described LT in a selected group of patients with locally advanced tumors who have responded to neoadjuvant therapy and have a period of disease stability. Currently, there are three prospective trials underway that will help clarify the role of LT in iCCA. This review seeks to explore the available studies involving LT for iCCA, the challenges of ongoing trials, and opportunities for the future.

INTRODUCTION

Cholangiocarcinoma (CCA) is the second-most common primary liver malignancy after HCC.[1] Within the CCA group, intrahepatic cholangiocarcinoma (iCCA) arises from intrahepatic bile ducts proximal to the second-order biliary division.[2] iCCA comprises up to 20% of all CCA, with the rest being extrahepatic, including perihilar CCA (pCCA) and distal CCA.[2] Over the past decades, the incidence of iCCA has increased

Abbreviations: AJCC, American Joint Committee on Cancer; BED, biological equivalent dose; CA 19-9, carbohydrate antigen 19-9; CCA, cholangiocarcinoma; EBRT, external beam radiation therapy; iCCA, intrahepatic cholangiocarcinoma; LC, local control; LNM, lymph node metastasis; LR, liver resection; LRTs, locoregional therapies; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; OPTN, Organ procurement and Transplantation Network; OS, overall survival; pCCA, perihilar cholangiocarcinoma; RFA, radiofrequency ablation; RFS, recurrence-free survival; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TNM, tumor, nodes, and metastases; UNOS, United Network for Organ Sharing; VI, vascular invasion.

globally across all age and ethnicity strata.[3–8] Paralleling this increase in incidence has been an increase in iCCA-specific mortality.[9,10] Though iCCA can arise in both cirrhotic and noncirrhotic livers, risk factors for its development are similar as for HCC and include cirrhosis, chronic hepatitis B and C, obesity, diabetes, and alcohol, the latter of which is on the rise and, along with better disease detection, are a contributing factor to the increased incidence.[11]

The staging of iCCA is based on the tumor, nodes, and metastases (TNM) staging system from the American Joint Committee on Cancer (AJCC). The staging, based on the AJCC 7th edition, was introduced in 2010 and has subsequently been revised as the AJCC 8th edition.[12–14] Whereas the node (N) and metastases (M) classification have remained essentially unchanged, except for modifying the lymph node metastasis (LNM) staging from IVA to IIIB, the tumor (T) categories classification has undergone significant reclassification.[14] This included stratifying T1 tumors into T1a (single lesion up to 5 cm without vascular invasion [VI]) and T1b (single lesion >5 cm without VI). T2 tumors comprise either a single lesion of any size with VI, or multiple lesions of any size or number, with or without VI. T3 tumors perforate the visceral peritoneum, and T4 tumors involve local extrahepatic structures by direct invasion.[14] A detailed outline of the staging of iCCA tumors according to the AJCC 7th and 8th editions is shown in Table 1.

According to the National Comprehensive Cancer Network guidelines, iCCA patients with resectable disease should undergo liver resection (LR) together with regional lymphadenectomy (RLA).[15] For patients with unresectable or metastatic disease, options include clinical trials, systemic therapy, external beam radiation therapy (EBRT) with concurrent fluoropyrimidine, locoregional therapy (LRT; such as arterially direct therapies), and best supportive care.[15]

Unfortunately, many patients have advanced or disseminated disease at diagnosis, which limits treatment options.[3,16] As a result, the 5-year overall survival (OS) for all comers is <10%.[17] LR represents the mainstay treatment option with curative potential for patients who meet criteria for resection (absence of diffuse bilobar involvement and satellite lesions, peritoneal carcinomatosis, distant metastases, underlying liver disease precluding safe resection, an estimated future liver remnant <20%–30% with inadequate response to portal vein occlusion, or severe comorbidities).[18] For patients who can undergo LR, >70% require a major hepatectomy (three or more segments) to achieve a microscopic negative margin resection (R0).[16,19,20] In

TABLE 1 iCCA AJCC staging 7th and 8th editions

	AJCC 7th Edition		AJCC 8th Edition
T category		T category	
T1	Solitary tumor without VI	T1a	Solitary tumor ≤5 cm without VI
		T1b	Solitary tumor >5 cm without VI
T2a	Solitary tumor with VI	T2	Solitary tumor with intrahepatic vascular tumors, with or without VI
T2b	Multiple tumors, with or without VI		
T3	Tumor perforating the visceral peritoneum or involving local hepatic structures by direct invasion	T3	Tumor perforating the visceral peritoneum
T4	Tumor with periductal invasion	T4	Tumor involving local extrahepatic structures
N category			
N0	No regional LNM	N0	No regional LNM
N1	Regional LNM present	N1	Regional LNM present
M category			
M0	No metastasis	M0	No metastasis
M1	Metastasis present	M1	Metastasis present
TNM stage		TNM stage	
I	T1 N0 M0	IA	T1a N0 M0
		IB	T1b N0 M0
II	T2 N0 M0	II	T2 N0 M0
III	T3 N0 M0	IIIA	T3 N0 M0
		IIIB	T4 and/or N1 M0
IVA	T4 N0 M0/any T N1 M0	IV	Any T any N M1
IVB	Any T1 any N M1		

addition to performing a margin negative resection, an RLA is recommended by the International Liver Cancer Association guidelines, which includes at least six nodes, to aid in prognostication.[2]

Given the poor outcomes, high recurrence rates, and the limited curative treatment options for patients with iCCA, LT has re-emerged as a therapeutic strategy. This has been fueled, in part, by the success of LT in the management of other hepatic malignancies that were previously contraindicated for LT. Within this context, there have been excellent oncological outcomes with LT for patients with HCC, even if standard criteria like the Milan criteria are exceeded. Success has also been demonstrated for selected patients with localized pCCA treated with neoadjuvant chemoradiotherapy followed by LT. In the past decade, there has been an accumulation of data on oncological outcomes of patients who have undergone LT for early iCCA, predominantly as an incidental diagnosis or for a presumed HCC.[21] More recently, efforts have been taken to push the envelope further and evaluate the outcomes for a select group of patients with locally advanced disease who have received neoadjuvant therapy for downstaging.[22] As a result of these efforts, several clinical trials are ongoing to further clarify the outcomes of patients with iCCA undergoing liver transplantation (LT) in a prospective fashion. Consequently, the current status of LT for iCCA warrants appraisal and whether it is ready to be considered a formal indication for LT.

This review will evaluate evidence related to the above-mentioned clinical scenarios.

