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Intrahepatic Cholangiocarcinoma: expert consensus statement

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Abstract

An American Hepato-Pancreato-Biliary Association (AHPBA)-sponsored consensus meeting of expert panellists met on 15 January 2014 to review current evidence on the management of intrahepatic cholangiocarcinoma (ICC) in order to establish practice guidelines and to agree on consensus statements. The treatment of ICC requires a coordinated, multidisciplinary approach to optimize survival. Biopsy is not necessary if the surgeon suspects ICC and is planning curative resection, although biopsy should be obtained before systemic or locoregional therapies are initiated. Assessment of resectability is best accomplished using cross-sectional imaging [computed tomography (CT) or magnetic resonance imaging (MRI)], but the role of positron emission tomography (PET) is unclear. Resectability in ICC is defined by the ability to completely remove the disease while leaving an adequate liver remnant. Extrahepatic disease, multiple bilobar or multicentric tumours, and lymph node metastases beyond the primary echelon are contraindications to resection. Regional lymphadenectomy should be considered a standard part of surgical therapy. In patients with high-risk features, the routine use of diagnostic laparoscopy is recommended. The preoperative diagnosis of combined hepatocellular carcinoma and cholangiocarcinoma (cHCC–CC) by imaging studies is extremely difficult. Surgical resection remains the mainstay of treatment, but survival is worse than in HCC alone. There are no adequately powered, randomized Phase III trials that can provide definitive recommendations for adjuvant therapy for ICC. Patients with high-risk features (lymphovascular invasion, multicentricity or satellitosis, large tumours) should be encouraged to enrol in clinical trials and to consider adjuvant therapy. Cisplatin plus gemcitabine represents the standard-of-care, front-line systemic therapy for metastatic ICC. Genomic analyses of biliary cancers support the development of targeted therapeutic interventions.

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Diagnosis and staging of intrahepatic cholangiocarcinoma

Clinical presentation

The clinical presentation of intrahepatic cholangiocarcinoma (ICC) is often not specific and patients with early-stage disease are usually asymptomatic. Patients may present with a wide array of symptoms that include weight loss, malaise, abdominal discomfort, hepatomegaly or a palpable abdominal mass in more advanced stages.[1] Biliary tract obstruction is relatively infrequent among patients with ICC.

Pathologic features

Whereas the clinical suspicion of ICC can be based on a combination of clinical presentation, laboratory analyses and radiologic evaluation, pathologic evidence is required for a definitive diagnosis. Although tissue biopsy is needed to confirm a histo-

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logic diagnosis, it is not routinely recommended or necessary in all patients in whom surgery is planned. In fact, liver biopsy is not routinely recommended or necessary for the surgeon to proceed with resection; however, pathologic diagnosis is necessary before systemic chemotherapy or radiation therapy can be started. Although a liver biopsy can help to establish a diagnosis, a 'negative' biopsy does not exclude ICC given the potential for sampling error. When a biopsy is performed, the most common histologic finding is adenocarcinoma with some associated fibrous stroma. The histologic appearance of ICC can be comparable with that of metastatic adenocarcinoma arising from other tumours of gastrointestinal or pancreatic origin. Most often, the differentiation of ICC from metastatic adenocarcinoma requires further immunohistochemical evaluation [e.g. negative: lung (TTF1), colon (CDX2), pancreas (DPC4); positive: biliary epithelium (AE1/AE3; CK7+ and CK 20)]. Differentiation between ICC and mixed hepatocellular tumours may require further evaluation of specific markers of hepatocellular or progenitor cell features (e.g. Hep-Par-1, GPC3, HSP70, EpCAM, etc.), although this distinction is difficult on biopsy specimens.[2] Plasma serum markers for ICC tend to have high specificity, but low sensitivity. For example, carbohydrate antigen (CA) 19-9 is elevated in only about 50% of ICC cases, whereas carcinoembryonic antigen (CEA) is elevated in 15–20% of cases.[1–3] As such, these markers are not sufficiently sensitive to definitively rule out ICC when they are within normal limits.

Extent of preoperative evaluation

When a biopsy reveals unspecified adenocarcinoma and the lesion is radiographically indeterminate of a primary ICC, as opposed to metastatic disease, the diagnostic work-up should include a search for the potential primary tumour. This evaluation may include cross-sectional imaging of the chest, abdomen and pelvis, and colonoscopy and upper endoscopy should be strongly considered to rule out a primary gastrointestinal tumour. In the setting of portal or coeliac adenopathy, an endoscopic ultrasound (EUS) with nodal sampling may also be helpful to define whether disease exists in the nodal basins.[4,5] A mammogram should also be performed in women, as well as appropriate gynaecologic evaluation.

By contrast, when biopsy (with immunohistochemical staining) and imaging strongly support the diagnosis of ICC, the additional work-up for a primary tumour described above may not be necessary as it is likely to yield very little information and obtaining these tests prolongs the time until definitive treatment can be completed.

