Calderon Novoa *et al. Hepatoma Res* 2023;9:33
DOI: 10.20517/2394-5079.2023.36

Hepatoma Research

Review

Open Access

Liver transplantation for intrahepatic cholangiocarcinoma: a narrative review of the latest advances

Francisco Calderon Novoa[1], Victoria Ardiles[1,2], Juan Pekolj[1,2], Juan Mattera[1,2], Martin de Santibañes[1,2]

[1]Department of general surgery, Hospital Italiano de Buenos Aires, Buenos Aires C1181ACH, Argentina.
[2]Department of Surgery, Division of HPB Surgery, Liver Transplant Unit, Hospital Italiano de Buenos Aires, Buenos Aires C1181ACH, Argentina.

Correspondence to: Dr. Martin de Santibañes, Department of Surgery, Division of HPB Surgery, Liver Transplant Unit, Hospital Italiano de Buenos Aires, Juan D. Perón 4190, Bunos Aires C1181ACH, Argentina. E-mail: martin.desantibanes@hospitalitaliano.org.ar

How to cite this article: Calderon Novoa F, Ardiles V, Pekolj J, Mattera J, de Santibañes M. Liver transplantation for intrahepatic cholangiocarcinoma: a narrative review of the latest advances. *Hepatoma Res* 2023;9:33. https://dx.doi.org/10.20517/2394-5079.2023.36

Received: 20 Apr 2023 **First Decision:** 6 Jun 2023 **Revised:** 28 Jun 2023 **Accepted:** 21 Jul 2023 **Published:** 28 Jul 2023

Academic Editors: Rong-Qian Wu, Bruno Nardo, Kelvin K Ng, Pierluigi Toniutto **Copy Editor:** Dan Zhang **Production Editor:** Dan Zhang

Abstract

Intrahepatic cholangiocarcinoma (iCCA) is a rare tumor that arises from second order or smaller bile ducts. Its incidence has been growing in the last couple of decades, in parallel with its mortality rates, both in America and Europe. The currently accepted gold treatment for iCCA is liver resection (LR). However, results are still poor, with 5-year survival rates ranging between 25% and 40%. In addition, more than half of the patients undergoing LR will relapse, particularly those who present with multifocal iCCA. Given the aggressiveness of this tumor, and the modest results seen with adjuvant and neoadjuvant therapies, the sights have been set on liver transplantation (LT) for this disease. Retrospective studies have shown encouraging results in select patients, especially those with very early-staged iCCA (< 2 cm) who underwent LT. The aim of this review is to analyze the current information regarding LT for iCCA, as well as future perspectives.

Keywords: Intrahepatic cholangiocarcinoma, LT, iCCA

INTRODUCTION

Intrahepatic cholangiocarcinoma (iCCA) is a rare entity, corresponding to less than 5% of all gastrointestinal malignancies worldwide[1]. It accounts for approximately 10% of all hepatobiliary malignancies, and its clinical course is quite distinct from hilar or distal cholangiocarcinoma (CCA). Its usual presentation is that of a mass-forming tumor in 65% of cases[2], and other subtypes include periductal infiltrating type and intraductal papillary infiltrating type[3,4]. As of the latest AJCC edition, early iCCA is considered to be < 5 cm with no vascular invasion, while that with vascular invasion of a larger size is considered advanced[3]. Global iCCA trends of incidence and mortality have been rising during the last decades, as shown by numerous studies[5-13]. A 2019 study from 32 countries using World Health Organization and Pan American Health Organization registries from 1995 to 2016 showed that mortality from iCCA reached its peak from 2010 to 2014, with rates of 1.5-2.5/100.000 in men and 1.2-1.7/100.000 in women[10]. A recent analysis of the SEER database revealed an increase in the incidence of iCCA from 0,6 per 100.000 in the year 2000 to 1.3 per 100.000 in 2018[13]. This rise in incidence and mortality is explained by several reasons, including diagnostic tool improvements, and a concomitant increase in risk factors associated with iCCA, such as viral hepatitis, obesity and metabolic syndrome[9-13], predominantly in Western countries. Hepatitis B virus remains a significant risk factor for the development of iCCA. Several meta-analyses consistently show that the pooled risk of developing iCCA in HBV patients is over three times higher when compared to the HBV-negative population (HR 3.17-3.42)[14,15]. Other recent studies have identified primary sclerosis cholangitis as a risk factor for iCCA, with as high as a 30-fold increase in the risk of developing any type of CCA compared to the general population[16,17]. Most cases of iCCA are diagnosed at advanced stages, with only 10 to 35% of patients being amenable to curative treatment upon diagnosis[18,19]. Furthermore, only 5% of all patients are alive at 5 years[20], due to this tumor 's high aggressiveness. Of those patients who are suitable candidates for liver resection (LR), 60% will relapse at 5 years, and only 10% of patients will be completely cured[20,21].

The high number of patients diagnosed at advanced stages, and the considerable amount of reports showing iCCA in liver specimens preoperatively interpreted as HCC show that correctly diagnosing iCCA remains challenging, to say the least. It remains an unfrequent tumor, even in high-risk cohorts, such as patients with liver disease, and non-invasive methods have discrete success rates. Conventional diagnosis of iCCA relies primarily on imaging, such as US, computed tomography and magnetic resonance imaging, preferably with contrast. Imaging features vary significantly between subtypes, and may present with either hypoatenuation or hyperatenuation, perilesional bile duct dilation and infiltrative contour[22-25]. Recent studies suggest morphologically distinct features for HBV-related iCCA such as capsule, frequent washout pattern, smaller size and homogeneous tumor signals, and are usually characterized as LR-M in the LI-RADS classification[26]. However, due to the shared risk factors between HCC and iCCA and the context of liver disease, the distinction between both entities may be a hardship[22].

