Review Article

Management of locally advanced intrahepatic cholangiocarcinoma: a narrative review

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Background and Objective: Intrahepatic cholangiocarcinoma (ICC) is an aggressive primary hepatic malignancy, which has increased in incidence over the past decades. While surgical resection is the standard of care for patients with early-staged disease, many patients present with locally advanced and unresectable tumors. Given the importance of locoregional control and the potential for downstaging to resectability, knowledge of advances in the management of locally advanced ICC is critical for optimizing outcomes.

Methods: This is a narrative review providing an up-to-date summary of the current literature regarding contemporary management of locally advanced ICC including systemic and liver-directed therapies.

Key Content and Findings: Along with systemic chemotherapy, several liver-directed therapies including transarterial chemoembolization, transarterial radioembolization, and hepatic artery infusion pumps, targeted therapies, and chemoradiation therapy have demonstrated promising results for improving local disease control and possibly extending survival. Unfortunately, successful downstaging to resection remains uncommon with no single treatment strategy established as standard of care. Although additional randomized controlled data are needed, multidisciplinary management using contemporary systemic and locoregional therapies improves outcomes for patients with locally advanced ICC.

Conclusions: The optimal management of locally advanced ICC remains uncertain. Despite this, novel treatment options and ongoing clinical trials are currently contributing to more effective treatment and improved patient outcomes. Future advancements are likely to explore further novel therapies in addition to elucidating optimal patient selection and sequencing of multidisciplinary therapy.

Keywords: Biliary tract neoplasms; systemic chemotherapy; hepatectomy; liver-directed therapy; conversion therapy

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is an aggressive primary hepatic malignancy that arises from the intrahepatic biliary tracts proximal to the secondary biliary radicals. It is the second most common primary liver tumor behind that of hepatocellular carcinoma (HCC) but is distinguished in that it arises in patients both with and without chronic liver disease (1). The current understanding of ICC pathogenesis suggests that genetic heterogeneity along with high concentrations of inflammatory mediators lead

Table 1 The search strategy summary

Items	Specification
Date of search	November, 2022
Databases and other sources searched	PubMed, Cochrane Library, and MEDLINE; NCCN guidelines; ClinicalTrials.gov
Search terms used	Intrahepatic cholangiocarcinoma, locally advanced, neoadjuvant therapy, liver-directed therapy, radiotherapy, liver transplantation, down-staging, chemotherapy, chemoembolization, radioembolization, resection
Timeframe	May 1990 to November 2022
Inclusion and exclusion criteria	Includes primarily retrospective data in addition to completed and ongoing prospective trials published in English
Selection process	The authors conducted the selection of data and relevant trials

NCCN, National Comprehensive Cancer Network.

to progressive mutations that foster cell proliferation (2-5). ICC is an aggressive cancer that often presents late and therefore leads to diagnosis at advanced stages. Indeed, a majority of patients with ICC present with metastatic disease in which treatment largely consists of palliative chemotherapy. Even among patients with localized disease, a significant proportion are unresectable and therefore deemed locally advanced. The management of locally advanced ICC is important since expanding indications for surgery and effective downstaging with systemic and liver-directed therapies can lead to curative-intent therapy in a subset of patients. Moreover, effective liver-directed therapy is important for long-term locoregional control even in the absence of surgical resection which is critical for palliative and oncologic purposes (6). Therefore, the purpose of this article is to provide an up-to-date summary of the current literature regarding the contemporary multidisciplinary management of locally advanced ICC. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-22-115/rc).

Methods

The current literature regarding management of locally ICC was based on an exhaustive literature search using the primary databases PubMed, Cochrane Library, and MEDLINE. This search was supplemented by examing reference lists for other pertinent studies and trials. Current guidelines were reviewed and the status of ongoing and completed clinical trials were assessed using ClinicalTrials.gov. The included data in the review were gathered from English, retrospective or prospective studies published from May 1990 to November 2022 (*Table 1*).

Background

Cholangiocarcinoma (CCA) broadly refers to a heterogenous group of cancers arising from epithelium within the biliary tract. CCA is anatomically grouped into intrahepatic, perihilar, or extrahepatic based on the origin of the tumor, each requiring its own distinct management approach (7). CCA occurs in the setting of chronic biliary inflammation and stasis and the causes of which differ in Eastern and Western countries. In Western countries, CCA is commonly associated with primary sclerosing cholangitis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cirrhosis, alcohol use, and smoking. In Eastern countries, risk factors for CCA commonly include chronic bile duct calculi (hepatolithiasis), liver fluke infection, and viral hepatitis (8). Although relatively rare, several studies have noted both an increasing incidence and mortality rate associated with ICC (9-11). The mainstay of treatment for ICC is surgical resection with negative (i.e., R0) microscopic margins. However, less than 20–30% of patients will be candidates for resection at the time of diagnosis due to either locally advanced or metastatic disease (12,13). As a result of the locally advanced nature of some cancers, extended resections during hepatectomy may be required. While extended resection may play a role in locally advanced ICC, the risks associated with major hepatic resection as well as importance of disease biology must be considered. Even among those who are able to safely undergo margin-negative resection, disease recurrence remains high, which suggests that improved systemic control, and not surgical resection alone, is needed

to achieve prolonged overall survival (OS). These factors suggest the need for major advances in the multidisciplinary management of ICC (14).

