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Original Article

Conversion therapy for intrahepatic cholangiocarcinoma and tumor downsizing to increase resection rates: A systematic review

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ABSTRACT

Intrahepatic cholangiocarcinoma (ICC) is a devastating malignant neoplasm with dismal outcomes. Several therapeutic modalities have been used with variable success to downsize these tumors for resection. Neoadjuvant therapy such as chemoembolization and radioembolization offer promising options to manage tumor burden prior to resection. A systematic review of the literature was performed with a focus on conversion therapy for ICC and tumor downsizing to increase resection rates among patients who have an initially unresectable tumor. Of 132 patients with initially unresectable ICC, we identified 27 who underwent conversion therapy with surgical resection. Adequate tumor downsizing was achieved with chemotherapy, chemoembolization, radioembolization, or combination thereof. Although negative tumor margins were possible in some patients, recurrence rates and survival outcomes were inconsistently reported. Twenty-three of 27 patients were alive at last reported follow-up. Conversion therapy for initially unresectable ICC may offer adequate tumor downsizing for resection.

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Key Words: Chemoembolization; Cholangiocarcinoma; Neoadjuvant therapy; Conversion therapy; Liver neoplasms

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Introduction

Cholangiocarcinoma, an adenocarcinoma or mucin-producing carcinoma of the biliary system, is the most common biliary tract malignant neoplasm accounting for approximately 3% of all gastrointestinal malignancies and the second most common hepatic malignancy accounting for 10%-20% of primary liver cancers.[1] Cholangiocarcinoma is an insidious neoplasm with no effective screening tools; it typically presents late with vascular invasion of the hepatic artery or portal vein and lacks effective therapeutic regimens. For resectable tumors, surgical intervention provides patients the only chance for a potential cure.[2] Intrahepatic cholangiocarcinoma (ICC) has a more aggressive pathophysiology than hepatocellular carcinoma; ICC is usually fatal with overall survival rates at 3-years and 5-years estimated at 30% and 18%, respectively.[3,4]

Cholangiocarcinoma arises from malignant transformation of the cholangiocytes lining the biliary epithelium as a result of chronic inflammation secondary to etiologies including viral and parasitic infection, sclerosis, cirrhosis, cholestasis and hepatolithiasis.[5-8] Worldwide incidence and prevalence vary based on geography and risk factors. In the United States, the incidence of cholangiocarcinoma is 1 to 2 cases per 100,000 persons and is attributable to risk factors including hepatitis B virus, hepatitis C virus, and liver cirrhosis. Comparatively, in Northern Thailand, the incidence of cholangiocarcinoma is greater than 80 cases per 100,000 persons, and is believed to be related to hepatolithiasis and biliary parasitic fluke infestations, most commonly *Opisthorchis viverrinni* and *Clonorchis sinenesis*.[9-11]

Cholangiocarcinoma is classified into 3 types based on location: perihilar, distal, and intrahepatic that represents 50%, 40% and 10% of cases, respectively.[12] Although ICC is the least common type of cholangiocarcinoma in the United States, the incidence in the population has risen 165% from the 1970s through the 1990s. The cause of this increase remains unclear.[13-15]

Intrahepatic cholangiocarcinoma originates from small intrahepatic ductules or large intrahepatic ducts proximal to the bifurcation of the right and left hepatic ducts.[16] Macroscopic growth patterns of ICC include mass forming (most common growth pattern associated with the worst prognosis), periductal and intraductal. Clinically, ICC generally remains silent and patients present with few nonspecific constitutional symptoms such as abdominal pain and malaise without other stigmata of biliary obstruction such as jaundice.[17] Routine laboratory tests often demonstrate hepatic function and alpha-feto-protein levels within normal limits. Most cases of ICC are discovered incidentally with diagnostic imaging when the disease process has reached an advanced stage and treatment options are limited.[18,19]

For patients with ICC, complete tumor resection is the only potentially curative therapy. Resectability is defined as complete tumor resection for curative intent with a negative tumor margin (R0) while leaving an adequate liver remnant. Extrahepatic extension, multifocal and multicentric tumors, and lymph node metastases beyond the local tumor basin are considered contraindications for resection.[2] Following an R0 resection, 5-year survival rates range from 23% to 42% vs 0% when an R0 resection is not possible.[12,20,21] For patients with microscopic tumor margins (R1) or residual local disease (R2 resection), adjuvant therapy provides outcomes similar to palliative therapy without tumor resection.[22] Despite an R0 resection, tumor recurrence rates remain high at approximately 50%, generally occurring within 10-20 months, most commonly due to residual disease in the liver remnant.

