REVIEW

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Hepatic Oncology

Monitoring outcomes in intrahepatic cholangiocarcinoma patients following hepatic resection

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Practice points

- Intrahepatic cholangiocarcinoma (iCCA) is the second most frequent primary liver cancer after hepatocellular carcinoma.
- R0 resection (negative microscopic surgical margins) offers the best potential for cure in patients with iCCA.
- Surgical resectability is determined based on preoperative cross-sectional imaging findings, calculated future remnant liver and patient's possible medical comorbidities.
- Routine staging laparoscopy before exploration of the abdomen for tumor resection is recommended in patients with high-risk features (e.g., high preoperative serum levels of CA 19-9 and CEA, multicentric disease or suspicious vascular invasion).
- Considering the strong prognostic value of lymph node (LN) involvement and potential of selecting high-risk patients for adjuvant therapy, universal removal of the regional LNs is recommended during surgery for iCCA.
- Adjuvant therapy is generally recommended in the management of patients with positive surgical margins (R1 or R2 resection), LN metastasis, or patients predicted to have high recurrence rate based on preoperative work-up (e.g., vascular invasion, large tumors, multicentricity).
- There are no clear guidelines regarding the duration and frequency of follow-up for surveillance after iCCA surgery. However, using some form of contrast enhanced cross-sectional imaging every 2–4 months for first 2 years after resection along with measurement of tumor markers such as CEA and CA 19-9 is generally recommended.
- Disease recurrence is common following surgical resection of iCCA (up to 50–60%), with liver known to be the most common site of recurrence (50–60%) followed by the locoregional LNs (20–30%) and peritoneum (20%).
- Five-year OS of patients with iCCA undergoing surgical resection is dependent on several factors and usually varies between 11 and 40%.
- Determining factors associated with disease recurrence and survival of the iCCA patients after surgical resection plays a critical role to accurately identify patients who will benefit from major surgical resections, stratify them for adjuvant therapies or clinical trials and guide surgeon–patient discussions in decision-making process. Recently, several iCCA-specific nomograms and prognostic models have been proposed for this purpose.

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Intrahepatic cholangiocarcinoma (iCCA) is one of the fatal gastrointestinal cancers with increasing incidence and mortality. Although surgery offers the only potential for cure in iCCA patients, the prognosis is not optimal with low overall survival rate and high disease recurrence. Hence, adjuvant therapy is generally recommended in the management of high-risk patients. Identifying factors associated with disease recurrence and survival of the iCCA patients after resection will improve understanding of disease prognosis and help in selecting patients who will benefit from surgical resection or stratifying them for clinical trials. Despite development of new methods for early detection of tumor recurrence, effective prognostic models and nomograms, and recent advances in management, significant challenges remain in improving the prognosis of iCCA patients.

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KEYWORDS

- intrahepatic cholangiocarcinoma
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- systemic therapy • tumor marker

Intrahepatic cholangiocarcinoma (iCCA) is a tumor arising from the malignant proliferation of epithelial cells lining the intrahepatic ducts located proximal to the second-degree branches of the bile ducts. iCCA is the second most frequent primary liver cancer after hepatocellular carcinoma (HCC) [1,2] with an incidence and mortality that is rising worldwide [3–5].

In this review we discuss the current management options of iCCA while highlighting the role of surgical resection as well as follow-up and monitoring of iCCA patients after resection. Furthermore, overall survival (OS) of these patients after hepatic resection and factors associated with prognosis and patient selection are examined.

Management modalities

• Surgical resection

Resectability criteria

Resection with negative microscopic margins (R0 resection) offers the best potential for cure in patients with iCCA. Without surgery prognosis is poor, with less than 5% of the patients alive 5 years after the diagnosis [6]. The median survival for patients with inoperable disease is generally short (7–12 months) [7], with reported median survival of as low as 1.8 months in some series of patients with advanced iCCA managed conservatively [8]. Preoperative cross-sectional imaging using contrast-enhanced multidetector computed tomography (MDCT scan) and/or MRI/magnetic resonance cholangiopancreatography (MRI/MRCP) plays a key role in the assessment of tumor extent along with its locoregional and distant spread, and thus helping to determine tumor resectability [9,10].

In general, iCCA is considered unresectable in the case of bilateral multifocal or multicentric tumors, extrahepatic disease, or involvement of

lymph nodes (LNs) beyond the regional basin (e.g., celiac and para-aortic nodes) [11–13]. Locally advanced tumors with involvement of vascular structures that will require major vascular reconstruction are still potentially resectable, depending on the extent of involvement/reconstruction needed [14,15]. Calculating future remnant liver function, especially in patients with underlying liver disease (e.g., cirrhosis), and thorough work-up of medical comorbidities are other important determinants of tumor resectability. The future liver remnant (FLR) of 40% is considered the minimum safe volume needed after extended hepatic resection in patients with underlying cirrhosis to prevent postoperative liver failure. This threshold volume reaches to 20% and 30% in patients with normal underlying liver and patients who receive extensive chemotherapy before resection, respectively [16,17]. Portal vein embolization is one of the proposed effective methods to increase FLR by redirecting flow to the liver remnant and increasing hypertrophy through clonal expansion of hepatocytes [18,19]. More recently, the Associating Liver Partition and Portal Vein Ligation for Staged (ALPPS) hepatectomy has been introduced for resection of otherwise inoperable tumors, especially in patients with limited FLR. In this technique, a two-stage liver resection combining *in situ* liver transection with portal vein transection is used to increase the resectability of marginally resectable or locally unresectable liver tumors through inducing faster hypertrophy of future liver remnant [20,21].

