Surgical Resection Criteria and Neoadjuvant Therapies for Intrahepatic Cholangiocarcinoma

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Abstract: The staging of intrahepatic cholangiocarcinoma (ICC) is complex, and there is no consensus among international cancer groups on how to most appropriately select candidates with nonmetastatic disease for surgical resection. Factors contributing to a higher stage of disease include larger tumor size, multiple tumors, vascular invasion (either portal venous or arterial), biliary invasion, involvement of local hepatic structures, serosal invasion, and regional lymph node metastases. For patients selected to undergo surgery, it is well-documented that R0 resection translates to a survival benefit. Estimating the risk of post-hepatectomy liver failure and post-surgical residual liver function is vital and may preclude some patients with significant tumor burden from undergoing surgery. Numerous serum and biliary biomarkers of the disease can help detect recurrence in patients undergoing surgical resection. Systemic and locoregional neoadjuvant treatments to facilitate better surgical outcomes have yielded mixed results regarding improving resectability and overall survival. Additional research is needed to identify optimal neoadjuvant treatment approaches and to evaluate which patients will benefit most from these strategies. Therapies targeting genetic mutations and protein aberrations found by tumor molecular profiling may offer additional options for future neoadjuvant treatment.

Keywords
Biomarkers, intrahepatic cholangiocarcinoma, locoregional therapy, neoadjuvant therapy, staging, surgical resection

Introduction

Cholangiocarcinoma (CCA) is a form of cancer originating from the epithelial cells of the biliary tract. This disease is rare in the United States, with approximately 8000 to 9000 new diagnoses each year, but the fatality rate is high.[1,2] The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program estimates that the 5-year relative survival rate for patients with intrahepatic bile duct cancers (all stages combined) is 9%.[3] CCA's poor prognosis is partly driven by the lack of effective screening methods. Furthermore, CCA is frequently asymptomatic at earlier stages, and by the time symptoms arise, the disease is often advanced and not amenable to definitive therapy.

Although CCA is rare, data suggest that its global incidence is rising in most countries.[4] East Asian countries are often disproportionately affected, with some of the highest age-standardized incidence rates of CCA worldwide reported in South Korea, Thailand, Japan, and China.[5] This is thought to be partly due to infections from endemic parasites (such as the river flukes of the genera *Clonorchis* and *Opisthorchis*) that can cause inflammation of the biliary tree and promote the development of malignancy.[6,7] There are many other risk factors for CCA, including primary hepatobiliary diseases (chiefly, primary sclerosing cholangitis[8]); inherited genetic disorders, such as Lynch syndrome[9]; and chronic tobacco or alcohol use.[10] Individuals with metabolic syndrome are also thought to be at increased risk for the development of CCA, which may help to explain the rising incidence of the disease.[11]

CCA may also be classified anatomically, with the 2 broadest categories being intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC). ECC may be further subdivided into perihilar, affecting the common hepatic duct, and distal, affecting the common bile duct. This review focuses specifically on ICC.

For localized disease, treatment is aimed at definitive surgical resection, often followed by adjuvant therapy with systemic chemotherapy or chemoradiotherapy. For patients with localized unresectable disease, neoadjuvant strategies are often employed to attempt downstaging of the tumor and eventual surgical cure. Determining candidacy for surgical resection in ICC is notoriously challenging, as the cancer commonly has invaded the bile ducts, the surrounding vasculature, and other local structures by the time of diagnosis. Furthermore, no unanimity exists regarding accurate disease staging and identification of surgical candidates. This review discusses existing ICC staging protocols and reviews data on the role of neoadjuvant medical therapies and locoregional approaches for disease downstaging.

Existing Staging Protocols for ICC

US Criteria

The American Joint Committee on Cancer (AJCC) publishes ICC staging guidelines. Its staging protocol establishes a framework for prognostication in patients with ICC and for determining who may be a candidate for surgical resection.

Before discussing surgical resection further, it is necessary to outline that histopathology is the gold-standard technique for analysis of the resection margin. An R0 resection is characterized by a microscopically margin-negative resection with no evidence of residual tumor in the primary tumor bed. An R1 resection is defined as the removal of all macroscopic disease but with some microscopic margins. An R2 resection reflects apparent macroscopic residual disease that was not successfully resected.