CA 19-9 antigen, a commonly employed biomarker for biliary tract malignancies, has been reviewed in a meta-analysis of 31 studies with over 3,100 individuals, having a sensitivity of 0.72 and a specificity of 0.84 for cholangiocarcinoma[27], and is not currently recommended for either screening or diagnosis. Micro-RNAs have been presented as a promising tool as biomarkers in several cancers, including CCA, and several studies have found the predictive value of different mi-RNA markers in iCCA, such as m6A[28]. A meta-analysis of 11 studies and 430 CCA[29] revealed that mi-RNA had a pooled specificity of 91.4% and a sensitivity of 75.6% with an AUC of 0.90 for the detection of CCA. However, mi-RNA assessment continues to be limited by costs, sample collection, and applicability.

Brushing samples obtained from endoscopic retrograde cholangiopancreatography (ERCP) has been described for the diagnosis of malignant biliary strictures. However, results in CCA are overall poor, with sensitivity below 60% in several reports[30-32]. This is most likely due to the desmoplasic characteristics of CCA[32]. Given the difficulties in the early detection of iCCA, it is no surprise that surgical results remain poor. With perioperative mortality ranging from 1%-9%[33-35], and five-year survival ranging between 20% to 45% at best[35-38], LR still lacks effectiveness, albeit being considered the gold standard for iCCA. The most frequent cause of death for resected patients is local recurrence in the liver, as shown by the low rates of disease-free survival (DFS) at 5 years, ranging from 2.1%-30%[33-38]. Most patients will die after a year of recurrence, in spite of locoregional treatment for the recurrence[30].

In the context of unfavorable results for LR in iCCA, LT has been proposed as a possible alternative. Theoretical benefits of LT for treatment of iCCA include the complete removal of the tumor and resolution of the underlying disease in cirrhotic patients. However, initial reports of LT for iCCA have been discouraging, with 5-year survival under 40%[39,40]. These numbers fall short of the expected 50%-60% LT survival defined as benchmark results. There have been several retrospective studies regarding LT and iCCA[41-47]. More recent studies from the last decade by Sapisochin *et al.* have shown extremely encouraging results for "Very early" stage iCCA, which have rekindled the attention and efforts towards iCCA and LT[48,49]. In spite of these efforts, high-yield evidence is lacking regarding the indication, patient selection and bridging therapies or adjuvant treatment for LT in iCCA. This article aims to review the road so far regarding LT for iCCA: Its initial poor results and contraindication for LT, followed by interesting findings regarding accidental iCCA in explant specimens from LT, and the encouraging results published regarding neoadjuvant therapies for LT in iCCA as well as future perspectives.

LIVER TRANSPLANT FOR INTRAHEPATIC CHOLANGIOCARCINOMA

Historical results for LT in Intrahepatic cholangiocarcinoma

Due to poor outcomes related to LR and the great advances in the field of transplant oncology, particularly regarding another primary liver tumor such as hepatocellular carcinoma (HCC), the last decade has seen a significant increase in the interest in LT in iCCA. Because of its rarity and non-specific imaging findings, most of the data regarding iCCA and LT is incidental. Initial publications regarding iCCA on explant specimens of LT date back to as early as the late 1980s, where outcomes were very poor[41,50]. O'Grady reported a total of 26 cholangiocarcinomas (13 "peripheral" and 13 "central"), with dismal 1-year OS results between 30%-38% for both groups, and almost 100% of recurrence for those patients who survived 1 year. Studies that followed the next 20 years also proved quite disappointing[39,40,42-44,51]. In light of these discouraging results, iCCA has been considered a relative and even absolute contraindication for LT in most centers for the last decades. The recent flare-up and increase in interest for LT in iCCA may be related to different factors: On one hand, it could be linked to the encouraging results observed in HCC using the BCLC staging system[52] and in perihilar cholangiocarcinoma and transplantation following the Mayo Clinic protocol[53]; On the other hand, it might be influenced by the work of Sapisochin *et al.*[48,49]. In 2014, a retrospective study analyzing outcomes of LT with specimen findings of an iCCA in 16 Spanish centers was published. Most centers enlisted patients according to Milan criteria. In a 10-year period, over 7000 patients were transplanted for end-stage liver disease (ESLD), of which 1% (29 patients) presented unexpected iCCA on the explant specimens, eight of which were classified as "Very early" iCCA (< 2 cm). With a mean follow-up of 3 years for the cohort, the recurrence rate was 24,1%, with a 5-year DFS of 71%. The 5-year actuarial rate was 45%. However, when performing a subgroup analysis of the 8 patients with very early iCCA, no patient experienced recurrence and had an impressive 5-year survival rate of 71%. Although the small sample size limited the statistical value of the study, a benefit for this population seemed evident, with a 2-cm size cutoff value univariately associated with poorer survival. This was perhaps the initial step towards the current paradigm shift regarding LT in iCCA. A couple of years later, in 2016, Sapisochin *et al.*