With application of the 7th edition of the American Joint Committee on Cancer Tumor Node Metastasis Staging System (Table 1), only 30–40% of patients with iCCA (stage one and two) were deemed to benefit from surgical resection [9,10]. Due to the technical complexity of R0 resection, often requiring hemihepatectomies

Table 1. The seventh edition of American Joint Committee on Cancer/Tumor Node Metastasis staging system for intrahepatic bile duct tumors.

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma <i>in situ</i> (intraductal tumor)		
T1	Solitary tumor without vascular invasion		
T2a	Solitary tumor with vascular invasion		
T2b	Multiple tumors, with or without vascular invasion		
T3	Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion T4 tumor with periductal invasion		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis		
N1	Regional lymph node metastasis present		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis present		
Anatomic stage groupings			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	Any T	N1	M0
Stage IVB	Any T	Any N	M1

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or extended hepatic resections in majority of patients (up to 70%) [12,22] combined with possible concomitant extrahepatic bile duct resection (in up to 20% of cases) [12,23], only a small subset of patients eligible for surgery are typically offered to have resection [10,24]. In one study, using the Surveillance Epidemiology and End Results database, retrospective review of medical information of 3756 iCCA patients revealed that only 446 patients (12%) underwent surgical resection [24]. Interestingly, only 91 patients (37%) out of 248 patients identified to have localized potentially resectable disease in this database were offered surgery [24]. Although factors such as medical comorbidities and complexity of operative procedure have been proposed as possible barriers to inadequate delivery of surgical care to these patients, further studies are warranted to explore other potential underlying causes (e.g., surgeons' and patients' attitude toward iCCA) [24,25].

Staging laparoscopy

A few studies have suggested a role for diagnostic laparoscopy in identifying peritoneal or intrahepatic metastasis that may be otherwise undetected

in preoperative investigations. Specifically, some studies have reported the yield for diagnostic laparoscopy to vary from 27 to 38% [13,27].

In a prospective cohort of 401 patients with hepatobiliary malignancy, D'Angelica *et al.* reported that laparoscopy spared one in five patients a laparotomy with an associated decrease in hospital stay and postoperative morbidity [28]. In another study, staging laparoscopy precluded an unnecessary laparotomy in 36% of patients with potentially resectable biliary malignancy based on preoperative imaging [29]. Although the role of routine staging laparoscopy before exploration of the abdomen for tumor resection is still controversial, its usage is recommended in patients with high-risk features (e.g., high preoperative serum levels of CA 19-9 and carcinoembryonic antigen (CEA), multicentric disease or suspicious vascular invasion) [9,10].

Combining laparoscopy with ultrasonography might further increase the yield of diagnostic laparoscopy in selected patients [9,10].

Resection of locoregional LN involved in iCCA

The incidence of locoregional LN (e.g., LNs of the hepatoduodenal ligament and the hepatic

artery) involvement in iCCA patients has been reported to be as high as 40% in some studies [12,22,30]. Nonetheless, performing routine lymphadenectomy in the surgical management of iCCA is still debated. In a large international multi-institutional study of 449 patients with iCCA who underwent surgery, De Jong *et al.* reported that just 248 patients (55.2%) had lymphadenectomy with the median number of harvested LNs of 3 [22]. In this study, LN metastasis (LNM) was associated with worse outcome with median survival of 30 months in patients without LN involvement versus 24 months in a group with LNM; ($p = 0.03$) [22]. While removing clinically suspicious LNs seems to be mandatory, some investigators have questioned the survival benefit of routine LN dissection [22,31–32].

However, considering the strong prognostic value of LN involvement and potential of selecting high-risk patients for adjuvant therapy [3,22,30,33–34], universal removal of the regional LNs is recommended during surgery for iCCA [9–10,34].

Furthermore, some studies have even suggested a therapeutic role for lymphadenectomy by decreasing the rate of locoregional recurrences [9,35]; although this role remains unclear.

Adjuvant chemotherapy

The survival benefit of adjuvant therapy after surgical resection of biliary duct tumors is not entirely supported by current randomized trials. In one study from Japan, postoperative chemotherapy did not show any statistically significant survival benefit in 508 patients with resected pancreatobiliary malignancy [36]. The same results were achieved when the data were stratified to include just the 118 patients with bile duct cancer, with 5-year survival rate of 26.7% in treatment group versus 24.1% in control group (p NS) [36]. In another international European trial (ESPAC)-3, the use of adjuvant therapy was not associated with a statistically significant survival advantage either in all patients with periaampullary malignancies or in the subset of patients with bile duct cancer [37]. In a recent meta-analysis of 20 studies (total of 6712 patients with biliary tract cancer who underwent curative-intent surgery), Horgan *et al.* reported a survival benefit among patients treated with adjuvant chemotherapy (OR: 0.39; 95% CI: 0.23–0.66) and chemoradiotherapy (OR: 0.61;

95% CI: 0.38–0.99), especially in patients with node-positive and margin-positive disease [38]. The major limitation of these studies was that they included broad categories of biliary tract cancers. More recently, several iCCA-focused studies have demonstrated a survival benefit of adjuvant therapy in postresection iCCA patients who had positive nodes and/or margins [39,40].