Defining locally advanced disease

Since margin-negative resection is one of the most critical prognostic factors for patients with ICC, defining locally advanced disease is important for standardizing resectability and clarifying treatment options. ICC was previously staged identically to that of HCC. Several retrospective studies including a 2009 SEER database study found that prognostic factors differed for ICC. For example, tumor size greater than 5cm was not a relevant prognostic factor for survival whereas the presence of multiple tumors, vascular invasion, and lymph node status were (15). As a result, the revised 7th edition of the American Joint Committee on Cancer (AJCC) staging system focused on multiple tumors, vascular invasion, and lymph node metastasis rather than tumor size alone for prognosis. These changes were validated from the AFC-IHCC study group in which the median survival was not reached for patients with stage I disease (no vascular invasion), 53 months for stage II (vascular invasion), and 16 months for stage III (violation of visceral peritoneum by tumor) (16). This framework of the new staging system resulted in some changes for the AJCC 8th addition but overall maintained the principle that vascular invasion and lymph node status are key prognostic factors for survival in ICC.

Resectability must be carefully considered across three domains: physiologic, biologic, and anatomic. Most importantly, patients' fitness for major surgery must be assessed based on one's comorbidities, performance status, frailty, and underlying liver quality. Oncologic resectability takes into account the biology of the tumor and likelihood for surgical resection to contribute to a meaningful disease-free and overall-survival benefit. Extrahepatic disease, tumor differentiation, significantly elevated tumor markers, tumor morphology, the presence of satellite lesions, and/or failure to respond to previous therapies are some indicators that a patient's disease is aggressive and possibly associated with early recurrence after surgery. Finally, anatomic resectability refers to the technical ability to remove the tumor with an R0 resection while leaving the remaining liver with sufficient vascular inflow (portal vein, hepatic artery), outflow (hepatic veins), biliary drainage, and future liver remnant (FLR) size. These technical considerations have been discussed at length elsewhere (17,18).

Briefly though, FLR refers to the volume of liver remaining following hepatic resection and can be measured pre-operatively through formal volumetry. Size is a surrogate for function and therefore the quality of liver parenchyma dictates the necessary FLR volume in order to prevent post-hepatectomy liver failure. In general, standardized FLR volumes of 20%, 30%, or 40–50% are necessary for patients with normal, compromised, or cirrhotic livers, respectively (19). Importantly, some systemic chemotherapies used in ICC and other gastrointestinal malignancies can be hepatotoxic, and therefore require higher planned FLR volumes after surgery. While several methods exist to stimulate hepatic lobar hypertrophy for those patients with insufficient or borderline FLRs, portal vein embolization is the most common intervention employed (20). In addition to inadequate anticipated FLR volume, other common reasons for unresectability include major vascular invasion, satellite metastases, contralateral vascular involvement, and inability to tolerate major surgery. In summary, while resectability is a complex and sometimes subjective determination that involves multiple domains, locally advanced cancers most often represent those that are anatomically or occasionally biologically non-amenable to upfront surgery. Radiographic examples of locally advanced ICC are demonstrated in *Figure 1*.

Systemic therapy

In clinical practice, systemic therapy remains the first line therapy for locally advanced ICC (21). The rationale for using systemic therapy before consolidative locoregional therapy is based on several observations: (I) sufficient downstaging to enable surgical resection can occur with contemporary cytotoxic chemotherapy alone, (II) prioritizing chemotherapy treats micrometastatic disease which is arguably the most common mode of failure even for patients with locally advanced disease, and (III) to enhance patient selection by ensuring no rapid progression of metastatic disease before consolidating with liver-directed treatments. Over the past several decades, major advances have been made in the development of both traditional and targeted systemic therapies. As a result, first line chemotherapy regimens for advanced ICC have evolved over time.

First line systemic therapy

While several early phase II trials demonstrated activities of fluoropyrimidines, cisplatin, and gemcitabine against