Imaging characteristics of ICC

On ultrasonography, ICC typically appears as a hypoechoic mass and may be associated with peripheral ductal dilatation, although these features are not specific. Hyperenhancement on contrast-enhanced ultrasound can identify tumours with an increased density of cancer cells, but lacks specificity for ICC.[6] Intrahepatic cholangiocarcinoma may be incidentally detected by cross-sectional imaging performed for other reasons. On computed tomography (CT), the typical appearance is that of a hypodense hepatic mass with irregular margins in the unenhanced phase, peripheral rim enhancement in the arterial phase, and progressive hyperattentuation on venous and delayed phases.[7] Computed tomography can show the presence of capsular retraction indicating hepatic atrophy. Intrahepatic cholangiocarcinoma is most often characterized by a progressive contrast uptake from the arterial to the venous phase, with increased uptake in the delayed phase. This finding may reflect fibrosis that is slow to enhance but retains the intravenous contrast agent. On magnetic resonance imaging (MRI), ICC typically appears hypointense on T1-weighted and hyperintense on T2-weighted images; T2-weighted images may also show central hypointensity corresponding to areas of fibrosis.[8] Dynamic images show peripheral enhancement in the arterial phase followed by progressive and concentric filling in of the tumour with contrast material. Pooling of contrast on delayed images is indicative of fibrosis and suggestive of ICC in the right clinical setting.[9] Magnetic resonance imaging with cholangiopancreatography (MRI/MRCP) can be helpful in visualizing the ductal system and vascular structures and thereby determining the anatomic extent of tumour.

Up to 80–90% of ICCs will be avid on fluorodeoxyglucose positron emission tomography (FDG-PET). Although PET can detect mass-forming ICCs with relatively high sensitivity, it is less useful for infiltrating ICC tumours. The clinical utility of PET-CT for diagnosis of ICC when CT or MRI has already been performed is controversial. In the absence of suspicious disease outside the liver on CT or MRI, some investigators have questioned the additional utility of PET.[10,11] Some small studies have, however, suggested that the use of FDG-PET may result in the identification of occult metastatic disease in up to 20–30% of patients and may even help to rule out an occult primary tumour.[10,12]

Staging

Traditionally, until the publication of the current 7th edition of the American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC) staging manual, there was no distinct staging system for ICC. Rather, ICC was staged according to the criteria derived from patients with hepatocellular cancer (HCC). Given the epidemiologic and biologic differences between ICC and HCC, there has been increasing realization of the importance of establishing a distinct staging system for ICC. The 7th edition of the AJCC/UICC staging manual largely reflects many of the proposals included in previous publications. Tumour size is no longer a prognostic factor; rather, T-classification is based on number of lesions, vascular invasion, intrahepatic metastasis and invasion of adjacent structures. Specifically, T1 tumours are solitary without vascular invasion; T2 disease includes multiple tumours (e.g.

multifocal disease, satellitosis, intrahepatic metastasis), as well as tumours associated with any type of vascular invasion (e.g. microvascular or major vascular invasion); T3 tumours directly invade adjacent structures, and T4 disease includes tumours with any periductal infiltrating component (Fig. 1). As with most other solid liver/biliary/gastrointestinal malignancies, AJCC/UICC staging also includes both an 'N' and an 'M' subclassification. Regional lymph node (LN) metastases in the hilar, periduodenal and peripancreatic nodes are considered N1 disease, whereas distant disease is considered M1 disease.[13]

Although the 7th edition of the AJCC/UICC manual is still relatively new, the validity of the staging system has been independently validated.[14] The 7th edition of the AJCC/UICC staging system for ICC was noted to be more discriminating in predicting survival than other staging systems.[15] Furthermore, patients were equally distributed among the AJCC/UICC 7th edition stages, which was not the case for the other staging systems studied. There are, however, undoubtedly limitations to the current 7th edition staging system for ICC. For example, multiple tumours are classified as representing stage T2b. From a clinical standpoint, it is difficult to distinguish among patients with 'multiple' tumours who have multifocal disease and those with an index lesion and intrahepatic metastases or satellite lesions. In addition, the impact of size on prognosis may be more nuanced and have a non-linear threshold effect. In a recent study, the effect of tumour size on risk for death was linear until the tumour reached a diameter of approximately 7 cm, after which the risk for death associated with further incremental increase in size plateaued.[16] Finally, the classification of T4 disease as any tumour with periductal infiltration requires further validation in future studies that specifically examine the impact of this prognostic factor.

Consensus statements

- Tumour markers are insufficient to make a diagnosis or rule out ICC.
- Biopsy is not necessary if the surgeon suspects ICC and is planning curative resection. Biopsy should be obtained before systemic or locoregional therapies are initiated in order to confirm the diagnosis in the setting of unresectable disease. When biopsy is obtained, immunostains are required to differentiate ICC from other possible metastatic lesions, as well as to differentiate ICC from mixed hepatocellular tumours.
- In the setting of a liver mass with a biopsy showing adenocarcinoma, an occult primary tumour should be ruled out in most instances, unless immunohistochemical staining and imaging are clearly consistent with ICC.
- Assessment of resectability and/or intra- and extrahepatic metastatic disease, as well as venous and arterial invasion, is best accomplished using radiographic studies such as CT and/or MRI.
- In view of the limited data, the role of PET for staging ICC is unclear and thus PET should be used selectively.
- The 7th edition of the AJCC/UICC ICC staging schema is the preferred staging system for ICC.