As such, adjuvant therapy is generally recommended in the management of patients with positive surgical margins (R1 or R2 resection), LN metastasis, or patients predicted to have high recurrence rate based on preoperative work-up (e.g., vascular invasion, large tumors, multicentricity) [41,42]. The local and distant relapse patterns after surgical resection of these tumors provide the rationale for both local and systemic adjuvant therapy [11,43–45]. However, according to current data there is no established preferred modality (e.g., chemotherapy alone vs chemotherapy plus chemoradiotherapy). While the choice of regimen (e.g., gemcitabine–, fluoropyrimidine-based chemotherapy, among others) is also not well supported by level 1 evidence from adjuvant trials, most often a gemcitabine–cisplatin regimen is used based on data from patients with advanced biliary cancers.

The application of neoadjuvant chemotherapy or chemoradiotherapy in iCCA patients is limited to a few cases reporting conversion of the large, locally advanced unresectable tumors to potentially resectable ones [15,46]. Other highly selected patients have been reported to undergo orthotopic liver transplantations (OLT) in a few centers with designed clinical protocols for these patients [47,48].

• OLT

Unlike well-described patient selection criteria, organ allocation system, neoadjuvant therapy protocols, and long term outcomes of patients associated with perihilar cholangiocarcinoma (pCCA) undergoing OLT [47], current data for patients with iCCA is limited to a few reports with variable patient selection criteria [10,48]. Of note, the overall reported survival of patients with iCCA is markedly less than OLT being performed for cirrhotic patients [49,50]. For example, in a multicentric Canadian retrospective study of ten patients who underwent OLT who were subsequently found to have an incidental iCCA, the 3-year survival was just 30% [49]. Most recently, an international multicentric cohort study reported better results for OLT performed for

cirrhotic patients who were noted to have a very early incidental iCCA (single tumor $\leq 2\text{cm}$) [23]. The reported 5-year actuarial survival and recurrence rate for 15 patients with very early iCCA (out of total of 48 patients with iCCA) were 65 and 18%, respectively [23]. The results of this study were consistent with findings of previous studies that also examine a limited number of patients [23,51]. As such, OLT for iCCA should not be considered a standard therapy and should only be considered in restricted centers to highly selected patients using designed clinical protocols.

• Systemic chemotherapy

The role of systemic chemotherapy in patients presenting with advanced cholangiocarcinoma not amenable to surgical resection is evolving. The survival benefit of chemotherapy relative to best supportive care alone has been demonstrated in several studies [52,53]. Sharma *et al.* in a randomized controlled study of patients with unresectable gall bladder cancer demonstrated that median OS of patients received chemotherapy (modified gemcitabine and oxaliplatin) was better than the patients with best supportive care without chemotherapy (9.5 vs 4.5 months, respectively; $p = 0.039$) [53]. However, there is still no definitive consensus regarding the standard regimen [9–10,34].

The two main factors hampering the results of current trials are limited number of cases, as well as heterogeneity of patients included in these studies. Overall, the combination of gemcitabine plus cisplatin (or oxaliplatin as a potentially better-tolerated agent) has been recommended by experts as a first-line chemotherapy regimen for patients with a good performance status [9,31,41,54]. In the ABC-02 trial, which included 410 patients with locally advanced mixed subset of biliary duct malignancies, gemcitabine plus cisplatin was associated with a significant survival advantage over gemcitabine alone without additional toxicity (11.7 months vs 8.1 months; HR: 0.64; 95% CI: 0.52–0.80; $p < 0.001$) [54]. Among patients with a refractory response to first-line therapies, there is no strong clinical evidence that further chemotherapy will improve the survival [55,56]. With the progressively evolving field of biliary cancer genetics [10,57–58], new molecular-targeted agents (e.g., erlotinib, bevacizumab) have been introduced recently with the potential of improving the effectiveness of

traditional chemotherapies – however, more data are needed [59,60].

• Hepatic artery-based locoregional therapy

Transarterial chemoinfusion (TACI) [61,62], transarterial chemoembolization (TACE) [61–63] and transarterial radioembolization (TARE) using Yttrium-90 (Y-90) tagged glass or resin microspheres [43,62–65] have been proposed as effective treatments with acceptable toxicities in patients with locally advanced inoperable iCCA. The fundamental rationale for all these therapies is the fact that the majority of the blood supply to an intrahepatic tumor is derived from the hepatic artery (80–100%) rather than the portal vein. In a retrospective review of 198 patients with advanced unresectable iCCA, treatment with hepatic artery based therapy (including conventional TACE, drug-eluting TACE and TARE) led to complete or partial response in 25.5% of patients and stable disease in 61.5% of patients [63]. In this study, the median OS was 13.2 months without any statistically significant differences between the different modalities [63]. More recently, Boehm *et al.* in a meta-analysis of data from 657 inoperable iCCA patients proposed that TACI offered the best outcomes in terms of tumor response and OS (22.8 months in TACI vs 13.9, 12.4 and 12.3 months in Y90, TACE and drug-eluting TACE, respectively), but therapy was limited due to toxicity [62]. Selecting a preferred modality among these therapies and demonstrating a clear advantage over other systemic and locoregional treatments will require further studies.