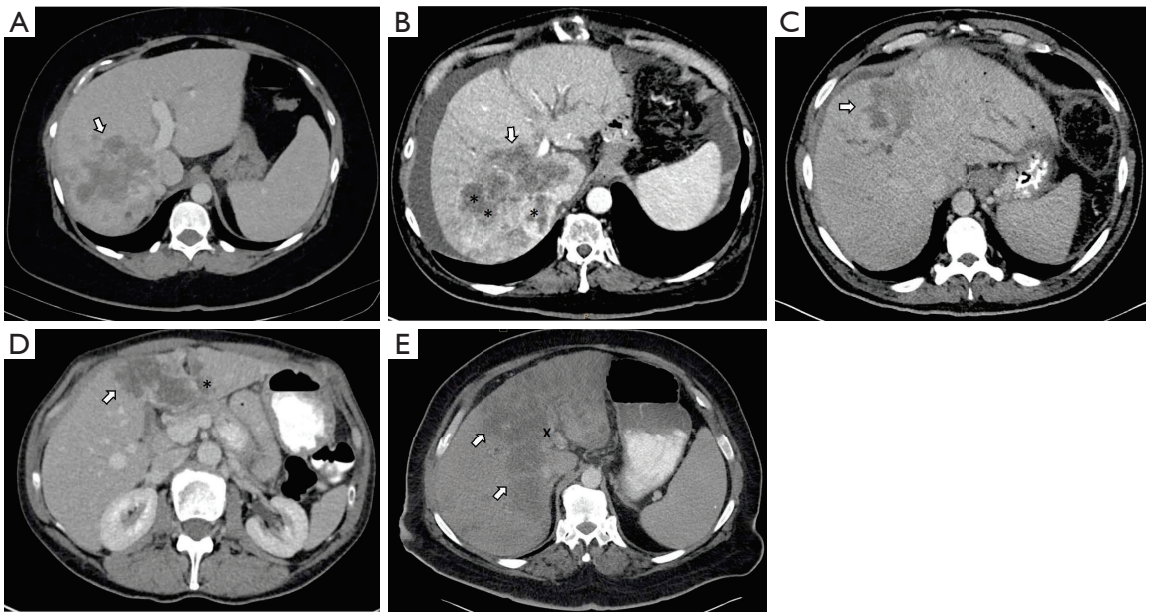

Figure 1 Locally advanced cholangiocarcinoma as demonstrated on CT. Representative examples of locally advanced intrahepatic cholangiocarcinoma. Arrows represents main tumor; asterisk represents satellite lesions; X indicates vascular occlusion. (A) Predominate right sided liver disease. (B) Right sided liver disease with multiple satellite lesions. (C) Centrally located disease. (D) Left sided disease with satellite lesions. (E) Left and right sided disease with vascular occlusion.

metastatic ICC, the ABC-02 trial established the doublet use of gemcitabine and cisplatin as the standard of care in patients with unresected advanced biliary tract cancer (BTC) (22). This randomized, phase III trial included 410 patients with locally advanced or metastatic CCA, gallbladder cancer, or ampullary cancer. Median OS was significantly greater among patients randomized to cisplatin-gemcitabine compared to gemcitabine alone (11.7 *vs.* 8.1 months; HR 0.64; 95% CI: 0.52–0.80; P<0.001). The rate of tumor control was also significantly increased in the dual therapy group with 81.4% of patients demonstrating stable disease compared to 71.8% in gemcitabine alone (P<0.05) (22). This trial however was not specific to ICC as all biliary tract cancers were included.

More recently, the TOPAZ-1 trial evaluated gemcitabine/cisplatin plus durvalumab in patients with previously untreated unresectable or metastatic BTC or those with recurrent disease. This double-blind, placebo-controlled, phase III study randomized 685 patients to gemcitabine/cisplatin with either durvalumab or placebo. The durvalumab group had an estimated 24-month overall survival of 24.9% (95% CI: 17.9–32.5%) compared to 10.4% (95% CI: 4.7–18.8%) for placebo. Overall survival in the durvalumab plus chemotherapy group was significantly increased compared to placebo (HR 0.8; 95% CI: 0.66–0.97; P=0.021) and an improvement in secondary outcomes of progression-free survival and objective response rate were also noted (23). This immunochemotherapy combination is the preferred first line regimen for managing cholangiocarcinoma.

In a separate phase II trial, the triplet regimen gemcitabine/cisplatin/nab-paclitaxel therapy was evaluated in 60 patients with BTCs, demonstrating a median progression-free survival of 11.8 months and median overall survival of 19.2 months in an intention-to-treat analysis (24). Based on these findings, a phase III randomized trial comparing nab-paclitaxel to placebo with gemcitabine and cisplatin is currently being conducted (SWOG S1815 trial). Other combinations such as FOLFIRINOX, NUC-1031 (activated form of gemcitabine) plus cisplatin, and gemcitabine/regorafenib were not beneficial over gemcitabine and cisplatin combination (25-28).

Neoadjuvant systemic therapy

Few trials have specifically evaluated the role of systemic chemotherapy in locally advanced ICC to determine the optimal neoadjuvant regimen. Therefore, regimens

established in the metastatic setting are typically applied for patients with locally advanced ICC. One difference is defining the goals of therapy since patients with locally advanced disease may still aim for curative-intent therapy particularly if sufficient downstaging occurs to reach surgical resection. As a result, there may be a desire to be particularly aggressive with systemic therapy regimens in order to optimize the potential for tumor response. In practice, this typically involves cisplatin-gemcitabine or gemcitabine-cisplatin-durvalumab with or without concomitant liver-directed therapy (29).

The conversion rates of locally advanced, unresectable disease to resectable disease in early trials were historically highly variable. For example, a retrospective study evaluating the use of gemcitabine for downstaging of locally advanced unresectable ICC achieved downstaging to the point of surgical resection in 36.4% of patients (30). A follow-up study evaluating gemcitabine/cisplatin found the dual regimen to achieve a conversion rate of 25.6% (31). A retrospective study from 2000 to 2013 included 186 patients with either locally advanced ICC not initially resectable and patients with upfront resectable disease. Patients with locally advanced disease underwent six chemotherapy cycles with 53% (N=39) able to eventually undergo resection. Not only were half of these patients down-staged to resectable disease, those who achieved resection experienced similar survival durations to those initially resectable (24.1 *vs.* 25.7 months) (32). Although the above mentioned conversion rates to surgery are encouraging, the highly variable range of conversion reported in retrospective studies indicates more data, ideally through clinical trials, are needed.

Several ongoing trials specifically investigating neoadjuvant and downstaging regimens in BTC are ongoing (33). For example, NCT03603834 is a phase II trial evaluating neoadjuvant FOLFOXIRI for potentially or borderline resectable cholangiocarcinoma with a primary outcome of overall response rate evaluated by MRI or CT according to RECIST 1.1 criteria (34). In addition, the Neoadjuvant Gemcitabine/Cisplatin/Nab-paclitaxel (NEO-GAP) trial examined gemcitabine, cisplatin, and nab-paclitaxel (GAP) chemotherapy in the neoadjuvant setting for resectable but high-risk ICC. This multi-institutional prospective single-arm phase II trial was conducted from 2018 to 2021 and focused on the primary endpoints of completion of all therapy including neoadjuvant chemotherapy and resection. Thirty-seven patients were enrolled and 77% (N=23; P=0.0026) completed all therapy, which demonstrated that neoadjuvant gemcitabine/cisplatin/nab-paclitaxel is feasible and safe prior to ICC resection (35). While results from this trial are anticipated, the routine use of neoadjuvant therapy (NT) for ICC is not recommended and instead reserved for those patients where downstaging is needed.