The latest edition of the AJCC cancer staging manual (the eighth edition, published in 2017) includes several revisions to the T categories that incorporate data from international cancer groups. The T1 category is subdivided into T1a and T1b, based on a solitary tumor size cutoff of 5 cm. This change reflects the more recent understanding that tumor size greater than 5 cm is likely associated with a poorer prognosis and an increased chance of recurrence after surgical resection.[12-14]

Since its publication in 2017, 3 major studies have evaluated the prognostic performance of the AJCC eighth edition ICC staging protocol. Kim and colleagues utilized the SEER cancer registry to identify patients who had undergone surgical resection for ICC between 1998 and 2013 (N=1008). They generated Kaplan-Meier 5-year overall survival (OS) curves for patients staged with AJCC seventh and eighth editions and used Harrell's concordance index (c-index) to compare relative discriminative abilities between stages. They concluded that the AJCC eighth edition protocol was comparable to that of the AJCC seventh edition and did not provide improved discriminative ability (c-index of 0.669 vs 0.667, respectively).[15]

Spolverato and colleagues conducted a similar analysis of patients who underwent surgical resection for ICC between 1990 and 2015 (N=1154). The investigators found that the AJCC eighth edition had a slightly better T-category c-index than the seventh edition (0.609 vs 0.590, respectively). The later edition also demonstrated a higher hazard ratio of death for T2a, T2b, and T4 patients than for T1 patients. However, the team also found that, according to the AJCC eighth edition, patients with T3 tumors had higher 5-year OS rates than those with T1b and T2 tumors.[16]

In a single-institution retrospective study of data collected over 20 years from patients who underwent R0 resection for ICC (N=626), Kang and colleagues similarly

questioned whether the AJCC eighth edition improved upon the seventh edition staging protocol. They showed similar c-indices between the AJCC seventh and eighth editions for both tumor recurrence (0.615 vs 0.625, respectively) and 10-year OS (0.626 vs 0.628, respectively). They also found no prognostic difference between eighth edition–defined T2 and T3 tumors, with patients having similar OS rates (25 vs 27 months) and median time to recurrence (14 vs 15 months). These findings indicate that the eighth edition definition of T3 does not suitably reflect the tumor biology. They also challenge the importance of tumor perforation of the visceral peritoneum as an independent prognostic factor.[17]

In general, c-indices of 0.7 to 0.8 are considered acceptable. In all the studies discussed above, c-indices do not surpass 0.7. In other words, the predictive accuracy of the AJCC seventh and eighth editions in identifying suitable candidates for surgery does not exceed 70%. Thus, sole reliance upon these tools has a significant chance of inappropriate selection and suggests a need for improvement in staging methods. That said, the imperfection of current staging protocols does not always affect the decision-making surrounding surgery, as surgical resection is the only curative option. Additionally, the increasing availability of efficacious neoadjuvant, adjuvant, and radiation therapies surrounding surgery will likely improve c-indices for these staging protocols in the future.

Japanese Criteria

The recent revisions reflected in the AJCC eighth edition staging protocol for ICC are influenced by data from the Liver Cancer Study Group of Japan (LCSGJ), including those from a large multivariate analysis published by Sakamoto and colleagues in 2016.[18] The Sakamoto study sought to evaluate the effectiveness of several existing ICC staging protocols, including the AJCC seventh edition and the LCSGJ fifth edition, through a retrospective analysis of 419 ICC patients undergoing surgical resection. The investigators proposed a novel staging protocol separate from the AJCC system. The protocol (Table 1) used 3 core criteria to assign T1 to T4 classifications as follows: (1) a solitary tumor was present; (2) the largest tumor was no more than 2 cm in the widest diameter; and (3) there was an absence of portal vein/arterial/major biliary invasion. The fulfillment of all 3 core criteria corresponded to T1, and the satisfaction of 2, 1, and 0 core criteria corresponded to T2, T3, and T4, respectively.