Surgical treatment of ICC

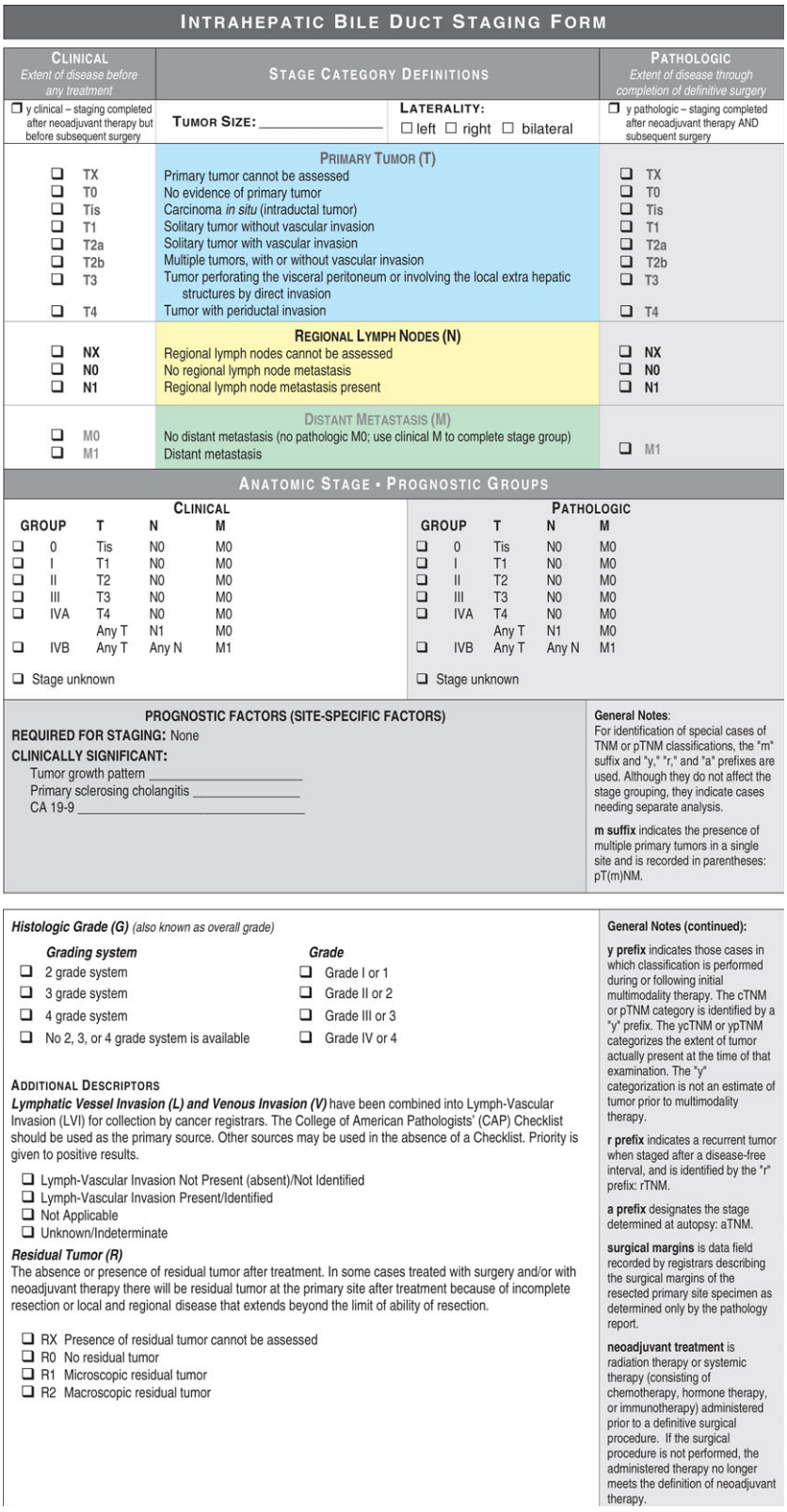
Many locoregional treatment modalities are available for patients with ICC. Unfortunately, most modalities, including ablation and hepatic intra-arterial therapies, have marginal therapeutic roles as a result of inherent limitations and/or the lack of a durable tumour response.[1] Therefore, surgical resection, as the only potentially curative treatment, remains the mainstay of therapy for patients with resectable disease.

Definition of resectability

Potentially resectable tumours include those that can be completely extirpated with negative histologic margins while a sufficient liver remnant is retained (i.e. a minimum of two contiguous segments with adequate perfusion, and venous and biliary drainage).[17–19] The presence of extrahepatic disease, including the involvement of LNs beyond the regional basin[13] (i.e. N2 nodes such as the coeliac and the para-aortic nodes), is a contraindication to resection.

Similarly, in patients with bilateral multifocal or multicentric disease, resection should be avoided. In fact, several studies have shown that multiplicity of tumours, a feature reported in up to 44% of patients,[3,17,18,20,21] portends a shorter period of survival as reflected in the tumour–node–metastasis (TNM) staging (i.e. T2 tumour).[13] It is currently less well understood whether satellite nodules, synchronous multicentric tumours and bilateral intrahepatic metastases, all of which are usually classified into the broad category of 'multiple tumours', have different natural histories. Theoretically, the worst prognosis may be associated with bilateral multifocal disease[22] because it is likely to represent systemic haematogenous metastatic intrahepatic dissemination, although there are no data to address the prognostic relevance of true peritumoral satellite lesions versus multifocal disease. Based on this definition of resectability, even patients with advanced complex tumours that will require extensive resections and major vascular and biliary reconstruction should be considered as potential candidates for resection.[23,24] Negative-margin (R0) resection rates can approach 85% with an aggressive surgical approach that often involves a major or extended hepatectomy (in up to 70% of cases) or a concomitant bile duct or vascular resection (in up to 20% and 5% of cases, respectively).[17]

