Ruff *et al. Hepatoma Res* 2023;9:17
DOI: 10.20517/2394-5079.2023.18

Hepatoma Research

Review

Open Access

Surgical management of intrahepatic cholangiocarcinoma

Samantha M. Ruff, Timothy M. Pawlik

Department of Surgery, Division of Surgical Oncology, The Ohio State University Wexner Medical Center and James Comprehensive Cancer Center, Columbus 43210, OH, USA.

Correspondence to: Prof. Timothy M. Pawlik, Department of Surgery, The Ohio State University, Wexner Medical Center, 395 W. 12th Ave., Suite 670, Columbus 43210, OH, USA. E-mail: tim.pawlik@osumc.edu

How to cite this article: Ruff SM, Pawlik TM. Surgical management of intrahepatic cholangiocarcinoma. *Hepatoma Res* 2023;9:17. https://dx.doi.org/10.20517/2394-5079.2023.18

Received: 14 Mar 2023 **First Decision:** 18 Apr 2023 **Revised:** 23 Apr 2023 **Accepted:** 8 May 2023 **Published:** 15 May 2023

Academic Editor: Georgios Tsoulfas **Copy Editor:** Yanbing Bai **Production Editor:** Yanbing Bai

Abstract

Intrahepatic cholangiocarcinoma (ICCA) is a rare tumor with a poor prognosis that arises from the intrahepatic biliary tract. Patients who present with locally advanced or metastatic ICCA are generally treated with first-line gemcitabine/cisplatin and/or liver-directed therapy with the hope of downstaging/downsizing the disease. Patients who present with resectable ICCA may be treated with upfront surgery and postoperative adjuvant capecitabine. Staging laparoscopy should be considered to evaluate for occult metastatic disease and laparoscopic ultrasound can be used to better evaluate the liver parenchyma. Resection with the goal of achieving an R0 margin, along with lymphadenectomy to adequately stage patients, should be the standard operative approach. Unfortunately, the surgical technique cannot overcome poor tumor biology, and ICCA has a high incidence of recurrence, with many patients developing metastatic disease. Targeted therapy with IDH and FGFR inhibitors has had promising results in early clinical trials. Future endeavors should strive to identify more effective systemic and targeted therapies, which will hopefully improve survival for patients with ICCA.

Keywords: Surgery, intrahepatic cholangiocarcinoma, margin status, lymphadenectomy

INTRODUCTION

Cholangiocarcinoma (CCA) is a rare tumor arising from the biliary tract that can be defined as either intrahepatic (ICCA) or extrahepatic (ECCA) based on its anatomic location. ICCA arises from the biliary

tracts within the liver and accounts for approximately 10% of CCAs[1]. ECCA is divided into either hilar (Klatskin) CCA arising from the common hepatic duct or distal ECCA arising from the common bile duct below the insertion of the cystic duct down to the level of the ampulla of Vater[1]. There is increasing evidence to suggest that ICCA and ECCA are biologically different and should be treated as different cancers[2].

The standard of care for patients with resectable ICCA at diagnosis is upfront surgery with adjuvant capecitabine[3]. Unfortunately, only approximately 15% of patients with ICCA present with resectable disease at the time of diagnosis, and even among individuals who undergo surgery and adjuvant capecitabine, there is a high rate of recurrent and metastatic disease[4]. Median overall survival is between 27 and 36 months for these patients[5]. For patients with advanced or metastatic disease at diagnosis, the combination of gemcitabine and cisplatin chemotherapy is currently the standard of care based on the ABC-02 trial[6]. In addition, for patients with ICCA, liver-directed therapy (e.g., hepatic artery infusion pump, Yttrium-90 radioembolization) can be used in combination with systemic therapy[7]. Given the poor prognosis of ICCA, research and clinical trial efforts have been focused on developing effective targeted therapy through molecular profiling of the tumor to target specific genetic aberrations[8].

For patients with resectable disease, upfront surgery is the best chance of cure. The goal of surgery for ICCA is to perform a margin-negative resection and regional lymphadenectomy with at least six lymph nodes harvested, and minimize the risk of complications or hepatic insufficiency. We herein review the critical aspects of the surgical management of ICCA to obtain a successful oncologic outcome.

DIAGNOSTIC WORK UP

While patients with extrahepatic CCA present with biliary obstruction (jaundice, pruritus, dark urine, light colored stool), patients with ICCA more commonly present with abdominal pain, generalized malaise, or weight loss. Abdominal pain is caused by displacement of the hepatic parenchyma stretching the liver capsule. Unfortunately, many patients who present with symptoms already have advanced disease, and given the frequently asymptomatic presentation or vague symptoms associated with ICCA, many individuals are diagnosed late in the course of disease[9]. A small subset of patients who have large ICCA tumors that encroach on the hepatic hilum can present with jaundice and hyperbilirubinemia, requiring biliary stenting. Risk factors for ICCA include primary sclerosing cholangitis, fibropolycystic liver disease, intrahepatic biliary stones, carcinogen exposure (e.g., 1,2 dichloropropane or dichloromethane from occupational exposure in the printing industry), and chronic inflammation secondary to hepatitis B or C[10-12]. Tumor markers like carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP) can help physicians narrow the differential diagnosis. Patients with ICCA are more likely to have an elevated CA19-9, while hepatocellular carcinoma (HCC) is associated with an elevated AFP. CA19-9 and CEA have also been reported to have prognostic value in ICCA[13,14].