The 3 core tumor criteria used in their staging protocol were validated by univariate and multivariate analyses of multiple possible prognostic factors for the entire cohort (N=419). Statistically significant factors influencing the 5-year OS rate included tumor size no greater than 2 cm (*P*=.011), the presence of a solitary tumor (*P*<.001), the absence of portal vein invasion (*P*=.009), the absence of arterial invasion (*P*=.003), the absence of major biliary invasion (*P*=.004), the absence of serosal invasion (*P*=.001), the absence of lymph node metastasis (*P*<.001), and the absence of distant metastasis (*P*<.001). Minor biliary invasion, defined as invasion of third-order or greater peripheral branches of the bile duct or second-order branches of the bile duct, was not shown to significantly affect 5-year OS (*P*=.07). Major biliary invasion was defined as the invasion of the common hepatic duct or a first-order branch of the bile duct. Similar analyses were performed for patients in the cohort with N0M0 disease (n=267) to clarify the influence of T-classification on 5-year OS. For these patients, statistically significant factors were the presence of 1 solitary tumor (*P*<.001), the absence of arterial invasion (*P*<.002), and the absence of major biliary invasion (*P*=.007).

For the 419 patients staged with the Sakamoto protocol, different ICC stages had distinct 5-year OS curves; stage III was statistically significantly distinct from stage IVA (*P*<.001) and stage IVA was statistically significantly distinct from stage IVB (*P*<.001). Similarly, for the 267 patients with N0M0 disease, 5-year OS curves for

Table 1. Staging of Intrahepatic Cholangiocarcinoma From Sakamoto and Colleagues According to the Modified Tumor, Node, Metastasis (TNM) Staging System

Variable	Parameter
Criteria	
1. Number of tumors	Solitary
2. Size of largest tumor	≤2 cm
3. Vascular or major biliary invasion	No portal vein invasion, no arterial invasion, no biliary invasion, or minor biliary invasion within the second-order bile duct branch
Tumor classification	
T1	3 of 3 criteria fulfilled
T2	2 of 3 criteria fulfilled
T3	1 of 3 criteria fulfilled
T4	0 of 3 criteria fulfilled
Nodal classification	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present
Stage	
I	T1N0M0
II	T2N0M0
III	T3N0M0
IVA	T4N0M0 or T1-T3N1M0
IVB	T4N1M0 or T1-T4N0-1M1

Sakamoto Y et al. *Cancer*. 2016;122(1):61-70.[18]

patients with T2 disease were statistically significantly distinct from T3 (*P*=.009) and T3 from T4 (*P*=.012). Notably, patients staged as T1 (having a solitary tumor ≤2 cm without vascular or major biliary invasion) had a 100% 5-year OS rate after surgical resection.

Influence of Vascular Invasion on Resectability

For ICC, vascular invasion is considered major if it affects the inferior vena cava (IVC) or portal vein (PV). Major vascular invasion has historically been considered a contraindication to surgery, although newer studies propose a possible survival benefit from surgical intervention in these cases.

For resection of tumors affecting the hepatic venous system, IVC resection is often concurrently indicated to achieve R0 resection. Although this approach offers an apparent cure, there are high intraoperative and perioperative complication rates. In a 2011 review of 23 patients undergoing hepatectomy with IVC resection for various hepatic malignancies, including ICC (n=3), investigators found that despite a 100% R0 resection rate, 39% of patients had significant surgical complications.[19] Accordingly, the survival benefit after surgery is modest. Another study of 258 patients undergoing combined hepatic and IVC resection for hepatic malignancy, including 51 patients with ICC, reported a 5-year OS rate of only 37%.[20]

Data on postoperative outcomes for patients with PV involvement are scantier than those for IVC involvement. A 2017 retrospective study of ICC patients who underwent surgical resection between 1990 and 2017 (N=1087) included 98 patients who received PV resection. Investigators found similar rates of major operative complications (odds ratio, 0.95; 95% CI, 0.49-2.00) and postoperative mortality (odds ratio, 1.05; 95% CI, 0.32-3.47). They also found a similar median OS time (33.4 vs 40.2 months; HR, 0.71; 95% CI, 0.36-1.40) between patients with PV and other major vascular involvement and patients without such involvement.[21]

Survival and Risk of Recurrence Predicted by Resection Grade and Margin

Factors related to the quality of the surgical resection itself also appear to influence survival in patients with ICC. To investigate the effect of the extent of resection (categorized as R0, R1, or R2, with further subcategories) on the survival of patients with ICC, Luo and colleagues performed a retrospective study of ICC patients who underwent surgery between 2007 and 2011 (N=1333). They found that the 5-year OS rate was higher among the 464 (34.8%) patients who received an R0 resection than among those with an R1 or R2 resection, at 28.7% vs 13.9% and 0.0%, respectively (*P* values not reported).[22]