With proper patient selection, rates of 5-year survival following resection range from 30% to 40%.[17,23,25,26] Recently, a large multi-institution series of 301 patients demonstrated that more than half of the patients experienced recurrence after resection and, in most instances (61%), this was within the liver.[19] The optimal treatment of recurrent disease is unclear, as is the issue of whether these patients should be considered



INTRAHEPATIC BILE DUCT STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS	PATHOLOGIC *Extent of disease through completion of definitive surgery*
❒ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE: _____ LATERALITY: ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)	
❑ TX	Primary tumor cannot be assessed	❑ TX
❑ T0	No evidence of primary tumor	❑ T0
❑ Tis	Carcinoma *in situ* (intraductal tumor)	❑ Tis
❑ T1	Solitary tumor without vascular invasion	❑ T1
❑ T2a	Solitary tumor with vascular invasion	❑ T2a
❑ T2b	Multiple tumors, with or without vascular invasion	❑ T2b
❑ T3	Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion	❑ T3
❑ T4	Tumor with periductal invasion	❑ T4
	REGIONAL LYMPH NODES (N)	
❑ NX	Regional lymph nodes cannot be assessed	❑ NX
❑ N0	No regional lymph node metastasis	❑ N0
❑ N1	Regional lymph node metastasis present	❑ N1
	DISTANT METASTASIS (M)	
❑ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
❑ M1	Distant metastasis	❑ M1

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL

GROUP	T	N	M
❑ 0	Tis	N0	M0
❑ I	T1	N0	M0
❑ II	T2	N0	M0
❑ III	T3	N0	M0
❑ IVA	T4	N0	M0
	Any T	N1	M0
❑ IVB	Any T	Any N	M1

❑ Stage unknown

PATHOLOGIC

GROUP	T	N	M
❑ 0	Tis	N0	M0
❑ I	T1	N0	M0
❑ II	T2	N0	M0
❑ III	T3	N0	M0
❑ IVA	T4	N0	M0
	Any T	N1	M0
❑ IVB	Any T	Any N	M1

❑ Stage unknown

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: None

CLINICALLY SIGNIFICANT:

Tumor growth pattern _____
Primary sclerosing cholangitis _____
CA 19-9 _____

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

Histologic Grade (G) *(also known as overall grade)*

Grading system	*Grade*
❑ 2 grade system	❑ Grade I or 1
❑ 3 grade system	❑ Grade II or 2
❑ 4 grade system	❑ Grade III or 3
❑ No 2, 3, or 4 grade system is available	❑ Grade IV or 4

ADDITIONAL DESCRIPTORS

Lymphatic Vessel Invasion (L) and Venous Invasion (V) have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists' (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

❑ Lymph-Vascular Invasion Not Present (absent)/Not Identified
❑ Lymph-Vascular Invasion Present/Identified
❑ Not Applicable
❑ Unknown/Indeterminate

Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

❑ RX Presence of residual tumor cannot be assessed
❑ R0 No residual tumor
❑ R1 Microscopic residual tumor
❑ R2 Macroscopic residual tumor

General Notes (continued):

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

neoadjuvant treatment is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

Figure 1 American Joint Committee on Cancer 7th edition staging system for intrahepatic cholangiocarcinoma

for repeat liver resection. Few studies have evaluated the impact of repeat hepatectomy, but some have suggested a survival benefit for highly selected patients who are considered to be eligible for repeat resection.[20,27,28] There are no studies that compare systemic, regional or local treatment strategies with repeat resection. Clearly, further studies are necessary to elucidate the ideal treatment of liver-only recurrent disease, which is a common pattern in ICC.

Prognostic factors following resection

Longterm survival after surgery is dependent on several factors. The majority of studies have identified completeness of resection (R0), number of tumours (single versus multiple), presence of vascular invasion and LN metastases as the most important determinants of prognosis.[3,17,18,21,25,26,29] In particular, multiple reports have indicated the presence of LN metastases as the most important independent predictor of survival.[17,18,21,25,26,29] Attesting to the impact of nodal disease, margin status is not predictive of outcome in the setting of LN involvement.[3]

Role of lymphadenectomy

The role of routine lymphadenectomy is still controversial, especially in the West. Recent data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) registry show that only 55% of patients have pathologic evaluation of at least one regional LN,[18,25] despite the fact that LN metastasis is universally cited as a negative prognostic factor.[3,17,18,25] In addition, the incidence of nodal disease is high, with some studies showing LN metastasis in as many as 40% of patients.[3,17,18,25] Because of its prognostic relevance and high incidence, many authors have argued in favour of including this procedure as a standard approach in all patients undergoing hepatectomy for ICC, although prospective trials have not addressed this issue.[1,17,18,25] Longterm survival is rare but possible even in the setting of LN metastasis,[29,30] although admittedly these longterm survivors are likely to be patients with occult nodal disease rather than grossly positive regional nodes on cross-sectional imaging. In addition to the essential role of lymphadenectomy for accurate staging, which, in turn, may assist in decision making regarding adjuvant therapy, some authors have suggested a therapeutic benefit in decreasing locoregional recurrence.[30,31] Based on the existing data for ICC, and on more developed data for many other tumour types including breast and melanoma, it is possible that lymphadenectomy improves staging and prognosis, but the role of lymphadenectomy in decreasing locoregional recurrence remains unclear. Because of the poor outcome in patients with nodal disease, in whom median survival is 7–14 months,[18,32] the best initial treatment for patients with grossly positive porta hepatis LNs is systemic chemotherapy, followed by restaging to assure no progression of disease, prior to any contemplation of resection.