Imaging is key to defining the diagnosis. While ultrasound is traditionally the initial modality to rule out common benign etiologies of right upper quadrant pain or biliary obstruction, contrast-enhanced computed tomography (CT) scans and/or magnetic resonance imaging (MRI) are the preferred methods to image hepatic pathology, define tumor extension, and evaluate resectability. HCC arises from the hepatocytes and will often demonstrate an arterial enhancement pattern on CT scan. In contrast, ICCA arises from hepatic parenchyma with desmoplastic features and its main blood supply is the portal system. In turn, ICCA is typically characterized by peripheral rim-like contrast enhancement during the arterial and portal phases and a more attenuated center during the delayed phase [Figure 1][15-18]. ICCA has three patterns of enhancement that correlate with different tumor biology: hypovascular, rim-like, and hypervascular.

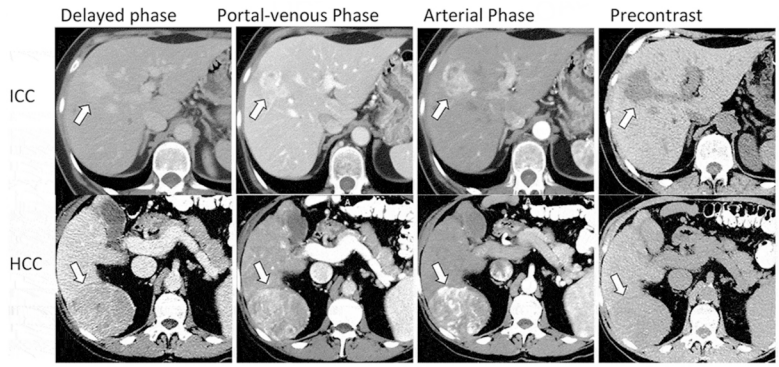

Figure 1. Hepatocellular carcinoma (lower panel) versus intrahepatic cholangiocarcinoma (upper panel) on computed tomography imaging[17]. The figure was reprinted from reference 17 with permission.

Hypovascular ICCAs commonly have lymphatic, perineural, or biliary invasion and worse overall survival, whereas hypervascular tumors have a lower incidence of invasion and better long-term survival[19]. MRI better detects locoregional spread of ICCA and can be used to further differentiate ICCA from HCC. Diffusion-weighted images often demonstrate rim enhancement during the arterial phase, also known as the target sign in ICCA[20].

FDG-PET may help ascertain the presence of intra- and/or extrahepatic disease including lymph node metastasis. ICCA is an FDG avid tumor, so FDG-PET in the preoperative setting should be considered, but there may be a risk of false positives in the setting of chronic inflammation. FDG-PET can sometimes help identify occult metastasis, which can result in a shift in the proposed treatment plan (i.e., use of preoperative chemotherapy) or change determinations of resectability[21].

UPFRONT SURGERY VERSUS NEOADJUVANT CHEMOTHERAPY

Currently, surgery offers the best potential for cure among patients with ICCA[22]. Unfortunately, even after resection, recurrence ranges from 42-70%[3,23,24]. Patients who present with resectable ICCA generally can proceed to upfront surgery with consideration of adjuvant capecitabine in the postoperative period. In the phase III clinical BILCAP trial, patients with ICCA were randomized to either adjuvant capecitabine or observation after curative resection[3]. The trial did not meet its primary endpoint, but did demonstrate improved overall survival in the capecitabine cohort (51.1 months) compared with the observation cohort (36.4 months).

Among patients with locally advanced ICCA who are not candidates for resection, chemotherapy with gemcitabine and cisplatin is typically employed. In fact, gemcitabine and cisplatin have been the standard-of-care first-line therapy for metastatic and locally advanced ICCA for the past decade based on the phase III ABC-02 clinical trial[6]. Following treatment with chemotherapy, patients should be re-imaged/staged as a subset may have disease cytoreduction and subsequently be candidates for hepatectomy. In conjunction with liver-directed therapies, chemotherapy can sometimes downstage/downsize ICCA to make it more amenable to resection from a technical/anatomic standpoint[25,26]. One retrospective study reported that 53% of patients with locally advanced ICCA were downstaged/downsized and were able to undergo resection; there was no difference in median overall survival between the downstaged/downsized patients versus patients who had upfront resectable ICCA[25]. A separate retrospective study similarly demonstrated that 36.4% of patients with advanced, unresectable ICCA became surgical candidates after preoperative chemotherapy and half of the patients who underwent resection had an R0 margin[26]. In addition, among

patients with high-risk tumors (poorly differentiated, vascular invasion, extrahepatic lymphadenopathy, large tumor size, high tumor burden, KRAS status, multifocality), chemotherapy may provide a "test of time" to better elucidate the underlying biology and help select patients who will benefit the most from an operation[27]. Specifically, patients who progress on chemotherapy would likely have progressed with or without an operation. Neoadjuvant chemotherapy affords these patients the opportunity to avoid a large operation that likely would not have changed their overall prognosis.

Surgical considerations

Staging Laparoscopy

Peritoneal metastatic disease or locally advanced/invasive disease is not always appreciated on preoperative imaging. A staging laparoscopy at the start of the operation can avoid unnecessary laparotomies in patients with occult metastatic disease. In a retrospective study, metastatic disease was detected in 29% of patients with hepatobiliary malignancy, including ICCA, on staging laparoscopy. In turn, one in five patients was spared a laparotomy and the associated increase in hospital length-of-stay and morbidity[28]. In a separate study, 36% of patients who underwent a staging laparoscopy for CCA or gallbladder cancer had advanced or unresectable disease[29]. Even though a short amount of additional operative time is often required, staging laparoscopy should be considered in patients with ICCA, given the high risk of occult metastatic disease or unresectable disease. Laparoscopic ultrasound of the liver should also be performed at the time of surgery for planning purposes and to help identify occult intrahepatic metastasis. Ultrasound is important to evaluate the anatomic relationship between the ICCA tumor and major vascular structures within the liver.