In a study by Bartsch and colleagues of 210 patients with ICC, 150 (71.4%) underwent surgical resection with curative intent between 2008 and 2018, with 131 (87.3%) of these patients achieving an R0 resection.[23] Given the size of the R0 group in their cohort, the investigators could further subcategorize the resection according to the width of the resection margin from the tumor. Within the R0 group, margins were greater than 1 cm in 22 patients (16.8%), from 0.5 to 1 cm in 11 patients (8.4%), from 0.1 to 0.5 cm in 49 patients (37.4%), and less than 0.1 cm in 49 patients (37.4%). OS and recurrence-free survival (RFS) in R0 patients with wide resection margins (>0.5 cm) were better than for R0 patients with narrow margins (≤0.5 cm). However, these improvements were nonsignificant, and this lack of significance was maintained even when patients with R0 resection with greater than 0.5 cm margins were compared with those with R1 resections. R0 and R1 resections showed greater OS and RFS benefits than nonresectable disease. They concluded that although R0 resection with wide margins may not always be feasible, careful consideration is warranted for all patients with potentially resectable disease, even if only narrow margins or margins with microscopic tumor involvement can be achieved.

Watanabe and colleagues similarly analyzed the effect of wide resection margins on OS and RFS in patients with ICC who received R0 resections from 2000 to 2007 (N=635).[24] They divided the cohort into quartiles according to the width of the resection margin: marginal (<0.1 cm), narrow (0.1-0.4 cm), intermediate (0.5-0.9 cm), and wide (≥1 cm). Similarly, they found that margin width had a limited effect on prognosis. The risk-adjusted hazard ratios for OS between the narrow, intermediate, and wide groups had a significant overlap of their 95% CIs, at 0.79 (95% CI, 0.51-1.24), 0.93 (95% CI, 0.59-1.47), and 0.70 (95% CI, 0.46-1.08), respectively. There was a similar overlap in 95% CIs when RFS was compared among groups. Patients without lymph node metastasis undergoing wide tumor resection had better HRs for OS than patients in other groups, although CIs still overlapped.

Residual Liver Function After Resection

Post-hepatectomy liver failure is likely to occur in patients with inadequate liver remnant following surgery and is associated with frequent mortality. The risk is greater in patients receiving more extensive resections, which often is necessary in ICC cases owing to the frequent involvement of multiple blood vessels (discussed briefly in the Influence of Vascular Invasion on Resectability section),

bile ducts, and adjacent hepatic parenchyma.[25]

Patients with ICC receiving extensive surgical resection are not necessarily at an elevated risk of perioperative complications. For example, Nathan and colleagues employed the SEER database to analyze a cohort of patients with ICC who received surgical resection between 1973 and 2002 (N=557). They divided their cohort into 2 groups. Group A consisted of 215 patients with a solitary tumor of less than 7 cm, and Group B consisted of 342 patients with a solitary tumor of greater than 7 cm and/or 3 or more lesions. Although patients in Group B were more likely to receive extensive hepatectomies than those in Group A (30.4% vs 16.9%, *P*<.001), the investigators found similar incidences of postoperative complications and mortality.[26]

Biomarkers for Tracking Disease Recurrence

Disease recurrence rates are high in patients undergoing surgical resection of ICC. Zhang and colleagues found that out of 933 patients who underwent hepatic resection with curative intent for ICC, 685 (73.4%) had recurrence during the study period (median follow-up, 22 months), with 279 (29.9%) experiencing new extrahepatic disease.[27] Their group defined early recurrence as occurring within 24 months of resection, whereas late recurrence was defined as occurring after 24 months. When their cohort was analyzed using this distinction, it was found that median OS was worse among patients who experienced early recurrence (10 vs 18 months; *P*=.029). Additionally, those with early recurrence were more likely to develop extrahepatic disease (44.1% vs 28.3%; *P*<.001).

