Editorial

Systemic management for patients with hepatobiliary tumors in a multi-dimensional view

Jianzhen Lin, Haitao Zhao

Department of Liver Surgery, Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS & PUMC), Peking Union Medical College Hospital, Beijing 100730, China

Correspondence to: Haitao Zhao. Department of Liver Surgery, Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS & PUMC), Peking Union Medical College Hospital, Beijing 100730, China. Email: zhaoht@pumch.cn.

Submitted Jul 23, 2019. Accepted for publication Jul 25, 2019.
doi: 10.21037/hbsn.2019.07.21
View this article at: http://dx.doi.org/10.21037/hbsn.2019.07.21

As one of the most leading causes of cancer-related mortality, hepatobiliary tumors (HBT) are featured as limited treatment and poor survival. Due to the complexity and heterogeneity of epidemiologic risk factors, clinicopathological characteristics and cancer genomics, it is still hard to form a normalized clinical management for patients with advanced HBT. Over a long period of time, surgery-oriented comprehensive treatment is the mainstream medical care for clinical treatment for HBT, which emphasizes to categorize HBT into resectable/transplantable stage or unresectable/untransplantable stage. In recent years, benefiting from unprecedented explosion in antitumor strategies, including small molecular chemical drugs targeted tyrosine kinase receptors and biological immunotherapy inhibited immune-checkpoints, therapeutic options for HBT patients are becoming more varied and effective (1). Neoadjuvant therapies in order to strive for surgical resection and to reduce recurrent risk are also widely explored. Hence, with increasing weapons for anti-HBT, it indispensable to achieve whole course management for HBT patients with a multi-dimensional vision. Herein, concentrating on systemic management of HBT patients, we briefly summary current manner to perform clinical treatment and exploration (expanding phase), and we also prospect the ideal mode (stereoscopic phase) in the future.

Current: expanding phase

The most crucial part of clinical management of the underlying HBT patients is primary prevention and early detection. Identification of HBT-associated population characteristics and carcinogenic factors highlights the essentiality of primary prevention for carriers with risk factors including chronic hepatitis [e.g., hepatitis B virus (HBV)/hepatitis C virus (HCV) infections], sustained hepatic inflammation and fibrosis (e.g., fluke), metabolic disorders (e.g., diabetes), hazardous material contact (e.g., aflatoxin, alcohol and tobacco) and hereditary susceptibility. For these people, regular examination by abdominal ultrasound scan and serum alpha-fetoprotein (AFP) contributes to the early diagnosis of hepatocellular carcinoma (HCC) (2). The improved early diagnosis leads to the improvement of excision rate of HBT and the elevation of survival rate in 5 or 10 years. Emerging techniques based on detecting cancer-specific abnormalities in blood circulating-free nucleic acid and tumor-originated cells, such as micro-RNA, methylation signature and genomic mutations, and circulating tumor cells (CTCs), are encouraging in remedying the negative diagnosis through serum tumor markers (3,4).

For resection of primary HBT, surgeons commonly concern about the diameter, number and metastatic status of the tumors and liver function of the patients, to make sure that only patients with resectable HBT could be sent into operating room. For patients with high-risk (e.g., multiple tumor sites or positive surgical margin) of recurrence, postoperative prophylactic treatments including radiotherapy, chemotherapy (e.g., orally capecitabine) (5) or transcatheter arterial chemoembolization (TACE) were adopted. For surgical techniques, approaches with more minimal invasion, such as laparoscopic resection and robotic resection, gradually become the routine applications in clinical practice. Reduced trauma caused by operations make surgeons to embrace the concept of "enhanced

recovery after surgery (ERAS)" (6).

Unfortunately, even HBT patients had undergone a radical resection with tumor-negative surgical margins, the median recurrence-free survival is still short (range from 6 months to 2 years) for most patients (7). For patients with refractory or recurrent HBT, limited by potent adjuvant treatment, the survival prognosis and quality of life (QOL) are always unsatisfied. For HCC, the molecular targeted drugs approved to use at first-line treatments include sorafenib and lenvatinib, for the increasing median survival in the study of SHRAP trial (8) and noninferiority antitumoral activity in the REFELCT trial (9). Other agents, such as everolimus, sunitinib, FOLFOX (fluorouracil, leucovorin and oxaliplatin), has failed to increase survival when compared with sorafenib. For second-line treatment of HCC patients, drugs including regorafenib, cabozantinib, ramucirumab and nivolumab (a PD-1 inhibitor) showed promising antitumor efficacy (10). As for patients with advanced bile tract cancer, only cisplatin plus gemcitabine was approved to use as the first-line treatment, while there is no recommended systemic second-line treatment.