Future Liver Remnant

An important preoperative consideration for ICCA is the patient's functional status and future liver remnant (FLR). Hepatectomy is a complex operation that stresses the body. Patients with multiple co-morbidities may not have the physiologic reserve to recover well or cope with potential complications. After the patient is deemed an appropriate candidate, it is crucial to ensure that the FLR is sufficient to prevent postoperative hepatic insufficiency[30]. Adequate FLR depends on the underlying functional status of the liver (e.g., determined through Child-Pugh score and baseline laboratory tests). In addition to traditional etiologies of liver damage (e.g., alcohol, hepatitis B, hepatitis C, non-alcoholic fatty liver disease), it is important to also account for hepatic damage secondary to chemotherapeutic agents. An adequate FLR in patients with a healthy liver typically is at least 20%, while patients with steatosis and/or cirrhosis often need an FLR of 30% to 40%[31-37]. Liver volume can be calculated using computed tomography or MRI to determine the postoperative FLR. In some cases, there may be a discrepancy between FLR volume and postoperative liver function. Technetium-99m mebrofenin hepatobiliary scintigraphy is a quantitative test that may be helpful in assessing FLR function[38]. Quantitative liver function assessment with an indocyanine green (ICG) clearance test can help predict hepatic functional reserve. A retention rate of 15 minutes has been associated with post-hepatectomy liver failure[39]. For patients that require a major hepatectomy with suboptimal FLR, preoperative FLR modulation strategies, such as portal vein embolization or associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), can be employed to instigate accelerated hypertrophy of the FLR to minimize the risk of postoperative hepatic insufficiency[38].

Minimally Invasive Approach

Minimally invasive surgery (MIS) has become the standard of care for many operations and is increasingly being used for liver resection, including for benign lesions, as well as hepatocellular carcinoma, colorectal liver metastases, and ICCA. The MIS approach often results in decreased postoperative pain, decreased blood loss, fewer postoperative complications, and faster recovery time with shorter hospital length-of-stay[40]. In well selected patients with ICCA, laparoscopic liver resection (LLR) has comparable oncologic outcomes to open resection. In well selected patients, LLR for ICCA may even be associated with decreased

blood loss and decreased Pringle maneuver time[41-43]. In addition, the data demonstrated that oncologic outcomes, such as the number of lymph nodes harvested, are comparable among patients undergoing a minimally invasive approach[42-44]. Despite the potential benefits of MIS and comparable long-term outcomes to open surgery, the success of the MIS approach is dependent on patient selection and surgeon experience/expertise. In addition, the oncologic success of the MIS approach for ICCA (defined as obtaining an adequate lymphadenectomy and R0 margin status) has been strongly associated with receipt of surgery at high-volume centers[20].

Anatomic vs Non-Anatomic Resection

The role of an anatomic resection (AR) versus non-anatomic resection (NAR) for HCC has been well established, but its role in ICCA remains controversial. A retrospective review of 702 patients with ICCA noted that patients who underwent anatomic versus non-anatomic resection had a similar incidence of complications (AR 26.6% versus NAR 25.1%, $P = 0.634$), yet 1-, 3-, and 5-year disease-free and overall survival was better among individuals who had an AR[23]. The benefit of anatomic resection was only noted, however, among patients with stage IB or stage II (without microvascular invasion) cancer. A separate retrospective study of 1,023 patients with ICCA who underwent curative-intent resection compared short- and long-term outcomes among patients who had a major versus minor hepatectomy[45]. Of note, overall and recurrence-free survival were the same, but the risk of postoperative complications was higher among patients who underwent a major (48.4%) versus minor (27.2%) hepatectomy ($P < 0.001$). The impact of AR versus NAR remains debated. Therefore, the main goal of resection for ICCA should be to spare hepatic parenchyma as long as a negative margin can be achieved.

Margin Status

A universal goal of curative intent surgery is to achieve an R0 resection margin. A positive microscopic (R1) or macroscopic (R2) margin is associated with a higher risk of recurrence. Spolverato *et al.* evaluated the relationship between margin status and survival in 583 patients from 12 major hepatopancreatobiliary centers[46]. Of note, one out of six patients had an R1 resection and R1 margin status was a predictor of both shorter recurrence-free (hazard ratio 1.61, $P = 0.01$) and overall (hazard ratio 1.54, $P = 0.01$) survival versus patients who had an R0 resection. A separate multi-institutional database study analyzed 449 patients with ICCA who underwent surgery[47]. In this study, again, 15.6% of patients had an R1 margin and a positive resection margin was associated with worse overall survival (hazard ratio 2.2, $P < 0.001$). Multifocal disease, vascular invasion, and lymph node metastases were also associated with worse overall survival. While the goal of surgical resection is to always achieve an R0 margin, an R1 margin may just be reflective of worse underlying tumor biology (e.g., larger tumors, multifocal disease, perineural or vascular invasion). To this point, in a retrospective study of 1,105 patients with ICCA, the relationship between overall tumor burden and margin status was examined[48].The tumor burden score was calculated with a formula that incorporated tumor size and number. With increasing margin width, patients with low or medium tumor burden had incrementally better survival. Patients with a high tumor burden did not, however, derive the same survival benefit from increasing margin width or from an R0 resection margin. In turn, while the goal should be an R0 margin, achieving microscopically negative margins cannot always overcome poor tumor biology.

