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Review Article

Neoadjuvant and Adjuvant Therapy in Intrahepatic Cholangiocarcinoma

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Abstract

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer and causes major economic and health burdens throughout the world. Although the incidence of ICC is relatively low, an upward trend has been seen over the past few decades. Owing to the lack of specific manifestations and tools for early diagnosis, most ICC patients have relatively advanced disease at diagnosis. Thus, neoadjuvant therapy is necessary to evaluate tumor biology and downstage these patients so that appropriate candidates can be selected for radical liver resection. However, even after radical resection, the recurrence rate is relatively high and is a main cause leading to death after surgery, which makes adjuvant therapy necessary. Because of its low incidence, studies in both neoadjuvant and adjuvant settings of ICC are lagging compared with other types of malignancy. While standard neoadjuvant and adjuvant regimens are not available in the current guidelines due to a lack of high-level evidence, some progress has been achieved in recent years. In this review, the available literature on advances in neoadjuvant and adjuvant strategies in ICC are evaluated, and possible challenges and opportunities for clinical and translational investigations in the near future are discussed.

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Keywords: Intrahepatic cholangiocarcinoma; Neoadjuvant therapy; Adjuvant therapy; Recurrence; Liver resection; Liver transplant.

Abbreviations: 3D-CRT, three-dimensional conformal radiotherapy; 5-FU, 5-Fluoropyrimidine; AE, adverse event; AJCC, the American Joint Committee on Cancer; AT, adjuvant therapy; AVT, antiviral therapy; CA19-9, carbohydrate antigen 19-9; CAP, capecitabine; CEA, carcino-embryonic antigen; CIS, cisplatin; CRT, chemoradiotherapy; CSS, cancer-specific survival; CT, chemotherapy; CTLA4, cytotoxic T-lymphocyte associated protein 4; DCC, distal cholangiocarcinoma; DFS, disease-free survival; DOX, doxorubicin; EBRT, external beam radiotherapy; ECC, extrahepatic cholangiocarcinoma; EFS, event-free survival; GEM, gemcitabine; GEMOX, gemcitabine + oxaliplatin; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; HR, hazard ratio; ICC, intrahepatic cholangiocarcinoma; IMRT, intensity-modulated radiotherapy; IPTW, inverse probability of treatment weighting; LN, lymph nodes; LR, liver resection; LRFS, local recurrence-free survival; LT, liver transplantation; mOS, median OS; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NAT, neoadjuvant therapy; NCCN, National Comprehensive Cancer Network; NCDB, National Cancer Database; ORR, objective response rate; OS, overall survival; OXA, oxaliplatin; PCC, perihilar cholangiocarcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PSM, propensity score matching; RCTs, randomized controlled trials; RFS, recurrence-free survival; RT, radiotherapy; SEER, Surveillance, Epidemiology, and End Results; TACE, transcatheter arterial chemoembolization; TNM, tumor-node-metastasis; VMAT, volumetric modulated arc therapy.

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Introduction

Intrahepatic cholangiocarcinoma (ICC), the second most common primary liver cancer, accounts for 6.4–12.0% of primary malignancies arising in liver itself.[1,2] Although most ICC cases are sporadic, some risk factors have been identified, including liver fluke infection, bile tract conditions (e.g., primary sclerosing cholangitis, choledochal cysts, choledocholithiasis, cholelithiasis, and cholecystocholithiasis), hepatitis B and C virus infection, cirrhosis, alcohol consumption, smoking, metabolism-related factors (e.g., nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), obesity, and diabetes mellitus), inflammatory bowel disease, thyrotoxicosis, hemochromatosis, gout, and environmental chemical exposure etc.[3–8] The incidence of ICC is relatively low, but an upward trend has been noted in the last few decades, in contrast to a stable or decreasing incidence of extrahepatic cholangiocarcinoma (ECC).[9,10] National Cancer Database (NCDB) records reveal that ICC cases rose from 1,194 in 2004 to 3,821 in 2015, with an average annual increase of 4.16%.[11] It has been suggested that the increase is linked to the mounting incidence of type 2 diabetes mellitus, cirrhosis, alcoholic liver disease, and cholelithiasis.[4] Significantly, a definitive association between cirrhosis and ICC occurrence has been confirmed by several studies and patients with cirrhosis,[3,4] mainly secondary to hepatitis B and C virus infection, who are a population at high risk of ICC, which can be detected in a timely manner with an appropriate surveillance modality, such as magnetic resonance imaging (MRI) with hepatocyte-specific Gd-based contrast agents.[12] The enlarging gap between ICC and ECC can be partially accounted for by the high incidence of metabolism-associated conditions, especially NAFLD. NAFLD affects approximately 24% of the global population and is now the leading cause of chronic liver