published a follow-up international study for external validation[49]. Now, with a total of 48 patients with iCCA, 15 with "very-early" and 33 with advanced iCCA. With a follow-up time of almost 5 years for the "very-early" group and over 2 years for the advanced iCCA group, tumor recurrence was seen in 13% of very early iCCA, while in 54% of the advanced iCCA ($P < 0.05$). The 5-year survival for the "very-early" group was indeed a staggering 65% compared to 45% in the advanced iCCA group. These values are above the arbitrarily stipulated threshold of 50% at 5 years suggested for oncological LT[54], and favor LT over LR as well. These findings clearly support LT as a viable and effective alternative for a select group of patients with iCCA. However, the low frequency of this tumor, difficulties in preoperative diagnosis and its contraindication for LT, as well as the limited organs available for allocation to patients without ESLD, make prospective trials for early iCCA a true challenge. These last findings have led transplant societies to include and consider iCCA as a potential indication for LT, given the correct scenario[55]. Table 1 summarizes the most important studies regarding iCCA in LT in the past 10 years. Currently, a single-armed clinical trial to determine the usefulness of transplantation in very early iCCA is ongoing (NCT0287847)[56].

A 2021 meta-analysis by Ziogas *et. al.* recollected and analyzed data from 18 studies and 355 patients with iCCA. The 1, 3 and 5-year OS rates were 75%, 56% and 42 %, respectively, coincident with previous reports[57]. RFS at 1, 3 and 5-years was 70%, 49% and 38%, meaning that over 60% of patients recur after 5 years. Subgroup analysis of very early stage (n = 29) and advanced stage (n = 79) showed relevant differences, with 5-year OS in the very-early group of 71% *vs.* 48% in the advanced iCCA group. However, the 5-year OS did not reach statistically significant differences, most likely due to the small sample size. RFS was also significantly higher in the very early group (67% *vs.* 34%), with an overall recurrence rate of 15% compared to 51% in the advanced group.

Tumor burden and nodal status

As described thus far, there are mainly two factors that have been shown to negatively affect survival after LT in iCCA: tumor size and the presence of nodal status.

Notwithstanding the encouraging results by Sapisochin *et al.*, preoperative diagnosis of iCCA continues to preclude LT in most centers worldwide, making large prospective analysis of the risk factors involved with survival and recurrence challenging, to say the least[48,49]. Small-sized tumors may be adequately treated by LT alone without previous or posterior adjuvant treatment. However, encouraging results such as those shown by the Methodist group with large 10 cm tumors adequately treated preoperatively appear to have similar results to smaller tumors. Perhaps, although size does matter and has been shown by several series to predict worse outcomes, The beneficial effect of neoadjuvant therapies may negate this. The authors believe that strict criteria such as tumor burden may potentially preclude many patients from receiving curative treatment in spite of their "unresectable" condition. Following the experience with HCC, there are many groups that no longer abide by the Milan criteria and have shown great results with patients using UCSF criteria. Such rules may also eventually apply to iCCA, and rather than only abide by tumor size, transplant groups should evaluate tumor biology by its response to neoadjuvant therapies in larger tumors.

Another key aspect is lymph node compromise. Lymph node assessment is, without a doubt, mandatory for LT in iCCA. Lymph node invasion has been shown to be an independent risk factor for worse DFS and OS in large LR series such as Kim *et al.*[33]. This can translate into LT, especially if we consider LT a form of extreme LR, in which one can achieve the best possible margins and cure underlying disease in the same procedure. Lymph node involvement can predict early recurrence and distant metastases, and should be ruled out either preoperatively by adequate imaging studies or intraoperatively by performing routine

Table 1. Literature review of studies in the last 10 years with patients with iCCA subject to LT

Authors	Study design	Year	*n*	NAT	5 yr DFS (%)	Overall survival (%)			Comments
						1 yr	3 yr	5 yr	
Valin *et al.*[80]	Retrospective	2013	10	No	-	80	60	24	
Sapisochin *et al.*[48]	Retrospective	2014	298 very early	8 TACE 3 RFA 2 PEI	29%	79%	61%	45%	very early survival 100%, 73% and 73%
Lindnér *et al.*[81]	Retrospective	2015	5	-	-	-	60%	-	no details on long-term outcomes
Facciuto *et al.*[82]	Retrospective	2015	32	69% 12 TACE 1 RFA 6 RFA + TACE 1 SRBT 1 TACE + SRBT	44%	71%	-	57%	only four biopsy-proven iCCA
Vilchez *et al.*[47]	Retrospective	2016	440	no	-	79%	58%	47%	
Takahashi *et al.*[60]	Retrospective	2016	13	no	-	-	-	-	
Sapisochin *et al.*[49]	Retrospective	2016	48 15 very early	48 15 very early	82% very early 39% advanced	93% 79%	84% 50%	65% 45%	**Very early** **Advanced**
Jung *et al.*[83]	Retrospective	2017	16	10 TACE 1 RFA 1 LR 2 LR + RFA	21.9	81.3	52,4	52,4	
Lunsford *et al.*[66]	Prospective single arm	2018	6	GEM-CIS	50	100	83.3	83.3	
Lee *et al.*[84]	Retrospective	2018	44	no	-	78.6	-	54.5	
De Martin *et al.*[61]	Retrospective	2020	49	62%	75	90	76	67	
Krasnodębski *et al.*[85]	Retrospective	2020	8	-	28,6	75	37,5	25	
MacMillan *et al.*[67]	Prospective single arm	2021	18	GEM-CIS 3 LR 4 SRBT 4 locoregional*	-	90%	61%	49	
Ito *et al.*[65]	Prospective single arm	2021	31	1- patients GEM-CIS + SRBT and TACE	42	80	60	49	

iCCA: Intrahepatic Cholangiocarcinoma; LT: Liver Transplantation; DFS: Disease-free survival; OS: overall survival; TACE: Transarterial Chemoembolization; PEI: percutaneous ethanol injection; RFA: Radiofrequency Ablation; LR: Liver resection; SBRT: Stereotactic Body radiation Therapy; GEM-CIS: Gemcitabine-Cisplatin; NAT: Neoadjuvant therapies. Locoregional therapies*: TACE, Transarterial radioembolization, RFA, and electroporation. Not specified in the manuscript.

lymph node dissection along with the explant. Given worldwide donor scarcity, it is of paramount importance to rule out lymph node involvement in order to avoid futile procedures.