Lymphadenectomy

Lymph node metastases are an important prognostic indicator of survival for patients with ICCA. The National Comprehensive Cancer Network (NCCN) guidelines recommend portal lymphadenectomy at the time of resection to ensure accurate staging [Figure 2][49]. In particular, at least six lymph nodes should be evaluated. The extent of lymphadenectomy should include the dissection of lymph nodes along the common hepatic artery and within the hepatoduodenal ligament[50]. A SEER database study evaluated 1,496

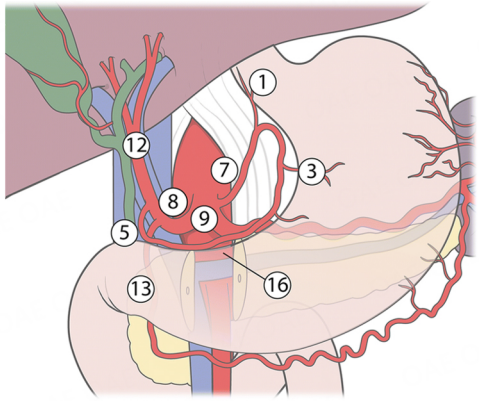

Figure 2. Lymph node drainage patterns for intrahepatic cholangiocarcinoma vary with tumor location. Left-sided cancers tend to drain to lymph nodes along the lesser curvature of the stomach and then to the celiac nodal basin. Right-sided cancers preferentially drain to portal/hilar lymph nodes and then to caval and peri-aortic lymph nodes[70]. This figure was reprinted with permission from reference 70.

patients who underwent curative-intent resection for ICCA[51]. This study noted that 52.4% of patients had at least one lymph node evaluated, 78.2% had 1-5 lymph nodes evaluated, and only 21.8% had at least six lymph nodes evaluated. Over time, as the guidelines have changed, the number of patients who had at least 6 lymph nodes harvested increased. Still, these data suggest that patients are often under-staged. Of note, while patients with higher T-category disease had an increased risk of lymph node metastases, the incidence of lymph node metastases did not directly correlate with the T-category. In fact, the highest incidence of lymph node metastases was noted among patients with T2a tumors. Therefore, T stage is not necessarily a reliable predictor of nodal disease, a point that further emphasizes that lymphadenectomy should be performed on all patients with ICCA to ensure adequate staging.

In a separate analysis of 603 patients from 15 high-volume institutions, Xu-Feng *et al.* investigated the association between lymph node metastases and prognosis[52]. Lymph node metastases were present in about 40% of patients who underwent surgical resection and an increasing number of lymph node metastases (0 *vs.* 1-2 *vs.* 3 or more) was associated with incrementally worse overall, disease-specific, and recurrence-free survival. These data further emphasize the importance of an adequate lymphadenectomy for staging purposes. In addition, this study highlighted the importance of lymph node metastasis location. Specifically, among patients with at least six lymph nodes examined, individuals with lymph node metastases beyond station 12 (hepatoduodenal ligament) had worse survival than patients with lymph node metastases limited to station 12. The eighth edition of the American Joint Commission on Cancer staging guidelines recommends sampling hepatoduodenal ligament, inferior phrenic, and gastrohepatic lymph nodes for left-sided ICCA and hepatoduodenal ligament, peri-duodenal, and peri-pancreatic lymph nodes for right-sided ICCA[52].

Clinical lymph node status should also be considered when deciding between upfront surgery versus chemotherapy as the first line of treatment. Patients who have portal lymph node involvement may benefit from receiving systemic chemotherapy with a re-staging scan prior to hepatectomy[30]. This therapeutic approach may provide a "test of time" to declare biology and help appropriately select patients who will most likely benefit from a resection relative to an oncologic perspective. In particular, lymph node involvement beyond the primary draining nodal basins (e.g., celiac or para-aortic lymph nodes) represents metastatic disease, and these patients should be treated with systemic therapy and only offered surgery in

select instances[5].

Vascular Resection

A subset of patients with ICCA may need a concomitant vein resection in order to achieve a satisfactory oncology outcome; however, this may increase morbidity/mortality. In a multi-institutional study of 1,087 patients who underwent curative intent hepatectomy for ICCA, Reames et al. reported that 128 (11.8%) patients required a major vascular resection (16.4% inferior vena cava resection, 76.6% portal vein resection, and 7% a combined resection)[53]. Interestingly, the authors noted that a major vascular resection did not increase the risk of complication or postoperative mortality. In addition, there was no difference in median recurrence-free or overall survival. Patients who required a vein resection were more likely to have been treated with neoadjuvant systemic therapy. In another retrospective review of 270 patients with ICCA, 31 patients (11.5%) required a vascular resection (15 portal vein resections, 16 inferior vena cava resections)[54]. In this study, patients who underwent a vascular resection did have increased morbidity and mortality. Of note, after adjusting for clinical and pathologic factors on multivariable analysis, vascular resection was not associated with worse long-term outcomes. In addition, patients who underwent an R0 resection and had no lymph node metastases yet required a vascular resection had equivalent survival to patients who did not undergo a vascular resection; in addition, patients who had a vascular resection to achieve an R0 margin had better survival than individuals who underwent an R1 resection. In yet another study, Ali et al. reported on 121 patients who underwent a major hepatectomy for ICCA and noted that 14 (12%) patients required vascular resection (5 portal veins, 9 inferior vena cava)[55]. There was no difference in postoperative complications or median overall survival among patients who did or did not have a vascular resection. As such, vascular resection should be considered for patients with ICCA if needed to achieve an R0 margin. Patients should have good performance status and, in general, have successfully completed neoadjuvant therapy without progression to ensure that the operation will provide an oncologic benefit. The addition of vascular resection and reconstruction can increase operative morbidity, and these types of operative procedures should be performed at high-volume centers.