Chemotherapy, radiation, and transarterial therapeutic modalities (including selective internal radiation therapy and transarterial chemoembolization) have demonstrated success in palliating unresectable ICC, whereas neoadjuvant chemotherapy, with or without radiation, followed by resection or liver transplantation has successfully treated extrahepatic cholangiocarcinoma.[17,18,22-26] Recently, neoadjuvant modalities including chemotherapy and transarterial embolization have been reported to effectively downsize an initially unresectable ICC, and subsequently allow for a potentially curative resection to occur.[27-37] For patients with unresectable ICC, neoadjuvant therapy aims to effect tumor control, but with increased tumor downsizing,

the focus may shift to conversion with tumor resection. The effectiveness of neoadjuvant therapy as a conversion therapy for patients with unresectable ICC may depend on its ability to enable subsequent tumor resection. Despite the pathological sequelae of ICC tumors, some patients may respond favorably to neoadjuvant therapy, such that a once deemed unresectable tumor may be downsized to resectable.

For patients diagnosed with ICC, tumor resection is the only chance for a potential cure. Investigators have capitalized on the downsizing effect of neoadjuvant therapy and have successfully resected ICC tumors that were previously deemed unresectable, without the need for orthotopic liver transplantation. For unresectable ICC, chemotherapy regimens include gemcitabine, usually in combination with platinum-based compounds (cisplatin or oxaliplatin), or fluoropyrimidines fluorouracil (5FU) with leucovorin, or capecitabine.[17,23,37,38] Embolization therapy, including transarterial chemoembolization and Yttrium-90 radioembolization, offers some success in treating hepatocellular carcinoma by reducing tumor volume and inducing hypertrophy of the contralateral liver remnant.[39] With palliative therapy, patient survival may be up to 12 months, whereas with untreated, unresectable disease, median survival is about 3-6 months.[40,41]

Orthotopic liver transplantation for ICC was first contemplated after transplant surgeons incidentally found ICC on pathology of explanted native livers when expecting hepatocellular carcinoma. Case reports of incidentally found ICC in post-transplant patients have shown mixed results.[24,42] Ghali et al noted in a retrospective study of incidentally found ICC following orthotopic liver transplantation, that overall survival was no better than patients with known ICC.[43] Robles et al, in a multicenter retrospective study of 23 transplant patients with ICC, reported 5-year survival rates and recurrence rates of 42% and 35%, respectively, with a mean time to recurrence of 22 months.[26] Facciuto et al conducted a retrospective study of 32 patients who met Milan criteria and underwent an orthotopic liver transplantation. Upon pathological discovery of ICC, the authors reported a 5-year survival and 5-year tumor recurrence rate of 78% and 10%, respectively.[42]

For unresectable hilar cholangiocarcinoma, orthotopic liver transplantation was thought initially to offer a possible cure. However, plagued with high levels of tumor recurrence within 2 years, modest survival secondary to advancement of disease and limited organ availability, transplant centers revisited cholangiocarcinoma and adopted strict criteria resulting in a highly selected patient population.[25,26] In particular, the Mayo Clinic Transplant Center and the University of California at Los Angeles Transplant Center devised protocols that incorporated neoadjuvant/adjuvant chemoradiation in conjunction with orthotopic liver transplantation for a highly selected patient population with perihilar cholangiocarcinoma.[44]

Taking into account the success with neoadjuvant therapy and orthotopic liver transplantation for perihilar cholangiocarcinoma and somewhat promising studies with neoadjuvant/adjuvant therapy and orthotopic liver transplantation for ICC, the International Liver Cancer Association suggested that, although orthotopic liver transplantation is not a futile intervention for ICC, results are suboptimal compared to cirrhotic patients undergoing orthotopic liver transplantation. Furthermore, the International Liver Cancer Association did not recommend orthotopic liver transplantation for ICC, but suggested that orthotopic liver transplantation may be offered in transplant centers with designed clinical research protocols that encompass neoadjuvant and adjuvant therapies.[23]

The aim of this study was to review the published literature regarding neoadjuvant or induction therapy to treat initially unresectable ICC and the association with tumor downsizing to increase resection rates. In an attempt to focus our review on patients with initially unresectable ICC, we acknowledge some overlapping terminology in studies that address neoadjuvant therapy, which implies an expectation that patients will subsequently undergo a potentially curative operation, and studies that address induction therapy, which implies that a tumor is unresectable. For purposes of this systematic review, we placed our emphasis on patients with an initially unresectable ICC who underwent treatment aimed to induce disease control, but achieved conversion to surgical resectability as the definitive treatment.