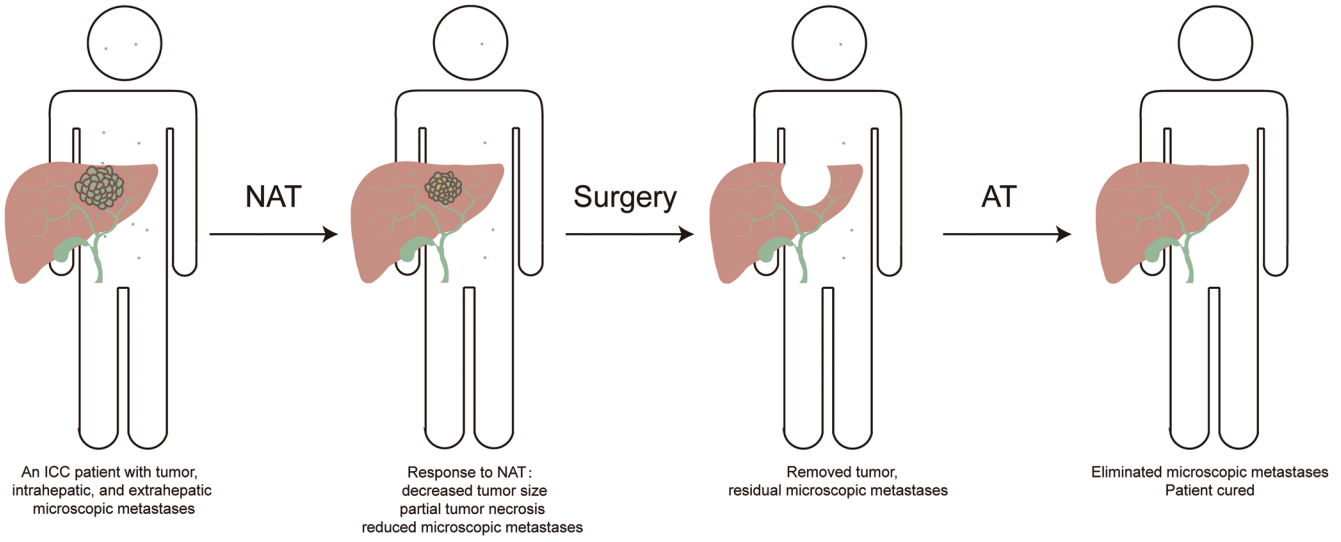

Fig. 1. Rationale for neoadjuvant and adjuvant therapy in ICC. AT, adjuvant therapy; ICC, intrahepatic cholangiocarcinoma; NAT, neoadjuvant therapy.

disease. Meanwhile, increasing studies indicate a definitive association between NAFLD and ICC, but not in ECC.[5,6,13,14] Owing to its highly aggressive biological behavior and the lack of specific symptoms and signs, most ICC patients present with relatively advanced disease at the initial diagnosis. An analysis of the Surveillance, Epidemiology, and End Results (SEER) database showed that 65.1–70.0% of ICC patients in the USA were classified as stage III or IV according to the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system.[15] Accordingly, only 23.0–53.0% of patients have the opportunity to undergo surgical resection and then experience long-term survival.[16,17] However, the high recurrence rate after curative treatment leads to a dismal prognosis. Even after radical resection, 57.9–73.4% of patients experience recurrence and 41.3–42.5% patients die of recurrence.[18–20] Postoperative recurrence occurs not only in the liver remnant, but also in adjacent and distant organs. Hu *et al*.[20] reported that intrahepatic-only recurrence was observed in 53.2% of patients, extrahepatic-only recurrence in 14.8% of patients, and both intrahepatic and extrahepatic recurrence in 32.0% of patients. Similar findings were observed in other studies.[18,19] While more than half recurrent ICC patients have liver involvement, extrahepatic recurrence is not an uncommon event. The most common recurrence sites outside the liver are the lungs, lymph nodes, and peritoneum.[18–20]

Owing to the scarce experience in liver transplantation (LT) for ICC patients and the shortage of donors, liver resection remains the main modality for curing ICC patients. However, because of the relatively advanced stage at diagnosis and the high recurrence rate after resection, both neoadjuvant and adjuvant therapies are necessary in those situations. Neoadjuvant chemotherapy or radiotherapy enables initially unresectable patients to be downstaged and converted to surgical candidates, which is frequently undertaken in other malignancies.[21] On the other hand, disseminated micrometastases in the liver remnant, lymph nodes, blood, or other organs can be eradicated by adjuvant chemotherapy or radiotherapy. The efficacy of neoadjuvant and adjuvant therapy has been validated in other types of cancer, and they are recommended as standard treatments in various guidelines.[21] In contrast, the benefits of neoadjuvant and adjuvant therapy in ICC are poorly understood. No standard neoadjuvant and adjuvant regimens are included in the latest National Comprehensive Cancer Network (NCCN) guidelines.[22] Thus, we endeavored to assess the available evidence on the use of neoadjuvant and adjuvant therapies in ICC patients undergoing resection or LT in this review.

Neoadjuvant therapy (NAT) for ICC

Neoadjuvant therapy is often used in other malignancies as an important modality to evaluate tumor response and biological nature, downstage initially borderline resectable or unresectable patients, and then select appropriate patients for resection. Nevertheless, NAT is not commonly used in ICC patients. The reported percentage of patients who received NAT is less than 10% in most studies.[19,23–45] Indeed, no high-level evidence supports the use of pre-operative chemotherapy or radiotherapy in ICC, and current guidelines do not recommend it in ICC patients undergoing resection or LT. However, the unique clinical manifestations of ICC resulting from its aggressive biology, including relatively advanced disease at diagnosis, and rapid recurrence in some cases after surgery, imply that NAT might be necessary before surgery (Fig. 1).

Chemotherapy and radiotherapy are frequently combined to obtain maximum neoadjuvant effectiveness in ICC. The first case of aggressive surgical resection following neoadjuvant chemoradiation therapy was reported by Kato *et al*.[46] in 2009, in which intravenous gemcitabine and three-dimensional conformation radiotherapy were administered to a patient with locally advanced disease. Decreased enhancement of the tumor on CT scan and decreased serum CA19-9 levels demonstrated an active treatment response, which was validated by extensive fibrosis in the resected tumor and lymph nodes. A similar case was reported in 2015, in which a complete pathological response was achieved by gemcitabine-based chemotherapy. The patient remained alive with no evidence of recurrence 6 months after surgery.[47] The first small-sample study was by Rayar *et al*.[48] in 2015, in which 10 patients with potentially resectable disease were given gemcitabine-based systemic chemotherapy and yttrium-90 radioembolization. Eight patients accepted R0 resection, and the conversion rate was 80%. Six patients achieved long survival, with one patient remaining alive 40 months after initial treatment. Similarly, Sumiyoshi *et al*.[49] reported a conversion rate of 71% (5/7) with S-1-based

chemoradiotherapy and two patients having an overall survival of more than 40 months. The long survival of the patients in those studies is encouraging. Investigators have begun to explore its impact of NAT on long-term outcomes by comparing patients receiving NAT and surgery with those undergoing upfront surgery.