Hepatic Artery Infusion Pump Therapy

For patients with locally advanced or unresectable ICCA, placement of a hepatic artery infusion pump (HAIP) can provide local control and potentially downstage patients. HAIP allows for direct delivery of chemotherapy to the liver, where it is preferentially distributed to the cancer cells through the hepatic artery and metabolized prior to entering the systemic circulation. This allows for directed treatment of the liver while diminishing the toxic side effects[56]. HAIP has primarily been studied in metastatic colorectal cancer, but has also shown promising results in early studies of patients with ICCA. In a study of 319 patients with multifocal ICCA, 141 patients received a HAIP and 178 underwent resection[56]. The 30-day postoperative mortality rate was higher in the resection cohort. There was no difference in overall survival between the two groups, even when stratified by number of lesions. In a retrospective study of patients with multifocal ICCA, there was no difference in overall or progression-free survival between patients who underwent intra-arterial therapy (transarterial chemoembolization, transarterial radioembolization, or HAIP) compared to resection[57]. However, patients who specifically underwent HAIP therapy were shown to have improved overall survival (39 months) compared to those who underwent surgery (20 months). Finally, in a single institution phase II trial, 38 patients with unresectable ICCA were given floxuridine and gemcitabine/oxaliplatin through the HAIP. Four patients were able to be downstaged and undergo resection, while 58% achieved an objective radiographic response and 84% achieved disease control[58]. HAIP is a promising liver-directed therapy that may help control disease growth and even downstage appropriately selected patients so that they may undergo curative resection.

RECURRENT DISEASE

Even after curative-intent resection of ICCA, the risk of recurrence is high ranging from 30-70%. Risk factors for recurrence include underlying liver disease (e.g., cirrhosis, primary sclerosing cholangitis), large tumor size, multifocal disease, positive surgical margin, vascular or perineural invasion, and metastatic regional lymph nodes[59]. In one study of 685 patients with ICCA who developed a recurrence, patients were divided into two cohorts based on the timing of recurrence: early (< 24 months) versus late (≥ 24 months)[60]. Individuals with early recurrence were more likely to have extrahepatic disease and worse overall survival. On a multivariable analysis, increased tumor size and the presence of satellite lesions were associated with an increased risk of early intrahepatic recurrence, whereas underlying liver cirrhosis was associated with late intrahepatic recurrence. Early recurrences may be due to occult residual disease at the time of the operation, while the late recurrences may have been related to background liver disease and de novo disease rather than a recurrence of the original tumor[60].

In another multi-institutional study of 920 patients with ICCA who underwent curative-intent resection, 607 (66%) developed a recurrence[61]. Among these patients, 24% recurred at the resection margin, 29% had an intrahepatic recurrence away from the margin, 15% had only extrahepatic recurrence, and 32% had both intra and extrahepatic recurrence. Intrahepatic margin recurrence and extrahepatic only recurrence commonly occurred within 6 months of resection, while distant intrahepatic recurrence occurred later within 2 years[61]. In turn, the authors speculated that early recurrence may be related to surgical technique (e.g., positive margin) or poor tumor biology (extrahepatic disease only).

In the setting of recurrent disease, additional systemic therapy, non-surgical liver-directed therapy (e.g., transarterial chemoembolization, Yttrium-90 radioembolization), or re-resection may be employed. Given that most recurrences are intrahepatic, re-resection may be a reasonable option in a subset of individuals. The selection of patients for repeat surgery depends on the size of the liver remnant, patient co-morbidities, and the anatomic location of the recurrent disease; in addition, the underlying biology (i.e., timing, location, and number) needs to be considered. In a study of 400 patients with ICCA recurrence, patients who underwent a re-resection had a better median survival (26.1 months) compared with individuals who received non-surgical locoregional therapy (9.6 months) or systemic chemotherapy (16.8 months). Among 41 patients who underwent re-resection, more than half developed additional recurrences within a median time of 11.5 months[62]. In a separate study of 156 patients with recurrent ICCA, 113 patients underwent re-resection and had a median survival of 65.2 months[63]. For patients who are not candidates for re-resection, Yttrium-90 radioembolization or other locoregional therapies may help to slow disease progression or palliate symptoms. In the setting of recurrence, treatment should be discussed in a multidisciplinary setting and clinical trials should be explored.

FUTURE DIRECTIONS FOR SYSTEMIC TREATMENT

Given the poor prognosis of ICCA, ongoing efforts are needed to identify effective systemic therapies to prevent disease recurrence and metastasis. Over the past few decades, immunotherapy has come to the forefront of cancer care with promising results. In order to successfully utilize immunotherapy, the tumor microenvironment needs to be characterized further to identify potential therapeutic targets. For example, Gani et al. demonstrated that some cells in the ICCA invasive tumor front and ICCA tumor macrophages stain positive for programmed death ligand 1 (PD-L1) expression and that PD-L1 expression was associated with worse survival, nodal metastases, and multifocal disease[64]. These data suggest that the PD-L1 pathway may be suppressing the host immune response in patients with ICCA. The TOPAZ-1 phase III trial evaluated whether the addition of durvalumab (a PD-L1 inhibitor) could improve survival when added to the cisplatin/gemcitabine regimen among patients with locally advanced or metastatic ICCA[65]. Indeed, the

addition of durvalumab improved overall survival and progression-free survival among patients with metastatic or unresectable biliary tract cancers, including ICCA. As a result, durvalumab was recently approved in combination with gemcitabine/cisplatin for this patient population.

