Editorial Commentary

Guidelines for hepatobiliary cancers: treatment strategies in the East and West

Yutaka Midorikawa^

Department of Surgery, National Center of Neurology and Psychiatry, Tokyo, Japan

Correspondence to: Yutaka Midorikawa, MD. Department of Surgery, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-higashi-cho, Kodaira-shi, Tokyo 187-8551, Japan. Email: mido-tky@umin.ac.jp.

Keywords: Clinical practice guidelines; hepatocellular carcinoma; biliary tract cancer

Submitted Apr 30, 2023. Accepted for publication Jul 05, 2023. Published online Jul 17, 2023.
doi: 10.21037/hbsn-23-225
View this article at: https://dx.doi.org/10.21037/hbsn-23-225

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer originating from hepatocytes, whereas intrahepatic cholangiocarcinoma (ICC) occurs in parts of the bile ducts within the liver and is the second most common primary malignant liver tumor. Extrahepatic cholangiocarcinoma develops in the bile ducts outside the liver and includes hilar and distal bile duct cancers. In a recent report from the National Comprehensive Cancer Network (NCCN), members of the NCCN Hepatobiliary Cancers Guidelines Panel summarized the clinical practice guidelines for hepatobiliary cancers, including HCC, gallbladder cancer, ICC, and extrahepatic cholangiocarcinoma (1). Most of the space is occupied by the etiology, screening, diagnosis, workup, pathology, and treatment options for HCC, which is nearly consistent with the guidelines offered by the Barcelona Clinic Liver Cancer (BCLC) strategy (2). Due to differences in the circumstances of medical insurance, donor shortage, and drug approval, there are variations in screening, treatments, and chemotherapies among the NCCN, BCLC, and Japan Society of Hepatology (JSH) guidelines (3), which are the focus of this commentary (*Table 1*).

Hepatocellular carcinoma

Most HCC patients have cirrhosis and chronic liver disease caused by viral infection with the hepatitis B virus, hepatitis C virus, alcohol abuse, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis. Therefore, the American Association for the Study of Liver Diseases (AASLD) and BCLC guidelines recommend ultrasound (US) screening every 6 months for patients with such risk factors. The NCCN panel and the Asian Pacific Association for the Study of the Liver (APASL) (4) recommend the measurement of serum alpha-fetoprotein (AFP) levels in addition to US screening every 6 months. If US shows nodules <10 mm in diameter without AFP elevation, this screening is repeated within 3–6 months. In addition to screening using a combination of US and AFP measurements, determination of serum protein levels induced by vitamin K absence-II (PIVKAII), also known as des-gamma-carboxy-prothrombin, is recommended in Japan, which could improve the diagnostic capability of screening for HCC in high-risk patients (5).

The consensus of the NCCN panel for treatment options for HCC is that liver resection or transplantation, if feasible, are preferred for patients who meet surgical or transplant selection criteria. Locoregional therapies such as radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), and external beam radiation therapy (EBRT) are recommended for patients who are not eligible for liver resection or transplantation. These treatment options except for transplantation are indicated for patients with Child A or B in the NCCN guidelines, while the Child-Pugh classification was already abandoned in the last BCLC version.

^ ORCID: 0000-0002-6662-0494.

© HepatoBiliary Surgery and Nutrition. All rights reserved.

Table 1 Indication for treatment options of hepatocellular carcinoma

Treatment options	NCCN (1)	BCLC (2)	JSH (3)
Liver resection			
Liver function	Child-Pugh A/B	Preserved liver function*	Child-Pugh A/B
Esophageal varices	–	–	–/+ (after treatments for varices)
Tumor No. and size	≤3 nodules (if resectable)	Single and ≤3 cm	≤3 nodules
Vascular invasion	–/+ (if resectable)	–	–/+ (if resectable)
Transplantation			
Liver function	Child-Pugh C	Preserved liver function	Child-Pugh C
Tumor No. and size	UNOS	Milan criteria	5-5-500 rule
Ablation			
Liver function	Child-Pugh A/B	Preserved liver function	Child-Pugh A/B
Tumor No. and size	Away from major vessels/bile ducts	≤3 nodules and ≤3 cm	≤3 nodules and ≤3 cm
Vascular invasion	–	–	–
TACE			
Liver function	Child-Pugh A/B	Preserved liver function	Child-Pugh A/B
Tumor No. and size	No limit	No limit	≥4 nodules
Vascular invasion	–/+ (selected patients)	–	–/+ (selected patients)
EBRT			
Liver function	Child-Pugh A/B		Child-Pugh A/B
Tumor No. and size	Unresectable and appropriate location	Not recommended	≤3 nodules and ≤5 cm
Chemotherapy			
Liver function	Child-Pugh A/B	Preserved liver function	Child-Pugh A
Tumor No. and size	Metastatic disease and extensive liver tumor burden	Diffuse, infiltrative, extensive, and bilobar liver involvement	Not indicated for surgery and locoregional therapies

*, liver function should be evaluated beyond the conventional Child-Pugh staging. NCCN, National Comprehensive Cancer Network; BCLC, Barcelona Clinic Liver Cancer; JSH, Japan Society of Hepatology; UNOS, United Network for Organ Sharing; TACE, transcatheter arterial chemoembolization; EBRT, external beam radiation therapy.