Buettner *et al*.[40] identified 1,057 patients with curative-intent resection for ICC in an international multi-institutional cohort, among whom 62 patients had received preoperative chemotherapy. Both overall survival (OS) and disease-free survival (DFS) in patients with and without preoperative chemotherapy were comparable in propensity-score matched cohorts. Similar results were reported by others.[19,24,27,29,34,43,50,51] However, the results should be interpreted with caution for several reasons. To begin with, the sample size was relatively small or the proportion of patients with NAT was low in these studies. Then, there might be selection bias regarding choosing candidates for NAT. It has been established that locally advanced patients or borderline resectable patients, who are deemed to have a dismal prognosis, are more likely to receive NAT. Finally, NAT regimens varied greatly among individuals in different studies and even in the same study in terms of the administration routine, dosage, and duration. Nevertheless, a recent study by Mason *et al*.[52] reported a positive effect of neoadjuvant chemotherapy, with a 23% decrease in the risk of death compared with surgery alone (HR=0.77, $p<0.05$). Similarly, Utuama *et al*.[53] observed that NAT prolonged survival (HR=0.58, $p=0.02$), but only in stage II–III disease. Both studies evaluated cases included in the NCDB database, and used propensity score matching to reduce the bias caused by the low proportion of patients with NAT. Another recent study from the USA confirmed the protective role of NAT in prolonging OS in ICC patients (HR=0.16, $p=0.001$).[54]

Traditionally, ICC is considered as a contradiction for LT because of unfavorable results. However, promising results were observed in a recent study, caused in part by NAT as the bridging treatment. Lunsford *et al*.[55] performed LT in six of 12 (conversion rate: 50%) locally advanced ICC patients, all of whom had received NAT in the waiting period and had stable disease or tumor regression after 6 months or more on NAT. Most NAT regimens included gemcitabine-based systemic chemotherapy, fluoropyrimidines, and targeted drugs. The 5-year OS and DFS were 83.3% and 50% respectively, indicating favorable long-term outcomes. That was the first study focusing on LT in locally advanced ICC patients in the setting of NAT, which implies that the tumor response to NAT can be useful to measure tumor biology and to select candidates who might benefit from LT. While a satisfying conversion rate and improved long-term survival indicate the effectiveness of preoperative therapy, well-designed prospective studies are still necessary to confirm the role of NAT prior to liver resection or transplantation.

Adjuvant therapy (AT) for ICC

While NAT is usually employed to downstage and convert initially unresectable patients to surgical candidates, immediate resection remains the first choice in ICC patients with resectable tumors and sufficient future liver remnant volume and function. However, recurrence is a relatively common event in patients who receive upfront surgery, which is associated with residual micrometastasis from the primary tumor or de novo carcinogenesis from the underlying liver background. Extrahepatic recurrence or metastasis is also not uncommon. Therefore, effective adjuvant therapy must address all those issues (Fig. 1).

Transcatheter arterial chemoembolization (TACE)

While TACE is thought to be safe, feasible, and effective as a palliative treatment in unresectable ICC patients, the role of TACE in adjuvant settings is less well understood. Nearly all relevant studies are from China (Table 1), and report mixed results. Shen *et al*.[56] published the first study in this field in 2011, in which patients receiving TACE after surgery had significantly better OS than those receiving surgery alone in an early recurrence subgroup, with a median OS of 12 vs. 5 months, $p<0.001$), but not in a late recurrence subgroup. The investigators concluded that TACE controlled early recurrence by eradicating recurrent foci in the remnant liver. Another study from the same center observed that TACE improved survival (3-year OS: 34% vs. 0%, $p<0.001$ and 3-year DFS: 27% vs. 0%, $p=0.008$) in patients with poor prognostic factors, while having no effect on the survival of patients without poor prognostic factors.[57] The positive effect of TACE in ICC patients at high risk of recurrence or death was also confirmed by other studies that included patients with high-risk features such as being in the lowest tertile of a prognostic nomogram, having a preoperative GGT of >54 U/L, arterial phase enhancement on CT scans, relatively advanced TNM stages, elevated CA19-9, and without lymphadenectomy.[58–63] Liu *et al*.[64] observed no survival benefit with TACE, which instead promoted recurrence, similar to the findings of Li *et al*.[59] in TNM stage I patients. The hypoxia caused by the blockage of liver blood flow during TACE may increase the malignant potential of residual tumor cells. Two meta-analyses also drew conflicting conclusions.[65,66] Randomized controlled trials (RCTs) are not available, but the findings of the above studies indicate that adjuvant TACE might benefit patients at high risk of recurrence or death.

Systemic chemotherapy

The NCCN or other guidelines do not include a standard adjuvant regimen, it is not uncommon for ICC patients to receive adjuvant chemotherapy after surgery.[22,67] The majority of relevant studies report that more than 30% patients receive systemic chemotherapy.[18,20,26,28,33,40] Owing to a lack of RCT results, chemotherapy regimens vary among centers, and include gemcitabine, 5-fluorouracil, capecitabine, S-1, oxaliplatine, and cisplatine, etc.[28,68–72] The most common regimens include gemcitabine and 5-fluorouracil. Detailed information on chemotherapy reagent dose, duration, and number of cycles is often not provided, and might partially explain inconsistent reports of treatment effectiveness.

Owing to the relatively low incidence of ICC, the role of adjuvant chemotherapy in resected biliary tract cancer including ICC has been evaluated in only two RCTs, neither of which achieved the primary endpoint of improving OS in the whole cohort as well as in the ICC subgroup. ICC only accounted for a minority (84/447,18.8%; and 86/194, 44.3%) of the entire study cohort in the two RCTs.[73,74] Given the fact that ICC differs from other bile duct cancers at the clinicopathological and molecular levels, studies with large groups of ICC patients are needed.[75] The first study focusing on AT in ICC patients was an analysis by Sur *et al*.[76] of 638 ICC patients with surgical resection who were included in the NCDB database. Seventy-five had received adjuvant chemotherapy alone and 147 had received adjuvant chemoradiation. The patients with significant benefits from adjuvant chemotherapy or chemoradiation had positive surgical margins (chemotherapy HR=0.44, $p=0.0016$ and chemoradiation HR=0.57, $p=0.0039$) or lymph node metastasis (chemotherapy HR=0.54, $p=0.0365$ and chemoradiation HR=0.50, $p=0.005$). Three other studies that included patients in the NCDB or SEER databases who were treated at