Recent research has also focused on identifying effective targeted therapies for ICCA. Through genetic analysis and molecular profiling, specific genetic aberrations within ICCA can be targeted[66,67]. Studies have identified common genetic aberrations in CCA, including isocitrate dehydrogenase (IDH), AT-rich interactive domain-containing protein 1A (ARID1A), BRCA1-associated protein (BAP1), tumor protein 53 (TP53), cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B), and fibroblast growth factor receptor (FGFR)[68,69]. Targeted therapy with IDH and FGFR inhibitors has had promising results in early clinical trials, but there is still much that is unknown about which patient populations will respond to these drugs and how to overcome mechanisms of resistance.

CONCLUSIONS

ICCA is an aggressive primary liver cancer. When feasible, surgical resection should be pursued as this therapeutic modality offers the best potential for long-term survival. Preoperative planning with volumetric analysis of the FLR and medical optimization is crucial to ensuring that patients will be able to tolerate surgery and minimize complications. In addition, high-risk tumor features may result in early recurrence and should therefore be used to select patients who may benefit from preoperative systemic chemotherapy prior to resection. In particular, patients with locally advanced or high-risk tumors (e.g., extrahepatic lymphadenopathy, poor differentiation, vascular invasion, multifocal disease) should be strongly considered for chemotherapy with gemcitabine/cisplatin (+/- durvalumab) with re-staging scans and delayed resection. For patients with favorable biology and resectable disease, upfront surgery with adjuvant capecitabine based on the BILCAP data should be considered.

At the time of surgery, staging laparoscopy should be considered to evaluate for occult metastatic disease and laparoscopic ultrasound can be used to better evaluate the liver parenchyma. Resection with the goal of achieving an R0 margin, along with lymphadenectomy to adequately stage patients, should be the standard operative approach. Unfortunately, the surgical technique cannot overcome poor tumor biology and ICCA has a high incidence of recurrence, with many patients developing metastatic disease. Therefore, future endeavors should strive to identify more effective systemic and targeted therapies, which will hopefully improve survival for patients with ICCA.

DECLARATIONS

Authors' contributions

Conceptualization, drafting, and critical revision of the manuscript: Ruff SM, Pawlik TM

Availability of data and materials

Not applicable.

Financial support and sponsorship

There was no financial support for this work.

Conflicts of interest

The authors do not have any potential conflicts of interest to declare.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

REFERENCES

1. Goyal L, Kongpetch S, Crolley VE, Bridgewater J. Targeting FGFR inhibition in cholangiocarcinoma. *Cancer Treat Rev* 2021;95:102170. DOI PubMed
2. Cardinale V, Semeraro R, Torrice A, et al. Intra-hepatic and extra-hepatic cholangiocarcinoma: new insight into epidemiology and risk factors. *World J Gastrointest Oncol* 2010;2:407-16. DOI PubMed PMC
3. Primrose JN, Fox RP, Palmer DH, et al; BILCAP study group. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol* 2019;20:663-73. DOI
4. Buettner S, van Vugt JL, IJzermans JN, Groot Koerkamp B. Intrahepatic cholangiocarcinoma: current perspectives. *Onco Targets Ther* 2017;10:1131-42. DOI PubMed PMC
5. Squires MH, Cloyd JM, Dillhoff M, Schmidt C, Pawlik TM. Challenges of surgical management of intrahepatic cholangiocarcinoma. *Expert Rev Gastroenterol Hepatol* 2018;12:671-81. DOI PubMed
6. Valle J, Wasan H, Palmer DH, et al; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;362:1273-81. DOI
7. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. *Nat Rev Clin Oncol* 2018;15:95-111. DOI PubMed PMC
8. Brown ZJ, Ruff SM, Pawlik TM. Developments in FGFR and IDH inhibitors for cholangiocarcinoma therapy. *Expert Rev Anticancer Ther* 2023;23:257-64. DOI PubMed
9. Doherty B, Nambudiri VE, Palmer WC. Update on the diagnosis and treatment of cholangiocarcinoma. *Curr Gastroenterol Rep* 2017;19:2. DOI PubMed
10. Masarone M, Persico M. Hepatitis c virus infection and non-hepatocellular malignancies in the daa era: a systematic review and meta-analysis. *Liver Int* 2019;39:1292-306. DOI
11. Tanaka M, Tanaka H, Tsukuma H, Ioka A, Oshima A, Nakahara T. Risk factors for intrahepatic cholangiocarcinoma: a possible role of hepatitis B virus. *J Viral Hepat* 2010;17:742-8. DOI PubMed PMC
12. Kubo S, Takemura S, Tanaka S, et al. Occupational cholangiocarcinoma caused by exposure to 1,2-dichloropropane and/or dichloromethane. *Ann Gastroenterol Surg* 2018;2:99-105. DOI PubMed PMC
13. Tao LY, Cai L, He XD, et al. Comparison of serum tumor markers for intrahepatic cholangiocarcinoma and hepatocellular carcinoma. *Am Surg* ;2010.76:p. 1210-3. PubMed
14. Moro A, Mehta R, Sahara K, et al. The impact of preoperative CA19-9 and CEA on outcomes of patients with intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2020;27:2888-901. DOI
15. Valls C, Gumà A, Puig I, et al. Intrahepatic peripheral cholangiocarcinoma: CT evaluation. *Abdom Imaging* 2000;25:490-6. DOI
16. Seo N, Kim DY, Choi JY. Cross-sectional imaging of intrahepatic cholangiocarcinoma: development, growth, spread, and prognosis. *AJR Am J Roentgenol* 2017;209:W64-75. DOI PubMed
17. Blechacz B. Cholangiocarcinoma: current knowledge and new developments. *Gut Liver* 2017;11:13-26. DOI PubMed PMC
18. Fábrega-Foster K, Ghasabeh MA, Pawlik TM, Kamel IR. Multimodality imaging of intrahepatic cholangiocarcinoma. *Hepatobiliary Surg Nutr* 2017;6:67-78. DOI PubMed PMC
19. Fujita N, Asayama Y, Nishie A, et al. Mass-forming intrahepatic cholangiocarcinoma: enhancement patterns in the arterial phase of dynamic hepatic CT - correlation with clinicopathological findings. *Eur Radiol* 2017;27:498-506. DOI
20. Hewitt DB, Brown ZJ, Pawlik TM. Surgical management of intrahepatic cholangiocarcinoma. *Expert Rev Anticancer Ther* 2022;22:27-38. DOI PubMed
21. Lamarca A, Barriuso J, Chander A, et al. ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) for patients with biliary tract cancer: Systematic review and meta-analysis. *J Hepatol* 2019;71:115-29. DOI
22. Spolverato G, Vitale A, Cucchetti A, et al. Can hepatic resection provide a long-term cure for patients with intrahepatic cholangiocarcinoma? *Cancer* 2015;121:3998-4006. DOI
23. Lamarca A, Edeline J, McNamara MG, et al. Current standards and future perspectives in adjuvant treatment for biliary tract cancers. *Cancer Treat Rev* 2020;84:101936. DOI
24. Zhang XF, Bagante F, Chakedis J, et al. Perioperative and long-term outcome for intrahepatic cholangiocarcinoma: impact of major versus minor hepatectomy. *J Gastrointest Surg* 2017;21:1841-50. DOI
25. Le Roy B, Gelli M, Pittau G, et al. Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. *Br J Surg*