OUTCOMES AND CHALLENGES WITH LIVER RESECTIONS FOR iCCA

LR is the standard of care and is currently the only curative treatment option in patients with iCCA. This typically consists of a segmental resection plus portal lymphad enectomy.[23–25] When possible, minimally invasive surgery may have a role in enhancing recovery and potentially reducing complications, though this is not always feasible, and comparative data between open and minimally invasive surgery in this setting are lacking.[26–28] Unfortunately, despite achieving a margin-negative resection, long-term oncological outcomes are poor, with 5-year survivals between 30% and 40% and low cure rates (9.7%; 95% CI, 6.1–13.4).[29–31] Recurrence rates after LR are high, with the initial recurrence being intrahepatic in 60%–70%.[19,32] Though patients with very early iCCA (≤2 cm; with no LNM or VI) can achieve excellent outcomes (100% at 5 years) based on a nationwide survey of the Liver Cancer Study Group of Japan, slightly larger tumors, defined as ≤5 cm, even in the absence of aggressive pathological features, such as VI, poor grade, LNMs, and periductal histology, only have a cure fraction of 25.8%.[29,33] Moreover, though LR represents the mainstay of therapy, most patients will not be candidates because of factors such as unfavorable tumor location, cirrhosis/portal hypertension, multifocal disease, or extrahepatic disease.[18] Based on a high-volume, single-institution experience of 564 patients, 66% of consecutive iCCA patients underwent resection.[34] On a population scale, however, only 15% of patients with iCCA underwent resection based on an analysis of the Surveillance, Epidemiology, and End Results (SEER) Program between 1983 and 2010.[35] These factors highlight that significant progress is needed to improve patient outcomes. Within this context, it is imperative to note that retrospective studies that perform comparative evaluations between LR and LT are likely to be subject to selection bias and both unmeasured and residual confounding, given the highly distinct patient populations across the two treatment modalities.

LT FOR iCCA

The role of LT in iCCA is relevant within two clinical scenarios. The first scenario includes very early iCCA in patients who are not amenable to LR, typically because of significant underlying liver dysfunction. The second scenario includes patients with more locally advanced iCCA, but where the extent of LR required would be unfeasible. The option for this latter group of patients typically includes neoadjuvant therapy tumor control and selection.

iCCA has long represented a formal contraindication for LT globally because of historically dismal outcomes.[36–40] Many available studies are based on single-center analyses with few patients with limited statistical power. Some studies analyze patients with both iCCA and pCCA, and patients with and without liver cirrhosis have been included in the analyses.[41,42] This heterogeneity in some of the analyzed patient populations has limited the inferences that can be made. There has, however, been a recent reappraisal of the role of LT with both single- and multi-institutional studies demonstrating favorable results in patients who underwent LT for other indications.[21,43] Given the contraindication of iCCA for LT, many of these patients were either diagnosed incidentally on explant pathology or were incorrectly diagnosed as having HCC before LT.

LT FOR SMALL UNRESECTABLE iCCA

Sapisochin et al., in 2014, performed a retrospective, multicenter study on 16 Spanish transplant centers, which identified 29 patients with cirrhosis with iCCA in the liver explant, many of whom had a pre-LT diagnosis

of HCC.[21] Of these patients, 8 had "very early" iCCA (≤2 cm), and 4 of these 8 were incidental tumors. Tumor recurrence risk was associated with larger tumor size and volume, microscopic VI, and poor tumor differentiation. Compared to patients with single tumors >2 cm, the very early iCCA group had no tumor recurrence versus 36.4% in the larger-tumor-size group with a median follow-up of 36.4 months (median follow-up of 51.9 months in the very early iCCA group). The actuarial survival for the very early iCCA group was excellent with 1-, 3-, and 5-year survival rates of 100%, 73%, and 73 versus 71%, 43%, and 34% in the larger-tumor-size group (p = 0.2).[21] This study was followed by a larger, retrospective, international multi-institutional series in 2016, including 17 major transplant centers.[43] The study cohort comprised patients who had undergone LT for HCC or decompensated cirrhosis and had iCCA incidentally identified at explant. In the study period 2000–2013, 48 patients had iCCA only. Of these, 15 (31%) were "very early" and 33 (69%) were larger (>2 cm) or multifocal iCCA. The 1-, 3-, and 5-year cumulative incidence of recurrence was 7%, 18%, and 18% for the very early iCCA group versus 30%, 47%, and 61% for the advanced group (p = 0.01). The corresponding 1-, 3-, and 5-year survival rates were 93%, 84%, and 65% in the very early iCCA group versus 79%, 50%, and 45% in the advanced group (p = 0.02).[43] It is noteworthy that the 5-year recurrence rate of 18% and 5-year survival of 65% are within the accepted standard oncological outcomes expected of HCC, a well-established indication for LT.

There have been several additional studies for LT in the setting of small iCCA, which have demonstrated overall mixed results regarding survival and recurrence rates (Table 2). There is significant heterogeneity in the study populations, with varying tumor sizes, inclusions (including patients with concomitant HCC nodules), and grouping iCCA with mixed HCC-CCA. The rationale for the latter grouping is that distinguishing between iCCA versus mixed HCC-CCA for a definitive presurgical diagnosis is challenging and may not be feasible and thus more consistent with real-life clinical practice.[44] It is worth noting that these mixed-type, or biphenotypic, tumors typically have a prognosis between pure HCC and pure CCA.[45] A recent meta-analysis from 2020 was based on 18 studies comprising 355 patients together with a registry-based study of 385 patients. The pooled 1-, 3-, and 5-year OS rates were 75% (95% CI, 64–84), 56% (95% CI, 46–67), and 42% (95% CI, 29–55), and corresponding recurrence-free survival (RFS) rates of 70% (95% CI, 63–75), 49% (95% CI, 41–57), and 38% (95% CI, 27–50).[46] Cirrhosis was positively associated with RFS (the higher the proportion of patients with cirrhosis, the higher the RFS), whereas an incidental diagnosis was not associated with RFS.[46] Moreover, neither cirrhosis nor an incidental diagnosis was associated with OS.[46] The researchers found a pooled overall recurrence rate of 43% (95% CI, 33–53) over a mean follow-up of 40.6 ± 37.7 months.[46] On a subgroup analysis of only patients with very early (single iCCA, ≤2 cm) disease, the pooled 5-year RFS (67%; 95% CI, 47–86) was better than in patients with more locally advanced iCCA (34%; 95% CI, 23–46).[46]

LR VERSUS LT

The favorable outcomes noted in some studies for LT in iCCA have led to some groups seeking to compare how these outcomes may compare to those of LR. Hue et al. evaluated the U.S. hospital-based National Cancer Database, which captures >70% of all newly diagnosed cancer cases in the USA,[47] in a contemporary era with modern chemotherapy (2010–2016), for a comparative evaluation of outcomes between iCCA patients who underwent LR and LT.[48] The researchers performed a propensity-score–matched analysis matching the two treatment groups (1879 LR and 74 LT) based on age, sex, race, ethnicity, insurance payor, income, education, Charlson-Deyo comorbidity score, facility type, clinical T stage, receipt of neoadjuvant single- or multiagent chemotherapy, and receipt of radiotherapy.[48] After 1:1 matching, there were 57 patients in each group. The groups were similar in postoperative outcomes and survival (1-, 3-, and 5-year survival 86.9%, 55.4%, and 38.8% for LT vs. 82.4%, 47.0%, and 34.9% for LR).[48] A subgroup analysis of patients with pathological T0-T2 disease (solitary tumor with intrahepatic VI or multiple tumors, with or without VI, regardless of size—presumably based on the AJCC [7th and 8th editions]) similarly demonstrated no differences in survival between the groups.[48] The researchers concluded that given similar outcomes between the groups, LR should remain the preferred treatment option for patients with localized iCCA. It should be emphasized that this represents results from a database analysis, and patients selected for LT were likely to have advanced underlying cirrhosis. The researchers also recognized, though, that there were limitations with the analysis, including the unavailability of a fibrosis/cirrhosis score, Model for End-Stage Liver Disease (MELD) score, functional status, detailed information on (neo) adjuvant therapy (such as the number of cycles completed), information about predicted future liver remnant, the number of tumors within the liver, and detailed operative information, such as blood loss, whether a tumor had been deemed to be surgically resectable, or information on any previous hypertrophic liver management such as portal vein embolization or associating liver partition and portal vein ligation for staged hepatectomy.[48] Moreover, the high rate of neoadjuvant chemotherapy (61.4% of LT patients) and neoadjuvant radiation (42.1% of LT patients) has raised some skepticism, especially given that iCCA does not represent an