Methods

We searched the PubMed (MEDLINE), EMBASE, Cochrane and Google Scholar databases for English-language articles published from January 2006 through June 2017 that addressed therapy aimed to induce disease control for an unresectable ICC. Search terms included "intrahepatic cholangiocarcinoma," "cholangiocarcinoma," "neoadjuvant," "downsize," "unresectable," and "resectable." No limits were used and searches were auto-exploded.

One author (MF) conducted the primary search and identified relevant articles by title, abstract, and keywords to identify studies for inclusion in the analysis. Inclusion criteria for study analysis focused on articles that described patients with an unresectable ICC who received conversion therapy and subsequently underwent an assessment of resection or surgical intervention including hepatic resection. Full text manuscripts included case reports. Excluded were manuscripts that described therapy for palliative care, extrahepatic cholangiocarcinoma, neoadjuvant therapy followed by orthotopic liver transplantation, and nonsurgical management.

Two authors (EHB and MF) independently reviewed the full-text version of all relevant studies for study inclusion. Disagreements about study inclusion were resolved by discussion of the manuscript's relevance to the study. Data extracted from the manuscripts included the following: number of patients, reason for unresectability, type of conversion therapy, type of surgical intervention, tumor resection margins, postoperative complications, survival, and local tumor recurrence.

Results

The initial search yielded 343 relevant clinical reports. Ten full-text articles including 5 case reports met our inclusion criteria and were selected for detailed review. Although case reports have limited generalizability, we included them in our analysis because ICC is a rare disease and the authors provided detailed explanations. Fig. 1 depicts the PRISMA diagram for the inclusion and exclusion of manuscripts in the systematic review. The articles included for analysis focused on patients who received conversion therapy for an unresectable ICC but who later underwent tumor resection or an assessment of tumor resection because of adequate tumor downsizing. Initial unresectability was typically related to tumor involvement of the hepatic veins or portal vein of the liver remnant.

Of the articles that met selection criteria, 2 were retrospective, single-center studies, 1 was a retrospective, multicenter study, 1 was a prospective study, and 1 was a prospective safety study.[28-30,32,33] All referenced studies reported outcomes from small patient cohorts. Additionally, we included 5 case reports.[31,34-37] for a total of 10 articles that are summarized in Table 1.

Retrospective studies of conversion therapy, tumor downsizing, and resection

Of the 3 retrospective studies, 14 patients meet our inclusion criteria. In 1 study, conducted from January 2004 to December 2010, 7 patients were treated with gemcitabine for an initially unresectable ICC.[29] In 4 of 7 patients, tumors were downsized based on response evaluation criteria in solid tumors and underwent subsequent resection. Three of the 4 patients underwent a tumor negative margin resection (R0) and were alive at the time of the last reported follow-up. The remaining patient underwent a tumor positive margin resection (R1) and died 10 months after surgery.

In the second study, conducted from January 2008 to October 2013, 2 of 12 patients who were treated with hepatic artery infusion of gemcitabine followed by oxaliplatin had tumors that were successfully downsized for resection.[28] In the third study, conducted from January 2008 to October 2013, 8 of 45 patients with hepatic vein invasion or portal vein invasion who received a combination of chemotherapy (gemcitabine with or without platinum salts) and radioembolization with Yttrium-90 had tumors that were successfully downsized to resection.[32] Two of the

Table 1
Summary of 27 patients with adequate tumor downsizing.