Table 1. Selected studies of adjuvant TACE in ICC

Reference	Study type	Arms and interventions	Patients, *n* intervention/ observation	Main findings	Remarks
Shen *et al*. (2011)[56]	Retrospective	TACE vs. observation	53/72	Patients with recurrence time ≤ 3 months: improved 1-, 3-, 5-year OS with TACE.	TACE can eradicate recurrent foci in remnant liver and control early recurrence.
Wu *et al*. (2012)[57]	Retrospective	TACE vs. observation	57/57	Patients with poor prognostic factors: improved 1-, 3-, 5-year OS and DFS with TACE.	Poor prognostic factors: tumor size ≥ 5 cm, advanced TNM stage (stage III or IV).
Li *et al*. (2014)[58]	Retrospective	TACE vs. observation	68/143	TNM stage II, III, and IV patients: improved OS with TACE.	TNM stage I patients: higher recurrence rate with TACE.
Li *et al*. (2015)[59]	Retrospective	TACE vs. observation	122/431	Patients with nomogram scores ≥ 77: improved 1-, 3-, 5-year OS and recurrence rate with TACE.	ICC nomogram: CEA, CA19-9, tumor diameter, tumor number, vascular invasion, lymph node metastasis, direct invasion and local metastasis; study with the largest sample size.
Jeong *et al*. (2017)[60]	Retrospective	TACE vs. observation	9/33	ICC with arterial phase enhancement on CT scans: improved 1-, 3-, 5-year OS with TACE.	HBV-associated ICC; preoperative CT scan manifestation can serve as a selection criterion for TACE candidates; limited by small sample. size
Lu *et al*. (2017)[61]	Retrospective	TACE vs. observation	89/183	Patients with GGT levels > 54 U/L: improved OS with TACE.	PSM; preoperative serum GGT level can serve as a selection criterion for TACE candidates.
Wang *et al*. (2020)[62]	Retrospective	TACE vs. observation	39/296	Patients with stage II, III or risk factors < 2: improved OS with TACE.	PSM; the incidence of patients having adjuvant TACE is relatively low (11.6%).
Cheng *et al*. (2021)[63]	Retrospective	TACE vs. observation	68/155	Patients with elevated CA19-9 or no lymphadenectomy: improved OS with TACE.	PSM and IPTW; all patients have microvascular invasion.
Liu *et al*. (2021)[64]	Retrospective	TACE vs. observation	35/234	TNM stage I patients: TACE cannot prolong OS; instead, TACE might increase the recurrence risk.	All patients have TNM stage I disease; relatively low proportions (13.0%) of patients receive adjuvant TACE.

CEA, carcino-embryonic antigen; CA19-9, carbohydrate antigen 19–9; DFS, disease-free survival; CT, computed tomography; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; ICC, intrahepatic cholangiocarcinoma; IPTW, inverse probability of treatment weighting; LR, liver resection; OS, overall survival; PSM, propensity score matching; TACE, transcatheter arterial chemoembolization; TNM, tumor-node-metastasis.

different time periods also reported that high-risk patients benefited from AT. The use of chemotherapy has increased from 33% of patients in 2000–2004, to 37% in 2005–2009 and 41% in 2010–2014 (p=0.027).[45,77–78] The findings are echoed by similar results from the Taiwan Cancer Registry database and a multi-institutional cohort.[79,80] Unlike the various high-risk characteristics of adjuvant TACE, those associated with adjuvant systemic chemotherapy are limited to positive margins, positive lymph nodes, or relatively advanced stage.[79,80] A study by Schweitzer *et al*.[81] could not evaluate high-risk subgroups because of a small sample size, but did report a survival advantage of adjuvant chemotherapy in a propensity-score matching analysis (median OS: 33.5 vs. 18.0 months, p=0.002). However, many studies did not find a significant positive or negative correlation between AT and patient survival.[19,20,29,31,33–35,82] However, the studies mainly focused on other factors, such as albumin and bilirubin, and AT was only an incidental variable. As no subgroup analysis or propensity-score matched analysis was used to evaluate AT, and the role of AT was underestimated. In these circumstances, the view that selected ICC patients can benefit from AT seems more convincing. Selected studies are presented in Table 2.

Radiotherapy

Radiotherapy is often combined with chemotherapy both in neoadjuvant and adjuvant settings of ICC patients. As chemotherapy has been discussed above, only radiotherapy is included in this section. The first study of adjuvant radiotherapy in ICC evaluated patients included in the SEER database. Those with surgery and adjuvant radiotherapy had significantly better OS then those with surgery alone (median: 11 vs. 6 months, p=0.014). However, information on the radiotherapy modality, dose, and duration and infor-

Table 2. Selected studies of adjuvant chemotherapy/radiotherapy/chemoradiotherapy for intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma

Category	Reference	Regimen	Study type	Patients, *n** intervention/ observation	ICC	ECC
Adjuvant CT	(i) Sur *et al*. (2015)[76]; (ii) Miura *et al*. (2015)[45]; (iii) Reames *et al*. (2017)[80]; (iv) Schweitzer *et al*. (2017)[81]; (v) Lee *et al*. (2019)[77]; (vi) Altman *et al*. (2020)[78]	(i) CT; (ii) CT; (iii) CIS/GEM/5-FU; (iv) GEM-based CT; (v) CT; (vi) CT	(i) Retrospective; (ii) Retrospective; (iii) Retrospective; (iv) Retrospective; (v) Retrospective; (vi) Retrospective	(i) 75/416; (ii) 985/1,766; (iii) 347/807; (iv) 39/171; (v) 1,189/1,624; (vi) 470/753	(i) Positive LN subgroup OS: HR=0.54, p=0.037; positive margin subgroup: HR=0.44, p=0.002. (ii) T3/T4 subgroup mOS: 21.3 vs. 15.6 months, p<0.001; N1 subgroup mOS: 19.8 vs. 10.7 months, p<0.001; R1/R2 subgroup mOS: 19.5 vs. 11.6 months, p=0.006. (iii) T3/T4 subgroup OS: HR=0.44, p<0.01; N1 subgroup: HR=0.24, p<0.001. (iv) PSM cohort OS: HR=0.33, p=0.002. (v) high-risk subgroup OS: HR=0.66, p<0.001. (vi) N1 subgroup OS: HR=0.46, p=0.001	(a) PCC; OS: HR=0.25, p=0.035. (b) ECC; positive LN subgroup OS: HR=0.85, p<0.05. (c) DCC; OS: HR=0.21, p=0.001; DFS: HR=0.34, p=0.002. (d) ECC; OS: HR=0.62, p=0.008; PFS, HR=0.62, p=0.007. (e) PCC; PSM cohort 5-year OS: 43.2% vs. 15.6%, p=0.001; 3-year RFS: 46.9% vs. 15.9, p=0.01. (f) ECC; OS: HR not reported, p=0.114; DFS: HR=1.64, p=0.035. (g) ECC; OS: HR=1.01, p=0.964; RFS: HR=0.9, p=0.693. (h) DCC; PSM cohort mOS: 26.3 vs. 43.3 months, p=0.340; mDFS: 15.5 vs. 14.7 months, p=0.790. (i) ECC; 5-year OS: 40.8% *vs* 44.6%, p=0.916; RFS, 30.9% vs. 38.4%, p=0.794. (j) PCC; early recurrence subgroup OS: HR=0.38, p=0.039. (k) PCC; OS: HR=0.47, p=0.001; DFS: HR=0.69, p=0.068
	(a) Murakami *et al*. (2009)[97]; (b) Hoehn *et al*. (2015)[98]; (c) Kim *et al*. (2016)[92]; (d) Im *et al*. (2016)[95]; (e) Mizuno *et al*. (2017)[99]; (f) Yin *et al*. (2018)[100]; (g) Ebata *et al*. (2018)[101]; (h) Bergeat *et al*. (2018)[102]; (i) Morino *et al*. (2019)[103]; (j) Zhao *et al*. (2020)[104]; (k) Im *et al*. (2021)[94];	(a) GEM-based CT; (b) CT; (c) 5-FU/DOX/GEM; (d) 5-FU/CIS/GEM; (e) GEM monotherapy; (f) GEM/CIS/OXA/S-1/CAP; (g) GEM monotherapy; (h) GEM-based CT; (i) GEM/S-1; (j) GEM/S-1; (k) 5-FU/GEM-based CT	(a) Retrospective; (b) Retrospective; (c) Retrospective; (d) Retrospective; (e) Retrospective; (f) Retrospective; (g) RCT; (h) Retrospective; (i) Retrospective; (j) Retrospective; (k) Retrospective	(a) 18/20; (b) 444/5,739; (c) 27/102; (d) 90/168; (e) 67/113; (f) 40/40; (g) 117/108; (h) 56/122; (i) 57/49; (j) 25/310; (k) 67/90		
Adjuvant RT	(i) Shinohara *et al*. (2008)[83]; (ii) Jiang *et al*. (2010)[84]; (iii) Hammad *et al*. (2016)[86]; (iv) Zheng *et al*. (2018)[85]	(i) RT; (ii) EBRT; (iii) RT; (iv) IMRT/VMAT	(i) Retrospective; (ii) Retrospective; (iii) Retrospective; (iv) Retrospective	(i) 286/948; (ii) 24/66; (iii) 525/2,372; (iv) 26/23	(i) mOS: 11 vs. 6 months, p=0.014. (ii) OS: HR=0.48, p=0.013.(iii) PSM cohort OS: HR=1.01, p=0.923. (iv) OS: HR=0.27, p=0.011	(a) ECC; OS: HR=0.89, p=0.074. (b) ECC; OS: HR=0.59, p=0.078; PFS, HR=0.57, p=0.045. (c) DCC; OS: HR=2.38, p=0.040; RFS: HR=1.42, p=0.361. (d) PCC; mOS: 22 vs. 23 months, p=0.978; mCSS, 17 *vs* 18 months, p=0.554. (e) ECC; OS: HR=0.49, p=0.085; LRFS, HR=0.31, p=0.043. (f) PCC; OS: HR=0.81, p=0.538; DFS: HR=1.32, p=0.368
	(a) Vern-Gross *et al*. (2011)[91]; (b) Im *et al*. (2016)[95]; (c) Kim *et al*. (2016)[92]; (d) Leng *et al*. (2017)[93]; (e) Kim *et al*. (2017)[96]; (f) Im *et al*. (2021)[94]	(a) RT; (b) 3D-CRT; (c) EBRT; (d) RT; (e) RT; (f) EBRT/IMRT	(a) Retrospective; (b) Retrospective; (c) Retrospective; (d) Retrospective; (e) Retrospective; (f) Retrospective	(a) 473/1,018; (b) 29/168; (c) 9/102; (d) 762/1,155; (e) 23/36; (f) 18/90		
Adjuvant CRT	(i) Sur *et al*. (2015)[76]	(i) CRT	(i) Retrospective	(i) 147/416	(i) positive LN subgroup OS: HR=0.50, p=0.005; positive margin subgroup: HR=0.57, p=0.004	(a) ECC; OS: HR=0.53, p=0.005; DFS: HR=0.55 p=0.005. (b) ECC; OS: HR=0.82, p<0.001. (c) DCC; OS: HR=0.25, p=0.024; DFS: HR=0.33, p=0.004. (d) PCC; OS: HR=0.46, p=0.003; PFS, HR=0.41, p=0.001. (e) PCC; OS: HR=0.26, p<0.001; DFS: HR=0.31, p<0.001
	(a) Kim *et al*. (2011)[105]; (b) Hoehn *et al*. (2015)[98]; (c) Kim *et al*. (2016)[92]; (d) Im *et al*. (2016)[95]; (e) Im *et al*. (2021)[94]	(a) 5-FU-based CT+EBRT; (b) CRT; (c) 5-FU/CAP/GEM+EBRT; (d) 5-FU/CIS/GEM+3D-CRT; (e) 5-FU/GEM-based CT+EBRT/IMRT	(a) Retrospective; (b) Retrospective; (c) Retrospective; (d) Retrospective; (e) Retrospective	(a) 115/53; (b) 1,902/5,739; (c) 20/102; (d) 49/168; (e) 21/90		