2018;105:839-47. DOI
26. Kato A, Shimizu H, Ohtsuka M, et al. Surgical resection after downsizing chemotherapy for initially unresectable locally advanced biliary tract cancer: a retrospective single-center study. *Ann Surg Oncol* 2013;20:318-24. DOI
27. Moris D, Palta M, Kim C, Allen PJ, Morse MA, Lidsky ME. Advances in the treatment of intrahepatic cholangiocarcinoma: an overview of the current and future therapeutic landscape for clinicians. *CA Cancer J Clin* 2023;73:198-222. DOI PubMed
28. D'Angelica M, Fong Y, Weber S, et al. The role of staging laparoscopy in hepatobiliary malignancy: prospective analysis of 401 cases. *Ann Surg Oncol* 2003;10:183-9. DOI
29. Goere D, Wagholikar GD, Pessaux P, et al. Utility of staging laparoscopy in subsets of biliary cancers: laparoscopy is a powerful diagnostic tool in patients with intrahepatic and gallbladder carcinoma. *Surg Endosc* 2006;20:721-5. DOI
30. Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. *HPB* 2015;17:669-80. DOI PubMed PMC
31. Shindoh J, Tzeng CW, Aloia TA, et al. Optimal future liver remnant in patients treated with extensive preoperative chemotherapy for colorectal liver metastases. *Ann Surg Oncol* 2013;20:2493-500. DOI PubMed PMC
32. Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *Br J Surg* 2007;94:274-86. DOI PubMed
33. Abdalla EK, Barnett CC, Doherty D, Curley SA, Vauthey JN. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. *Arch Surg* 2002;137:675-80; discussion 680. DOI PubMed
34. Abdalla EK. Resection of colorectal liver metastases. *J Gastrointest Surg* 2011;15:416-9. DOI PubMed
35. Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery* 2000;127:512-9. DOI
36. Kubota K, Makuuchi M, Kusaka K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 1997;26:1176-81. DOI
37. Thirunavukarasu P, Aloia TA. Preoperative assessment and optimization of the future liver remnant. *Surg Clin North Am* 2016;96:197-205. DOI PubMed
38. Rassam F, Olthof PB, van Lienden KP, et al. Comparison of functional and volumetric increase of the future remnant liver and postoperative outcomes after portal vein embolization and complete or partial associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). *Ann Transl Med* 2020;8:436. DOI PubMed PMC
39. Li M, Wang J, Song J, et al. Preoperative ICG test to predict posthepatectomy liver failure and postoperative outcomes in hilar cholangiocarcinoma. *Biomed Res Int* 2021;2021:8298737. DOI PubMed PMC
40. Owen ML, Beal EW. Minimally invasive surgery for intrahepatic cholangiocarcinoma: patient selection and special considerations. *Hepat Med* 2021;13:137-43. DOI PubMed PMC
41. Lee W, Park JH, Kim JY, et al. Comparison of perioperative and oncologic outcomes between open and laparoscopic liver resection for intrahepatic cholangiocarcinoma. *Surg Endosc* 2016;30:4835-40. DOI
42. Wei F, Lu C, Cai L, Yu H, Liang X, Cai X. Can laparoscopic liver resection provide a favorable option for patients with large or multiple intrahepatic cholangiocarcinomas? *Surg Endosc* 2017;31:3646-55. DOI PubMed
43. Uy BJ, Han HS, Yoon YS, Cho JY. Laparoscopic liver resection for intrahepatic cholangiocarcinoma. *J Laparoendosc Adv Surg Tech A* 2015;25:272-7. DOI PubMed
44. Ratti F, Cipriani F, Ariotti R, et al. Safety and feasibility of laparoscopic liver resection with associated lymphadenectomy for intrahepatic cholangiocarcinoma: a propensity score-based case-matched analysis from a single institution. *Surg Endosc* 2016;30:1999-2010. DOI
45. Neoptolemos JP, Moore MJ, Cox TF, et al; European Study Group for Pancreatic Cancer. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA* 2012;308:147-56. DOI
46. Spolverato G, Yakoob MY, Kim Y, et al. The impact of surgical margin status on long-term outcome after resection for intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2015;22:4020-8. DOI
47. de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol* 2011;29:3140-5. DOI
48. Endo Y, Sasaki K, Moazzam Z, et al. Higher tumor burden status dictates the impact of surgical margin status on overall survival in patients undergoing resection of intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2023;30:2023-32. DOI
49. NCCN guidelines version: hepatobiliary cancers. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1438 [Last accessed on 12 May 2023].
50. Cloyd JM, Ejaz A, Pawlik TM. The landmark series: intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2020;27:2859-65. DOI PubMed
51. Zhang XF, Chen Q, Kimbrough CW, et al. Lymphadenectomy for intrahepatic cholangiocarcinoma: has nodal evaluation been increasingly adopted by surgeons over time? a national database analysis. *J Gastrointest Surg* 2018;22:668-75. DOI
52. Zhang XF, Xue F, Dong DH, et al. Number and station of lymph node metastasis after curative-intent resection of intrahepatic cholangiocarcinoma impact prognosis. *Ann Surg* 2021;274:e1187-95. DOI
53. Reames BN, Ejaz A, Koerkamp BG, et al. Impact of major vascular resection on outcomes and survival in patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis. *J Surg Oncol* 2017;116:133-9. DOI