Technical issues regarding lymphadenectomy

The ideal lymphadenectomy should include all regional nodal stations. Clinical and pathologic data indicate that LNs of the hepatoduodenal ligament and the hepatic artery are the first to become involved in the metastatic process and should be removed in all patients.[13] For ICC originating in the right hemiliver, the retropancreatic LNs, which are still considered as first echelon nodes, may be involved;[13] as a consequence, their routine removal is recommended. Another direct lymphatic pathway is recognized as running from the left hemiliver to the stomach through the lesser omentum.[33] Therefore, in patients with ICC originating from the left hemiliver, the nodes around the cardiac portion of the stomach and along the lesser curvature have a higher likelihood of involvement and thus should also be removed for adequate lymphadenectomy.[13]

At present, there is no specific evidence for the minimum number of LNs required to facilitate accurate staging. Complicating this discussion, the number of nodes retrieved is likely to vary according to age, anatomy, and the thoroughness and method of pathologic examination of the specimen.[34]

Staging laparoscopy

The yield of staging laparoscopy in patients with ICC varies from 27% to 38%.[13,26,35] Two prospective studies[36,37] found staging laparoscopy precluded resection in 25–36% of patients as a result of findings of occult metastatic disease. Therefore, a substantial number of unresectable patients will benefit from staging laparoscopy, the costs of which are acceptable and which incurs only a moderate increase in operative time in patients with presumed resectable disease.[37] Thus, staging laparoscopy should be routinely utilized in high-risk patients (i.e. patients with multicentric disease, high CA 19-9, questionable vascular invasion or suspicion of peritoneal disease) because of the risk that occult metastatic disease will be discovered at the time of surgery. Use of laparoscopic ultrasonography may further increase the utility of staging laparoscopy because unresectability may reflect intrahepatic metastases or extensive vascular invasion that can only be assessed with ultrasound. Therefore, in selected high-risk patients, use of laparoscopic ultrasonography is also recommended.

Consensus statements

- Resectability for ICC is defined by the ability to completely remove the disease with curative intent (R0) while leaving an adequate liver remnant. Extrahepatic disease, multiple bilobar or multicentric tumours, and LN metastases beyond the primary echelon are formal contraindications to resection.
- Regional lymphadenectomy should be considered a standard part of surgical therapy for patients undergoing resection of ICC.
- For patients with high-risk features, the routine use of diagnostic laparoscopy with selective use of laparoscopic ultrasonography is recommended.

Combined hepatocellular carcinoma and cholangiocarcinoma

Combined hepatocellular carcinoma and cholangiocarcinoma (cHCC–CC) is a rare primary cancer in which dual differentiation toward hepatocytes and bile duct epithelia coexists in the same tumour or in the same liver. Combined HCC–CC was first described by Wells in 1903, and classified into three categories by Allen and Lisa in 1949.[38] It was further classified by Goodman *et al.* in 1985.[39]

Aetiology

The most common primary liver cancer is HCC, which accounts for more than 90% of all primary hepatic malignancies. The second most frequent is ICC, which accounts for 5–10% of cases. The incidence of cHCC–CC has been reported to range from 0.7% to 14.0% in clinical and autopsy cases.[39–42] Reports from Asian countries have shown that 60–70% of patients with cHCC–CC have hepatitis C or B virus and 54–73% have cirrhotic livers.[43,44] However, in a Western report, the incidence of hepatitis virus infection was 15% and no cirrhosis was found in 27 patients.[45] Because of the rarity of this tumour, there has been no large-scale investigation of the risk factors for development of cHCC–CC; however, conditions commonly found in patients with HCC or ICC, such as cirrhosis, hepatitis virus infection, alcoholic liver disease and metabolic syndrome, are common in cHCC–CC.

A recent SEER study evaluating incidence over three decades found no difference in the incidence of cHCC–CC over time. Overall, cHCC–CC accounted for 0.87% of all liver tumours.[46] Although there was no difference in incidence, there did appear to be an improvement in outcome over time.[46]

Pathology and classification of cHCC–CC

Allen and Lisa classified cHCC–CC into types based on its histologic features.[38] They proposed three types of cHCC–CC: in type A, HCC and CC are present at different sites within the same liver; in type B, HCC and CC are present at adjacent sites and mingle with continued growth, and in type C, HCC and CC are combined within the same tumour.

Goodman *et al.*[39] proposed a new classification involving three types: type I involves 'collision tumours' that contain two distinct or merging nodules with separate histologies of HCC and ICC; type II involves 'transitional tumours' that exhibit distinct HCC- and ICC-like areas, each of which also contain intermediate features and transition from one morphologic phenotype to another, and type III, in which 'fibrolamellar tumours' exhibit a combination of HCC and ICC differentiation throughout the tumour, with crypts and pseudocrypts of excretion mucus and without separate areas of one or the other. Clinically, type I and II tumours are more like HCC than ICC.

In a strict sense, true cHCC–CC are thought to be tumours corresponding to type C of Allen and Lisa[38] and type II of Goodman *et al.*,[39] in which the morphologies of HCC and CC, respectively, are distinct but are intermingled within the tumour.[40,41,43–45,47] The World Health Organization (WHO) classification describes cHCC–CC as a tumour containing unequivocal, intimately mixed elements of both HCC and CC. This tumour should be distinguished from separate HCC and CC arising in the same liver. Such tumours may be separated or intermixed ('collision tumour').[48]

Symptoms

The symptomatology of cHCC–CC is similar to that of HCC or ICC in that most patients will have no specific symptoms. In advanced stages, patients may experience abdominal pain, weight loss or general fatigue. Patients with tumours involving the hepatic hilum may present with obstructive jaundice, similarly to patients with hilar cholangiocarcinoma.