TABLE 2 LT for iCCA

Author	Year	Tumor Size	Total	Incidental, n (%)	Misdiagnosed as HCC, n (%)	Pre-LT Known iCCA, n (%)	Cirrhosis, n (%)	Patient Survival Years (%)			Recurrence-Free Survival Years (%)			Recurrence Rate Years (%)		
								1	3	5	1	3	5	1	3	5
O'Grady et al.[35]	1988	—	13					38.4	10	—	—	—	—	—	—	—
Yokoyama et al.[76]	1990	—	2	—	—	—	—	50	0	—	—	—	—	—	—	—
Pichlmayr et al.[77]	1996	(Sizes not detailed) T1: ductal wall, 2 pts T2: perimuscular connective tissue, 10 pts T3: adjacent structures, 13 pts N1, hepatoduodenal ligament, 8 pts	25	7	—	18	—	60	21.4	17.1	—	—	—	—	—	—
Casavilla et al.[36]	1997	T1, solitary, ≤2 cm, without VI ± regional nodes or T2: solitary,≤2 cm, with VI. Multiple, one lobe, ≤2 cm, without VI. Solitary, >2 cm, without VI, 3 pts T2: solitary, ≤2 cm, with VI. Multiple, one lobe, ≤2 cm, without VI. Solitary, >2 cm, without VI with regional nodes or T3 solitary, >2 cm, with VI. Multiple, one lobe, >2 cm, with or without VI, 4 pts T4: multiple, more than one lobe. Invasion of major branch of portal or hepatic veins, 10 pts Distant metastasis, 3 pts	20	—	—	20 —	8 (40)	70	29	18	67[a]	31[a]	31[a]	—	—	—
Shimoda et al.[78]	2001	pTNM stage I (single ≤2 cm, no VI), 2 pts II (single ≤2 cm with VI or multiple tumors in one lobe all ≤2 cm no VI; or solitary tumor >2 cm without VI), 2 pts III (tumor[s] of any size with or without VI with regional LNM), 3 pts IVa (mutiple tumors in more than one lobe or tumor invasion of major portal or hepatic venous branch with or without regional LNMs), 7 pts IVb (any tumor number, size and regional LNMs and metastatic disease), 2 pts	16	5	—		8	62	39	39	70	35	35	—	—	—

(Continues)

TABLE 2 (Continued)

Author	Year	Tumor Size	Total	Incidental, n (%)	Misdiagnosed as HCC, n (%)	Pre-LT Known iCCA, n (%)	Cirrhosis, n (%)	Patient Survival Years (%)			Recurrence-Free Survival Years (%)			Recurrence Rate Years (%)		
								1	3	5	1	3	5	1	3	5
Robles et al.[61]	2004	T1N0M0,[b] 4 pts T2N0M0,[b] 9 pts T3N0M0,[b] 4 pts T4N0M0,[b] 4 pts T4N1M0,[b] 2 pts	23	10 (44)	10	13	4 (17)	77	65	42	68	45	27	—	—	—
Sotiropoulos et al.[79]	2008	—	10	—	3	7	3 (30)	70	50	33	—	—	—	—	—	—
Hu et al.[80]	2011	>5 cm, 16 pts	20	20 (100)	—	—	4 (20)	84.2	32.7	21.8	55.6	28.8	18.8	—	—	—
Hong et al.[37]	2011	≥5 cm, 16 pts	25	—	—	25	—	—	—	—	69	42	32	—	—	—
Fu et al.	2011	TNM version unclear I: 3 pts II: 2 pts IIIA: 3 pts IIIC: 3 pts	11	—	3	8	6 (55)	50.5	50.5	—	51.9	51.9	—	—	—	—
Friman et al.[81]	2011	Not detailed	33	16 (49)	—	—	—	68[c]	42[c]	33[c]	—	—	—	—	—	—
Vallin et al.[82]	2013	Single ≤2 cm, 3 pts ≤2 cm and multiple, 1 pt Single >2 cm, 5 pts >2 cm and multiple, 1 pt	10	6 (60)	4 (40)	—	10 (100)	80	60	24	40	50	50	—	—	—
Patkowski et al.[83]	2014	Tumor size ranged from 2 to 6 cm; 5 of 6 pts had solitary lesions, and 2 of 6 pts had poorly differentiated tumors.	6	6 (100)	—	—	—	78	22	—	60	0	—	—	—	—
Sapisochin et al.[17]	2014	Overall, 29 pts ≤2 cm, 8 pts Multiple or single >2 cm, 21 pts	29	23 (79)	—	—	29 (100)	79 100 71	61 73 43	45 73 43	89 0 74	71 0 58	71 0 58	—	—	—
Facciuto et al.[84]	2015	Combined iCCA/mixed HCC-CCA for analyses iCCA, 7 pts Goodman type I: iCCA and HCC separate nodules, 9 pts Goodman type II: mixed HCC-CCA in same nodule or mixed HCC-CCA + concomitant HCC nodules, 12 pts	7			4		71	57	57	—	—	44	—	—	—

TABLE 2 (Continued)