Bridging/neoadjuvant therapies for LT in Intrahepatic Cholangiocarcinoma

The ever-growing and cumulative experience and trials have led to great advances in transplant oncology. Particularly regarding hepatocellular carcinoma (HCC), the most common primary malignancy of the liver, there are many studies that show benefit for cirrhotic patients with HCC, when correctly studied and stratified. Milan criteria[58], UCSF[59] and BCLC[52] staging system are different methods used to stratify cirrhotic patients with HCC, and determine the best treatment for each scenario. Patients with HCC and a BCLC staging score of "A" (tumors within Milan criteria in cirrhotic child A/Super A patients) have a clear indication for LT. However, due to donor shortage and "good" health status, these patients often suffer disease progression and migrate to a higher BCLC class due to either tumor growth or metastases while on the waitlist, missing the opportunity for a LT. Due to this issue, there have been many advances regarding neoadjuvant treatments (NAT) for patients with HCC who await a LT. " Bridging" therapies refer to these

locoregional treatments used to control local progression before transplant (transarterial chemoembolization, radioembolization, radiofrequency ablation, or even LR), while " downstaging" refers to the same therapies used to bring a patient from a higher BCLC score (usually BCLC B) to be considered for LT.

One of the questions related to iCCA and LT is if these therapies can be taken from the experience with HCC and reproduced for iCCA. As mentioned, prospective trials regarding NAT and LT in iCCA are limited due to low prevalence and exclusion from transplant when preoperative assessment identifies large iCCA-compatible masses in most centers. Takahashi *et al.* analyzed results for 13 patients with incidental iCCA in the specimen of LT, and were matched to patients with HCC in the explant specimen[60]. Four patients underwent TACE and one RFA. However, NAT before LT showed no benefit, with the RFS rate for these patients being worse than those without locoregional treatment (14 months *vs.* 24.6 months, $P = 0.91$). Recent publications have also studied neoadjuvant therapies. De Martin *et al.* recently published a study on 14 years of cirrhotic patients who underwent LT with specimen findings of iCCA previously interpreted as HCC[61]. 49 patients had an iCCA in the LT, and 31 of these (63%) had received some kind of preoperative treatment (mainly TACE). Almost a third of the patients with iCCA or mixed iCCA-HCC had vascular invasion or satellite nodules. Overall survival for the LT with iCCA population was 67% at 5 years, with a 75% DFS at 5 years, significantly better than the matched LR patients for this study. A trend favoring preoperative therapies as a protective factor for tumor recurrence was identified in the univariate analysis (HR 0.67, $P = 0.06$), but failed to reach statistical significance in the multivariate ($P = 0.12$). This study reaffirmed that tumor burden was the most important predictor of recurrence, and failed to find a significant protective value of preoperative TACE treatment over OS or DFS.

Rayar *et al.* have shown promise for both for treatment while on waitlist and downstaging using radioembolization with Yttrium-90[62,63]. However, as far as this review is concerned, there are only two centers that have published prospective results with standardized neoadjuvant protocols in patients with preoperatively confirmed iCCA: UCLA and the Houston Methodist-MD Anderson.

The first results presented by Hong *et al.* from UCLA in 2011 showed encouraging results of 25 locally advanced iCCA undergoing LT. This group was compared to 12 iCCA with LR[64]. Nine of these received NAT and adjuvant therapy, while 7 received only adjuvant after the LT. NAT consisted of stereotactic body radiation with a total of 40 Gy, delivered shortly in 7-12 days within five sessions. Following SBRT, patients continued with Capecitabine, Fluoracil or Gemcitabine-based regimes until the time of transplant. For those patients with iCCA larger than 3.5 cm, the locoregional therapy of choice was TACE instead of SRBT. Survival rates were significantly improved in patients who received combined adjuvant and NAT compared to no therapy or adjuvant therapy alone (8% recurrence *vs.* 40% and 50%, respectively). The same group has recently published their follow-up on these patients until 2019[65]. 31 patients were now enrolled, 23 of these received NAT, and 29 received adjuvant therapy. OS for the 31 patients was 49% at 5 years, with a DFS at 5 years of 42%. There was a trend for better survival in those patients who were transplanted in the "new era" (after 2007), and the best survival rates were associated with patients receiving both NAT and adjuvant therapies, independently of the era or tumor size. This may suggest that the use of perioperative therapies may level the field for patients with more advanced stages, and may make LT an option for a larger number of patients with significantly higher tumor burden.