*Numbers of patients in the intervention/observation groups. i–vi are studies of adjuvant CT/RT/CRT in ICC; a–k are studies of adjuvant CT/RT/CRT in ECC. 3D-CRT, three-dimensional conformal radiotherapy; 5-FU, 5-Fluoropyrimidine; CAP, capecitabine; CIS, cisplatin; CRT, chemoradiotherapy; CSS, cancer-specific survival; CT, chemotherapy; DCC, distal cholangiocarcinoma; DFS, disease-free survival; DOX, doxorubicin; EBRT, external beam radiotherapy; ECC, extrahepatic cholangiocarcinoma; GEM, gemcitabine; HR, hazard ratio; ICC, intrahepatic cholangiocarcinoma; IMRT, intensity-modulated radiotherapy; LN, lymph nodes; LRFS, local recurrence-free survival; mOS, median OS; OS, overall survival; OXA, oxaliplatin; PCC, perihilar cholangiocarcinoma; PFS, progression-free survival; PSM, propensity score matching; RCT, randomized controlled trial; RFS, recurrence-free survival; RT, radiotherapy; VMAT, volumetric modulated arc therapy.

mation on other variables such as adjuvant chemotherapy and lymph node metastasis was missing, which is an inherent drawback of the SEER database.[83] Jiang *et al*.[84] reported that adjuvant radiotherapy improved the prognosis of patients with resected ICC and concurrent macroscopic lymph node metastases, and Zheng *et al*.[85] reported a similar role of radiotherapy in ICC patients with tumors adhering to major vessels. The survival of patients with narrow margins and adjuvant radiotherapy was comparable to that of patients with wide margins and no adjuvant radiology, and adjuvant radiotherapy improved the survival of patients who had narrow margins. The results indicated that adjuvant radiotherapy overcame the negative impact of narrow margins to some extent. However, an analysis of patients in the NCDB database did not find a survival benefit of adjuvant radiotherapy, even in patients with positive resection margins or node-negative disease.[86] Even though RCTs of adjuvant radiotherapy in ICC are lacking, the findings of current studies support the use of adjuvant radiotherapy in high-risk patients.

Antiviral therapy (AVT)

The role of viral hepatitis is not as prominent in ICC as it is in HCC, and is involved in only 6.1–7.0% of all cases.[42,43] To the best of our knowledge, Lei *et al*.[87] published the only study on adjuvant antiviral therapy in ICC patients. Of 1,064 consecutive patients with liver resection for ICC and concurrent HBV infection, 198 received antiviral therapy. Eighty-seven of the 198 patients began AVT before surgery and all continued it after surgery. The remaining 111 patients initiated AVT after liver resection. That is to say, all 198 received AVT as AT and some also received AVT as NAT. AVT regimens included lamivudine, adefovir, telbivudine, and entecavir, and interferon alpha. The patients were required to receive an AVT regimen for at least 3 months. AVT reduced postoperative viral reactivation to 3.3%; viral reactivation occurred in 8.3% of patients who did not receive AVT. Compared with patients who had high HBV-DNA levels and no AVT, those with AVT had significantly better long-term outcomes (5-year OS: 43.0% vs. 20.5%, $p<0.001$), but the difference was not significant in patients with low HBV-DNA levels. In that study, neoadjuvant and adjuvant AVT decreased viral reactivation and improved long-term outcomes in ICC patients with a high viral burden.[88] AVT should thus be considered in such ICC patients.

AT in ICC and ECC

Owing to the low incidence of biliary cancer, ICC and ECC are often reported together and are not evaluated separately in many studies even though they have distinct anatomical, clinical, and molecular characteristics. The outcomes of AT in ICC and ECC in selected studies are shown and compared in Table 2.[73,74,88–111] Both ICC and ECC patients are more likely to receive adjuvant chemotherapy than radiotherapy, as there are more studies on adjuvant chemotherapy than radiotherapy in ICC as well as ECC. In both ICC and ECC, most AT regimens include gemcitabine- or fluorouracil, and the results are mixed in both diseases. Overall, there are far more differences than similarities between ICC and ECC studies. First, more studies have evaluated AT in ECC than in ICC, regardless of the treatment modalities (i.e., adjuvant chemotherapy, radiotherapy, or chemoradiotherapy). There is even one RCT of adjuvant chemotherapy for ECC. Secondly, it seems to be easier for ECC patients to benefit from AT. In studies reporting positive results, it was often the case that the benefit emerged in the analysis of the whole ECC cohort, while the benefit was only apparent in subgroup analyses of high-risk ICC patients. Five studies included both ICC and ECC patients, with subgroup analysis of each cancer type.[73,74,88–90] In the two of three retrospective studies, ICC patients benefitted from AT but ECC patients did not. This difference was not observed in the two RCTs and in another retrospective study. In the RCTs, neither ICC nor ECC benefitted from AT. In the third retrospective study, only ECC patients with distal cholangiocarcinoma benefitted from AT. Finally, owing to the anatomical location of ICC (buried inside the liver) and a proportion of patients having a background of HBV infection, ICC patients can be given TACE and antiviral therapy as AT, but that is obviously not the case for ECC patients.