• Radiation

Conventional external beam irradiation (EBRT), with or without concomitant chemotherapy, has been shown to have palliative effects (relieving pain or biliary decompression) in patients with advanced biliary cancer and intrahepatic malignancies. However, its role in patients with iCCA is not well defined [44,66].

In one study, Zeng *et al.* reported an objective response in 36% of patients and pain relief in 90% of the 22 unresectable iCCA patients who underwent EBRT. A similar retrospective study of 84 patients with inoperable iCCA revealed complete and partial response of the primary tumor in 8.6 and 28.5% of the patients receiving EBRT, respectively [44]. In a more recently published large cohort of 1636

patients with nonmetastatic unresectable iCCA using National Cancer Database, the addition of radiation to chemotherapy was associated with improved OS (26 vs 20%, respectively) [67]. Although current technical advances with development of transluminal brachytherapy, 3D conformal radiation therapy, or stereotactic body radiotherapy (SBRT) have enabled the delivering of higher doses of radiation therapy more precisely to a tumor while sparing adjacent normal tissue, there are no strong data to establish its role as standard therapy in the management of patients with unresectable iCCA. For example, in the case of SBRT, the experience has been limited to a few single-institutional retrospective series involving both iCCA and pCCA [68–70]. In one recent study, the authors noted that among 34 patients with unresectable iCCA and pCCA who received SBRT, the local control rate was 79% with median OS of 17 months [70]. Similarly, Chen and associate demonstrated that transluminal brachytherapy is a safe palliative therapy in patients with malignant obstructive jaundice, with potential to prolong the stent patency ($p < 0.05$) and to extend the survival of patients (mean survival 9.6 months vs 6.4 months in control group; although this difference was not statistically significant) [71].

• Ablation

Tumor ablation, either radiofrequency ablation (RFA) or microwave, is recommended by several studies as an effective modality to treat small (<3 cm) locally advanced unresectable iCCA [72–74]. In a study of 17 patients with unresectable iCCA who underwent RFA, early tumor necrosis was noted in 96.2% of patients with median recurrence-free and OS of 17 and 33 months, respectively [73]. The reported 5-year survival in this study was 28.9% with an overall complication rate of 3.6% [73]. Ablation as standard treatment for small iCCA tumors requires, however, further investigation.

Follow-up

There are no clear guidelines regarding the duration and frequency of follow-up for surveillance after iCCA surgery. Studies on iCCA recurrence following resection generally utilize some form of contrast enhanced cross-sectional imaging every 2–4 months for first 2 years after resection along with measurement of tumor markers such as CEA and CA 19-9. Thereafter, clinicians generally performed continued imaging

surveillance every 3–12 months for a variable duration [11,75–76].

• Imaging methods

As tumor recurrence is very common [76], early detection and diagnosis is necessary so that additional therapy can be performed. Various radiological examinations are done for postoperative monitoring. Most widely used modalities are CT, MRI, endoscopic retrograde cholangiopancreatography and FDG-PET.

CT scan

CT is probably the most commonly used surveillance tool postoperatively. Even though no study has determined the efficacy of CT in detecting recurrent iCCA, CT scans are often utilized in the postoperative setting in an attempt to detect tumor recurrence. The interval of CT scan follow-up may depend upon various factors such as initial tumor stage, timing of adjuvant therapy, and even considerations around medical insurance and cost effectiveness [77]. MDCT with its extremely fast scanning capabilities allows thin sliced sections to be obtained that are helpful for visualizing coronal reformation, curved multiplanar reconstructive image (MPR) and vascular reconstruction [78–81].

MRI/MRCP

MRI is a widely used modality for postsurgical follow-up of iCCA. Besides the conventional sequence, the addition of heavily T2-weighted images can provide MRCP images, which allow delineation of dilated ducts and diagnose biliary tract pathology [5,9,78,82]. By virtue of its superior contrast resolution, MR Imaging with MR cholangiography has been found to be superior to CT for the assessment of intraductal lesions [83].

Over the last few years, several studies have suggested improved lesion conspicuity and superior lesion characterization with addition of hepatobiliary contrast agents such as gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid [84–86]. Diffusion-weighted imaging (DWI) enables qualitative and quantitative assessment of tissue diffusivity without the use of gadolinium chelates. It can further strengthen MRI capability by improving characterization of lesion as benign versus malignant since restricted diffusion is a marker of dense cellularity as seen in malignant tumors [87]. DWI can increase lesion conspicuity even in the absence of MR contrast agents [88]. Hence, it is very useful in patients with hepato

renal dysfunction where risk of nephrogenic systemic fibrosis is high secondary to use gadolinium products.