Targeted therapy

In the era of precision oncology, there is significant interest in the development and use of targeted therapies among patients with unresectable ICC (36). Two studies exemplify the early interest in targeted therapy for CCA by identifying the presence, or lack thereof, of common oncogenes in cases of ICC. In 2014 Ross *et al.*, using next-generation DNA sequencing, found that up to two-thirds of ICC specimens in their study harbored genomic alterations associated with targeted therapies (37). An even earlier 2013 study by Voss *et al.* utilized mass spectrometry to detect oncogenic mutations, which were identified in 24% of specimens and increased to 43% when combined with IDH1/2 mutation data (38). A separate study, the MOSCATO-01 trial, is of particular importance as it evaluated advanced cancers including ICC and included only patients who were considered non-curable by a multidisciplinary board. Overall, 68% of patients had a targetable gene mutation on genetic testing (39). Although these studies do not provide precise treatment recommendations, they strongly contribute to the foundation on which the use of targeted therapy has been explored for further personalizing ICC treatment.

Numerous studies have collectively recognized isocitrate dehydrogenase 1 (IDH1), fibroblast growth factor receptor (FGFR), EGFR, VEGF, NTRK, BRAF-V600E, RET, and HER2/neu mutations as well as mismatch repair deficiency to be among the most prevalent molecular alterations present in ICC (2,37-42). Among these, FGFR and IDH1 appear to be the most studied and actionable (2). A recently completed phase III randomized trial which evaluated ivosidenib, an IDH1 inhibitor, found an increased median OS of 10.3 months (95% CI: 7.8–12.4 months) with ivosidenib *vs.* 5.1 months with placebo [95% CI: 3.8–7.6 months; hazard ratio, 0.49 (95% CI: 0.34–0.70); 1-sided P<0.001], when adjusted for crossover (43).

Several phase II trials have evaluated the utility of pemigatinib (anti-FGFR2) in patients with FGFR rearrangements. A multicenter, open-label, phase II study (FIGHT-202) evaluated the safety and efficacy of

pemigatinib in patients with previously treated, locally advanced or metastatic CCA with and without FGFR2 mutations (44). Among 146 enrolled patients, 36% achieved an objective response with either complete (3/38) or partial (35/38) responses. As a continuation of the FIGHT-22 study, pemigatinib is currently being examined in an international phase III study as an addition to gemcitabine/cisplatin as first line therapy for unresectable or advanced ICC in patients with FGFR2 fusions/rearrangements (45,46).

In April 2020, the US Food and Drug Administration (FDA) approved pemigatinib for the treatment of patients previously treated for advanced ICC who have a FGFR2 fusion or rearrangement. Currently, there are approximately ten FGFR inhibitor and four IDH inhibitor clinical trials that are ongoing and are evaluating their use in patients who have advanced on previous therapy. The effect of these targeted therapies on overall and progression-free survival are yet to be known; therefore, ongoing studies are needed in order to determine their efficacy.

Until more comparative trials are performed of targeted therapies in the first line, most guidelines will likely continue to recommend standard cytotoxic chemotherapy for newly diagnosed advanced ICC (47). FGFR and IDH inhibitors have largely been explored as palliative targeted therapy, and frequently, in patients who have already failed multiple lines of treatment. Furthermore, few trials have been conducted in the first line or among resectable patients. Therefore, the role of targeted therapies in the neoadjuvant setting clearly remains undefined. Fortunately, steps are being made in this direction. The PROOF-Trial (NCT03773302) is a current phase III study evaluating the efficacy of oral infigratinib (FGFR inhibitor) *vs.* standard of care chemotherapy (gemcitabine-cisplatin) in the first line treatment of unresectable locally advanced ICC with FGFR2 fusion/rearrangement (48). It is currently active and no longer recruiting with an expected completion date in 2026. Additional studies of this nature are needed. In addition to the evaluation of targeted therapies for first line use, future clinical trials should also consider their potential as adjuncts to current neoadjuvant regimens.

The use of immune-checkpoint inhibitors are restricted to microsatellite instability-high (MSI-H) patients in the first line and in those with tumor mutational burden (TMB) >10 in the second line (49-51). Nivolumab can be used in patients if there are no effective options post-gemcitabine/cisplatin (if durvalumab was not used earlier) (52). Combination of stereotactic body radiation therapy (SBRT) with immunotherapy showed reasonable response and tolerable toxicity in managing ICC (53,54). Chemotherapy options in subsequent lines include FOLFOX, nanoliposomal irinotecan/5FU, and FOLFIRINOX (55-58).

Transarterial therapies

There is increasing interest in the use of transarterial therapies for locally advanced ICC whether following induction chemotherapy or in combination with systemic chemotherapy. Indeed, data is emerging for the use of liver directed therapy in ICC for the purpose of downstaging tumors in a neoadjuvant fashion, optimizing local control, and possibly improving both duration and quality of life (59). The poor survival of ICC is largely attributable to liver failure and thus liver directed therapy remains a modality of interest in controlling locally advanced tumors. Liver directed transarterial therapies include chemoembolization, bland embolization, Yttrium-90 (Y-90), and hepatic artery infusion.