Diagnosis

Preoperative diagnosis of cHCC–CC can be made in only a minority of cases because of both the complex imaging features of the two entities and the rarity of this tumour.[49] The imaging characteristics of cHCC–CC include not only features typical of HCC, such as arterial enhancement, washout and pseudocapsule, but also features typical of ICC, such as an irregular tumour surface, peripheral arterial enhancement or late central enhancement.

The tumour markers, α-fetoprotein (AFP), protein induced by vitamin K absence or antagonists-II (PIVKA-II), CEA and CA 19-9, are useful in making the diagnosis of cHCC–CC. Discordance between tumour marker elevation and imaging morphology may be suggestive of cHCC–CC.[45] For instance, in a tumour with the imaging features of HCC, but with elevated serum CA 19-9, suspicion for cHCC–CC should be increased. Unfortunately, no studies have evaluated the sensitivity and specificity of tumour markers to assess tumour histology in patients with cHCC–CC.

Surgical treatment

Hepatic resection

Surgical resection remains the only curative option for patients with cHCC–CC. Resection of cHCC–CC involves hepatectomy, which is occasionally combined with resection of the extrahepatic bile duct and/or portal vein in order to achieve an R0 resection. Preoperative portal vein embolization is necessary in patients with a small future liver remnant (FLR) volume to increase the safety of major hepatectomy.

The role of lymphadenectomy is unclear. The incidence of nodal metastases varies and these data are limited based on the small patient numbers reported. Yin *et al.*[41] reported that the incidence of nodal metastasis in 103 patients with

cHCC–CC was 13.2%, which was higher than that in 6679 patients with HCC (2.1%) and lower than that in 386 patients with ICC (21.4%). In a series from Italy, the incidence of nodal metastasis was 44%, which was comparable with that in ICC (36%).[50] There are few data on the prognostic importance of nodal disease in patients with cHCC–CC. Because of the rarity of this tumour, there is no definitive evidence available to elucidate the role of nodal dissection, but it is likely that nodal staging will give additional prognostic information.

Liver transplantation

Combined HCC–CC is considered a relative contraindication to transplantation. A recent analysis of SEER data evaluated 3432 patients (3378 with HCC and 54 with cHCC–CC) submitted to liver resection or liver transplantation for hepatic tumours.[51] There was no difference in 3-year survival rates between cHCC–CC patients submitted to liver transplantation and those submitted to resection (48% and 46%, respectively; $P = 0.56$), although no multivariate analysis was performed to control for tumour stage or other prognostic factors. Median survival following liver transplant for HCC was markedly improved (68 months) in comparison with that in patients with cHCC–CC (36 months), and this difference was sustained when other factors including stage and tumour size were controlled [hazard ratio (HR) for death in cHCC–CC patients compared with HCC patients: 2.5, 95% confidence interval (CI) 1.2–5.1; $P = 0.01$]. Because of the scarcity of donor organs, and worse outcomes following transplantation, cHCC–CC should remain a contraindication to transplant. Improvements in the ability to accurately preoperatively diagnose cHCC–CC, as opposed to HCC, are necessary in order to direct patients to resection.

Comparison of prognoses after hepatectomy for cHCC–CC, HCC and ICC

In several series, the survival of patients with cHCC–CC has been noted to be worse than that of patients with HCC or ICC.[40,47] However, in other reports, the survival of patients with cHCC–CC was intermediate in comparison with that in HCC and ICC patients.[4,6] In most reported series, however, the survival of cHCC–CC patients is worse than that of HCC patients (5-year survival rates: 8–36% versus 37–66%, respectively).[40,41,43,45]

Conclusions

Combined HCC–CC is a rare hepatic cancer in which dual differentiation toward hepatocytes and bile duct epithelia coexists in the same tumour. The preoperative diagnosis of cHCC–CC by imaging studies is difficult and the evaluation of tumour markers may be helpful in identifying components of HCC or ICC. Surgical resection remains the mainstay of treatment. The survival of patients with cHCC–CC after hepatectomy is worse than that in patients with HCC.

Consensus statements

- Combined HCC–CC is a rare primary cancer in which dual differentiation toward hepatocytes and bile duct epithelia coexists in the same tumour.
- The preoperative diagnosis of cHCC–CC by imaging studies is extremely difficult. Evaluation of tumour markers may help to identify the components of HCC or CC, but data to evaluate the sensitivity and specificity of tumour marker evaluation to assess tumour type are limited.
- Surgical resection remains the mainstay of definitive treatment.
- The survival of patients with cHCC–CC after hepatectomy is likely to be worse than that of patients with HCC, but survival data are limited by small series and thus definitive evidence on outcomes in HCC and ICC, respectively, are lacking.

Adjuvant and systemic therapy for ICC

Intrahepatic cholangiocarcinoma is an uncommon entity, albeit with a rising incidence, in part related to the hepatitis C epidemic.[18,52,53] A recent review of the SEER database demonstrated that there has been a 10-fold increase in cholangiocarcinoma-related mortality since 1973.[54] Treatment recommendations in both the adjuvant and metastatic settings are based on a paucity of Phase III trial data. Complicating this further, most of these datasets include patients with gallbladder disease, and extra- as well as intrahepatic cholangiocarcinoma, and, in some cases, patients with ampullary cancer.