Discussion

Although substantial progress has been made in understanding the epidemiology, risk factors, and molecular characteristics of ICC in the past few decades, the management of ICC remains extremely challenging.[3–10,75] Radical resection remains the main treatment for ICC patients to achieve long-term survival, but only a minority of patients are diagnosed at an early stage eligible for surgery because of a lack of specific symptoms and method suitable for an early diagnosis.[16,17] Relatively advanced disease at diagnosis means that NAT should be used to downstage patients and select appropriate candidates with tumor biology allowing hepatectomy. On the other hand, the aggressive behavior of ICC leads to a high recurrence rate even after radical resection, which calls for the use of AT.[18–20] Unfortunately, owing to the relatively low incidence and then the paucity of conclusive evidence in neoadjuvant as well as adjuvant settings, the latest guidelines do not recommend routine use of neoadjuvant or adjuvant regimens in managing ICC.[22,67]

NAT, as a means to downstage relatively advanced patients to resection or a bridge therapy before LT, has a relatively high objective response and conversion rates. Patients who respond to NAT also experience satisfying long-term outcomes similar to or superior to those with upfront surgery. The main challenge of promoting these conclusions lies in the fact that the sample size is relatively small, and the criteria for selecting candidates for NAT and NAT regimens vary greatly among different centers. Well-designed prospective trials are needed to identify those who will benefit from NAT, as well as the efficacy of various regimens. In comparison, there is evidence that supports adjuvant strategies in ICC, including TACE,[55–66] systematic chemotherapy,[76–81] radiotherapy,[83–86] and antiviral therapy.[87] Notably, most studies support the use of AT in ICC patients with high-risk features like positive margins or positive lymph nodes, indicating that not all patients can benefit from AT.[55–66,76–81] Instead, AT might harm selected ICC patients for some unknown reasons.[59,64] Future prospective studies on the role of AT are more likely to have positive results if they are designed to include candidates at high risk of recurrence or death. For HBV-infected ICC patients, especially these with high viral levels, active antiviral therapy before and after surgery can improve outcomes and should be implemented.[87] It is worth noting that all evidence in support of NAT and AT was obtained in retrospective studies and needs to be further confirmed by carefully designed prospective trials. Because the study of NAT and AT in ICC lags behind that in ECC, and that ICC has clinical and molecular characteristics distinct from ECC, prospective trials including only ICC patients are especially anticipated.

During our review of existing evidence for NAT and AT in ICC, we noticed some limitations of the available therapeutic modalities. The disadvantages of systemic chemotherapy include relative insensitivity to currently available

Table 3. Selected clinical trials of neoadjuvant and adjuvant therapy in ICC

Trial identifier	Regimen/intervention	Estimated enrollment	Study type	Primary outcome	Country	Setting
NCT04506281	Toripalimab (PD-1 antibody) + GEMOX + lenvatinib vs. observation	128	Phase 2, RCT	EFS	China	Neoadjuvant
NCT04523402	GEMOX vs. observation	100	Phase 2, RCT	EFS	China	Neoadjuvant
NCT04546828	Gemcitabine + cisplatin + nab-paclitaxel	34	Phase 2, single arm	Increased rate of R0 resection	Korea	Neoadjuvant
NCT04669496	Toripalimab (PD-1 antibody) + GEMOX + lenvatinib vs. observation	178	Phase 2–3, RCT	EFS	China	Neoadjuvant
NCT04989218	Gemcitabine + cisplatin + durvalumab (PD-L1 antibody) + tremelimumab (CTLA4 antibody)	20	Phase 1–2, single arm	ORR	USA	Neoadjuvant
NCT03579771	Gemcitabine + cisplatin + nab-paclitaxel	34	Phase 2, single arm	Completion of all therapy rate, AE	USA	Neoadjuvant
NCT04295317	SHR-1210 (PD-1 antibody) + capecitabine	65	Phase 2, single arm	RFS	China	Adjuvant
NCT03820310	Traditional therapy plus autologous Tcm cellular immunotherapy vs. traditional therapy alone	20	Phase 2, RCT	PFS, OS	China	Adjuvant
NCT04782804	Tislelizumab (PD-1 antibody) + capecitabine vs. capecitabine alone	30	Phase 1–2, non-randomized	RFS	China	Adjuvant
NCT04077983	Nab-paclitaxel + gemcitabine	40	Phase 2, single arm	DFS	China	Adjuvant

AE, adverse event; CTLA4, cytotoxic T-lymphocyte associated protein 4; DFS, disease-free survival; EFS, event-free survival; GEMOX, gemcitabine + oxaliplatin; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RCT, randomized controlled trial; RFS, recurrence-free survival.

chemotherapy regimens, toxic side effects, and the development of drug resistance.[73,74] Compared with systemic chemotherapy, TACE, as a locoregional therapy, causes fewer general side effects than systemic chemotherapy agents, but also increases the chance of liver-related complications and an inability to control disease outside the liver, such as metastasis in the lungs and lymph nodes.[56,61] Radiotherapy, usually with an enlarged irradiation volume that includes surrounding organs like the kidneys and pancreas, can control micrometastasis with direct spread from the primary tumors, but also can harm those fields.[84,85] Radiotherapy, however, fails to manage distant metastasis. Antiviral therapy, given either before or after resection, improves outcomes in ICC patients with a background HBV infection. Recurrence after surgery depends on different mechanisms that include intrahepatic metastasis from the primary tumor and de novo carcinogenesis from the underlying inflammation or cirrhosis caused by HBV infection. Antiviral therapy can control neocarcinogenesis, but is less effective in eradicating intrahepatic metastasis.[87]

Given the limited effectiveness and drawbacks of existing therapeutic modalities, more effective strategies based on immunotherapy and targeted agents should be pursued. Immunotherapy, including inhibitors of immune checkpoints such as programmed death 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen-4, (CTLA-4), cancer vaccines, and adoptive cell transfer, have received ongoing attention in recent years. No immunotherapy has been approved for treating ICC, but the evidence has been increasing. Job *et al*.[112] confirmed the existence of an inflamed ICC subtype characterized by massive T lymphocyte infiltration and activation of inflammatory and immune checkpoint pathways and classification of the tumor microenvironment that showed a high response rate to immune checkpoint inhibitors. High expression of PD-1/PD-L1 in ICC has been observed in several studies, and was negatively correlated with unfavorable prognosis, which indicated a promising role of immunotherapy in ICC.[112–115] Although no conclusive results yet been reported, clinical trials of NAT and AT of ICC with immunotherapy alone or in combination with other therapeutic reagents are now underway (Table 3). Considering the limited treatment options and efficacy of existing therapeutic modalities, the outcomes of ongoing clinical trials are eagerly anticipated. Two drugs, pemigatinib and infigratinib, have been approved by the FDA for the targeted treatment of advanced or metastatic cholangiocarcinoma patients with *FGFR2* fusions or rearrangements. Relatively high objective response rates indicate promising anticancer activity of the two drugs in cholangiocarcinoma,[116,117] but no clinical trials of either FGFR inhibitor for NAT and AT of ICC have been registered. Given that FGFR2 fusions or rearrangements almost exclusively occur in ICC, the use of pemigatinib and infigratinib for NAT and AT warrants exploration.