Author	Year	Tumor Size	Total	Incidental, n (%)	Misdiagnosed as HCC, n (%)	Pre-LT Known iCCA, n (%)	Cirrhosis, n (%)	Patient Survival Years (%)			Recurrence-Free Survival Years (%)			Recurrence Rate Years (%)		
								1	3	5	1	3	5	1	3	5
Lindner et al.[85]	2015	—	5	2 (40)	—	—	—	—	60	—	—	—	—	—	—	—
Sapisochin et al.[39] (advanced)	2016	Single >2 cm or multiple tumors, 33 pts	33	8 (24)	—	—	33 (100)	79	50	45	—	—	—	30	47	61
Sapisochin et al[39] (very early)	**2016**	Single ≤2 cm, 15 pts	15	7 (47)	—	—	15 (100)	93	84	65	—	—	—	7	18	18
Elshamy et al.[64]	**2017**	Combined iCCA/mixed HCC-CCA for analyses Pathology lesion number, 1.0 ± 0.0 Pathology largest lesion (cm), 2.7 ± 0.4 Tumor differentiation well/moderate/poor 0/3/1	4	2 (50)	2 (50)	4	—	85[k]	51[k]	51[k]	68[k]	51[k]	41[k]			
Jung et al.[86]	**2017**	Single ≤2 cm, 4 pts ≤2 cm and multiple, 2 pts Single >2 cm, 10 pts	16	1 (6)	14 (88)	—	12 (13)	81.3 62.5[d]	52.4 62.5[d]	52.4 —	—	—	—	56.2 50.0[d]	56.2 50.0[d]	78.1 —
Lee et al.[40]	2018	Single ≤2 cm, 16 pts (on pathology) Multiple or single >2 cm, 28 pts (on pathology)	44	3 (18)	—	—	—	78.6 87.5[e] 77.0[f] 63.6[g]	— 62.5[e] 69.0[f] 63.6[g]	54.5 37.5[e] 62.5[f] 63.6[g]	—	—	—	21.0[e] 30.0[f] 29.0[g]	47.5[e] 58.0[f] 42.0[g]	47.5[e] 58.0[f] 42.0[g]
Lunsford et al.[18]	2018	Locally advanced disease status after neoadjuvant therapy Multiple and >2 cm, 5 pts Single and >2 cm, 1 pt	6	—	—	6 (100)	1 (17)	100	83.3	83.3	50	50	50	—	—	—
Krasnodebski et al.[87]	2020	Single ≤2 cm, 1 pt Multiple or single >2 cm, 7 pts	8	4 (50)	4 (50)	—	8 (100)	75	37.5	25	71.4	28.6	28.6	—	—	—

(Continues)

TABLE 2 (Continued)

Author	Year	Tumor Size	Total	Incidental, n (%)	Misdiagnosed as HCC, n (%)	Pre-LT Known iCCA, n (%)	Cirrhosis, n (%)	Patient Survival Years (%)			Recurrence-Free Survival Years (%)			Recurrence Rate Years (%)		
								1	3	5	1	3	5	1	3	5
De Martin et al.	2020	Combined iCCA/mixed HCC-CCA for analyses	24 iCCA total (49 total iCCA and mixed HCC-CCA)	5 (10)	44		49 (100)	90	76	67	87	79	75	—	—	—
		Largest nodule ≤5 cm, 49 pts						88[h]	65[h]	65[h]	81[h]	74[h]	74[h]			
								92[i]	87[i]	69[i]	78[i]	69[i]	55[i]			
								87[j]	65[j]	65[j]	80[j]	75[j]	75[j]			

Abbreviations: cHCC, combined hepatocellular-cholangiocarcinoma; HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma; LT, liver transplant; pts, patients; pTNM, pathological TNM.

[a]Tumor-free survival.

[b]TNM 5th edition, Sobin et al., Union for International Cancer Control.

[c]Based on patients undergoing LT after 1995 (*n* = 19).

[d]Patients with iCC alone (*n* = 8).

[e]Patients with single ≤2 cm based on pathology (*n* = 16).

[f]Patients multiple or single >2 cm based on pathology (*n* = 28).

[g]Patients with single ≤2 cm (*n* = 12) based on pre-LT imaging.

[h]iCCA and cHCC-CCA combined tumor size >2 but ≤5 cm (*n* = 24).

[i]≤2 cm iCCA and mixed HCC-CCA combined tumors (*n* = 25).

[j]>2 and ≤5 cm iCCA and cHCC-CCA combined tumors (*n* = 24).

[k]iCCA and mixed HCC-CCA combined tumors (*n* = 13).

accepted LT indication in the USA and hence receiving such treatments would be unlikely, given that most would presumably only be identified incidentally on the liver explant.[49] Though smaller case series have evaluated outcomes of LT in iCCA patients who received previous neoadjuvant therapy, these numbers are significantly lower than those presented.[22,48,50] This may be related to issues inherent to large registries, such as misclassification. Some pCCA or HCC may have been classified as iCCA, which would explain the discrepancies in neoadjuvant therapy use, given that pre-LT therapies are common in these entities in the Mayo Clinic protocol (which has been used as a basis for approving pCCA as an indication for LT as approved by the Organ Procurement and Transplantation Network [OPTN] and the United Network for Organ Sharing [UNOS])[51] and as bridging therapy in patients with HCC.[52,53] Notwithstanding these limitations, this demonstrates at least equipoise between the treatment modalities. Finally, it is important to mention that LR and LT in this setting are complementary given that LT is offered to patients with nonresectable disease.

Recently, De Martin et al. performed a multicenter study, including three French Tertiary Hepatobiliary centers, comparing outcomes of patients with cirrhosis who underwent LT or LR between 2002 and 2015 with iCCA or mixed HCC-CCA found incidentally.[54] The researchers included iCCA and mixed HCC-CCA in their analyses, with all tumors being ≤5 cm. There were 49 patients in the LT group and 26 in the LR group.[54] Overall, LT had a higher 5-year RFS (75% vs. 36%; $p = 0.004$). Similarly, for the subgroup of tumors >2 and ≤5 cm, LT had a nonstatistically significantly higher 5-year RFS (74% vs. 40%; $p = 0.06$) and a nonstatistically significantly lower recurrence rate (21% vs. 48%; $p = 0.06$).[54] Based on forward step-wise regression modeling, the researchers found that LT was associated with a lower risk of recurrence (HR, 0.23; 95% CI, 0.07–0.82; $p = 0.02$), with factors being associated with a higher risk being the size of the largest nodule and tumor differentiation.[54] The 5-year OS rate for patients who underwent LT and had tumors ≤2 cm and >2 to ≤5 cm was 69% and 65%, with no differences in survival noted between the LT patients who had pure iCCA and those with mixed HCC-CCA ($p = 0.29$).[54] The effect of preoperative treatments, the proportion of which was higher in the LT group (TACE, 55% vs. 4%; $p = 0.005$), the response to such therapies, and the impact and response of biomarkers such as carbohydrate antigen 19-9 (CA 19-9) is not clear.[54] Moreover, the analysis was by design per protocol, evaluating the outcomes from the time of LT rather than the time of listing. As such, it remains unclear what proportion of iCCA and/or mixed HCC-CCA patients may experience waitlist dropout attributable to tumor progression.

Despite several recent studies that have evaluated comparative outcomes between LR and LT for iCCA, as mentioned previously, it is unlikely that a fair comparison between the groups is possible given the selection bias that is likely inherent in the retrospective design. Moreover, a randomized controlled study between the two modalities is challenging. Given that iCCA does not represent a formally accepted indication for LT, the patients were either preoperatively determined (erroneously) to have HCC or had iCCAs discovered incidentally on explant pathology. Given the prevailing organ scarcity, a patient with an iCCA amenable to LR should undergo LR.[2] However, the clinical scenario involving a patient with localized disease, who has a contraindication to undergoing LR, is more challenging and remains to be fully elucidated. The options, in this case, include a potential LT, currently only in a clinical trial setting, LRTs, or palliative systemic therapy.