In 2018, Lunsford *et al.* from Houston Methodist-MD Anderson published a prospective case series of gemcitabine-cisplatin based NAT followed by LT in 12 patients with biopsy-proven unresectable iCCA[66]. Using livers that would have been discarded (extended criteria donors or domino living donors), 6 patients

were transplanted. Neoadjuvant protocol for these patients consisted of first-line gemcitabine in combination with cisplatin, with optional locoregional therapy, mainly comprising SRBT. In order to be included in the protocol and listed, patients required a 6-month period of disease stability with neoadjuvant protocol. These patients presented with an 83% OS at 5 years and a 50% RFS, with no recurrences after the first year. This is the second of the prospective series of patients with a preoperative diagnosis of iCCA, and shows excellent results for a select few patients, using disease stability and treatment response as a surrogate for tumor biology. Follow-up with 36 patients enrolled on the waiting list using the same adjuvant protocol was published by this team in 2022[67]. Of these patients, 18 were eventually transplanted, with tumor size mean values of 10.4 cm, and multifocality present in 56% of transplanted patients. OS continued to show good results in this cohort, with rates of 100%, 71% and 57% at 1, 3 and 5 years respectively. 38% of LT patients recurred, with a median time to recurrence of 11 months. Another interesting information about this paper is that out of the 37 listed patients, 5 were resected after downstaging with NAT. Upon specimen analysis, one patient was found to have a complete pathological response. This protocol requires further investigation and external validation with robust data and eventually a randomized trial in order to confirm the findings. It would seem that neoadjuvant systemic therapy can potentially negate the effect of tumor burden, as this prospective series had comparable results to the very-early series by Sapisochin *et al.*, while presenting locally unresectable tumors with a mean size of 10 cm. Better refined prospective protocols with locoregional therapies are necessary in order to determine their real impact on iCCA[48,49]. It is the authors' opinion that although tumor size may be one factor that contributes to worse outcomes, a correct assessment of patients with iCCA as candidates for LT must focus not only on size but on other key factors such as lymph node invasion and response to neoadjuvant therapies. Disease stability or conversion towards resectable disease may be clear indicators for favorable outcomes and should prompt multidisciplinary teams to consider such patients for LT, as shown by the Houston Methodist's results with large locally advanced iCCA. Given the molecular similarities between iCCA and hCCA and other bile tract cancers, and the success of Gemcitabine-based regimes as shown by Lunsford[66], Macmillan[67] and S-1 adjuvant therapy by Nakachi *et al.*[68], we believe that tumor burden may serve initially as a cutoff value for neoadjuvant therapy, rather than a contraindication for LT. Patients with "very early" iCCA should be enlisted without the use of NAT, while patients with larger tumors could potentially benefit from Gemcitabine-based regimes and possibly local therapies, such as SRBT, and show evidence of stable disease before enlisting.

Follow-up after Liver Transplantation

As mentioned, recurrence rates after LT remain high. Following LR, recurrence location is most frequently intrahepatic, with over 60% of patients having intrahepatic recurrence either at the surgical margin or satellite nodules. This shows the effect of the pathological liver on the course of the disease, and the potential benefits of LT. Less than 15% of patients will have extra hepatic recurrence alone[69]. The time to recurrence varies depending on the recurrence pattern: intrahepatic margin recurrence as well as extrahepatic recurrence alone tend to be very early recurrences (6 months), possibly explained by either suboptimal surgery or unrecognized metastases at the time of resection. Non-marginal intrahepatic recurrences tend to happen slowly during the first two years of LR[70,71]. Given these typical patterns of recurrence, follow-up should be kept in an exhaustive manner for the 2-3 years, with gradual spacing out following this peak in recurrence. There are multiple known risk factors for recurrence after LR, such as tumor size, amount of lesions and vascular invasion[72,73], and preoperative CA 19.9 values, which may serve as a biological surrogate for disease burden[74,75]. In the last years, there have been several studies that have developed different tools in order to identify patients at higher risk of recurrence following a curative intent LR. Preoperative neutrophil-to-lymphocyte ratio, a very popular and easily obtainable parameter, has been found to have independent prognostic value for early recurrence (< 1 year) in resected iCCA[76]. Several groups are beginning to explore the applicability of AI and machine learning models to assist in predicting recurrence[77-79]. Machine learning radionics has been found to accurately predict recurrence using

radiological features in a cohort of 127 patient[77]. The field of AI and its applicability in oncology is a growing one and will likely affect follow-up regimes, shifting the paradigm towards patient-tailored follow-up. If we consider LT an extremely radical resection with R0 margins, many of the risk factors and outcomes from LR are likely to be shared, and nomograms and calculators such as the "metro ticket" may help the team in deciding follow-up timing and imaging, which should likely be performed routinely every three months for the first year with high-quality imaging such as CT or MRI scans, and then reassessed depending on each patient's individual risk factors.

CONCLUSIONS

There is not enough evidence to consider LT the gold standard for iCCA. However, there seem to be promising results when patients are correctly selected, and prospective trials combining systemic NAC and locoregional treatments with LT have shown very interesting long-term results.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study, literature search writing, and proofreading: Calderon Novoa F
Conception and design of the study, proofreading: de Santibañes M
Design of study, literature search, and writing: Ardiles V
Conception and design of the study, proofreading: Matera J
Literature search, writing, and proofreading: Pekolj J

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Gupta A, Dixon E. Epidemiology and risk factors: intrahepatic cholangiocarcinoma. *Hepatobiliary Surg Nutr* 2017;6:101-4. DOI PubMed PMC
2. Kendall T, Verheij J, Gaudio E, et al. Anatomical, histomorphological and molecular classification of cholangiocarcinoma. *Liver Int* 2019;39 Suppl 1:7-18. DOI
3. Liao X, Zhang D. The 8th edition american joint committee on cancer staging for hepato-pancreato-biliary cancer: a review and update. *Arch Pathol Lab Med* 2021;145:543-153. DOI
4. Nakanuma Y, Kakuda Y. Pathologic classification of cholangiocarcinoma: new concepts. *Best Pract Res Clin Gastroenterol* 2015;29:277-93. DOI PubMed