In conclusion, more effort should be addressed the improvement of multidisciplinary management of ICC, despite advances that have been made in recent years. The flow diagram in Figure 2 illustrates proposed ICC treatment based on the current evidence. Liver resection remains an important treatment with curative-intent, but additional neoadjuvant and adjuvant therapies might increase the number of surgical candidates, reduce recurrence rates after surgery, and improve the long-term outcomes. Progress has been achieved in the use of NAT and AT for ICC, future investiga-

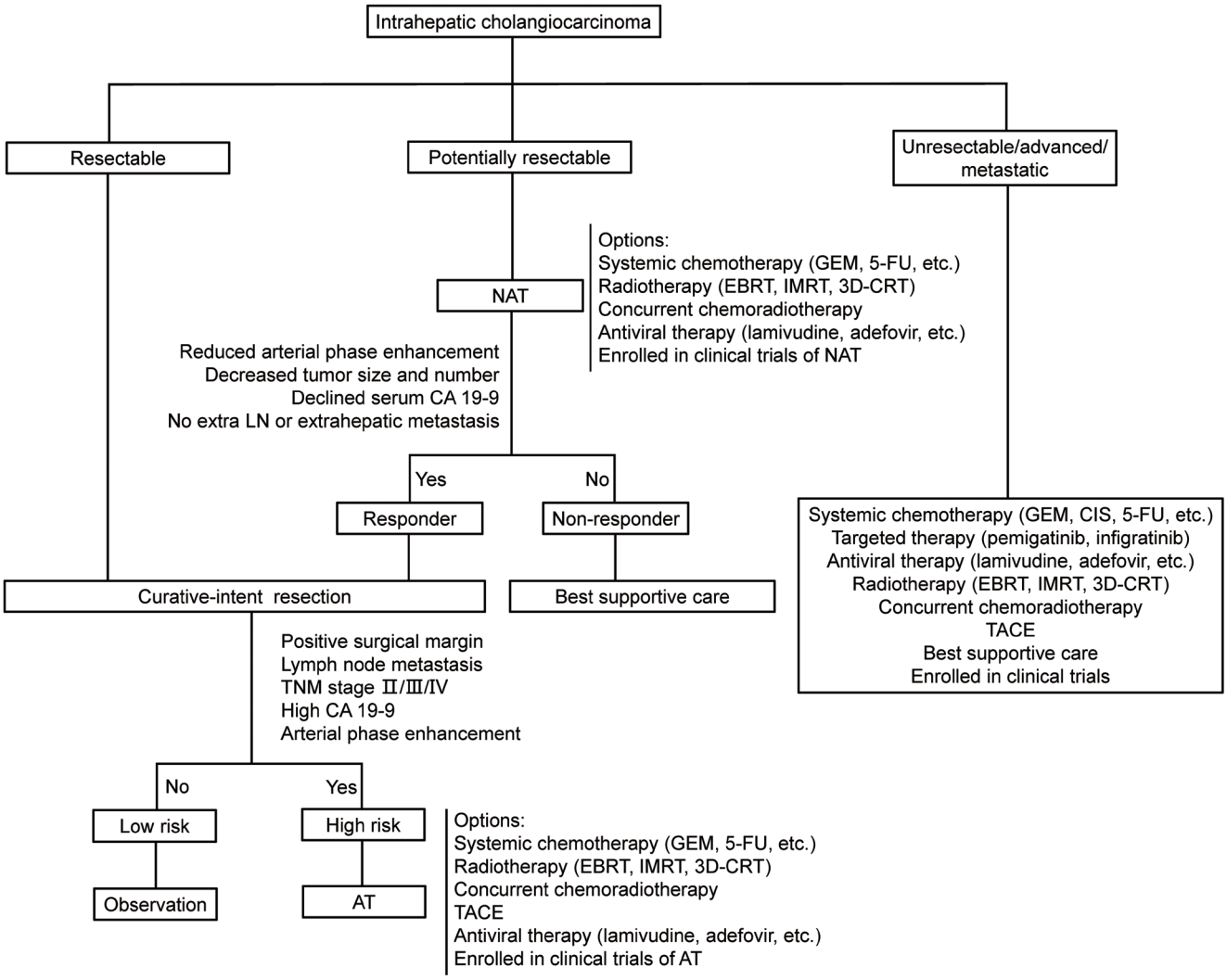

Fig. 2. Proposed treatment flow for ICC. 3D-CRT, three-dimensional conformal radiotherapy; 5-FU, 5-Fluoropyrimidine; AT, adjuvant therapy; CIS, cisplatin; EBRT, external beam radiotherapy; GEM, gemcitabine; IMRT, intensity-modulated radiotherapy; NAT: neoadjuvant therapy; TACE, transcatheter arterial chemoembolization; TNM, tumor-node-metastasis.

tion is needed to identify the optimal therapeutic regimens, including chemotherapy, radiotherapy, TACE, immunotherapy, targeted therapy, and antiviral therapy, or an appropriate combination of those modalities.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

XC, KY and YZ were responsible for the study concept and design, XC, JD and JH, were responsible for acquisition of data, analysis and interpretation of data, XC and JD drafted the manuscript, XC, KY and YZ performed critical revisions of the manuscript, and KY and YZ supervised the study.

Data sharing statement

The clinical data used to support the findings of this study are included within the cited articles.

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