Author year	No. patients	Neoadjuvant therapy	Resection assessment	Margin status	Patient follow-up
Rayar et al[32] 2015	8	Yttrium-90 radioembolization plus gemcitabine with or without platinum salts	8 patients downsized to resection: 2 right hepatectomy with caudate lobectomy; 5 right trisectionectomy with caudate lobectomy;1 left trisectionectomy	8 patients with R0 margin	2 patients died before discharge; 1 died at 6.5 mo without recurrence, 5 alive at mean follow-up of 8.2 mo
Ghiringhelli et al[28] 2013	2	Hepatic arterial infusion of gemcitabine plus oxaliplatin	2 patients downsized to resection	2 patients with R0 margin	Not available
Kato et al[29] 2013	4	Gemcitabine	4 patients downsized to resection and underwent hepatectomy	3 patients with R0 margin, 1 with R1	3 patients alive at 66, 44, and 13 mo; 1 patient died at 10 mo
Mouli et al[30] 2013	5	Yttrium-90 radioembolization	5 patients downsized to resection; 3 right lobectomy; 2 trisegmentectomy	5 patients with R0 margin	5 of 5 patients alive at months ranging from 5.6 to 47.1
Schiffman et al[33] 2011	3	Drug eluting bead therapy loaded with irinotecan	3 patients downsized to resection and underwent hepatectomy with radiofrequency ablation	3 patients with complete response; 100% loss of PET scan activity	1 patient disease-free at 33.8 mo, 2 patients alive with disease at 33.3 mo and 80 mo, respectively
Wu et al[37] 2007	1	Transcatheter arterial chemoembolization with degradable starch microspheres	Right trisegmentectomy with extra-hepatic bile duct excision	Not available	1 patient without recurrence at 21 mo after first operation
Poggi et al[31] 2008	1	Failed neoadjuvant chemotherapy with gemcitabine; underwent TACE microspheres loaded with oxaliplatin; OEM-TACE	Pt declined surgery for removal of nectotic liver lesion	Serum level CA 19-9 was 19 UI/ml; PET-CT showed no uptake of radiotracer	No residual hepatic disease 24 mo after TACE and 34 mo after initial diagnosis
Servajean et al[34] 2014	1	Tumor remained stable after chemotherapy underwent radioembolization 90Y-resin microspheres (SIRS)	Left hepatectomy enlarged to segment VIII	R0 resection	Alive without recurrence at 1 y
Tran et al[35] 2015	1	Neoadjuuvant chemotherapy: gemcitabine and cisplatin	Left hepatic trisectionectomy, caudate lobectomy, and porta hepatis, lymphadenectomy	Surgical margins were negative	Patient remains alive with no evidence of disease 6 mo after surgery
Uji et al[36] 2016	1	Chemotherapy with capecitabine plus oxaliplatin (CAPOX) combined with bevacizumab followed by embolization	Left hepatic trisectionectomy	Tumor positive for CK7 and CK19	Discharged from the hospital 79 d following surgery

Abbreviations: CA, cancer antigen; IVC, inferior vena cava; OEM, Oxaliplatin-eluting microspheres; PV, portal vein; PET, positron emission tomography; SIRS, selective internal radiation spheres (SIRS-Spheres Sirtex Medical, Lane Cove, Australia); TACE, trans-arterial chemoembolization.