PET scan

Several authors have reported that fludeoxyglucose-PET (FDG-PET) is more useful in diagnosing recurrent iCCA than CT [89,90] as it helps to detect malignant tumors by visualizing hypermetabolic rate of malignant cells. Use of FDG-PET/CT may have some benefits in response monitoring and recurrence detection as shown by Reinhardt *et al.* in patients with Primary Sclerosing Cholangitis and Klatskin's tumor [91]. There are also studies showing use of tumor specific PET isotopes such as ¹⁸F-fluorodeoxythymidine that may help overcome the inability of FDG to differentiate between inflammation and malignancy [92].

• Imaging findings

Recurrent iCCA can present as a local recurrence of cancer, liver metastasis, LN metastasis and peritoneal metastasis [78–82,89,93]. Post iCCA resection patients with recurrence may present with an irregular mass at the surgical site and imaging may show tumor invasion into the adjacent structures like the portal vein, pancreas, bowel and bile duct causing obstruction.

On CT scan, as the fibrotic component of tumor stroma accumulates contrast media, it is better appreciated in delayed images versus arterial and portal phases. On T1-weighted images (WI) iCCA are either isointense or hypointense while on T2-WI iCCA are variably hyperintense depending on the amount of mucinous material, fibrous tissue, hemorrhage, and necrosis. Like CT, due to the desmoplastic nature of iCCA, the tumors enhance on delayed phase during post-Gadolinium imaging. Local recurrence can be differentiated from postoperative changes by visualizing features such as invasion of fat between mesenteric vessels, encasement of vessels and adjacent bowel obstruction. Doubts regarding recurrence versus benign postoperative change can be clarified with a repeat follow-up scan. If the mass increases in size then it should be considered a recurrence; in contrast, if the area decreases or remains stable then a benign postoperative change may be considered [77].

Radiologic findings alone may not always be successful in differentiating postoperative biliary strictures from malignant stricture. However, on MRCP and endoscopic retrograde

cholangiopancreatography, certain features are known to favor malignancy: hyperenhancement >12 mm in length, >3 mm wall thickness, asymmetric narrowing of bile ducts and irregular margins. FDG-PET may be helpful in indeterminate cases [77]. Of note, the accuracy of PET varies based on iCCA morphologic subtype, with greater sensitivity for mass-forming iCCA versus intraductal growth subtype (85 vs 18%, respectively) [94]. Several studies have shown that sensitivity of PET-CT in detecting occult distant metastasis is higher than sensitivity of MRI and CT alone [95,96]. Gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid can provide positive T1-weighted intrabiliary contrast imaging during biliary excretion phase [97] and thus be helpful in further characterization of the stricture as benign or malignant. DWI can also provide aid in this differentiation [98].

• Common sites of recurrence

Recurrence is common following curative resection of iCCA as determined by recurrence rates of 60% at median follow-up of 21 months [88] and 80% at 5 years [76]. Recurrence may occur at various sites with most common sites being liver, LNs and lung. Liver metastasis presents as multiple nodules that appear as hypodense on CT while hypointense or hyperintense on T1-W and T2-W MR, respectively. These may sometimes show peripheral rim enhancement. In a study by Tabrizian *et al.*, which had a 79% rate of recurrence at 5 years following resection, the liver was found to be the most common site (65%) [76]. In another study, among all recurrences, 64.5% patients developed recurrences in remnant liver and/or locoregional LNs [88]. LN metastasis should be considered on CT scan when the LN is more than 1 cm in short axis diameter and is gradually increasing in size or did not shrink in size on follow-up CT. Sometimes imaging features of LN metastasis overlap with reactive hyperplasia, with a sensitivity of 47–78% and specificity 65–95% in preoperative stage workup. Gil *et al.* reported that 35.5% of recurrences in their study were in the form of distant metastasis and the most common site was found to be lung [99].

• Emerging techniques for treatment response assessment

With advances in functional imaging such as perfusion CT/MRI and DWI, other means to assess tumor therapeutic response are emerging.

For example, diffusion weighted and dynamic contrast enhanced imaging may be useful for assessing early response in cholangiocarcinoma treated with TACE (Figures 1 & 2). Halappa *et al.* in a study on volumetric changes ADC demonstrated among cholangiocarcinoma tumors treated with TACE that an increase in ADC was associated with favorable response to therapy and improved survival [100]. Tissue perfusion parameters such as blood flow, blood volume, mean transit time and tissue permeability that serve as physiological markers of tumor angiogenesis may provide quantitative assessment before and after antiangiogenic therapy [101,102]. With more advanced research in molecular imaging we can expect radiolabeled imaging agents like VCAM – 1 to become clinically useful to help measure angiogenesis and treatment response [103].

• Tumor markers

Previous studies have shown that CA 19-9 expression is also prevalent in iCCA [104]. According to a study by Yoo *et al.*, a higher incidence of recurrence (81%) was seen in association with high postoperative CA 19-9 levels compared with patients who had a normalized postoperative levels (53%). This study suggested that patients with high postoperative CA 19-9 levels could be considered for adjuvant chemotherapy and irradiation even without LN metastasis or positive resection margin status. This study also showed that a considerable number of iCCA patients with normal preoperative CA 19-9 have normal CA 19-9 levels after recurrence suggesting that patients with normal preoperative CA 19-9 levels should be followed closely with other tumor marker tests as well as radiologic studies [105].

