Editorial Commentary

The Japanese Clinical Practice Guidelines for intrahepatic cholangiocarcinoma: a comparison with Western guidelines

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The Liver Cancer Study Group of Japan (LCSGJ) recently published the first version of the clinical practice guidelines for intrahepatic cholangiocarcinoma (iCCA) (1). The study group followed the GRADE methodology for evidence-based medicine. Japan is a world leader in the treatment of cholangiocarcinoma, with Japanese medical centers realizing superior results compared to other developed countries and many landmark articles originating from these centers. While there are differences between the Japanese iCCA population and patients in other countries, these guidelines contain important lessons for healthcare providers across the world.

The guidelines cover a treatment algorithm, 5 background statements, 16 clinical questions, and a clinical topic. The treatment algorithm is straight-forward; resection for patients with solitary node-negative tumors and systemic treatment for all other patients. Patients with limited multifocal or limited nodal disease could also be considered for resection. Patients with Child-Pugh C are ineligible for any treatment. The 16 clinical questions delve into the details of diagnosis and treatment and are discussed after the background statements.

Background statement 1 and 2 cover the rising incidence and risk factors for iCCA. Japan, like many Asian countries, is known to have a three-fold higher incidence of cholangiocarcinoma compared to Western countries. The mortality rate in Japan is 6 per 100,000 inhabitants (2). Geographical as well as genetic risk factors probably play a role in this difference. In East Asia, the most significant risk factor is posed by Clonorchis sinensis and Opisthorchis viverrini. Although C. sinensis has in the past been endemic in Japan, this is no longer the case (3). Other risk factors are shared by both Japanese and Western patients, including cirrhosis, hepatitis B and C, hepatolithiasis, choledochal cysts, and Caroli disease (4). The reasons for the vast difference in incidence between Japan and the west is not fully understood, as most patients do not present with any risk factors.

Background statement 3 concerns staging. Staging differences exist between the Japanese General Rules for the Clinical and Pathological Study of Primary Liver Cancer (Revised 6th edition) and the AJCC TNM Classification of Malignant tumors (8th edition). Both staging systems are based on the number of liver tumors (solitary *vs.* multiple), size of the largest tumor, the presence of vascular invasion, nodal disease, and distant metastatic disease. The Japanese staging considers biliary invasion as an additional risk factor. These patients present with painless jaundice and require

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challenging biliary drainage prior to any treatment. The size cut-off in the Japanese system is 2 versus 5 cm in the AJCC system. Tumors of less than 2 cm, however, involved only 6% of Japanese patients undergoing a resection of iCCA. Moreover, iCCA of less than 2 cm is typically diagnosed only at pathological examination after resection or transplantation. These small lesions are asymptomatic and detected with surveillance of patients with cirrhosis and treated as hepatocellular carcinoma. Patients with multiple liver tumors can be classified as stage II in both staging systems. A recent large study, however, found that survival of iCCA patients with multiple liver tumors is so poor that it should be classified as M1 (5). This would be consistent with the recommendation of both Japanese and Western guidelines against resection in patients with multiple liver tumors. The LCSGJ staging appears to have little relevance for the proposed treatment algorithm that considers only distant metastases, lymph node metastases, and number of liver tumors.

In background statement 4, pre-malignant lesions are discussed focusing on IPNB and BilIN. Finally, background statement 5 discussed liver lesions that can masquerade as iCCA, such as IgG4-mediated cholangitis. The clinical topic at the end of the guideline could have been the 6th background statement. It discusses the difficulty of distinguishing perihilar cholangiocarcinoma (pCCA) from iCCA involving the liver hilum. The guideline discusses six means of differentiating between pCCA and iCCA; careful sectioning, location of the stenosis, tumor volume and invasion, presence of BilIN, elastic fibers surrounding the hilar region, and clinical imaging findings.