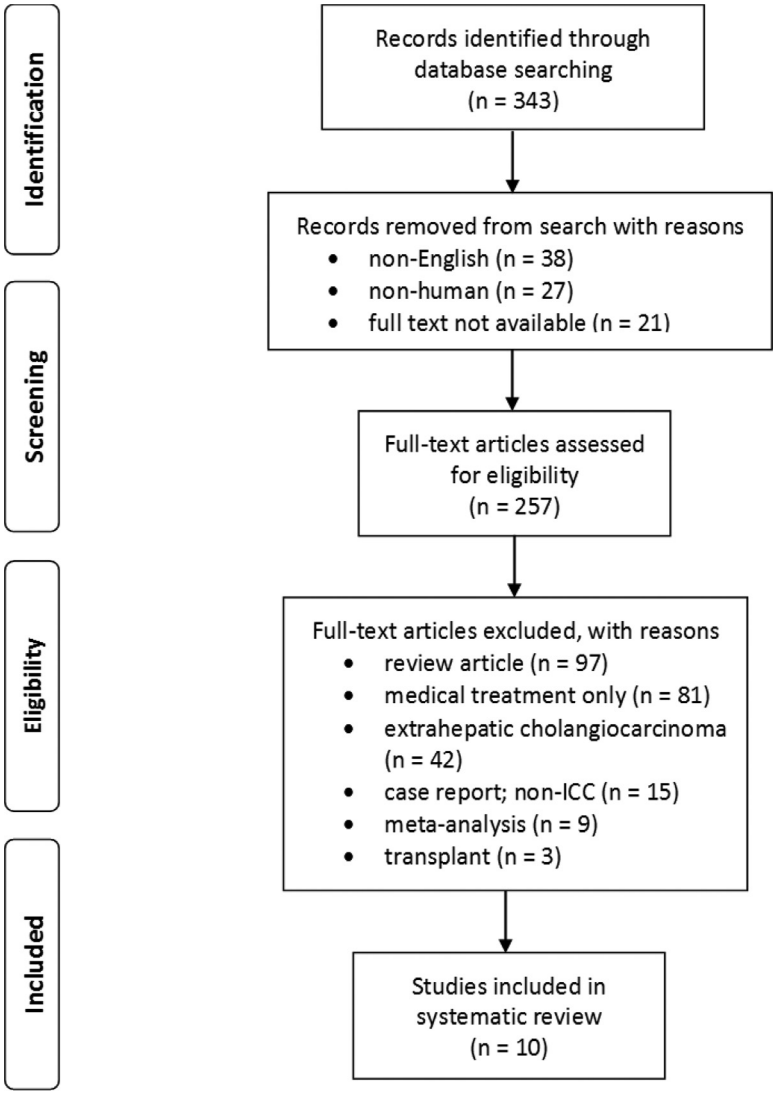

Fig. 1. Flow chart for identifying and screening manuscripts.

8 patients died in the immediate postoperative period, and 1 died 6.5 months after surgery (14 months after initiation of treatment). Of the 5 patients who remained alive, 2 had tumor recurrence; 1 patient developed metastases to the lung, and another patient developed metastasis to the lung, liver and lymph nodes. These 2 patients received adjuvant chemotherapy.[32]

Prospective studies of conversion therapy, tumor downsizing, and resection

Of 2 prospective studies, 8 patients met eligibility criteria. One prospective study conducted from July 2003 to May 2011, reported the use of Yttrium-90 radioembolization in 24 patients with ICC.[30] Prior to treatment with Yttrium-90, none of the patients had an adequate future

Table 2
Summary of patients who underwent conversion therapy and percentage of tumor downsizing.

	Number of patients	Number of patients downsized	Percentage downsized
Chemotherapy alone	22	4	18.2
Trans-arterial chemoembolization	36	5	13.9
Trans-arterial radioembolization alone	24	5	20.8
Chemotherapy and radioembolization	45	8	17.8
Total	127	22	17.3

[a]Includes 2 prospective studies and 3 retrospective studies that met our inclusion criteria: Rayar et al,[32] Ghiringhelli et al,[28] Kato et al,[29] Mouli et al,[30] Schiffman et al.[33]

liver remnant due to the tumor abutting major hepatic veins or the portal vein. Of these 24 patients, 5 patients were downsized to resection. In another prospective study, 3 of 24 patients who underwent transarterial chemoembolization with drug-eluting bead therapy loaded with irinotecan were adequately downsized to undergo resection and radiofrequency ablation.[33] At 80 months follow-up, 2 of the 3 patients were alive but not disease-free, whereas 1 patient remained disease-free.

Case studies of conversion therapy, tumor downsizing, and resection

Five case reports, each describing 1 patient, met eligibility criteria.[31,34-37] Two case reports described the use of conversion chemotherapy alone, 2 described an initially failed attempt at chemotherapy but successful results with subsequent chemoembolization or radioembolization, and one described successful results with trans-catheter arterial chemoembolization.[31,34-37] Four of the 5 patients underwent surgical resection.[34-37] The remaining patient showed no residual hepatic disease after the last trans-arterial chemoembolization procedure and declined surgical intervention for removal of a necrotic liver lesion.[31] Histologically negative resections margins (R0) were reported in 2 of the 4 patients who underwent resection.[34,35] Survival outcomes were as follows: 1 patient was alive without tumor recurrence at 6 months, 1 patient was alive without recurrence at 1 year, and 2 patients were alive without recurrence at 2 years.[31,34,35,37] The remaining case report lacked patient follow-up after hospital discharge.[36] The downsizing effect of various conversion therapies with respect to patients with ICC identified in the prospective and retrospective studies is shown in Table 2.