The goal of transarterial therapy is to precisely deliver chemotherapeutic agents to hepatic tumors while reducing damage to surrounding liver parenchyma and minimizing systemic toxicity (1). Interest in its utility has developed mostly from its use in HCC and neuroendocrine metastases to the liver (60,61). Multi-institutional retrospective data supports the use of intra-arterial therapy for advanced ICC. This study by Hyder *et al.* included 198 patients with advanced ICC who received conventional transarterial chemoembolization (64.7%), drug-eluting beads (5.6%), bland embolization (6.6%), or Y-90 radioembolization (23.2%) (62). Complete or partial response was noted in 25.5% and 61.5% had stable disease. Median overall survival was 13.2 months and was not significantly different based on intra-arterial modality. Although retrospective, this data supports further investigation of intra-arterial therapies in the setting of a clinical trial (62). Rates of conversion and other primary outcomes from select clinical trials are summarized in *Table 2*.

Transarterial chemoembolization

While transarterial chemoembolization (TACE) has been explored as an adjuvant therapy following surgical resection, it is most commonly used for ICC patients with unresectable disease (77). While typically performed to enhance local control, recent evidence has progressively shown its potential for downstaging of disease too.

An early study regarding the palliative role of TACE

Table 2 Selected studies of transarterial therapies for locally advanced intrahepatic cholangiocarcinoma

Author	Institution	Design	Modality/agents	Sample size	Tumor response	Conversion to resection	Outcomes
Burger, 2005 (63)	John Hopkins Hospital, United States	Retrospective	TACE–Cisplatin, Doxorubicin, Mitomycin-C	17	NR	12% (2/17)	Median OS: 23 months (95% CI: 15.4–30.6 months)
Vogl, 2012 (64)	Johann Wolfgang Goethe-University Frankfurt Theodor-Stern-Kai, Germany	Retrospective	Neoadjuvant TACE–Mit-C only, Gemcitabine only, Mit-C/Gem, or Mit-C/Gem/Cis	115	10 PR, 66 SD, 39 PD	NR	Median OS: 13 months
Aliberti, 2017 (65)	Agency Reunited Hospital of North Marche, Italy	Retrospective	DEB- and PEG-TACE with Doxorubicin	127	19 PR, 101 SD, 7 PD	4% (4/127)	PEG-TACE median OS: 14.53 months (95% CI: 9.17–15.23) DEB-TACE median OS: NR
Yuan, 2022 (66)	Zhongda Hospital, China	Retrospective	TACE + Lenvatinib	44	NR	64% (28/44)	Median OS: 55 months for all patients (including those unsuccessfully down staged)
Ibrahim, 2008 (67)	Northwestern Memorial Hospital, United States	Prospective	TARE-Y-90	24	6 PR, 15 SD, 1 PD	4% (1/24)	Median OS: 14.9 months for the entire cohort
Mouli, 2013 (68)	Northwestern Memorial Hospital, United States	Prospective/ Retrospective	TARE-Y-90	46	11 PR, 33 SD, 1 PD	11% (5/46)	Median OS: 15.6 months with peripheral tumor morphology Median OS: 6.1 months with infiltrative tumor morphology
Rayar, 2015 (69)	Rennes University Hospital, France	Retrospective	Systemic Gemcitabine + TARE-Y-90	10	NR	80% (8/10)	NR
Edeline, 2019 (70)	Centre Eugène Marquis, France	Phase II trial	TARE-Y-90 + Gemcitabine/Cisplatin	41	39–41% RR	22% (9/41)	Median OS: 22 months (95% CI: 14–52 months) Median PFS: 14 months (95% CI: 8–17 months)
Buettner, 2017 (71)	Erasmus MC University Medical Center, Netherlands	Retrospective	TARE-Y-90–Resin and glass microspheres	115	7 PR, 63 SD, 26 PD	4% (5/115)	Median OS: 11 months (95% CI: 8–13) Median PFS: 5 months for entire cohort (95% CI: 3–7)
Jarnagin, 2009 (72)	Memorial Sloan-Kettering Cancer Center, United States	Phase II trial	HAI FUDR/ Dexamethasone	26	14 PR, 11 SD, 1 PD	4% (1/26)	Median OS: 29.5 months Median PFS: 7.4 months for overall cohort (including HCC)
Kemeny, 2011 (73)	Memorial Sloan-Kettering Cancer Center, United States	Phase II trial	HAI FUDR/Dex + Bevacizumab	18	7 PR, 11 SD	17% (3/18)	Median OS: 31.1 months (CI: 14.14–33.59) Median PFS: 8.45 months (CI: 5.53–11.05) for overall cohort (including HCC)
Massani, 2015 (74)	Regional Hospital of Treviso, Italy	Retrospective	HAI Fluorouracil + Oxaliplatin	11	5 PR, 2 SD, 4 PD	27% (3/11)	Median OS: 17.6 months
Cercek, 2020 (75)	Memorial Sloan-Kettering Cancer Center, United States	Phase II trial	HAI FUDR + Gemcitabine and Oxaliplatin	38	1 CR, 22 PR	11% (4/38)	Median OS: 25.0 months (95% CI: 20.6–not reached) Median PFS: 11.8 months (1-sided 90% CI: 11.1)
Franssen, 2022 (76)	Erasmus MC Cancer Institute, Netherlands	Retrospective cohort	HAI FUDR	141	NA	NA	Median OS: 20.3 months

OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; NR, not reported; DEB, drug-eluting bead; PEG, polyethylene glycol drug eluting spheres; PR, partial response; CR, complete response; RR, response rate; SD, stable disease; PD, progressive disease; TARE, transarterial radioembolization; Y-90, Yttrium-90; HAI, hepatic artery infusion; FUDR, floxuridine; HCC, hepatocellular carcinoma; MC, medical center; NA, not available.

compared it to standard supportive treatment and found that partial response was achieved in 23% of the patients and survival was significantly longer among those who received TACE (12.2 *vs.* 3.3 months; P<0.0001) (78). This study helped to establish both the safety and possible survival benefit associated with TACE for ICC. In an even earlier study investigating its utility, data from Burger *et al.* has supported the neoadjuvant role of TACE for ICC conversion to resectable disease. This study was broadly designed to assess the safety and efficacy of conventional TACE using cisplatin, doxorubicin, and mitomycin-C for ICC in 17 patients with unresectable disease. The study showed an increase in median overall survival to 23 months with two patients becoming resectable (63). Other studies have been unable to convincingly establish a role for downstaging to surgical resection (79,80).

The optimal TACE regimen remains unclear as well. Vogl *et al.* found no statistically significant difference in outcomes between patients who receive TACE with Mitomycin C only, Gemcitabine only, Mitomycin C with Gemcitabine, or a combination of Gemcitabine, Mitomycin C and Cisplatin (64). Drug eluting bead-TACE has also been evaluated for unresectable ICC with comparable success to conventional TACE (65,81). A retrospective study by Kuhlmann *et al.* comparing three independent prospective studies found that DEB-TACE resulted in a progression-free survival (PFS) of 3.9 months and OS of 11.7 months compared with a PFS of 1.8 months and OS of 5.7 months in conventional TACE, with only 1 (4%) of patients converting to resectable disease (82). Given the lack of a standardized TACE regimen, the choice of treatment is often deferred to local institutional experience and preference.

Transarterial radioembolization with Y-90

Transarterial radioembolization (TARE) with Y-90 is an additional transarterial therapy that has been applied to locally advanced, unresectable ICC. Data over the past decade have generally noted good local control with most cases reaching stable disease using TARE; however, the conversion rate to resectable disease remains low (59). In an open-label cohort study observing 24 patients undergoing TARE with Y-90 microspheres, Ibrahim *et al.* determined that on imaging follow-up of 22 patients, six demonstrated a partial response, fifteen had stable disease, one had progressive disease, and one patient (4%) was converted to resectable disease (67). Two additional studies evaluating Y-90 for unresectable ICC, found conversion rates to successful R0 resection within their relatively small patient cohorts to be about 8–10% (68,83). Rayar *et al.* further evaluated the use of Y-90 in addition to systemic therapy in 45 patients with unresectable ICC and found that 8 (17%) of their patients converted to eventual R0 resection (69). Additional studies have collectively determined TARE to be an effective and safe strategy in the management of unresectable ICC (84-87).

More recently, a phase II clinical trial termed the Yttrium-90 Microspheres in Cholangiocarcinoma (MISPHEC) trial further evaluated the concurrent use of first line chemotherapy (cisplatin and gemcitabine) in addition to TARE with Y-90 for patients with unresectable ICC (70). The results displayed a conversion rate to eventual R0 resection of 20% along with a disease control rate of 98%, as well as a response rate of 39% according to RECIST criteria and 93% by Choi criteria (70). As a result of such encouraging data, a randomized phase III trial has been initiated to further evaluate the role of TARE with Y-90 in combination with gemcitabine and cisplatin (88). In the meantime and based on these data, some centers have moved to recommend concomitant TARE with systemic chemotherapy upfront to maximize the potential for local control and downstaging.

Hepatic artery infusion

Hepatic artery infusion (HAI) involves surgical placement of a catheter into the proper hepatic artery via the gastroduodenal artery connected to a subcutaneous pump, which allows for the delivery of high concentrations of local chemotherapy with fewer systemic side effects. Early evidence for HAI's utility in ICC treatment came from a phase II clinical trial at Memorial Sloan-Kettering Cancer Center in 2009 where 26 patients with unresectable ICC were treated with HAI floxuridine (FUDR). Of these 26 patients, 53.8% experienced a partial response, 42.3% developed stable disease, 3.8% experienced progression of disease, and 3.8% or one patient responded sufficiently to undergo surgical resection (72).

Kostantinidis *et al.* notably compared HAI plus systemic therapy versus systemic therapy alone and found an OS increase of 30.8 *vs.* 18.4 months, respectively (P<0.001); although there was no difference in tumor response by RECIST criteria (89). A follow-up study by Kemeny *et al.* added systemic bevacizumab to HAI FUDR and found no clear improvement in outcomes (median PFS 8.45 *vs.*

7.3 months, and median survival 31.1 *vs.* 29.5 months, for HAI + Bev *vs.* HAI alone groups, respectively) (73). Notably, the study was terminated early due to increased biliary toxicity. Another study by Massani *et al.* also supported the downstaging potential of HAI as three of eleven patients with initially unresectable disease had partial response and were able to undergo resection (74).

In a more recent 2014 meta-analysis including 20 articles and 657 patients, Boehm *et al.* compared the relative effectiveness between the various intra-arterial therapies and found HAI to have the highest median overall survival and response rate, although limited by the highest rate of toxicity (90). More recent data has come from another Phase II clinical trial at Memorial Sloan-Kettering Cancer Center completed between 2013–2019, involving the treatment of 38 patients with unresectable ICC with combination HAI FUDR and systemic chemotherapy (gemcitabine and oxaliplatin). Twenty-two patients (58%) achieved partial response, 32 patients (84%) achieved disease control at 6 months, and four patients (11%) were converted to resectable disease (75).