Tsilimigras and colleagues introduced more specific definitions of recurrence in their cohort of patients who received hepatic resections for ICC across multiple institutions from 1990 to 2016 (N=880).[28] They recognized that the time to recurrence was an important predictor of OS. However, the investigators suggested that the definition of early vs late recurrence based on the 24-month threshold may have been overly reliant on previous studies of HCC, as most patients experience recurrence of ICC sooner than 24 months. Tsilimigras coined a new term, "very early recurrence" (VER), defined as occurring within 6 months of resection. Out of the 880 patients in their cohort, 196 (22.3%) experienced VER, and the remaining 684 (77.7%) were combined into a "non-VER" group (>6-month recurrence). The median OS and 5-year survival rate were worse for patients with VER than for non-VER, at 13.8 (interquartile range, 11.6-15.3] vs 59.7 months (interquartile range, 48.2-73.8), respectively, and 8.9% vs 49.8%, respectively (*P*<.001).

The utility of CA19-9 as a tumor marker was first recognized for colorectal cancer, and it is now an established serum marker for CCA diagnosis. However, CA19-9 has a wide range of sensitivity and specificity for CCA detection, and it may be elevated in other nonmalignant conditions of the biliary system.[29] Still, Tsilimigras and colleagues found that before surgical resection, the median baseline CA19-9 concentration of their VER group (60.9 U/mL) was significantly higher (*P*=.008) than the non-VER group (44.8 U/mL).[28] This suggests that an elevated CA19-9 level in a patient with radiographic evidence or biopsy-proven ICC may portend a poorer prognosis.

Additional studies have substantiated the usefulness of CA19-9 in predicting ICC recurrence. In their retrospective analysis of data collected over 9 years from ICC patients (N=74) treated with surgical resection, Yoo and colleagues found that postoperative serum CA19-9 levels of 37 U/mL or less corresponded to a median OS of 43 months following surgery, which was significantly greater than the median OS of 11 months in patients with a serum level greater than 37 U/mL (*P*<.001).[30] The investigators also found significant differences in median survival time according to preoperative CA19-9 levels (47 months for CA19-9 levels ≤37 U/mL vs 22 months for CA19-9 levels >37 U/mL; *P*=.039). In their retrospective study of data collected over 16 years from patients who underwent ICC resection but had postoperative ICC recurrence (N=237), Xing and colleagues found significant differences in survival time when the cohort was stratified by CA19-9 level. At the time of resection, those with CA19-9 levels greater than 200 U/mL were found to have significantly worse post-recurrence survival than those with CA19-9 levels of 200 U/mL or less (post-recurrence survival HR, 2.51; *P*<.001).[31]

Carcinoembryonic antigen (CEA) is a glycoprotein commonly used as a tumor marker for stomach, colon, and pancreas cancers. Tsilimigras and colleagues found that the baseline median serum CEA concentration was higher in patients who eventually developed VER (2.8 ng/mL) than in those with non-VER (2.4 ng/mL). However, the difference was statistically less significant (*P*=.03) than for baseline levels of CA19-9.[28] In a separate study, Li and colleagues found that on assessing baseline CEA levels before CCA resection, patients with levels of 5 ng/mL or lower had significantly higher 1-year OS rates after surgery than those with levels greater than 5 ng/mL (54.5% vs 30.4%, respectively; *P*<.01).[32]

Data on Neoadjuvant Therapy

Chemotherapy may benefit patients with advanced disease, who generally are not amenable to surgery. In 2010, Valle and colleagues conducted a landmark study of 410 patients with locally advanced or metastatic biliary tract cancer who received either a combination of gemcitabine and

Table 2. Ongoing Clinical Trials Investigating Systemic Neoadjuvant Therapies for ICC

Trial	Phase	Estimated patient enrollment	Neoadjuvant agents	Description
NCT03603834[40]	2	25	mFOLFOXIRI	Single-group analysis of borderline resectable CCA
NCT04506281[41]	2	128	Lenvatinib, torpalimab, gemcitabine, and cisplatin	Comparison of neoadjuvant therapy vs upfront surgery for resectable ICC with high-risk recurrence factors
NCT03673072 (GAIN)[42]	3	300	Gemcitabine and cisplatin	Comparison of neoadjuvant plus adjuvant therapy vs adjuvant therapy alone for gallbladder or biliary tract cancer
NCT04308174 (DE-BATE)[43]	2	45	Durvalumab, gemcitabine and cisplatin	Comparison of neoadjuvant durvalumab, gemcitabine, and cisplatin vs gemcitabine and cisplatin for localized biliary tract cancer
NCT04989218[44]	1/2	20	Durvalumab, tremelimumab, gemcitabine, and cisplatin	Single-group analysis of resectable ICC with high-risk recurrence factors