Discussion

For advanced cholangiocarcinoma, the downstaging literature primarily focuses on patients with perihilar tumors and extrahepatic tumors, whereas a paucity of data exist for ICC. Success reported with neoadjuvant therapy prior to liver transplantation to treat perihilar cholangiocarcinoma opened the door for therapeutic modalities to treat ICC.[24,26,45] Several authors have reported improved outcomes with the use of neoadjuvant/adjuvant chemotherapy combined with liver transplantation in locally advanced ICC.[46] Various therapeutic modalities such as transarterial chemoembolization and Yttrium-90 have been used to downsize unresectable ICC tumors for curative resection.[37] The current National Comprehensive Cancer Network guidelines for unresectable ICC include gemcitabine/cisplatin combination, clinical trial, fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen, fluoropyrimidine chemoradiation, locoregional therapy, and supportive care.[47]

We conducted a systematic review of the literature on the topic of neoadjuvant (or conversion) therapy for unresectable ICC and its association with adequate tumor downsizing to enable resectability. Ten manuscripts were identified that met inclusion criteria. Of the 132 patients

included for review, 27 patients responded to conversion therapy and 26 patients underwent resection; 1 patient who showed no residual disease after therapy declined surgical intervention.[31] Of these 27 patients, 23 were alive at the time of the last reported follow-up. No standard conversion regimen existed across any of the studies; therapy included single and multiagent chemotherapy, radioembolization, and chemoradiation. Despite disparities in treatment protocols, outcomes were promising for adequate tumor downsizing enabling resection. Excluding individual case reports, 22 of 127 patients (17.3%) had successful tumor downsizing; based on treatment modality, tumor downsizing rates ranged from 13.9% (transarterial chemoembolization alone) to 20.8% (transarterial radioembolization alone) (Table 2). Despite promising rates in downsizing tumor burden, investigators have yet to determine whether a survival benefit is associated with these various treatment modalities.

Some authors reported no survival benefit associated with resection following neoadjuvant therapy of ICC. In 2017, Buettner et al reported results from a retrospective multicenter, international study evaluating the effect of neoadjuvant chemotherapy followed by surgery vs surgery alone in treating ICC.[27] The authors found no statistically significant difference on overall survival and disease-free survival. Furthermore, the use of preoperative chemotherapy was not associated with improved margin negative (R0) resection rates.[27] This study was excluded from our analysis because the lesions were not described as initially "unresectable" and the purpose of neoadjuvant therapy was not clearly defined in terms of downsizing tumor burden.

In addition, Gelli et al retrospectively evaluated 186 patients with ICC who were allocated to 3 cohorts: 95 patients with resectable tumors, 43 patients with an initially unresectable tumor who responded to neoadjuvant chemotherapy and later underwent resection, and 37 patients with unresectable tumors who did not respond appropriately to neoadjuvant therapy and continued with medical management.[48] Gemcitabine was used to treat 70% of the patients receiving neoadjuvant therapy. No difference in disease-free and 5-year survival was observed between the 2 cohorts who underwent surgery, suggesting that patients who were successfully converted from unresectable tumor to resectable tumor derived a substantial benefit.[48] This study was excluded from our analysis because it consisted of a conference abstract.

Limitations to the present study are similar to those cited by the authors of the referenced studies including: a limited number of patients; retrospective study design; selection bias for downsizing tumor burden; and limited follow-up. In addition, there was a lack of description of the neoadjuvant regimen (timing, cycles, and follow-up assessment of therapy response), intraoperative findings, operative details, operative complications, follow-up radiologic imaging, and recurrence rates. Surgeon-to-surgeon differences for resectability or nonresectability may have influenced treatment approaches. Given the lack of available evidence regarding neoadjuvant or induction therapy for ICC, additional well-designed trials should be conducted to study the efficacy of conversion therapy for ICC. Our summary of the 10 studies included in this systematic review may guide future research that enhances our understanding of how to improve patient outcomes.

Conclusion

Intrahepatic cholangiocarcinoma is a complex malignant neoplasm; surgical resection is the only potentially curative treatment. Neoadjuvant (or conversion) therapy offers promising options to adequately improve tumor resection rates and achieve a negative tumor margin; however, the optimal treatment strategy and associated survival benefit remain unclear. The limited number of published reports on conversion therapy for ICC leading to adequate tumor downsizing as well as the heterogeneity of therapeutic modalities limits a comparative appraisal at present. Therefore, a prospective, multicenter trial is needed to determine the optimal conversion therapy, subsequent resection rates, and if a survival benefit is associated with these medical and surgical interventions.

Conflict of Interest

Authors declare that they have no conflict of interest.

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