• Management of recurrence

Studies have shown that patients who underwent R1 resection had a survival similar to patients who were treated with palliative therapy (5 vs 7 months) and that local recurrence is a common problem with R1 resection [106,107]. Even after R0 resection, many studies have reported recurrence rates of more than 50% and therefore other treatment options such as radiation and systemic chemotherapy should be considered along with resection [6,108–113].

According to National Comprehensive Cancer Network recommendations, patients who undergo an R0 resection should be observed while some type of adjuvant therapy is generally recommended for patients who had

an R1 or R2 resection. However, a study by Gil *et al.* reported that recurrence was as high as 60.8% patients even after complete R0 resection [88], suggesting that adjuvant treatment may be considered even in this setting. Among the recurrences, locoregional metastases were present in the hypothetical radiotherapy field in less than 20% patients. Hence, these authors suggested that postoperative radiotherapy might be a useful adjuvant therapy by sterilizing the field and lowering the recurrence rates, especially for tumors more than 5 cm undergoing R0 resection.

Limited data exists on the treatment of recurrence after primary resection of iCCA [33,72,114–117]. In recent years emerging modalities like RFA, TACE and TARE have found to be effective and safe in the treatment of recurrent iCCA [64,118–120]. In one study involving 20 patients, Kim *et al.* reported a median OS of 27.4 months in the treatment of recurrent iCCA with RFA after curative resection [111]. In another study, Sulpice *et al.* demonstrated a survival benefit for recurrent iCCA with the use of TARE with Y-90 [110]. While Saxena *et al.* [113] could show disease control in 72% of patients, Whitney *et al.* [121] reported tumor downstaging using Y90. Keifer *et al.* reported local tumor control using TACE [122].

The data on repeat resection of recurrent disease are scarce. However, there are a few series that have reported resection of recurrent iCCA in 8.5–30% of patients [6,72,99,108–110].

Prognosis

• Overall survival

Five-year OS rate of patients with iCCA undergoing surgical resection is dependent on several factors and usually varies between 11 and 40% [3,33,35,75,97,102,105,123–125]; although one study did report an OS of 63% among patients who had an R0 resection with node-negative disease (Table 2) [126]. Considering the high rates of disease recurrence following surgical resection (up to 50–60%), the disease-free survival (DFS) rate is even lower with reported median DFS as low as 14.5 months. In a multi-institutional study of 301 patients undergoing surgery for iCCA, the incidence of recurrence was 53.5% with a median DFS of 20.2 months and a 5-year DFS of 32.1% [8]. In study by Wang *et al.*, which had a median follow-up time of 39.3 months, the median time to recurrence was 13.8 months and the postoperative recurrence at 1, 3 and 5 years

Figure 1. Pre-transarterial chemoembolization MRI images. Large right hepatic lobe lesion proven on pathology to be cholangiocarcinoma appearing as hyperintense lesion on T2-weighted imaging (A) and hypointense on T1-weighted imaging (B). Arterial (C), venous (D) and delayed (E) phase images on post-Gadolinium imaging shows progressive central enhancement of the lesion consistent with the desmoplastic nature of cholangiocarcinoma. Diffusion-weighted imaging (F) shows restricted diffusion in the form of bright lesion as compared with surrounding normal liver parenchyma with apparent diffusion coefficient map (G) showing absolute apparent diffusion coefficient value. The liver also had presence of multiple satellite nodules (arrows in [H]) near the dome, which is an indicator of poor prognosis.

were 48.9, 62.5 and 67.3%, respectively [75]. Determining factors associated with disease recurrence and survival of the iCCA patients after surgical resection plays a critical role in

accurately identifying patients who will benefit from major surgical resections, stratifying them for adjuvant therapies or clinical trials, and guiding surgeon–patient discussions in

Figure 2. Post-transarterial chemoembolization MRI images. Patient underwent right lobe transarterial chemoembolization (TACE) and 1 month post-treatment scan shows large central areas of necrosis (A). However, there was no significant increase in apparent diffusion coefficient post-TACE (B), which is a predictor of poor response to TACE. The patient survival from the time of diagnosis was 2 months.

decision-making process.

• Available prognostic models & nomograms

In an effort to help physicians to improve understanding of the disease prognosis, disease-specific nomograms have been proposed for a number of malignancies including pancreatic adenocarcinoma [129], esophageal adenocarcinoma [130] and HCC [131]. The advantage of nomogram over traditional prognostic staging system is its ability in predicting survival for the individual patient rather than a patient population [114].