OUTCOMES WITH LRTs FOR PATIENTS WITH LIVER-ONLY iCCA NOT AMENABLE TO LR

There are several LRT options for patients that have disease localized to the liver. Given that LT represents a potential alternative for these patients, a discussion of oncological outcomes with nonsurgical therapies is warranted.

Ablation

There are limited data on the use of ablation for iCCA compared to HCC. For nonsurgical patients with small lesions, ablation may represent a valuable option, though the main limitation is a high recurrence rate.[55] Using data from the SEER database, Xiang et al. evaluated patients with small ≤5-cm iCCA and compared OS and cancer-specific survival (CSS) between LR ($n = 150$) and radiofrequency ablation (RFA; $n = 34$).[55] The 1-, 3-, and 5-year OS were 87.4%, 73.3%, and 61.5% for LR versus 89.9%, 42.4%, and 23.9% for RFA ($p < 0.001$), and corresponding CSS rates of 91.5%, 73.8%, and 66.1% for LR versus 93.5%, 53.4%, and 30.0% ($p < 0.001$).[55] The difference was greater between the groups in the single iCCA <5-cm group ($p = 0.001$, favoring LR) compared with the single-iCCA <3-cm group ($p = 0.27$).[55] Diaz-Gonzalez et al. recently evaluated ablation outcomes for iCCA based on data from a single center.[56] Differences in survival were noted with a greater median OS of patients with a single lesion ≤2 cm (94.5 months) versus a single lesion >2 cm (24.3 months; $p = 0.04$).[56] There was a nonstatistically significantly shorter time to recurrence in patients with a single lesion >2 cm than those with a single lesion ≤2 cm ($p = 0.1$).[56] Brandi et al., from Italy, similarly found that a tumor size ≥2 cm is associated with lower local tumor progression-free survival and

may represent a cutoff for the use of RFA in this setting.[57] In a systematic review and meta-analysis from 2015, including seven observational studies comprising 84 patients, the pooled 1-, 3-, and 5-year survival rates were 82%, 47%, and 24% for RFA in patients with unresectable iCCA.[58]

Transarterial chemoembolization, Radioembolization, Hepatic artery infusion of chemotherapy, and Transarterial Radioembolization

A meta-analysis of transarterial chemoembolization (TACE) in patients with unresectable iCCA, including 16 articles (n = 542), found that median survival times from the time of diagnosis and first treatment was 15.7 ± 5.8 and 13.4 ± 6.7 months, respectively.[59] The weighted 1-year survival rate was 58.0% ± 14.5%.[59] A recently published systematic review and pooled analysis of LRTs in iCCA found a pooled mean weighted OS of 18.9 months (95% CI, 14.2–23.5) for EBRT, 14.1 months (95% CI, 12.1–16.0) for radioembolization, 15.9 months (95% CI, 12.9–19.0) for TACE, and 21.3 months (95% CI, 15.4–27.1) for hepatic artery infusion.[60] Another recent systematic review and meta-analysis by Mosconi et al. specifically evaluated intra-arterial therapies such as TACE and transarterial radioembolization (TARE).[61] Thirty-one articles comprising 1695 patients (TACE, n = 906; TARE, n = 789) were identified.[61] Median survival was similar between TACE (14.2 months; 95% CI, 11.6–17.6) and TARE (13.5 months; 95% CI, 11.4–16.1).[61] Unfortunately, the significant heterogeneity in the available literature precludes the development of firm recommendations for selecting one LRT over another.

Proton beam therapy

Proton beam therapy represents a newer possible treatment option for patients with iCCA. A multi-institutional phase II study from the USA evaluated high-dose hypofractionated proton beam therapy in patients with localized, unresectable HCC and iCCA.[62] In the 37 patients with iCCA, the local control rate (as defined by the Response Evaluation Criteria in Solid Tumors 1.0 criteria) at 2 years was 94.1% with an OS rate at 2 years of 46.5%.[62] Favorable results have been replicated in subsequent studies. Parzen et al. evaluated a prospective U.S. Proton Collaborative Group registry (nine institutions between 2013 and 2019), with 25 unresectable and treatment-naïve iCCA patients demonstrating a local control rate at 1 year of 90.9% and a 1-year OS rate at 81.8%.[63] A study from Japan evaluated outcomes in 37 unresectable iCCA patients and found 1- and 2-year OS rates of 60.3% and 41.4%, with 1- and 2-year local control (LC) rates of 100% and 71.5%, respectively.[64] Though short-term tumor control appears favorable with proton beam therapy, the durability of oncological outcomes remains to be clarified.

EBRT and stereotactic body radiation therapy

There is a role of EBRT and stereotactic body radiation therapy (SBRT) for patients with unresectable iCCA.[15] Within this, a combination of chemotherapy and radiotherapy may be beneficial, particularly for purposes of downstaging.[65,66] Tse et al. from the University of Toronto described the outcomes of SBRT for 10 patients with unresectable iCCA and Child-Pugh A cirrhosis not suitable for standard therapies from 2003 to 2006.[67] In this study, a median survival of 15.0 months (95% CI, 6.5–29.0) and a 1-year overall survival rate of 58% (95% CI, 23–83) were reported.[67] Thereafter, Chen et al. performed a larger, albeit retrospective, evaluation of 84 patients with unresectable iCCA from 1998 to 2008.[68] Of these, 35 received EBRT (five times weekly with a median dose of 50 Gy), and the remaining 49 patients comprised the non-EBRT group.[68] The researchers noted a complete response and partial response rate of the primary tumor in 9% and 29% of patients, with corresponding proportions in the LNMs of 20% and 40%.[68] Median survival of the EBRT group was 9.5 versus 5.1 months in the non-EBRT group.[68] More recently, Tao et al., from the MD Anderson Cancer Center, evaluated a retrospective cohort of 79 consecutive unresectable iCCA patients who received definitive radiation therapy from 2002 to 2014.[69] Median tumor size was 7.9 cm, and the majority (n = 70; 89%) of patients had received systemic chemotherapy before the radiation therapy. Median OS from the time of diagnosis was 30 months with a 3-year OS of 44%.[69] The researchers noted that higher radiation doses correlated with an improved LC and OS rate. When stratified by the biological equivalent dose (BED) of 80.5 Gy (deemed to represent an ablative dose), the 3-year OS was 73% in the higher-dose group (>80.5 Gy) versus 38% for the lower-dose group (≤80 Gy; p = 0.02).[69] Similarly, the LC rate was statistically significantly higher for the higher-BED group (78%, >80.5 Gy vs. 45%, ≤80.5 Gy; p = 0.04).[69] The BED delivered was associated with a favorable LC and OS hazard on multivariable analysis.[69] More recently, in 2019, Frakulli et al. performed a systematic review of the role of SBRT in advanced CCA.[70] The researchers included 10 studies (231 patients), with a primary outcome being OS and secondary outcomes being LC and toxicity rates.[70] The pooled 1-year OS was 58.3% (95% CI, 50.2–66.1) and 2-year pooled OS 35.5% (95% CI, 22.1–50.1).[70] The pooled 1-year LC was 83.4% (95% CI, 76.5–89.4), with the reported toxicities being

deemed to be acceptable and manageable. The researchers concluded that SBRT may yield outcomes equivalent to standard chemotherapy and radiotherapy options and could be considered a therapeutic option for patients with advanced CCA.[70] It should be noted, however, that the studies included in this systematic review were heterogeneous, and both primary intra- and extrahepatic CCA were included, as well as recurrent or metastatic disease.[70]

