Editorial

Pushing the limits for the surgical treatment of intrahepatic cholangiocarcinoma

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Introduction

In February 2022, Kubo *et al.* and the Liver Cancer Study Group of Japan published a clinical practice guideline for the treatment of intrahepatic cholangiocarcinoma (iCCA) (1). Their guideline consists of a treatment algorithm for iCCA with five background statements, 16 clinical questions and one clinical topic discussion (1). The background statements highlight (I) the rising incidence of iCCA worldwide despite subtracting the perihilar cholangiocarcinoma (pCCA) cases which were reclassified in the International Classification of Diseases for Oncology (ICD-O) 3rd edition; (II) how Asian ethnicity might be an independent risk factor for iCCA; (III) the differences in the iCCA staging criteria, patient characteristics, and clinical practice between Japan and Western countries [i.e., re-inclusion of 5-cm cut-off as a criterion for T-stage in the Union for international cancer control (UICC) 8th edition]; (IV) the definition of different pre-cancerous lesions; (V) how to differentiate intrahepatic pseudotumors from iCCAs (1). The clinical questions, answered with their recommendation and strength of evidence are listed in *Table 1*. This guideline concludes with a clinical topic discussion, describing how to differentiate hilar cholangiocarcinoma from an iCCA involving the hepatic hilum using pathological techniques and information such as correct sectioning, location of stenosis, detecting the presence of biliary intraepithelial neoplasia and elastic fibers in the hilar region, and interpreting them with radiological features (1). We commend the authors for writing this up-to-date, evidence-based clinical guideline for the treatment of iCCA (1). Few discussion points arose from our point of view.

Incidence of iCCA

We agree that the true incidence of iCCA has always been in question, as pCCA has been lumped together into the iCCA category through all the ICD 9&10 and ICD-O editions (3). Researchers from the United Kingdom recently have shown this by conducting a chart review of patients diagnosed with iCCA using ICD-10 codes between 2015 to 2017, and reported that 92% of pCCAs were incorrectly coded as iCCAs, and only 43% of the iCCA diagnosis were true iCCAs (3). Even with the adoption of ICD-O-3rd edition, the misclassification risk remains as pCCA can be cross-referenced to either iCCA or extrahepatic CCA

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Table 1 Clinical guideline published from Kubo *et al.* and the Liver Cancer Study Group of Japan (1) compared with the NCCN guidelines (2)

Q#	Clinical question	Recommendation from Liver Cancer Study Group of Japan	Strength of evidence	NCCN Guidelines v. 3.2022 Biliary Trac Ca: intrahepatic cholangiocarcinoma
1	Is there an effective screening method?	No effective screening method has been established. However, patients with risk factors may need regular screening using liver function tests, tumor markers, and abdominal ultrasonography	Weak	None. May be detected incidentally as an isolated intrahepatic mass on imaging
2	What blood tests are used to detect iCCA	Persistent elevation of serum bilirubin and alkaline phosphatase can suggest the presence of malignant biliary stenosis (weak recommendation). CA19-9 and CEA are recommended as tumor markers for early detection and diagnosis of iCCA	Weak/Strong	CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis. Consider AFP
3	What imaging modalities are effective for diagnosing iCCA?	Abdominal US, CT, and MRI are effective imaging modalities for diagnosing iCCA	Strong	Multiphasic abdominal/pelvic CT/MRI with IV contrast
4	What testing modalities are useful for diagnosing the degree of tumor extension (T-stage)?	Contrast-enhanced CT and EOB-MRI can be used. If bile duct invasion is suspected, imaging modalities for examining the bile ducts may be useful	Strong	Contrast-enhanced MRI with MRCP is preferred for evaluating the extent of biliary tract involvement. Imaging with multiphasic CT or MRI with thin cuts, or multiphase CT or MRI of the liver and biliary tree should specifically address the anatomy of the biliary tree, hepatic arteries, and portal veins and their relationship to the tumor. Delayed phase imaging is preferred when the diagnosis of iCCA is suspected or confirmed
5	What imaging modalities are useful in detecting lymph node metastasis?	CT, MRI, and FDG-PET are useful for detecting LNM, although their diagnostic accuracy is not necessarily high	Strong	
6	What imaging modalities are useful for detecting distant metastasis?	CT is useful in detecting lung metastasis. If bone metastasis is suspected, bone scintigraphy or FDG-PET may be useful	Strong	Chest CT ± contrast. Diagnostic laparoscopy to rule out unresectable disseminated disease should be considered
7	In which patients should tumor biopsy be performed?	In unresectable cases, tumor biopsy should be considered when deemed necessary for the purposes of differential diagnosis and drug therapy selection	Strong	A preoperative biopsy is not always necessary before proceeding with a definitive, potentially curative resection. A suspicious mass on imaging in the proper clinical setting should be treated as malignant
8	What types of iCCA are indicated for surgical treatment in terms of tumor condition?	A solitary tumor with no LNM is the best indication for hepatectomy. There is no restriction on tumor size	Strong	In highly selected cases with limited multifocal disease resection can be considered. Gross lymph node metastases to the porta hepatis portend a poor prognosis and resection should only be considered in highly selected cases