The first 7 clinical questions pertain to diagnosis and staging. The Japanese recommendations about blood tests, imaging, and biopsy are similar to those in other guidelines. FDG-PET is recommended to detect nodal and bone metastases. The diagnostic accuracy, however, is low with particular concern for false-positive results (6). In a recent systematic review of 10 non-randomized studies, FAPI-PET appeared superior to FDG-PET for staging of patients with iCCA (7).

Clinical questions 8–11 and 15 concern locoregional treatments focusing on surgical resection. The treatment algorithm recommends resection for solitary node-negative iCCA. The guideline recommends to be reluctant with resection in patients with multifocal liver lesions or node-positive iCCA, reporting a 5-year survival of only 11% in patients with 3 liver lesions or node-positive iCCA. Patients with multifocal liver lesions often require extended liver resections with a 90-day mortality that was also 11% in a recent meta-analysis (8). The American National Comprehensive Cancer network guideline for Hepatobiliary Cancers recommends a lymphadenectomy of at least 6 nodes. The motivation for this recommendation is mainly diagnostic, as therapeutic benefit is controversial (9). The Japanese guidelines agree with the advantage of superior staging, but also mention the increased operative risk in patients with liver cirrhosis and inflammation in the porta hepatis. Percutaneous ablation and radiation are recommended for small lesions in patients ineligible for surgery. This concerns only a very small proportion of patients with iCCA, in particular, those with underlying liver disease who are in surveillance program for liver tumors. Intra-arterial treatments for iCCA have not been considered in the Japanese guideline. A recent systematic review investigated radioembolization (SIRT), trans-arterial chemo-embolization (TACE), and hepatic arterial infusion chemotherapy (HAIC) for patients with unresectable iCCA (10). HAIC had the highest median survival. In a meta-analysis of HAIC for unresectable iCCA, the 3-year OS was 40%, which compared favorably with 3% after chemotherapy alone (11).

Clinical questions 12 to 14 evaluated the evidence for systemic treatment. For patients with unresectable iCCA, the Japanese guidelines recommend gemcitabine with cisplatin, with or without S-1. This recommendation is based on the KHBO1401-MIT-SUBA randomized controlled trial that found a superior response rate (42% versus 15%) by adding S-1 (12). Survival, however, was similar after adding S-1. Two key studies were published after the Japanese guidelines. The TOPAZ-1 trial investigated the addition of durvalumab to gemcitabine with cisplatin for patients with advanced biliary tract cancer (13). The hazard ratio for survival was 0.80 in favor of adding durvalumab (95% CI: 0.66–0.97, P=0.021). The ABC-06 trial found that FOLFOX was superior to best supportive care as second-line chemotherapy in patients with advanced biliary tract cancer (adjusted HR 0.69, 95% CI: 0.50–0.97, P=0.031) (14). All recommendations for systemic treatment were based on trials for all patients with advanced biliary tract cancer in which iCCA was only a small subgroup. The Japanese guideline included no recommendation for patients with genomic alterations in the FGFR or IDH genes.

The Japanese guidelines recommend that adjuvant chemotherapy "may be considered". This recommendation is notably weaker than those in the NCCN guidelines

("preferred"), and the ASCO clinical practice guideline ("patients should be offered adjuvant capecitabine"). The BILCAP trial included 447 patients, 19% of whom had iCCA, and showed superior OS (hazard ratio 0.74, P<0.01) with adjuvant capecitabine versus observation in a prespecified, adjusted intention-to-treat analysis (15). Because the treatment effect was not statistically significant in the unadjusted intention-to-treat analyses, experts across the world disagree whether adjuvant capecitabine should be the standard of care. A Japanese study comparing S-1, like capecitabine a pro-drug of 5-FU, versus observation is currently accruing with a targeted sample size of 440 (ASCOT study).

In conclusion, the iCCA guidelines of the LCSGJ form a concise but complete overview of the evidence for the diagnosis and treatment of iCCA for an international audience. While patient and disease factors are different from Western patients, the literature overview and the Japanese recommendation statements are mostly applicable to patients with iCCA across the world.

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Footnote

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