5. Dodson RM, Weiss MJ, Cosgrove D, et al. Intrahepatic cholangiocarcinoma: management options and emerging therapies. *J Am Coll Surg* 2013;217:736-750.e4. DOI
6. Poultsides GA, Zhu AX, Choti MA, Pawlik TM. Intrahepatic cholangiocarcinoma. *Surg Clin North Am* 2010;90:817-37. DOI PubMed
7. 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;125:1489-98. DOI PubMed PMC
8. Wu L, Tsilimigras DI, Paredes AZ, et al. Trends in the incidence, treatment and outcomes of patients with intrahepatic cholangiocarcinoma in the USA: facility type is associated with margin status, use of lymphadenectomy and overall survival. *World J Surg* 2019;43:1777-87. DOI
9. Xing H, Tan B, Yang C, Zhang M. Incidence trend and competing risk analysis of patients with intrahepatic cholangiocarcinoma: a population-based study. *Front Med* 2022;9:846276. DOI PubMed PMC
10. Khan SA, Genus T, Morement H, Murphy A, Rous B, Tataru D. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. *J Hepatol* 2019;71:1261-2. DOI PubMed
11. Bertuccio P, Malvezzi M, Carioli G, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. *J Hepatol* 2019;71:104-14. DOI
12. Clements O, Eliahoo J, Kim JU, Taylor-Robinson SD, Khan SA. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: A systematic review and meta-analysis. *J Hepatol* 2020;72:95-103. DOI PubMed
13. Petrick JL, Yang B, Altekruse SF, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based study in SEER-Medicare. *PLoS One* 2017;12:e0186643. DOI PubMed PMC
14. Zhou Y, Zhao Y, Li B, et al. Hepatitis viruses infection and risk of intrahepatic cholangiocarcinoma: evidence from a meta-analysis. *BMC Can-cer* 2012;12:289. DOI PubMed PMC
15. Li M, Li J, Li P, et al. Hepatitis B virus infection increases the risk of cholangiocarcinoma: a meta-analysis and systematic review. *J Gastroenterol Hepatol* 2012;27:1561-8. DOI
16. Chinchilla-López P, Aguilar-Olivos NE, García-Gómez J, et al. Prevalence, risk factors, and survival of patients with intrahepatic cholangiocarcinoma. *Ann Hepatol* 2017;16:565-8. DOI
17. Barner-Rasmussen N, Pukkala E, Hadkhale K, Färkkilä M. Risk factors, epidemiology and prognosis of cholangiocarcinoma in Finland. *United European Gastroenterol J* 2021;9:1128-35. DOI PubMed PMC
18. Izquierdo-Sanchez L, Lamarca A, La Casta A, et al. Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA registry. *J Hepatol* 2022;76:1109-21. DOI
19. Amini N, Ejaz A, Spolverato G, Kim Y, Herman JM, Pawlik TM. Temporal trends in liver-directed therapy of patients with intrahepatic cholangiocarcinoma in the United States: a population-based analysis. *J Surg Oncol* 2014;110:163-70. DOI PubMed
20. Spolverato G, Vitale A, Cucchetti A, et al. Can hepatic resection provide a long-term cure for patients with intrahepatic cholangiocarcinoma? *Cancer* 2015;121:3998-4006. DOI
21. Edeline J, Hirano S, Bertaut A, et al. Individual patient data meta-analysis of adjuvant gemcitabine-based chemotherapy for biliary tract cancer: combined analysis of the BCAT and PRODIGE-12 studies. *Eur J Cancer* 2022;164:80-7. DOI
22. Choi SH, Lee SS, Kim SY, et al. Intrahepatic cholangiocarcinoma in patients with cirrhosis: differentiation from hepatocellular carcinoma by using gadoxetic acid-enhanced MR imaging and dynamic CT. *Radiology* 2017;282:771-81. DOI
23. Park S, Lee Y, Kim H, et al. Subtype classification of intrahepatic cholangiocarcinoma using liver MR imaging features and its prognostic value. *Liver Cancer* 2022;11:233-46. DOI PubMed PMC
24. Rhee H, Kim MJ, Park YN, An C. A proposal of imaging classification of intrahepatic mass-forming cholangiocarcinoma into ductal and parenchymal types: clinicopathologic significance. *Eur Radiol* 2019;29:3111-21. DOI
25. Seo N, Kim DY, Choi JY. Cross-Sectional imaging of intrahepatic cholangiocarcinoma: development, growth, spread, and prognosis. *AJR Am J Roentgenol* 2017;209:W64-75. DOI PubMed
26. Sheng R, Wang H, Zhang Y, et al. MRI for hepatitis B-Associated intrahepatic cholangiocarcinoma: A multicenter comparative study. *J Magn Reson Imaging* 2023:Online ahead of print. DOI
27. Liang B, Zhong L, He Q, et al. Diagnostic accuracy of serum CA19-9 in patients with cholangiocarcinoma: a systematic review and meta-analysis. *Med Sci Monit* 2015;21:3555-63. DOI PubMed PMC
28. Wei F, Zhang JN, Zhao YQ, Lyu H, Chen F. Expression of m6A RNA methylation regulators and their clinical predictive value in intrahepatic cholangiocarcinoma. *Front Biosci* 2023;28:120. DOI PubMed
29. Liang Z, Liu X, Zhang Q, Wang C, Zhao Y. Diagnostic value of microRNAs as biomarkers for cholangiocarcinoma. *Dig Liver Dis* 2016;48:1227-32. DOI
30. Tanaka H, Matsusaki S, Baba Y, et al. Usefulness of endoscopic transpapillary tissue sampling for malignant biliary strictures and predictive factors of diagnostic accuracy. *Clin Endosc* 2018;51:174-80. DOI PubMed PMC
31. Nanda A, Brown JM, Berger SH, et al. Triple modality testing by endoscopic retrograde cholangiopancreatography for the diagnosis of cholangiocarcinoma. *Therap Adv Gastroenterol* 2015;8:56-65. DOI PubMed PMC
32. Kobayashi M, Ryozawa S, Araki R, et al. Investigation of factors affecting the sensitivity of bile duct brush cytology. *Intern Med* 2019;58:329-35. DOI PubMed PMC
33. Kim DH, Choi DW, Choi SH, Heo JS, Kow AW. Is there a role for systematic hepatic pedicle lymphadenectomy in intrahepatic cholangiocarcinoma? *Surgery* 2015;157:666-75. DOI