CCA, cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma, mFOLFOXIRI, modified leucovorin, 5-fluorouracil, oxaliplatin, and irinotecan.

cisplatin (n=204) or gemcitabine monotherapy (n=206). They found that the median OS and progression-free survival (PFS) were better in the gemcitabine/cisplatin group than in the gemcitabine monotherapy group (OS, 11.7 vs 8.1 months [*P*<.001]; PFS, 8.0 vs 5.0 months [*P*<.001]).[33] Later, the landmark TOPAZ-1 trial evaluated the benefit of adding durvalumab (Imfinzi, AstraZeneca) to systemic chemotherapy for patients with advanced biliary tract cancers, including ICC. Patients were randomized to receive either durvalumab plus gemcitabine/cisplatin (n=341) or a placebo plus gemcitabine/cisplatin (n=344). The patients receiving durvalumab had a better PFS (HR, 0.75; 95% CI, 0.63-0.89; *P*=.001) and 24-month OS rate (24.9%; 95% CI, 17.9%-32.5% vs 10.4%; 95% CI, 4.7%-18.8%) than those receiving the placebo.[34]

Few studies have assessed the benefit of chemotherapy in a neoadjuvant setting, and existing studies tend to have small sample sizes and limited power to determine its value accurately. One study compared neoadjuvant gemcitabine/cisplatin with alternative regimens (gemcitabine, capecitabine, or leucovorin/5-fluorouracil/irinotecan) in 18 patients with locally advanced unresectable CCA undergoing evaluation for a liver transplant. When comparing the 10 patients who received combination gemcitabine/cisplatin with the 8 patients who received alternative regimens, the length of time to recurrence and 5-year OS rate after transplant trended toward being greater in the gemcitabine/cisplatin group, at 20.1 vs 9.5 months, respectively (*P*=.18) and 75% (95% CI, 13%-96%) vs 63%, respectively (95% CI, 23%-86%).[35]

Gemcitabine can be used with alternative platinum-based chemotherapy regimens. In one retrospective single-center study of 74 patients with locally advanced ICC, 39 (52.7%) underwent surgical resection after a median of 6 cycles of neoadjuvant gemcitabine/oxaliplatin chemotherapy, and 35 received chemotherapy alone.[36] The median OS was considerably greater for patients who underwent surgery than for those who were not able to undergo surgery (3 years vs 11 months, respectively; HR, 4.58; 95% CI, 2.59-8.09; *P*<.001).

For patients unable to tolerate multidrug chemotherapy, Kato and colleagues found significant unresectable biliary tract tumor downsizing in 9 out of 22 patients treated with gemcitabine monotherapy; 8 patients (36.3%) ultimately underwent tumor surgical resection, and R0 resections were achieved in 4 of these.[37]

In a large retrospective study, Yadav and colleagues analyzed data from 1450 patients with stage I to III CCA (842 with ICC) registered in the National Cancer Database (NCDB) between 2006 and 2014. Of the 1450 patients, 299 received neoadjuvant treatment and 1151 received adjuvant treatment. Using matched cohort analyses, the investigators showed that neoadjuvant therapy resulted in superior median OS (40.3 vs 32.8 months, respectively; *P*=.01) and a higher probability of R0 resection (71.2% vs 61.6%, respectively; *P*=.02).[38] Chemotherapy regimen details (type, dose, and duration) were not reported.

A similar NCDB retrospective cohort study of 4456 ICC patients receiving surgical resection between 2006 and 2016 compared neoadjuvant treatment (n=607) with upfront surgery (n=3849). Neoadjuvant therapies included single-agent chemotherapy (n=72), combination chemotherapy (n=327), unspecified chemotherapy regimens (n=36), and chemoradiation (n=172). Single-agent neoadjuvant chemotherapy was not associated with a decreased risk of death relative to upfront surgery (HR,

0.81; 95% CI, 0.58-1.14). However, combination neoadjuvant chemotherapy (HR, 0.81; 95% CI, 0.69-0.95) and chemoradiation (HR, 0.69; 95% CI, 0.54-0.88) demonstrated a significantly decreased risk of death.[39]

Multiple ongoing clinical trials are investigating systemic neoadjuvant therapies for ICC, including immunotherapy agents. Current ongoing trials are summarized in Table 2.