Immunotherapy

The role of immunotherapy, particularly checkpoint inhibition in patients with advanced CCA, continues to emerge and represents an exciting potential future therapeutic option in patients with iCCA. Recently, the TOPAZ-1 phase III clinical trial (randomized, double-blind, placebo-controlled, multicenter, global trial) demonstrated durvalumab (an immune checkpoint inhibitor and human monoclonal antibody that blocks the interaction of programmed death ligand 1 on tumor cells with programmed cell death 1 and CD-80 on T cells) in combination with standard-of-care chemotherapy (gemcitabine plus cisplatin) to have a statistically significant OS benefit versus chemotherapy alone as the first-line therapy in patients with advanced biliary tract cancer (iCCA, extrahepatic CCA, and gallbladder cancers).[71] The study is still ongoing, and the estimated study completion date is the middle of 2022.[72]

LOCALLY ADVANCED UNRESECTABLE iCCA AND NEOADJUVANT THERAPY

LT for large, locally advanced, unresectable iCCA is generally contraindicated, given the high recurrence rate and low OS rates.[1-3] The largest series was a multicenter report from Spain, which included 23 patients with iCCA and noted a 5-year survival of 42%, with superior survival noted in those with smaller tumors and those without perineural invasion.[73]

However, whether the addition of neoadjuvant therapy can result in acceptable outcomes is an area of renewed interest following the publication of a prospective series of 6 patients transplanted following neoadjuvant therapy by Lunsford et al., in 2018.[22] In this series, the neoadjuvant therapy involved a heterogenous strategy consisting of gemcitabine and cisplatin for all patients. Three patients also received erlotinib; 1 received FOLFIRI (folinic acid, fluorouracil, and irinotecan), and 1 received fluorouracil (*n* = 1). There was a mandatory minimum period of 6 months showing sustained response after the chemotherapy. The protocol included repeat imaging (including contrast-enhanced CT or MRI of the abdomen and pelvis, CT of the chest, and bone scans) every 3 months, which should demonstrate stable or regressing disease and absence of extrahepatic disease. Two patients underwent resection before LT, and 1 was treated with radiation consisting of 40 Gy in five fractions to a surgical margin that was microscopically positive after initial resection. Median time to transplant from the time of diagnosis was 22 months. Following LT, all patients received adjuvant therapy consisting of gemcitabine (*n* = 4), capecitabine (*n* = 1), and gemcitabine plus capecitabine (*n* = 1). Recurrence occurred in 3 of 6 patients at a median of 7.6 months, whereas the remaining 3 patients have had no recurrence. One patient died at 13 months post-LT, whereas the remaining 2 with recurrence remained stable on systemic therapy after resection of metastasis at the time of publication. Tumor size was not related to recurrence, and the median cumulative diameter among transplanted patients was 14.2 cm, and no patient had a cumulative tumor diameter of <5 cm. Genetic mutation analysis was performed and published for all patients. Results of 3 additional transplanted patients, for a total of 9, were presented in abstract form in 2019.

An earlier experience using neoadjuvant therapy followed by LT for iCCA was reported by Hong et al. in 2011.[41] In this report, 38 patients underwent LT, including 25 with iCCA, with the remaining patients having pCCA. However, only 9 of 25 patients with iCCA received any neoadjuvant therapy, whereas 9 had no therapy and 7 had adjuvant therapy only. Of the 25 patients with iCCA who underwent LT, mean tumor size was 6.5 cm, and 16 of 25 (61%) had multifocal disease. Specific outcomes from this analysis are not reported separately for iCCA versus pCCA, though the overall 5-year survival was 33% for patients undergoing LT for CCA. Improved outcomes were noted in those with pCCA compared to iCCA. The heterogeneity of the patients, including both iCCA and pCCA, as well as those who did and did not receive neoadjuvant or adjuvant therapy, pose a significant limitation to interpreting the data.

The same group from UCLA recently published an updated experience of 53 patients, including 31 with iCCA.[42] In this new analysis, they separated the cohorts into those recently transplanted (*n* = 7; 2008–2019) compared to those transplanted previously (*n* = 22; 1985–2007). In the most recent era, they treated ~70% of patients with neoadjuvant therapy, whereas in the previous era, only 22% received neoadjuvant therapy. In the most recent era, patients with iCCA <6 cm received stereotactic beam radiotherapy whereas those with tumors >6 cm or multifocal tumors were treated with neoadjuvant chemotherapy consisting of a 5-fluorouracil-, capecitabine-, or gemcitabine-based regimen in combination with oxaliplatin, leucovorin, and cisplatin. The researchers note a trend toward improved survival in the most recent era, though

this was not significant. However, there were 4 patients with iCCA who received both neoadjuvant chemotherapy and liver-directed therapy in the most recent era who had a statistically significant survival advantage.

ONGOING PROSPECTIVE TRIALS FOR LT FOR iCCA

There are currently three ongoing trials (Table 3) that aim to evaluate the role of LT for ICCA in patients not amenable to LR: one for early iCCA, one for primary or recurrent iCCA, and one for locally advanced disease requiring downstaging therapy. Of note, though not registered as a clinical trial, the largest experience to date with LT for locally advanced iCCA is a prospective case series based on an LT protocol established by the Methodist-MD Anderson Joint Cholangiocarcinoma Collaborative Committee (MMAJCCC).[22]

NCT02878473 (Liver Transplantation for Early Intrahepatic Cholangiocarcinoma) is based in the University Health Network in Toronto, Canada and the Hospital Clinic of Barcelona, Spain. The enrollment goal is 30 patients, and 2 have been enrolled. The primary outcome is 5-year patient survival. The inclusion criteria include liver cirrhosis and a biopsy-proven iCCA ≤2 cm not amenable to LR. Additional criteria include a CA 19-9 ≤100 ng/mL.

NCT04556214 (Liver Transplantation for Non-Resectable Intrahepatic Cholangiocarcinoma: a Prospective Exploratory Trial [TESLA]) is based in Oslo University (Oslo, Norway). It is a single group, open-label study design with a planned enrollment of 15 participants. The primary outcome is overall survival from screening. To meet the inclusion criteria, patients must be ineligible for LR based on tumor location or underlying liver dysfunction, have no extrahepatic disease, and have good performance status. First-time iCCA and liver-only recurrent iCCA after previous LR is allowed.