34. Nakagohri T, Kinoshita T, Konishi M, Takahashi S, Gotohda N. Surgical outcome and prognostic factors in intrahepatic cholangiocarcinoma. *World J Surg* 2008;32:2675-80. DOI PubMed
35. Lang H, Baumgart J, Heinrich S, et al. Liver resection for intrahepatic cholangiocarcinoma-single-center experience with 286 patients undergoing surgical exploration over a thirteen year period. *J Clin Med* 2021;10:3559. DOI PubMed PMC
36. Sotiropoulos GC, Bockhorn M, Sgourakis G, et al. R0 liver resections for primary malignant liver tumors in the noncirrhotic liver: a diagnosis-related analysis. *Dig Dis Sci* 2009;54:887-94. DOI
37. Si A, Li J, Yang Z, et al. Impact of anatomical versus non-anatomical liver resection on short- and long-term outcomes for patients with intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2019;26:1841-50. DOI
38. Paik KY, Jung JC, Heo JS, Choi SH, Choi DW, Kim YI. What prognostic factors are important for resected intrahepatic cholangiocarcinoma? *J Gastroenterol Hepatol* 2008;23:766-70. DOI PubMed
39. Becker NS, Rodriguez JA, Barshes NR, O'Mahony CA, Goss JA, Aloia TA. Outcomes analysis for 280 patients with cholangiocarcinoma treated with liver transplantation over an 18-year period. *J Gastrointest Surg* 2008;12:117-22. DOI PubMed
40. Goldstein RM, Stone M, Tillery GW, et al. Is liver transplantation indicated for cholangiocarcinoma? *Am J Surg* 1993;166:768-71; discussion 771. DOI
41. O'Grady JG, Polson RJ, Rolles K, Calne RY, Williams R. Liver transplantation for malignant disease. Results in 93 consecutive patients. *Ann Surg* 1988;207:373-9. DOI PubMed PMC
42. Yokoyama I, Todo S, Iwatsuki S, Starzl TE. Liver transplantation in the treatment of primary liver cancer. *Hepatogastroenterology* 1990;37:188-93. PubMed PMC
43. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation* 2000;69:1633-7. DOI PubMed
44. Shimoda M, Farmer DG, Colquhoun SD, et al. Liver transplantation for cholangiocellular carcinoma: analysis of a single-center experience and review of the literature. *Liver Transpl* 2001;7:1023-33. DOI
45. Robles R, Figueras J, Turrión VS, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg* 2004;239:265-71. DOI PubMed PMC
46. Ghali P, Marotta PJ, Yoshida EM, et al. Liver transplantation for incidental cholangiocarcinoma: analysis of the Canadian experience. *Liver Transpl* 2005;11:1412-6. DOI
47. Vilchez V, Shah MB, Daily MF, et al. Long-term outcome of patients undergoing liver transplantation for mixed hepatocellular carcinoma and cholangiocarcinoma: an analysis of the UNOS database. *HPB* 2016;18:29-34. DOI PubMed PMC
48. 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;14:660-7. DOI
49. Sapisochin G, Facciuto M, Rubbia-Brandt L, et al; iCCA International Consortium. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: International retrospective study supporting a prospective assessment. *Hepatology* 2016;64:1178-88. DOI
50. Pichlmayr R. Is there a place for liver grafting for malignancy? *Transplant Proc* 1988;20:478-82. PubMed
51. Sotiropoulos GC, Kaiser GM, Lang H, et al. Liver transplantation as a primary indication for intrahepatic cholangiocarcinoma: a single-center experience. *Transplant Proc* 2008;40:3194-5. DOI
52. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol* 2022;76:681-93. DOI PubMed PMC
53. Gores GJ, Darwish Murad S, Heimbach JK, Rosen CB. Liver transplantation for perihilar cholangiocarcinoma. *Dig Dis* 2013;31:126-9. DOI PubMed
54. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A; OLT for HCC Consensus Group. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012;13:e11-22. DOI PubMed PMC
55. Sapisochin G, Javle M, Lerut J, et al. Liver transplantation for cholangiocarcinoma and mixed hepatocellular cholangiocarcinoma: working group report from the ILTS transplant oncology consensus conference. *Transplantation* 2020;104:1125-30. DOI
56. Liver Transplantation for Early Intrahepatic Cholangiocarcinoma (LT for iCCA). Available from: https://clinicaltrials.gov/ct2/show/NCT02878473 [Last accessed on 27 Jul 2023].
57. Ziogas IA, Giannis D, Economopoulos KP, et al. Liver transplantation for intrahepatic cholangiocarcinoma: a meta-analysis and meta-regression of survival rates. *Transplantation* 2021;105:2263-71. DOI
58. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693-9. DOI
59. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;33:1394-403. DOI
60. Takahashi K, Obeid J, Burmeister CS, et al. Intrahepatic cholangiocarcinoma in the liver explant after liver transplantation: histological differentiation and prognosis. *Ann Transplant* 2016;21:208-15. DOI
61. 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;26:785-98. DOI
62. Rayar M, Sulpice L, Edeline J, et al. Intra-arterial yttrium-90 radioembolization combined with systemic chemotherapy is a promising method for downstaging unresectable huge intrahepatic cholangiocarcinoma to surgical treatment. *Ann Surg Oncol* 2015;22:3102-8. DOI