One of the earliest such prognostic systems created for iCCA patients was proposed by Fundan *et al.* [132]. The score was generated based on five preoperative prognostic factors (alkaline phosphatase, CA 19-9, number of tumors, tumor size and tumor boundary type) [28], that were derived from the data of 344 iCCA patients who underwent hepatic resections in a single institution. All five variables were transformed to binary categorical variables and 1 point was assigned for each factor in the final scheme. The overall score calculated for each patient was used to stratify patients into four risk groups according to the total score and the relative risk of death: low risk for score 0, intermediate risk for score of 1, high risk for score of 2–3 and extremely high risk for score of 4–5 with a 5-year survival rate of 90.1, 77.4, 54.0 and 16.4%, respectively, in each group. One of the major limitations of

this scoring system was the use of a very subjective measure to describe tumor boundary type (distinct, defined as a regular border, versus obscure with worse prognosis, described as an ill-defined border of the lesion), which limited the study due to substantial interobserver variability [133]. Furthermore, the role of LN metastasis, which has been established as a strong prognostic factor in many studies [2,9,11,22,33], was neglected in this scoring system. The major advantage of the scoring system was the use of preoperative factors over the surgical-pathologic factors in the prognostic tool, which enables providers to identify patients with poor prognosis before surgical resection [121].

In 2013, Wang *et al.* proposed a prognostic nomogram for iCCA patients based on the data of 367 patients who underwent partial hepatectomy [75]. This nomogram was composed of preoperative serum CEA and CA 19-9 levels, tumor size, as well as three surgical-pathologic binary variables (LN metastasis, lymphovascular invasion, direct invasion or local metastasis), and tumor number as an ordinal variable (solitary/1–2/ >3) [75]. The reported C-index of the nomogram for predicting survival was 0.74 (95% CI: 0.71–0.77), which was better than other iCCA staging and prognostic tools such as the 7th edition American Joint Committee on Cancer manual, Liver Cancer Study Group of Japan classification. In 2014, another nomogram was proposed from a largely Western multi-institutional cohort of 515 patients from 13 major hepatobiliary centers [33]. Six variables

(age, tumor size, tumor number, lymphovascular invasion, LN status and underlying cirrhosis) were used to predict patients' survival. In addition to fundamental differences in design and methodology (cohort multicentric versus retrospective single-institution) as well as the number of study participants (515 vs 376) between two nomograms, the two nomogram variables vary significantly as well [33,75]. While the Wang nomogram modeled the effect of tumor size as a linear coefficient, suggesting that survival worsened consistently with increasing tumor diameter, the nomogram by Hyder *et al.* suggested that there might be a threshold effect of size on

long-term outcome. Specifically, this threshold was revealed to be 7 cm for tumor diameter [33]. While the influence of diameter on the survival was linear below 7 cm, the risk of death did not seem to increase above the 7 cm threshold. These data were consistent with findings of several previous studies [11,123]. Also, while Wang *et al.* included preoperative serum CEA and CA 19-9 levels along with direct extrahepatic invasion in their nomogram [75], the nomogram by Hyder *et al.* lacked either of these factors and instead incorporated age (with nonlinear threshold effect on prognosis, similar to tumor size) and underlying cirrhosis [33,122]. Likewise, the

Table 2. Factors prognostic of overall survival of patients with intrahepatic cholangiocarcinoma treated with curative intent, as reported in the latest published series.

Study	Study period	Number of patients	Poor prognostic factors			Ref.
			<i>Not associated with overall survival</i>	<i>Univariate prognostic factors</i>	<i>Independent prognostic factors</i>	
De Jong <i>et al.</i>	1973–2010	449	Biliary invasion Direct invasion	Large tumor size Multiple tumors Vascular invasion Lymph node metastasis	Multiple tumors Vascular invasion Lymph node metastasis	[22]
Ribero <i>et al.</i>	1990–2008	434	Age Sex Serum CEA Tumor macroscopic type Perineural invasion Adjuvant treatment	High serum CA 19-9 Poor tumor differentiation Lymph node metastasis Vascular invasion Large tumor size Multiple tumors Radical resection	High serum CA 19-9 Lymph node metastasis Multiple tumors	[12]
Wang <i>et al.</i>	2002–2007	367	Age Sex Hepatitis B Vascular invasion Surgical margin (<1 versus ≥ 1) Presence of intact capsule Cirrhosis Microvascular invasion	Elevated laboratory values (Serum CEA, CA 19-9, total bilirubin, albumin, GGT) Blood transfusion Large tumor size Multiple tumors Lymph node metastasis Vascular invasion Direct invasion Local extrahepatic metastasis	High serum CEA and CA 19-9 Large tumor size Multiple tumors Lymph node metastasis Vascular invasion Direct invasion Local extrahepatic metastasis	[75]
Jiang <i>et al.</i>	1998–2008	344	Age Sex Hepatitis B Vascular invasion	Low serum albumin High serum ALP and serum CA 19-9 Multiple tumors Large tumor size (≥10 cm) Obscure tumor boundary	Multiple tumors Large tumor size Obscure tumor boundary High serum ALP and CA 19-9	[123]
Farges <i>et al.</i>	1998–2008	212	NR	Pathologic TNM staging Large tumor size Satellite nodules Vascular invasion Lymph node metastasis R1 resection	Pathologic TNM staging	[127]

ALP: Alkaline phosphatase; CA: Carbohydrate antigen; CEA: Carcinoembryonic antigen; CN: China; FR: France; GGT: Gamma glutamyl transferase; ICC: Intrahepatic cholangiocarcinoma; IT: Italy; MC: Multicenter; MN: Multinational; NR: Not reported; OS: Overall survival.
Reproduced with permission from © American Medical Association (2016) [128].