Liver resection is the most effective option for patients with preserved liver function; however, the indications for resection differ in each guideline. According to the BCLC guidelines, liver resection is indicated only for patients with single nodule without macrovascular invasion, whereas according to the NCCN guidelines, resection can be considered even for patients with resectable multifocal disease or major vascular invasion, because complete removal of HCC by surgical treatment could still benefit patients. Patients with portal hypertension are contraindicated for resection because of poor surgical outcomes according to both the NCCN and BCLC guidelines. In contrast, the JSH guidelines recommend liver resection for patients with up to three nodules and vascular invasion of the first portal branch. Notably, HCC patients with portal hypertension could be candidates for liver resection because liver resection after the treatment of esophageal varices can be safely performed and beneficial for patients (6). The expected indication for liver resection for HCC is partly because there are severely insufficient donors for liver transplantation in Japan, though this might improve as public awareness about organ transplantation grows.

Patients with multifocal small HCC (≤3.0 cm) with up to three nodules can also be candidates for surgery according

© HepatoBiliary Surgery and Nutrition. All rights reserved.

to both the NCCN and JSH guidelines, while the BCLC strategy recommends RFA for such patients. Given that several studies have shown that survival outcomes do not differ significantly between liver resection and RFA, RFA may become the first treatment approach for small HCC if tumors are located appropriately away from other organs and major vessels/bile ducts (7).

Liver transplantation is commonly contraindicated for HCC patients with macrovascular invasion and extrahepatic disease, although the specific tumor conditions in the liver are described differently in the various guidelines. In the NCCN guidelines, liver transplantation is recommended for patients who meet the UNOS selection criteria in which patient has a single tumor 2–5 cm in diameter or 2–3 tumors 1–3 cm in diameter with serum AFP level ≤1,000 ng/mL. The BCLC guidelines recommend liver transplantation for patients fulfilling the Milan criteria, and sometimes employ extended criteria. In contrast, patients who meet the 5-5-500 rule (nodule size ≤5 cm in diameter, nodule number ≤5, and AFP level ≤500 ng/mL) are candidates for living-donor liver transplantation (LDLT) in Japan. This is partly because the outcomes of transplantation did not differ between the 5-5-500 rule and Milan criteria based on a Japanese nationwide survey (8), and partly because donors with brain death are insufficient and LDLT is mainly performed for patients with Child-Pugh C classification, which consequently relaxes the tumor condition.

According to the NCCN guidelines, TACE, including TAE, conventional TACE, and drug-eluting bead TACE, is indicated for patients with Child A or B disease who cannot be treated by liver resection, ablation, or transplantation. Similar to the JSH guidelines, the NCCN panel recommends that patients with portal invasion are candidates for TACE, in contrast to the BCLC guidelines, in which only patients who are classified into the intermediate stage are treated with TACE.

EBRT is recommended for patients with 1–3 unresectable HCC according to the NCCN guidelines. On the other hand, indication of EBRT is more specifically provided in the JSH guidelines: for patients with 1 to 3 nodules ≤5 cm in diameter and with/without vascular invasion when liver resection or RFA is difficult. In the BCLC guidelines, EBRT is not recommended as a first treatment option.

Since the US Food and Drug Administration (FDA) approved sorafenib for patients with advanced HCC in 2007 based on data from the SHARP trial (9), systemic therapy has been the most developed area in the treatment of HCC in a number of clinical trials, and NCCN and JSH recommends the following chemotherapies for advanced disease in patients with Child A. According to each guideline, an immune checkpoint inhibitor with a molecular target drug is the first-line chemotherapy. Combined atezolizumab and bevacizumab (Atezo-Bev) is listed as the preferred regimen, while sorafenib and lenvatinib (10) are other recommended regimens as first-line treatments in each guideline. This is because Atezo-Bev confers a superior survival benefit compared with sorafenib (IMbrave150 trial) (11), although it has yet to be evaluated head-to-head *vs.* lenvatinib. Patients treated with sorafenib were transferred to a second-line setting of regorafenib (if tolerant to sorafenib), cabozantinib, or ramucirumab (AFP level, >400 ng/dL). Cabozantinib is an effective third-line therapy. In addition to Atezo-Bev, combined durvalumab and tremelimumab is also the first-line treatment based on data from the phase III HIMALAYA trial (12) in BCLC. Each guideline recommends that the tumor response to chemotherapy be evaluated using Response Evaluation Criteria in Solid Tumours (RECIST) or modified RECIST, which estimates the enhanced area in the arterial phase of dynamic computed tomography.