63. Rayar M, Levi Sandri GB, Houssel-Debry P, Camus C, Sulpice L, Boudjema K. Multimodal therapy including Yttrium-90 radioembolization as a bridging therapy to liver transplantation for a huge and locally advanced intrahepatic cholangiocarcinoma. *J Gastrointestin Liver Dis* 2016;25:401-4. DOI PubMed
64. 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;146:683-9. DOI
65. 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 Transpl* 2022;28:386-96. DOI
66. Lunsford KE, Javle M, Heyne K, et al; Methodist0-MD Anderson Joint Cholangiocarcinoma Collaborative Committee (MMAJCCC). Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. *Lancet Gastroenterol Hepatol* 2018;3:337-48. DOI
67. McMillan RR, Javle M, Kodali S, et al. Survival following liver transplantation for locally advanced, unresectable intrahepatic cholangiocarcinoma. *Am J Transplant* 2022;22:823-32. DOI
68. Nakachi K, Ikeda M, Konishi M, et al; Hepatobiliary and Pancreatic Oncology Group of the Japan Clinical Oncology Group (JCOG-HBPOG). Adjuvant S-1 compared with observation in resected biliary tract cancer (JCOG1202, ASCOT): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet* 2023;401:195-203. DOI
69. Hu LS, Zhang XF, Weiss M, et al. Recurrence patterns and timing courses following curative-intent resection for intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2019;26:2549-57. DOI
70. Tsilimigras DI, Sahara K, Wu L, et al. Very early recurrence after liver resection for intrahepatic cholangiocarcinoma: considering alternative treatment approaches. *JAMA Surg* 2020;155:823-31. DOI PubMed PMC
71. Doussot A, Gonen M, Wiggers JK, et al. Recurrence patterns and disease-free survival after resection of intrahepatic cholangiocarcinoma: preoperative and postoperative prognostic models. *J Am Coll Surg* 2016;223:493-505.e2. DOI PubMed PMC
72. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: epidemiology and risk factors. *Liver Int* 2019;39 Suppl 1:19-31. DOI PubMed
73. Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. *Hepatology* 2011;54:173-84. DOI PubMed PMC
74. Hyder O, Marques H, Pulitano C, et al. A nomogram to predict long-term survival after resection for intrahepatic cholangiocarcinoma: an Eastern and Western experience. *JAMA Surg* 2014;149:432-8. DOI
75. Sahara K, Tsilimigras DI, Mehta R, et al. A novel online prognostic tool to predict long-term survival after liver resection for intrahepatic cholangiocarcinoma: the "metro-ticket" paradigm. *J Surg Oncol* 2019;120:223-30. DOI
76. Choi WJ, Perez FM, Gravely A, et al. Preoperative neutrophil-to-lymphocyte ratio is prognostic for early recurrence after curative intrahepatic cholangiocarcinoma resection. *Ann Hepatobiliary Pancreat Surg* 2023;27:158-65. DOI PubMed PMC
77. Bo Z, Chen B, Yang Y, et al. Machine learning radiomics to predict the early recurrence of intrahepatic cholangiocarcinoma after curative resection: a multicentre cohort study. *Eur J Nucl Med Mol Imaging* 2023;50:2501-13. DOI
78. Alaimo L, Lima HA, Moazzam Z, et al. ASO visual abstract: development and validation of a machine learning model to predict early recurrence of intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2023:Online ahead of print. DOI
79. Chu H, Liu Z, Liang W, et al. Radiomics using CT images for preoperative prediction of futile resection in intrahepatic cholangiocarcinoma. *Eur Radiol* 2021;31:2368-76. DOI
80. Vallin M, Sturm N, Lamblin G, et al. Unrecognized intrahepatic cholangiocarcinoma: an analysis of 993 adult cirrhotic liver explants. *Clin Transplant* 2013;27:403-9. DOI
81. Lindnér P, Rizell M, Hafström L. The impact of changed strategies for patients with cholangiocarcinoma in this millenium. *HPB Surg* 2015;2015:736049. DOI PubMed PMC
82. Facciuto ME, Singh MK, Lubezky N, et al. Tumors with intrahepatic bile duct differentiation in cirrhosis: implications on outcomes after liver transplantation. *Transplantation* 2015;99:151-7. DOI
83. 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. DOI
84. Lee DD, Croome KP, Musto KR, et al. Liver transplantation for intrahepatic cholangiocarcinoma. *Liver Transpl* 2018;24:634-44. DOI
85. Krasnodębski M, Grąt M, Jastrzębski M, et al. Unsatisfactory long-term results of liver transplant in patients with intrahepatic cholangiocarcinoma. *Transplant Proc* 2020;52:2463-7. DOI