NCT04195503 (Liver Transplant for Stable, Advanced Intrahepatic Cholangiocarcinoma) is based at the University Health Network in Toronto. It aims to evaluate the outcomes of LT for locally advanced, unresectable, nonmetastatic iCCA treated with neoadjuvant systemic therapy. Five-year patient survival is the primary outcome measure, and the enrollment goal is 10 patients. Since the study start date on December 10, 2019, 1 patient has been transplanted and 1 is awaiting transplant workup. To be eligible for inclusion in the trial, patients must have a histologically confirmed iCCA, not be candidates for LR, and have a living donor available.

MMAJCCC PROSPECTIVE CASE SERIES

In this series, Lunsford et al. reported their experience of an LT protocol for unresectable locally advanced iCCA. The protocol is based on receiving neoadjuvant therapy, achieving stable disease (determined based on a minimum of 6-month radiographic response or stability), followed LT.[22] To be eligible, patients needed to have tumors confined to the liver with a solitary tumor >2 cm or have multifocal disease without vascular or lymph node involvement. The group has published outcomes for 6 patients and reported on a total of 9 in abstract form.[22]

Nonetheless, there are several challenges with these ongoing trials. The rarity of these tumors makes recruitment difficult, particularly when only a few sites are participating in the study. Moreover, eligible patients must not only fulfill size and number criteria, but also have an absence of any extrahepatic disease, in some cases have a living donor available, and also not be candidates for LR. As evidenced by the several studies evaluating the outcomes of LT for iCCA, a consensus is lacking regarding whether iCCA and mixed HCC-CCA should be considered jointly or separately. The argument for considering them jointly is that a reliable pre-LT assessment of these two entities is not always possible, either with imaging or a percutaneous biopsy.[74,75] This difficulty in diagnosis is highlighted well in the studies shown in Table 2, where the iCCA was predominantly diagnosed incidentally (Table 2). However, the argument against considering the two entities jointly would be that combining the two may yield survival and recurrence estimates that are overly favorable, particularly if the dominant tumor phenotype is HCC. The difficulty in these patients is also the potential of several lesions being unrecognized before LT. As a result, several lesions may be present in the explant, including iCCA, mixed HCC-CCA, and HCC can be present in any given liver.[76] Deducing which lesion is the driver of adverse oncological outcomes and recurrence in this setting may be challenging or even impossible. Limiting heterogeneity in the study cohorts is critical to ensure that treatment guidelines based on them are as generalizable as possible. Donor scarcity is another challenge, and though a patient meets other inclusion criteria, they may not have a living donor available or be able to receive a deceased donor transplant in a timely manner if their physiological MELD score is low.

Several considerations will be relevant for ongoing and future trials that seek to clarify the role of LT for iCCA. Interdisciplinary collaborations and advances in radiology will be imperative to allow an accurate diagnosis that can be used to base future treatment decisions on. This may require nontraditional methodologies such as machine learning and radiomics, a field of imaging-based research to extract data from imaging as an imaging-based biomarker, to improve discrimination between lesions such as iCCA, HCC, and mixed HCC-CCA.[77,78] Next-generation

TABLE 3 Ongoing clinical trials evaluating LT in iCCA registered on www.clinicaltrials.gov

Population	Study Title	NCT No.	Inclusion Criteria	Lead Center(s)	Primary Outcome	Secondary Outcomes
Very early iCCA	Liver transplantation for Early Intrahepatic cholangiocarcinoma	NCT02878473	• Biopsy-proven iCCA ≤2 cm • Liver cirrhosis not amenable to LR • CA 19-9 ≤100 ng/mL	• University Health Network • Toronto, Canada • Hospital Clinic of Barcelona • Barcelona, Spain	Five-year patient survival	• Five-year disease recurrence after LT
Primary or recurrent iCCA after LR	Liver Transplantation for Non-Resectable Intrahepatic Cholangiocarcinoma: a Prospective Exploratory Trial (TESLA)	NCT04556214	• Ineligible for LR based on tumor location or underlying liver dysfunction • No extrahepatic disease • Good performance status	• Oslo University • Oslo, Norway	OS from screening and until 36 months after inclusion	• OS from relapse • DFS • Start of new treatment/ change of strategy • Time to decrease in physical function and global health score • LT complication • Development of other malignancies • Survival in relation to biological markers
Locally advanced iCCA	Liver Transplant for Stable, Advanced Intrahepatic Cholangiocarcinoma	NCT04195503	• Locally advanced, unresectable, nonmetastatic iCCA that is histologically confirmed • Treated with neoadjuvant systemic therapy • Demonstration of disease stability/regression for a minimum of 6 months • Have a living donor available	• University Health Network • Toronto, Canada	Five-year patient survival	• Five-year DFS • One-year patient survival

Abbreviations: DFS, disease-free survival; NCT, the National Clinical Trial number.

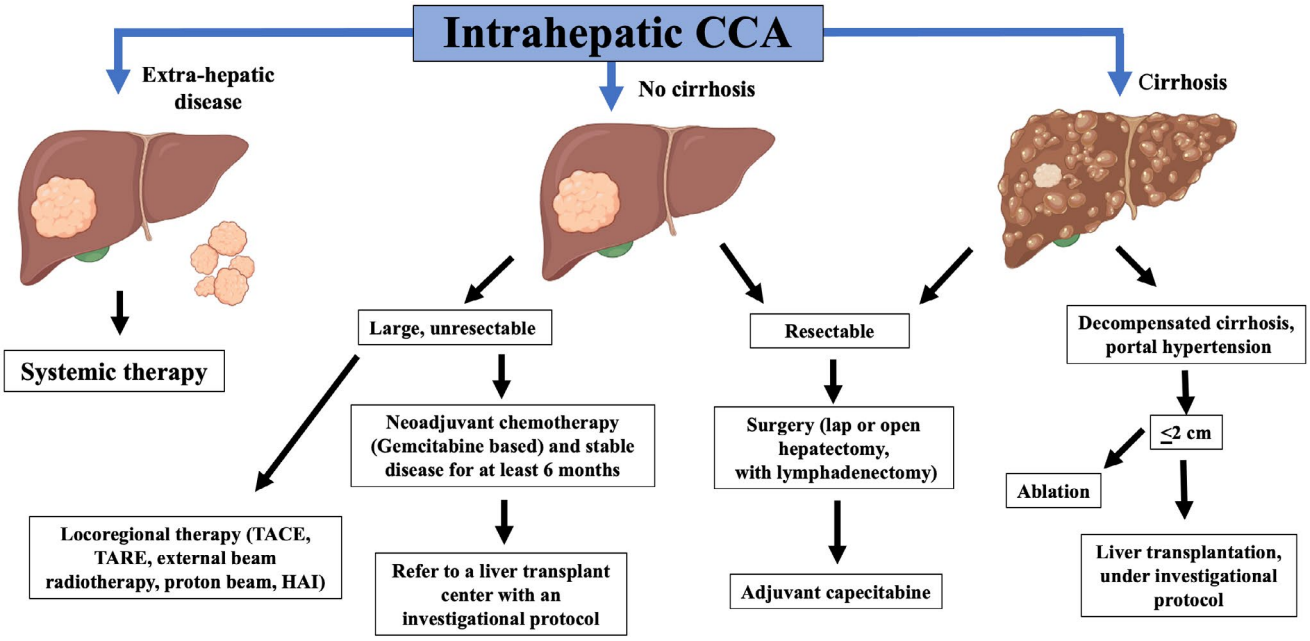

FIGURE 1 Proposed treatment approach to patients with iCCA and the role of LT (images created with BioRender.com)

sequencing methods can improve risk stratification when selecting patients for trials and treatment and potentially offer more targeted neoadjuvant therapy options.[79–81] Both the static and dynamic role of biomarkers such as CA 19-9 should be evaluated, which has been demonstrated to be associated with mortality in iCCA similar in magnitude to nodal metastases and positive resection margins.[82]