Table 1 (*continued*)

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Q#	Clinical question	Recommendation from Liver Cancer Study Group of Japan	Strength of evidence	NCCN Guidelines v. 3.2022 Biliary Trac Ca: intrahepatic cholangiocarcinoma
9	What are safe and reasonable surgical techniques?	The extent of liver resection should be performed to achieve negative surgical margins and sufficient remaining liver function	Strong	Hepatic resection with negative margins is the goal of surgical therapy. While major resections are often necessary, wedge resections and segmental resections are all appropriate given that a negative margin can be achieved
10	Is there any significance to lymph node dissection?	The significance of LN dissection is currently unclear	None	A regional lymphadenectomy of the porta hepatis is carried out
11	What are the indications of percutaneous ablation therapy?	Percutaneous ablation therapy may be considered for patients with iCCA who are ineligible for surgical resection or chemotherapy, owing to deteriorated hepatic functional reserve or comorbidities	Weak	
12	What drug therapies are recommended for unresectable iCCA?	The recommended drug therapies for unresectable iCCA are gemcitabine + cisplatin + S-1, gemcitabine + cisplatin, and gemcitabine + S-1 combination therapies	Strong	Gemcitabine + cisplatin or durvalumab + gemcitabine + cisplatin (durvalumab + gemcitabine + cisplatin is also a recommended treatment option for patients who developed recurrent disease >6 months after surgery with curative intent and >6 months after completion of adjuvant therapy)
13	Is neoadjuvant chemotherapy recommended?	There is no evidence for a benefit of neoadjuvant chemotherapy	None	No preferred regimen. Decision needs to be individualized and in close consultation with surgical oncologist and multidisciplinary team. A period of 2 to 6 months with reassessment every 2 to 3 months is reasonable. There are limited clinical trial data to define a standard regimen or definitive benefit
14	Is adjuvant chemotherapy recommended?	Adjuvant chemotherapy may be considered because some regimens have demonstrated tolerability and suggested efficacy	Weak	Capecitabine. Adjuvant therapy up to 6 months
15	Is stereotactic radiotherapy recommended for unresectable iCCA?	Stereotactic radiotherapy may be considered for unresectable iCCA with tumor diameter ≤5 cm in the absence of metastasis	Weak	All tumors irrespective of the location may be amenable to EBRT (3D-CRT, IMRT, or SBRT)
16	Is particle radiotherapy recommended for unresectable iCCA?	Particle radiotherapy may be considered for unresectable iCCA without metastasis	Weak	See above

NCCN, National Comprehensive Cancer Network; iCCA, intrahepatic cholangiocarcinoma; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; IV, intravenous; EOB-MRI, gadoxetic acid-enhanced magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; FDG-PET, fluorodeoxyglucose-positron emission tomography; LNM, lymph node metastasis; LN, lymph node; EBRT, external beam radiation therapy; CRT, conformal radiation therapy; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

(eCCA) (3). However, a recent study used the Surveillance, Epidemiology, and End Results (SEER) national database to trend iCCA from 2001 to 2017 using both ICD-10 and ICD-O-3 codes and still demonstrated the increasing age-adjusted incidence of iCCAs by 148.8% (0.80 to 1.99) (4). The true incidence of iCCA remains to be revealed and will be more accurately measured with the implementation of topography and morphological diagnosis codes that clearly separates between iCCA, pCCA, and eCCA.

Tumor markers for iCCA

The authors of this guideline reported a "strong recommendation" to use carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) for early detection and diagnosis of iCCA (1). The National Comprehensive Cancer Network (NCCN) guidelines reports otherwise, how both CA19-9 and CEA should not be used to confirm diagnosis, but only as baseline tests (2). Traditional tumor markers like CA19-9 greatly lack specificity for iCCA in the screening of high-risk population, especially in the presence of primary sclerosing cholangitis and jaundice, and we question its diagnostic or screening use for iCCAs (5,6). We do agree, however, on its value as another tool to monitor treatment response and relapse post-surgical resection. Soon, circulating-tumor DNA (ctDNA) may become the tumor marker of choice, as the ctDNA level showed up to 89% sensitivity and 97% specificity to diagnose CCAs, outperforming both CA19-9 and CEA (7). Further research is on its way to determine the impact of liquid biopsy in this setting.

Diagnostic or staging laparoscopy

In this guideline written by Kubo *et al.*, the role of diagnostic laparoscopy was not discussed (1). Even though the evidence supporting routine use of diagnostic laparoscopy is not there, there are suggestions of its role in some circumstances (8). NCCN guidelines recommends "diagnostic laparoscopy to rule out unresectable disseminated disease should be considered" (2). Western clinical guidelines also recommend staging laparoscopy for high-risk iCCA patients (high CA19-9 or major vascular invasion) (6). In our opinion, when there is a suspicion of peritoneal disease or presence of multifocal disease, staging laparoscopy prior to resection may play a role. Furthermore, as laparoscopic liver resections are becoming more prevalent, with studies suggesting similar outcomes to those of open approach in well-selected cases, staging laparoscopy will become easier to implement (8).