54. Conci S, Viganò L, Ercolani G, et al. Outcomes of vascular resection associated with curative intent hepatectomy for intrahepatic cholangiocarcinoma. *Eur J Surg Oncol* 2020;46:1727-33. DOI
55. Ali SM, Clark CJ, Zaydfudim VM, Que FG, Nagorney DM. Role of major vascular resection in patients with intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2013;20:2023-8. DOI PubMed
56. Franssen S, Soares KC, Jolissaint JS, et al. Comparison of hepatic arterial infusion pump chemotherapy vs resection for patients with multifocal intrahepatic cholangiocarcinoma. *JAMA Surg* 2022;157:590-6. DOI PubMed PMC
57. Wright GP, Perkins S, Jones H, et al. Surgical resection does not improve survival in multifocal intrahepatic cholangiocarcinoma: a comparison of surgical resection with intra-arterial therapies. *Ann Surg Oncol* 2018;25:83-90. DOI
58. Cercek A, Boerner T, Tan BR, et al. Assessment of hepatic arterial infusion of floxuridine in combination with systemic gemcitabine and oxaliplatin in patients with unresectable intrahepatic cholangiocarcinoma: a phase 2 clinical trial. *JAMA Oncol* 2020;6:60-7. DOI PubMed PMC
59. Bekki Y, Von Ahrens D, Takahashi H, Schwartz M, Gunasekaran G. Recurrent intrahepatic cholangiocarcinoma - review. *Front Oncol* 2021;11:776863. DOI PubMed PMC
60. Zhang XF, Beal EW, Bagante F, et al. Early versus late recurrence of intrahepatic cholangiocarcinoma after resection with curative intent. *Br J Surg* 2018;105:848-56. DOI
61. Hu LS, Zhang XF, Weiss M, et al. Recurrence patterns and timing courses following curative-intent resection for intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2019;26:2549-57. DOI
62. Spolverato G, Kim Y, Alexandrescu S, et al. Management and outcomes of patients with recurrent intrahepatic cholangiocarcinoma following previous curative-intent surgical resection. *Ann Surg Oncol* 2016;23:235-43. DOI
63. Bartsch F, Eberhard J, Rückert F, et al; German ICC Collaboration Group. Repeated resection for recurrent intrahepatic cholangiocarcinoma: a retrospective German multicentre study. *Liver Int* 2021;41:180-91. DOI
64. Gani F, Nagarajan N, Kim Y, et al. Program death 1 immune checkpoint and tumor microenvironment: implications for patients with intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2016;23:2610-7. DOI
65. Oh D, He AR, Qin S, et al. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. *JCO* 2022;40:378-378. DOI
66. Zhu AX, Borger DR, Kim Y, et al. Genomic profiling of intrahepatic cholangiocarcinoma: refining prognosis and identifying therapeutic targets. *Ann Surg Oncol* 2014;21:3827-34. DOI PubMed PMC
67. Chmiel P, Gęca K, Rawicz-Pruszyński K, Polkowski WP, Skórzewska M. FGFR inhibitors in cholangiocarcinoma-a novel yet primary approach: where do we stand now and where to head next in targeting this axis? *Cells* 2022;11:3929. DOI PubMed PMC
68. Lowery MA, Ptashkin R, Jordan E, et al. Comprehensive molecular profiling of intrahepatic and extrahepatic cholangiocarcinomas: potential targets for intervention. *Clin Cancer Res* 2018;24:4154-61. DOI PubMed PMC
69. Javle MM, Abou-alfa GK, Macarulla T, et al. Efficacy of derazantinib in intrahepatic cholangiocarcinoma patients with FGFR2 mutations or amplifications: interim results from the phase 2 study FIDES-01. *JCO* 2022;40:427-427. DOI
70. Kim SH, Han DH, Choi GH, Choi JS, Kim KS. Extent of lymph node dissection for accurate staging in intrahepatic cholangiocarcinoma. *J Gastrointest Surg* 2022;26:70-6. DOI PubMed