ICC harbors targetable mutations in *KRAS*, *BRAF*, *EGFR*, *PI3K*, *FGFR*, *IDH1/IDH2*, and *HER2/neu*. US Food and Drug Administration–approved targeted treatments for ICC include pemigatinib (Pemazyre, Incyte) for *FGFR*-mutated ICC and ivosidenib (Tibsovo, Agios) for *IDH1*-mutated ICC. Targeted therapies can be used as single agents or combined with existing neoadjuvant chemotherapy regimens, but further investigation is necessary to determine their efficacy in the neoadjuvant setting.

Additional neoadjuvant strategies for ICC include locoregional therapies, such as transarterial radioembolization (TARE), transarterial chemoembolization (TACE), and hepatic arterial infusion (HAI). These therapies rely on the fact that the normal liver parenchyma derives most of its blood supply from the portal vein, whereas the tumors, in general, are disproportionally supplied by the hepatic artery. TARE involves blocking branches of the hepatic artery supplying the tumor, usually with minute glass or resin beads filled with the radioactive isotope yttrium-90, resulting in a higher radiation dose to the tumor than the adjacent normal liver parenchyma; TACE involves embolization with a chemotherapeutic agent(s) and various embolic particles; and HAI allows arterial delivery of chemotherapy agents contained within a surgically implanted pump.

TARE, TACE, and HAI are more commonly used in patients with primary liver cancers such as HCC, and their use in ICC is generally limited to inoperable or palliative therapy cases. Some smaller studies have sought to understand the role of these therapies in downstaging disease. A retrospective review analyzing the use of TARE in patients with unresectable ICC (N=115) showed a median OS of 11 months, with only 4% of patients subsequently undergoing curative-intent tumor resection.[45] TARE has also been used in the neoadjuvant setting with chemotherapy. In a group of 45 patients with unresectable ICC receiving neoadjuvant TARE with gemcitabine plus a platinum agent, 8 patients later underwent surgical resection with a 100% R0 resection rate.[46] In a similar phase 2 clinical trial, 41 patients with unresectable ICC were treated with TARE and gemcitabine/cisplatin, and 9 of these patients were downstaged sufficiently to allow for surgical interventions, 8 of which were R0 resections.[47]

Burger and colleagues prospectively analyzed 17 patients with unresectable CCA who received at least 1 cycle of TACE using cisplatin, doxorubicin, and mitomycin C, in addition to other standard-of-care therapies. Three patients whose ICC was previously deemed unresectable could be downstaged, and 2 patients subsequently underwent successful R0 resection.[48]

Cercek and colleagues conducted a phase 2 clinical trial of HAI pump chemotherapy with floxuridine plus systemic chemotherapy with gemcitabine/oxaliplatin in 38 patients with unresectable ICC. Downstaging to resectable disease was achieved in only 4 patients, although 22 patients had achieved a partial response by 6 months.[49]

Overall, the locoregional approaches described in this paper have shown some ability to downstage unresectable disease to the point of potentially curative surgical resection. However, the rates of downstaging followed by R0 resection are still low.

Conclusion

In conclusion, protocols for ICC staging still need refining, and the ones currently available come with their advantages and disadvantages. Meanwhile, when surgery is indicated, R0 resections offer the best survival benefit when possible. In cases of advanced disease, tumor downstaging using neoadjuvant therapy with chemotherapy, chemotherapy plus targeted therapy, TARE plus chemotherapy, or TACE seems to offer the chance of R0 resection and extended survival, but this only applies to a handful of patients, and additional studies are needed. Patients with ICC have more hope today than ever before. However, our ability to cure or, at the very least, extend the survival of most patients with advanced disease is still poor, and much more work is required.

Limitations

This manuscript is intended as a broad qualitative literature review and does not represent a systematic review. Studies were chosen based on their statistical power and relevance to the topics discussed. However, study selection may be prone to author bias.

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