Minimally invasive resections for iCCA

While the role of minimally invasive surgery (MIS) was not discussed, in carefully selected cases, MIS hepatectomy maybe appropriate for iCCAs (8). The outcomes depends on the centers and their expertise as it requires a learning curve, but MIS hepatectomy has a potential to reduce both hospital length of stay and postoperative complications in resecting less extensive iCCAs (i.e., smaller tumors with no biliary/vascular invasions or reconstructions) (8). The long-term oncological outcomes of MIS hepatectomy will need to be better characterized with well-designed prospective randomized clinical trials.

Regional lymphadenectomy

The routine use of portal lymphadenectomy when resecting an iCCA is still a matter of debate. Kubo *et al.* made no recommendation regarding routine lymph node (LN) dissection, when on the contrary, both the NCCN and UICC guidelines recommend regional LN dissection (6 or more node resection) of the porta hepatis (1,2). It is well-established that LN metastasis (LNM) is associated with poor overall survival (OS) in patients who undergo resection for iCCAs, and that both the count and location of LNM matters as they incrementally affect the OS (9). We side with Zhang *et al.*, that while it is still unclear if the LN dissection itself improves survival, the detection of LNM is needed to identify high-risk patients who might benefit from adjuvant therapies or better surveillance strategies (9). This is supported by the most recent study from Sposito *et al.* showing survival benefits in patients who underwent adequate lymphadenectomies with clinical N0 stage but found to have positive nodes on final pathology (10). For centers that do not routinely offer adjuvant chemotherapy to patients who had curative-intent iCCA resections, adequate lymphadenectomies might be even more necessary to guide treatment decisions. In support of the UICC and NCCN recommendation, we believe the harvesting of at least 6 LN during iCCA resection should be routinely endorsed given that the increased morbidity should be low in experienced hands.

Multifocal disease

In general, multifocal iCCA is considered a formal

contraindication for surgery, especially if bi-lobar; and therefore, we agree with the authors of this guideline that multifocal iCCA treatment should be carefully selected based on multidisciplinary team discussions (1). The evidence is clear that resecting multiple tumors have worse prognosis compared to solitary tumors for iCCAs (11). In comparing resection to non-surgical therapies, a recent observational study (n=580) used the SEER database to compare liver resection *vs.* non-resection treatments for patients who had multifocal iCCA but no distant metastasis, and showed that after propensity-score matching, the resection group (26% had disease in multiple lobes) had a better 5-year OS (14% *vs.* 0%, P<0.001) compared to the non-resection group (12). However, in another multicenter retrospective study (n=102), patients who received associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure were propensity-score matched with those who got chemotherapy-only for locally advanced iCCA, and in the subgroup analysis for multifocal iCCAs, no survival difference was found (13). Furthermore, resection showed no benefit in patients with multifocal iCCA compared to intra-arterial therapies alone in a single-center retrospective study (n=116), yet to note that 47.4% of these resection patients had bi-lobar disease (14). Although the overall level of evidence is suboptimal, we believe that the surgical resection (and potentially liver transplantation) should continue to be explored, especially in uni-lobar multifocal iCCA that could be down-staged using neoadjuvant therapies (15).

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy has three theoretical benefits: (I) down-stage the tumor to make it resectable and/or increase R0 resection rate; (II) treat micro-metastatic disease that might be the culprit to early cancer recurrence; (III) test tumor biology before surgery to select out aggressive disease that might not benefit from an operation (8). We agree with the Kubo *et al.* of this guideline that level I evidence is required for the role of neoadjuvant chemotherapy in "resectable" cases and not only in downstaging initially unresectable cases. Several phase II clinical trials are underway for neoadjuvant chemotherapy (i.e., Gemcitabine, Cisplatin, and Nab-Paclitaxel, NCT03579771), targeted therapies (Pemigatinib for FGFR2 fusions, NCT05565794), and combined (including immunotherapy) therapies (Gemcitabine + Oxaliplatin + Lenvatinib + Toripalimab, NCT04506281) for resectable, high-risk iCCAs and the results are highly awaited (16). Indeed, several centers worldwide are utilizing systemic therapy as the initial treatment option in marginally resectable cases (16).

Conclusions

The guideline written by Kubo *et al.* and the Liver Cancer Study Group of Japan is very comprehensive and well-tailored to their patient population in Japan. It highlights very well the practice differences compared to the western hemisphere, which leaves room for future research and collaboration. Future studies incorporating novel tumor biomarkers, neoadjuvant/adjuvant therapies, liver transplantation, and minimally invasive techniques should incorporate both the East and the West for a unified result.

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