Adjuvant therapy

Evaluating patterns of failure is instructive in providing insight regarding what might be the best approach to adjuvant therapy. For ICC, by contrast with hilar and distal cholangiocarcinoma, local/regional and intrahepatic failure are major issues, and systemic failure is a secondary consideration.[55,56] In fact, following resection, recurrence occurs in the liver in 50–60% of patients, in the peritoneum in about 20%, and in the portal LNs in 20–30%.[19,32,57] Thus, both locoregional modalities and systemic therapy are valid options in the adjuvant setting.

Regarding adjuvant radiation, most studies to date are limited in design, there have been no adequately powered prospective randomized trials, and much of the insight derives from single-institution prospective series.[58] Most studies evaluating radiation utilized external beam radiation with or without brachytherapy. Studies have typically included a mix of patients, among whom most patients have undergone an R0 or R1 (positive margin) resection, but some have had an R2 resection. Additionally, trials have included both cholangiocarcinoma as well as gallbladder cancer patients. One small study evaluated surgery versus surgery in combination with external beam radiation therapy.[59] Three-year survival rates of 10%

(surgery) and 31% (chemoradiation) ($P = 0.0005$), respectively, were observed in these two populations.[59] Unfortunately, 90% of patients in this series had a positive margin resection, which brings into question the involvement of the resection margin in these results. Demonstrating this point, a separate series evaluated a similar adjuvant therapy strategy in margin-negative patients and observed no difference in median overall survival (18.4 months and 20.0 months, respectively).[60] Thus, the overall role of adjuvant radiation and which specific patient populations it may benefit remain to be defined.

With regard to adjuvant systemic therapy, two randomized trials have been conducted but were limited by the inclusion of multiple tumour types, and thus were not adequately powered to detect differences in ICC patients alone. One study evaluated a regimen of surgery and 5-fluorouracil (5-FU)/mitomycin followed by oral 5-FU in comparison with surgery alone in patients with resected pancreas, bile duct, gallbladder and ampullary cancers.[61] In the 118 patients with bile duct cancer, 72 of whom underwent curative resection, there was no difference in overall survival between the groups (41% in the adjuvant therapy group and 28% in the surgery-only group; $P = 0.48$). More recently, the results of the European Study Group for Pancreatic Cancer (ESPAC)-3 periampullary trial were reported.[62] In a preplanned subset analysis, no differences in outcome were observed between the surgery-alone group and the adjuvant treatment arm in patients with bile duct cancer (96 patients, 22% of enrolees).[62]

A systematic review and meta-analysis of adjuvant therapy involving over 6000 patients in 20 studies, many of which were retrospective, was recently published.[63] There was a non-statistically significant beneficial trend for adjuvant therapy over observation (HR 0.75, 95% CI 0.55–1.01; $P = 0.06$). Patients who received systemic therapy with or without the addition of radiation therapy had greater benefit than those who received radiation alone [odds ratio (OR) 0.39, 95% CI 0.39–0.98; $P = 0.02$]. The analyses also supported adjuvant chemotherapy or chemoradiotherapy in positive-margin resection (R1) (OR 0.36, 95% CI 0.19–0.68; $P = 0.002$) and patients with LN metastasis (OR 0.49, 95% CI 0.3–0.8; $P = 0.004$).

Three ongoing or recently completed studies will define prospective data on the role of adjuvant therapy. The BILCAP study evaluated capecitabine compared with observation (NCT00363584) in 360 patients. The UNICANCER trial of 190 patients evaluated gemcitabine/oxaliplatin compared with observation (NCT01313377), and a Japanese study (BCAP) is evaluating gemcitabine compared with observation (NCT000000820). In addition, in North America, the Southwestern Oncology Group (SWOG) has recently completed a single-arm, non-randomized Phase II study of four cycles of adjuvant gemcitabine/capecitabine followed by capecitabine-based external beam radiation in resected extrahepatic cholangiocarcinoma and gallbladder patients (NCT00789958). These latter data may provide a contemporary reference arm for future randomized controlled trials.

To summarize the existing adjuvant therapy data, there are no definitive data to provide recommendations regarding the optimal adjuvant therapy for patients with ICC. Current data suggest that for patients with margin-positive and node-positive resected cholangiocarcinoma, systemic therapy with gemcitabine or 5-FU, or 5-FU-based radiation should be considered. There are insufficient data to guide recommendations for node-negative and margin-negative patients. For all patients, when possible, enrolment in a clinical trial should be strongly encouraged.

Metastatic cholangiocarcinoma

Similar to the situation in the adjuvant setting, most trials in the context of advanced disease have typically included patients with not only intra- and extrahepatic cholangiocarcinomas but also gallbladder and ampullary cancers. Pooled analyses from nearly 3000 patients included in 104 trials from 1985 to 2006 suggest that combination cytotoxic therapy has a role and that gemcitabine and a platinum-based therapy is a reasonable option.[64] The Advanced Biliary Cancers (ABC)-02 randomized Phase II–III trial provided concrete support for gemcitabine and cisplatin, demonstrating improvements for the combination compared with gemcitabine alone both in overall survival (11.7 months versus 8.1 months; $P < 0.001$) and in progression-free survival (8.0 months versus 5 months; $P < 0.001$).[65] This trial included patients with intra- and extrahepatic cholangiocarcinoma, gallbladder and ampullary cancer, and patients with both locally advanced and metastatic disease. In the subset of bile duct cancer patients, benefits similar to the results of the overall trial were observed. These results have led to the use of gemcitabine and cisplatin as the standard of care in patients with metastatic ICC. Multiple other cytotoxic options have been studied, mostly in Phase II settings, suggesting that other gemcitabine-based combinations and 5-FU-based combinations also have value, although none have been compared with cisplatin and gemcitabine.[66]