approach of the two nomograms to model common variables was different (e.g., N0/N1/Nx vs N0/N1 for LN involvement, solitary/multiple vs solitary/1–2/>3 for number of tumors and micro/macro/no vs yes/no for vascular invasion). In a subsequent study performed by the Memorial Sloan Kettering Cancer Center group, a comparison between the two nomograms to externally validate the different prognostic tools in iCCA patients did not reveal any statistically significant difference [133]. This study reported that despite the aforementioned discrepancies, both nomograms have significant value in predicting the prognosis of patients and accurately stratifying them according to their death risk level after surgical resection [133].

• Other prognostic factors

Macroscopically, iCCA has been divided into mass forming, periductular infiltrating and intraductal papillary types [134–136]. Intraductal papillary type have better survival rate than non intraductal papillary tumors with aggressive curative resection being associated with longer survival [63]. Molecular biomarkers serve as independent prognostic factors for predicting OS in postoperative patients with gradually increasing iCCA as they are linked mechanistically to the pathogenesis of the disease and serve as potential targets for CCA therapy.

Mucins

Mucins are a heterogeneous family of heavy O-glycosylated high molecular weight glycoproteins whose abnormal Apo protein expression and glycosylation states have been mutually related with epithelial cancer progression and prognosis.

MUC 1

MUC1 is a Transmembrane Apo protein, which is a statistically significant risk factor for predicting poor survival outcome after surgery in mass forming iCCA [137,138].

Ki – 67 index

In a multivariate analysis Ki-67 has been demonstrated to be a marker of cell proliferation activity, is a significant independent risk factor for poor prognosis in iCCA [139].

MUC 4

MUC 4 is a novel intramembrane ligand and modulator for ErbB2 receptor tyrosine kinase pathway, which stimulates growth factor signaling to

suppress tumor cell apoptosis and promote tumor cell progression [140,141]. Shibahara *et al.* [142] reported that patients with MUC 4 and ErbB2 double positive iCCA have a significantly worse outcome after surgical resection than those with MUC4 and ErbB2 double negative tumors.

MUC 5AC

The expression of MUC 5AC has been reported by Boonla *et al.* [131] not to be an independent prognostic factor for liver fluke associated iCCA but median survival has been reported to be worse in iCCA patients with high serum MUC 5AC than in those with low serum MUC 5AC [143].

MUC 6

Elevated expression of MUC 6 in iCCA also has independent correlation with poor prognosis after surgical resection [144].

• Matrix metalloproteinases

MMP-7

MMP-7 is expressed in malignant cholangiocytes [145], suggesting its intrinsic value as a hepatobiliary tumor cell marker. It is more frequently expressed in invasive nonpapillary CCA's than papillary CCA. Particularly, MMP-7 appears to be a specific prognostic factor for poor survival in CCA patients after surgery [78,146].

MMP-9

At least one reported study suggests that increased MMP-9 immunoreactivity is correlated with poor survival and LN metastasis in surgically resected cases of iCCA with LN metastasis recurrence being more common in MMP-9 positive tumors than MMP-9 negative tumors.

• CCN proteins

CTGF

Gardini *et al.* [147] showed that patients with iCCA expressing increased levels of CTGF had a better prognosis with less chance of tumor recurrence. However, identification of specific mechanisms and pathways relating CTGF as a potential prognostic biomarker for iCCA has not yet been done.

WISP 1

A splice variant of Wnt – inducible secreted protein 1 was shown by Tanaka *et al.* [148] to be overexpressed in 49% cases of human iCCA compared with adjacent uninvolved liver tissue and was significantly associated with lymphatic

and perineural invasion as well as with poor clinical prognosis and reduced survival.

Conclusion

iCCA is a tumor that is increasing in incidence and is associated with a high case fatality. Even in the setting of resectable disease, recurrence is common among patients undergoing surgical resection. Various prognostic markers and nomograms can help stratify patients with regards to risk of recurrence, as well as OS. Monitoring outcomes among patients with iCCA is critical and typically involves the use of cross-sectional imaging with either CT or MRI. To date, systemic therapeutic options for iCCA have had limited efficacy and future studies will need to identify more effective agents to treat this disease.

Future perspective

Despite all recent progresses in diagnosis and management of patients, iCCA still is considered a fatal tumor with low OS rate, even after curative resection. Some of the potential areas of future evolution (direction for future studies) that might help to better understand the pathogenesis of the tumor and improve the prognosis of iCCA patients are as follows:

- Investigating the reasons of current global rise in incidence and mortality of the tumor;
- Further genomic analysis with identification of new tumor biomarkers to help in early detection of the tumor/ tumor recurrence and direct the therapy;
- Exploring new prognostic biomarkers;
- Standardizing patient selection criteria as well as adjuvant/neoadjuvant therapy with liver transplant as definite treatment;
- Randomized clinical trials to establish first-line locoregional treatment options;
- Randomized clinical trials to establish systemic chemotherapy as standard of care in patients with inoperable tumors.

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