Interestingly, a recent cohort study from a single institution compared the overall survival of patients with multifocal ICC who underwent surgical resection to those who had HAIP FUDR. Median overall survival was 20.3 months in HAIP group compared to 18.9 months in resection group which was not statistically significant. Post-operative 30-day mortality was significantly higher in the resection group at 6.2% compared to 0.8% in HAIP group (P=0.01). Five-year survival in patients with 2 or 3 lesions was 23.7% in HAIP group compared to 25.7% in resection. In this study, patients with multifocal ICC had similar survival regardless of whether they underwent HAIP or resection with significantly higher 30-day mortality in surgical group (76). Taken together, these findings suggest that HAI in addition to systemic chemotherapy may play a valuable role in the treatment of locally advanced ICC. Unfortunately, data is still lacking from randomized control trials, especially multicenter, and therefore further information from such studies are needed prior to implementation of HAI into the standard of care.

External beam radiotherapy

While still controversial in the adjuvant setting, external beam radiotherapy (EBRT) is commonly used for local control of locally advanced ICC following induction systemic chemotherapy. In 2010, a retrospective analysis of 84 patients with unresectable ICC, with 35 of the patients receiving EBRT, observed that 8.6% of patients experienced a complete response while 28.5% of patients experienced a partial response. Median survival times were 5.1 months in the non-EBRT group and 9.5 months in the EBRT group (P=0.003) with improved one-and two-year survival rates as well (91). In another retrospective study, Kim *et al.* noted that capecitabine-cisplatin chemotherapy with concurrent radiotherapy was well-tolerated and associated with longer PFS (4.3 *vs.* 1.9 months, P=0.001) and OS (9.3 *vs.* 6.2 months, P=0.048) than chemotherapy alone (92).

More recent studies include the use of modern EBRT treatment planning and delivery to permit ablative radiation therapy doses. The use of hypofractionated radiation therapy, SBRT, and proton beam therapy highlight the potential utility of radiation therapy in the management of locally advanced ICC. Further, there is mounting evidence on the role of radiation dose escalation for hepatic malignancies including ICC (93). Tao *et al.* reported on the impact of radiation dose escalation on local control and OS in patients with inoperable ICC (94). This retrospective single institution study included 79 patients treated at MD Anderson Cancer Center for inoperable ICC with 89% of patients receiving systemic therapy prior to radiation therapy. The median tumor size was 7.9 cm and the radiation doses delivered were 35–100 Gy in 3–30 fractions with a median of 58.05 Gy. The median biologic equivalent dose (BED) delivered was 80.5 Gy. Radiation dose was the most important prognostic factor with statistically significant improvement in 3-year OS (73% *vs.* 38%) and 3-year local control (78% *vs.* 45%) observed in patients receiving BED greater than 80.5 Gy compared to lower doses. Treatment was well-tolerated with no significant treatment-related toxicities.

SBRT permits the delivery of conformal high-dose external beam radiation therapy over five or fewer fractions, and has been found to be a safe and effective treatment for unresectable ICC. A prospective phase I study performed at Princess Margaret Hospital evaluated SBRT in patients with unresectable primary hepatic tumors, ten of which were ICC, and found favorable survival outcomes with a median OS of 15.0 months (95% CI: 6.5–29.0 months) in patients with ICC (95). No cases of radiation-induced liver disease or dose-limiting toxicities were observed. However, much of the supportive data for SBRT in ICC is based off of retrospective series (96-99). In a large retrospective series, Brunner *et al.* reported on 31 patients treated with SBRT for ICC. Their findings confirmed those of Tao

Table 3 Selected studies of liver transplantation for intrahepatic cholangiocarcinoma

Author	Institution	Design	Intervention	Sample size	Survival rates (1, 3, and 5 years)	RFS rates (1, 3, and 5 years)	Tumor recurrence
Robles, 2004 (104)	Virgen de la Arrixaca University Hospital, Spain	Retrospective	OLT alone	23	77%, 65%, and 42%	68%, 45%, and 27%	8/23 (35%)
Sapisochin, 2016 (105)	Toronto General Hospital, Canada	Retrospective	OLT alone for single tumors <2 cm	15	93%, 84%, and 65%	NR	2/15 (13.3%)
Lunsford, 2018 (106)	Houston Methodist Hospital and Research Institute, United States	Prospective Case-Series	Neoadjuvant gemcitabine-based therapy prior to OLT	6	100%, 83.3%, and 83.3%	50% at 1, 3, and 5 years	3/6 (50%) at a median of 7.6 months
Krasnodebski, 2020 (107)	Medical University of Warsaw, Poland	Retrospective Cohort	OLT alone	8	75%, 37.5%, and 25%	71.4%, 28.6%, 28.6%	NR
McMillan, 2022 (108)	Houston Methodist Hospital, United States	Prospective	Neoadjuvant therapy prior to OLT	18	100%, 71%, and 57%	NA	7/18 (39%)

RFS, relapse-free survival; OLT, orthotopic liver transplantation; NR, not reported; NA, not available.

et al. noting that the delivered radiation dose was found to be a prognostic factor for both local control and OS. Local control rates at 24 months were 80% for BED_{max} >91 Gy_{10} compared to 39% for lower doses, P=0.009 while patients with a BED_{max} >91 Gy_{10} had a median OS of 24 months *vs.* 13 months for those receiving lower doses (P=0.008) (98). The ABC-07 trial, a phase II clinical trial evaluating the use of gemcitabine-cisplatin with or without the addition of SBRT for patients with advanced biliary tract cancers recently completed accrual. The results are highly anticipated as prospective, randomized data for the use of radiotherapy in locally advanced ICC is currently limited. A second prospective trial, NRG Oncology GI001, was a randomized phase III study designed to evaluate the role of focal radiation therapy for patients with unresectable and localized ICC, but was terminated early due to poor accrual.