Gallbladder cancer and cholangiocarcinoma

Some patients with gallbladder cancer, and most patients with cholangiocarcinoma, experience obstructive jaundice. The NCCN panel recommends biliary drainage for patients with jaundice prior to biopsy, resection, and systemic therapy, while preoperative biliary drainage remains a matter for debate and some of guidelines refer to only total bilirubin concentration before drainage.

Complete removal of the disease with lymphadenectomy is the only potentially curative treatment for patients with gallbladder cancer or cholangiocarcinoma, and the general principle of surgical resection in the NCCN guidelines is not different from that in most of the other guidelines. To obtain a clear margin for patients with gallbladder cancer, hepatic resection and bile duct resection are recommended, if necessary, whereas lymphadenectomy should be performed to clear all lymph nodes in the porta hepatis. Given that multifocal liver disease and lymph node metastasis are prognostic factors for worse survival in patients with ICC, liver resection is recommended for highly selected cases with limited multifocal disease or lymph node metastasis to the porta hepatis. Lymphadenectomy of the porta hepatis is

© HepatoBiliary Surgery and Nutrition. All rights reserved.

recommended in patients with ICC; however, its clinical effect is yet to be elucidated. Extended hemihepatectomy with caudate resection is necessary in patients with hilar cholangiocarcinoma. To avoid postoperative liver failure, the NCCN recommends biliary drainage and portal vein embolization before surgery.

Systemic therapy is recommended for patients with unresectable gallbladder cancer or cholangiocarcinoma. Patients with ICC are not candidates for RFA or TACE in the NCCN guidelines, while RFA could be considered for selected patients who could not undergo liver resection due to poor liver function or recurrent ICC in the JSH guidelines. Combined gemcitabine (GEM) and cisplatin (CDDP) has been the global standard regimen for biliary tract carcinoma since the ABC-02 study in 2010 (13). NCCN and other guidelines still recommend the combination of GEM and CDDP chemotherapy as the standard first-line treatment for patients with unresectable biliary tract carcinoma. Furthermore, immunotherapy using durvalumab with GEM and CDDP is listed as first-line chemotherapy based on data from the TOPAZ-1 trial (14) in the NCCN guidelines.

Owing to the development of chemotherapies, such as immunotherapy and targeted therapy, the treatment strategy for HCC has changed. Surgical resection and liver transplantation are curative options. The indications for surgery and local therapies will differ depending on drug development for HCC, as well as medical insurance and the supply capacity of donors in each country in the future.

Acknowledgments

Funding: This work was mainly supported by a Grant-in-Aid for Scientific Research (YM) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan [(C) 21K08807]. The funding body has no role in the design of the study and analysis and interpretation of data and in writing the manuscript.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-225/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. NCCN Guidelines for Hepatobiliary Cancers, Version 3.2022. In press.
2. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol 2022;76:681-93.
3. Clinical Practice Guidelines for Hepatocellular Carcinoma 2021 Version. JSH HCC Guidelines 2021. KANEHARA & Co., LTD.
4. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317-70.
5. Kim DY, Toan BN, Tan CK, et al. Utility of combining PIVKA-II and AFP in the surveillance and monitoring of hepatocellular carcinoma in the Asia-Pacific region. Clin Mol Hepatol 2023;29:277-92.
6. Ohkubo T, Midorikawa Y, Nakayama H, et al. Liver resection of hepatocellular carcinoma in patients with portal hypertension and multiple tumors. Hepatol Res 2018;48:433-41.
7. Takayama T, Hasegawa K, Izumi N, et al. Surgery versus Radiofrequency Ablation for Small Hepatocellular Carcinoma: A Randomized Controlled Trial (SURF Trial). Liver Cancer 2021;11:209-18.
8. Shimamura T, Akamatsu N, Fujiyoshi M, et al. Expanded living-donor liver transplantation criteria for patients with hepatocellular carcinoma based on the Japanese nationwide survey: the 5-5-500 rule - a retrospective study. Transpl Int 2019;32:356-68.

© HepatoBiliary Surgery and Nutrition. All rights reserved.

9. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
10. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-73.
11. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
12. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid 2022;1. doi: 10.1056/EVIDoa2100070.
13. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273-81.
14. Oh DY, He AR, Qin S, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evid 2022;1. doi: 10.1056/EVIDoa2200015.

Cite this article as: Midorikawa Y. Guidelines for hepatobiliary cancers: treatment strategies in the East and West. HepatoBiliary Surg Nutr 2023;12(4):580-584. doi: 10.21037/hbsn-23-225

© HepatoBiliary Surgery and Nutrition. All rights reserved.