The expanded use of marginal grafts, which have shown significantly improved outcomes over time,[83] and the use of normothermic machine perfusion to salvage grafts that would otherwise have been discarded, may alleviate some of the prevailing scarcity, though, in most countries, organ allocation policy does not yet grant additional priority for iCCA. The recently established National Liver Review Board in the USA includes a guidance document intended to ensure consistency in submitting and reviewing nonstandard MELD exception requests. The guidance document is subjected to ongoing review and revision by the OPTN Liver Intestine Committee, including a period of public comment and submission to the OPTN Governing Board for any recommended changes. Currently, there is no guidance for LT in the setting of iCCA. However, as further evidence accumulates either in support of LT in iCCA or for settings where LT should not be considered for iCCA, revision of the NLRB guidance document to include such guidance may be needed.[49] The use of living donor liver transplant (LDLT) is another option that would secure a graft for the patients enrolled in the trials, though not all patients have a suitable living donor, and not all centers offer LDLT. Certain countries such as Norway, with a less pronounced organ scarcity, may be instrumental in further accelerating trial results and exploring the limits of patient selection, as has been observed with the previous SECA trials with LT for patients with colorectal liver metastases.[84] The TESLA trial is a good illustration of these opportunities, given that it allows the inclusion of patients with histologically verified iCCA regardless of size, either first-time iCCA or with liver-only recurrence after previous LR.[85] The role of bridging therapy in these patients remains to be clarified and could potentially prolong the time these patients can spend on the waitlist and possibly improve outcomes. An evaluation of intention-to-treat survival will also be necessary to gauge the proportion of patients listed for LT but who drop out for tumor progression. Within this context, survival benefit may represent an endpoint, which can help clarify the difference in survival with LT compared with other modalities. Finally, given the rarity of the disease, national and international collaborative efforts between institutions are vital to ensure that providers are aware of the trials and can refer their patients to be screened for possible inclusion.

SUMMARY: READY FOR PRIME TIME?

LT has emerged as a potential treatment option with curative potential for a highly select group of patients with iCCA. These include patients with very early disease (≤2 cm) who are not eligible for LR because of significant liver dysfunction and those with locally advanced

tumors without cirrhosis who can tolerate neoadjuvant chemotherapy. If disease stability can be demonstrated for at least 6 months, indicative of favorable biology, LT can be considered under investigational protocols, as highlighted in Figure 1.

The tumor biology of iCCA is typically more aggressive than HCC. Though a comparative evaluation of waitlist outcomes between the two is naturally unable to be performed at this time, patients with pCCA, a well-established LT indication, have been noted to have a higher cumulative incidence of dropout at 6 and 12 months (pCCA 6-month, 13.2% vs. HCC 7.3% and pCCA 12-month, 23.9% vs. HCC 12.7%) based on a USA population-based analysis of listing outcomes from the UNOS registry.[86] It is possible that these inferences can be extended to iCCA patients as well. Consequently, strategies for how to mitigate potential adverse waitlist outcomes while simultaneously improving posttransplant outcomes for potential future patients listed for LT with iCCA will therefore have to be carefully considered. Options to improve outcomes of patients that are potential LT candidates may include improved patient selection based on biology using enhanced staging techniques, including cell-free DNA and effective neoadjuvant therapies.[87] Tumor biology will be a critical determinant of patient outcomes before and after LT. Within this context, certain histological growth patterns, like the tubular growth pattern of iCCA, have a higher association with metastatic disease than the papillary type.[88] In addition, specific genetic determinants, such as tumor protein p53, KRAS, and cyclin-dependent kinase inhibitor 2A, may portend a worse prognosis in unresectable iCCA patients and may be helpful in further stratifying patients and aiding in refining treatment selection. At this time, however, there is a lack of studies available on tumor growth patterns and doubling times, which represents a significant impediment to a better understanding of this disease in the setting of transplant listing.

There are recently published consensus statements from the International Liver Transplantation Society Working Group on Transplant Oncology regarding the role of LT in iCCA.[89] These include a moderate-strength conditional recommendation regarding upfront LT in patients with very early iCCA (≤2 cm) and consideration for LT candidacy in patients without cirrhosis in the presence of locally advanced disease with disease stability after neoadjuvant therapy.[89] Moreover, based on moderately strong evidence, a strong recommendation was put forth to pursue a biopsy in patients with cirrhosis being considered for LT with a liver nodule that has atypical radiological features for HCC on cross-sectional imaging.[89] Genomic profiling through whole-genome sequencing was conditionally recommended based on low-level evidence to aid in identifying new molecular pathways and risk stratification.[89] Last, the treatment choice for iCCA should be LR, with the highest level of evidence and a strong recommendation, and that LT should be reserved for patients with unresectable disease only in the setting of strict clinical trial protocols (moderate evidence, strong recommendation).[89]

Historically, a 5-year survival exceeding 50% has been considered acceptable when considering an indication for LT.[90] This outcome can likely be achieved in a select group of patients with very early disease.[43] Though several studies evaluating LT for iCCA have failed to reproduce these results, the study cohorts have been highly heterogeneous regarding both histological and tumor morphometric groupings. Consequently, the only ways to demonstrate that outcomes are acceptable are robust prospective trials with strict selection criteria to limit such heterogeneity. Within this context, LT for iCCA should not be viewed in a vacuum. Instead, the option of LT in this select group of patients should be considered in light of the outcomes of alternative treatments such as various LRTs and systemic therapies, which have generally shown inferior outcomes, though, importantly, these therapies continue to evolve. Direct comparative analyses between LT and such therapies are currently unavailable. Radiological and genomic advancements will aid in increasing diagnostic precision, improving risk stratification, and refining patient selection. Given the rarity of iCCA and the strict selection criteria, dissemination of ongoing prospective trials is imperative to maximize patients' access to them and accelerate the accrual process. In light of all these considerations, though LT for iCCA is not currently ready for prime time, significant progress has been made in the field. As a result, these efforts have helped pave a promising path forward in improving future outcomes for patients afflicted with this disease.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Gonzalo Sapisochin: manuscript review; Tommy Ivanics: literature review and manuscript writeup; and Julie Heimbach: manuscript writeup.

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