Proton beam therapy has shown promising results for management of unresectable ICC. Hong *et al.* performed a multi-institutional phase II study of patients with either unresectable HCC or ICC. The local control rate at two years was a robust 94.1% with a two-year OS of 46.5% for those with unresectable ICC (100). In a retrospective study of 66 patients treated with hypofractionated radiotherapy for cases of unresectable ICC, Smart *et al.* reported a two-year local control of 84% and an OS of 58% (101). On multivariate analysis, there was a trend towards improved OS for patients treated with proton beam therapy compared to photons (HR =0.50, P=0.05).

Overall, data to this point have demonstrated the potential for radiation therapy to improve overall outcomes related to locally advanced ICC. While not typically used to downstage as radiation can lead to a more technically challenging operation, limited prospective data and primarily retrospective data suggests radiotherapy may provide long-term disease control. In addition, with ablative doses achieved using hypofractionated EBRT or SBRT, there is a potential for long-term survival and this approach may even be considered curative in select patients. As with all local therapy, a multidisciplinary discussion is needed regarding timing and selection of appropriate candidates for consideration of radiation therapy for ICC.

Liver transplantation

The role of liver transplantation (LT) in the management of ICC is controversial but greater experience with transplantation for hilar cholangiocarcinoma and renewed interest in transplant oncology in general has generated increased interest in LT for ICC in recent years. Historically, outcomes of patients with ICC who underwent LT were very poor (102,103). Recent studies, however, have challenged such early data and shown favorable outcomes for LT in ICC. Survival and recurrence patterns from select trials regarding liver transplantation for ICC are summarized in *Table 3*.

A recent 2021 meta-analysis and meta-regression of survival rates by Ziogas *et al.* summarizes the current use of LT for ICC and concludes that cirrhotic patients with very early ICC or select patients with advanced ICC following neoadjuvant therapy may benefit from transplantation

under research protocols (109). Previous studies give much support to this claim that early disease is more receptive to an effective liver transplantation. In a large international retrospective study, Sapisochin *et al.* evaluated patients found to have ICC on explant pathology. Patients with only ICC on pathology were divided into "very early" or "advanced" disease (single tumor >2 cm or multifocal disease) with 1-, 3-, and 5-year survival rates following transplantation of 93%, 85%, and 65% in the very early group versus 79%, 50%, and 45% in the advanced group (P=0.02) (105).

More recently however, studies have begun to evaluate the role of LT following NT for locally advanced ICC. In a prospective case-series by Lundsford *et al.*, patients with locally advanced, unresectable ICC without extrahepatic disease or vascular involvement were given neoadjuvant gemcitabine-based chemotherapy followed by liver transplantation upon demonstrating at least six months of radiographic response or stability. Of the 21 patients referred for evaluation, six underwent transplantation and have shown OS to be 100% (95% CI: 100–100%) at one year, 83.3% (27.3–97.5%) at three years, and 83.3% (27.3–97.5%) at five years. Three patients developed recurrent disease at a median of 7.6 months [interquartile range (IQR), 5.7–8.6] after transplantation, with 50% (95% CI: 11.1–80.4) RFS at one, three, and five years (106). Such recent data highlights the value of patient selection that neoadjuvant therapy provides beyond only downstaging intent. While a finite number of organs will continue to limit the routine use of LT for unresectable ICC, efforts to expand the pool of donors while improving the patient selection for those most likely to benefit will improve outcomes for this important therapeutic option.

Conclusions

ICC is an aggressive biliary tract cancer that often presents late and therefore at advanced stages. Indeed, most patients with ICC present with metastatic disease in which treatment largely consists of palliative chemotherapy. Even among those without metastatic disease, a significant proportion are unresectable and locally advanced. The management of locally advanced ICC is important since expanding indications for surgery and effective downstaging with systemic and liver-directed therapies can lead to curative-intent therapy in a subset of patients. Even if downstaging does not occur, local control in the liver is important given that liver failure is a primary cause of morbidity and mortality in patients with locally advanced ICC. Fortunately, with advances in systemic, targeted, and liver-directed therapies, patients with ICC have more effective treatment options available today which is leading to improved outcomes.

Despite these advances, numerous questions remain for the optimal management of locally advanced ICC. For example, what is the optimal induction (ie initial) systemic therapy? Gemcitabine/cisplatin has been the standard for the past decade; have recent trial results been sufficiently convincing to add durvalumab? For those with targetable mutations, should targeted therapies and/or immunotherapy be used in the first line or reserved for treatment failure? What is the optimal liver-directed therapy for unresectable ICC and should they be offered concurrent with or following systemic therapy? In addition to investigating novel therapies, the next few years will hopefully elucidate answers to these questions focused on patient selection and sequencing of therapies. Novel biomarkers, such as circulating tumor DNA, to aid in treatment selection and measuring response will hopefully be developed in the near future. At the same time, future research needs to be patient-centered, incorporating patient preferences and goals into treatment planning, while maximizing quality of life. In conclusion, while long-term outcomes remain guarded for patients with unresectable ICC, the availability of novel treatment options and ongoing clinical trials signal hope for major advances coming in the treatment of locally advanced ICC.

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Footnote

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