The genomics and molecular pathology of biliary cancers have been increasingly defined and a broad spectrum of mutations in tumour suppressor genes and oncogenes identified, particularly in terms of the recent identification of *IDH1* mutations in ICC. These observations have provided the underpinnings of an evaluation of targeted therapy in this disease, with a particular focus on anti-angiogenic therapy and disruption of the epidermal growth factor receptor (EGFR) pathway.[67–70] A South Korean Phase III study of 268 patients evaluated the addition of erlotinib 100 mg daily to gemcitabine/oxaliplatin.[71] For the primary endpoint of progression-free survival, there was no statistically significant difference between the chemotherapy-alone arm (4.2 months for gem/ox versus 5.8 months for erlotinib/gem/ox; HR 0.80, 95% CI 0.51–1.03; $P = 0.087$). Patients with cholangiocarcinoma

achieved progression-free survival of 3.0 months with chemotherapy alone compared with 5.9 months with chemotherapy and erlotinib (HR 0.73, 95% CI 0.53–1.00; $P = 0.049$), suggesting that there may be value in adding erlotinib in advanced cholangiocarcinoma. A limited analysis of the *KRAS* genotype did not provide a correlation with outcome in the erlotinib-treated patients. An extensive series of Phase I–II studies are underway evaluating other anti-EGFR targeting agents with panitumumab, cetuximab and afatinib. Additional studies currently in progress examine the role of MEK, Her-2 inhibition and anti-angiogenic agents such as sorafenib and bevacizumab.

Other approaches to advanced cholangiocarcinoma include regional treatment strategies, such as hepatic arterial infusion (HAI) therapy and embolization therapies including both bland embolization and transarterial chemoembolization (TACE) with or without drug-eluting beads (DEBs), and yttrium-labelled selective internal radiation therapy (SIRT). In a variety of studies using TACE or DEB–TACE with various chemotherapeutic approaches, median survival has ranged from 9 months to 30 months, but with significant toxicity in more than 20% of patients.[72–76] Outcomes of SIRT have been evaluated in limited numbers of patients, and median survival has ranged from 9 months to 22 months.[77–79] Encouraging data have been observed in a single-institution Phase II trial of HAI of regional floxuridine and dexamethasone,[80] which showed a median survival of 29 months and a response rate of 47%. Further evaluation is underway to examine the combination of systemic therapy with HAI therapy (NCT01525069), as well as to conduct an early evaluation in the adjuvant setting of resected ICC. Clearly, a major limitation of the HAI approach is the limited availability of oncologists experienced with its use outside select institutions. Regional therapy remains an important treatment option for patients with liver-only unresectable ICC, but current recommendations are limited by a lack of prospective trials. Rigorous evaluation of these strategies in a clinical trial is essential.

To summarize, based on Phase III data, systemic therapy utilizing cisplatin and gemcitabine represents the standard of care for metastatic ICC. More intensive cytotoxic therapies (e.g. FOLFIRINOX) are under study, as are a variety of targeted agents, including anti-EGFR-based therapies. For select patients in whom disease is confined to the liver, regional treatment strategies are attractive options, but lack prospective comparative data. Thus, recommendations for the type of regional therapy should be based on institutional experience. Well-designed prospective randomized trials evaluating regional strategies, such as TACE, the use of DEBs, SIRT and others, are desperately needed. These trials should be designed to provide insight into the value of these therapies in comparison and in combination with systemic therapy, as well as to delineate the ideal sequencing of treatment modalities. Finally, future trials in the adjuvant and metastatic settings must take into account the origin of the underlying tumour, as well as its histology.

Consensus statements

Adjuvant therapy

- There are no adequately powered, prospective randomized Phase III trials that can provide definitive recommendations for adjuvant therapy.
- There is no known benefit to adjuvant therapy in margin-negative and node-negative ICC. Therefore, patients with high-risk features (lymphovascular invasion, multicentricity or satellitosis, large tumours) should be encouraged to enrol in clinical trials.
- For resected margin-positive or node-positive ICC, systemic therapy with either gemcitabine or 5-FU, or 5-FU-based radiation should be considered. In patients with high-risk features (satellitosis/multiple tumours, poor differentiation), adjuvant therapy should also be considered.
- Randomized trials in the adjuvant setting evaluating gemcitabine, capecitabine, and gemcitabine and oxaliplatin compared with observation will mature over the next few years.

Treatment of advanced ICC

- Cisplatin plus gemcitabine represents the standard-of-care, front-line systemic therapy for metastatic ICC, based on Phase III data, with an improvement in median survival of 3.6 months, compared with gemcitabine alone.
- Early data suggest a value for regional treatment of unresectable cholangiocarcinoma confined to the liver. Options include embolization, chemoembolization, SIRT therapy and HAI therapy, all of which can be considered as viable options, given the lack of prospective comparative trials. The choice of therapy is highly dependent on institutional experience.
- Genomic analyses of biliary cancers support the development of targeted therapeutic interventions.

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Conflicts of interest

None declared.

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