Multi-omics researches on cancer genomics, transcriptomics, epigenomics and proteomics are unveiling the actionable targets and therapies countering cancer-specific alterations. Mutations in *TP53*, *TERT*, *CTNNB1*, and activation of oncogenic signaling (e.g., *RAS* mitogen-activated protein kinase; *MET* amplification; *AKT*-mammalian target of rapamycin) frequently occur in HCC. Besides, identified actionable mutations including *IDH*-1/2, *FGFR* fusion and germline/somatic *BRCA* pathogenic alterations have been investigated in several randomized controlled clinical trials for patients with bile tract cancers (11). The ideology of the umbrella experiment offers to accumulate available treatments for HBT patients, which derives the concept of biomarker-guided clinical management. Efficacy-related biomarkers facilitate the decision-making for cancer patients with advanced stage. For example, patients with over 400 ng/mL AFP are more sensitive for ramucirumab (12); HBTs with high microsatellite instability (MSI-H) are recommended to receive pembrolizumab (13); fibroblast growth factor (FGF) is correlated with response for sorafenib and lenvatinib; and expression patterns of plasma proteins and micro-RNAs were associated with survival outcomes of patients with HCC following treatment with regorafenib in the RESORCE trial (14).

So far, it is still hard to permeate the molecular-guided strategy into classical clinical management. With the encouraging antitumoral efficacy and survival outcomes brought by the advancements of molecular and biological drugs, we proposed that the clinical thinking of hepatobiliary surgery should be an all-sided consideration, rather than an immediate assessment. Surgeons ought to switch their role from surgical operators to surgical oncologists, with the re-classification of HBT from resectable/unresectable status to controllable/uncontrollable status.

Prospective: stereoscopic phase

The stereoscopic phase of HBT clinical management will be contributed by the successful achievements of evidence-based clinical practice and proof-of-concept trials at current expanding phase, underlying a systemic, whole-course and full-time assessing, treating and monitoring for each patient at every clinical stage.

In our opinion, surgery still plays the core role of HBT treatment, meanwhile more attention should be paid to preoperative neoadjuvant therapy and decision making in the operation timing. Through integrating clinical background characteristics, imaging information and histopathological/molecular-pathological features, patients with a high risk of recurrence could be identified. Plenty of well-designed clinical investigations should be proceeded to define the best approaches of neoadjuvant therapy. For instance, neoadjuvant radiotherapy was demonstrated to improve postoperative survival for patients with resectable HCC and portal vein tumor thrombus (15). Neoadjuvant chemoembolization, targeted therapy or immunotherapy are also prospectively investigated in numerous clinical trials (e.g., NCT03867370 and NCT03847428). Moreover, since more drugs with increasing antitumor efficacy are developed, we can still expect the effect of down staging of neoadjuvant radiotherapy, to transform unresectable HBT into resectable HBT.

For postoperative patients, immediate evaluations for pathological, biological, and genomic features are necessary. In view of multi-dimensional clinical management, we propose that it is more appropriate to classify HBT as controllable or uncontrollable status. For controllable HBT patients with limited metastasis, who are expected to have an effective and long-lasting therapeutic strategy so that long-term tumor stabilization is warranted, it is worthy to reconsider the significance of reducing tumor surgery. While for uncontrollable HBT with highly malignant biological behaviors, clinical benefits brought from

aggressive surgeries are limited, clinical management needs to improve the QOL as the starting point, focusing more on providing the best supportive medical care and minimizing tumor-induced complications. Overall, Through multi-disciplinary team (MDT) to develop a holistic therapeutic plan which is expected to be effective and adaptable to make sure the patient's first-line, second-line and follow-up treatment could be orderly and sequential. Comprehensive (how and when) application of various antitumoral approaches through a multi-dimensional view is an aesthetics of clinical management which is determined by surgical oncologists and MDT.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

References

1. Villanueva A. Hepatocellular carcinoma. N Engl J Med 2019;380:1450-62.
2. Zhou J, Sun HC, Wang Z, et al. Guidelines for diagnosis and treatment of primary liver cancer in china (2017 edition). Liver Cancer 2018;7:235-60.
3. Macias RIR, Kornek M, Rodrigues PM, et al. Diagnostic and prognostic biomarkers in cholangiocarcinoma. Liver Int 2019;39 Suppl 1:108-22.
4. Pezzuto F, Buonaguro L, Buonaguro FM, et al. The role of circulating free DNA and microRNA in non-invasive diagnosis of HBV- and HCV-related hepatocellular carcinoma. Int J Mol Sci 2018;19. doi: 10.3390/ijms19041007
5. Primrose JN, Fox RP, Palmer DH, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol 2019;20:663-73.
6. van Dijk DPJ, van Woerden V, Cakir H, et al. ERAS: improving outcome in the cachectic HPB patient. J Surg Oncol 2017;116:617-22.
7. Tabrizian P, Jibara G, Shrager B, et al. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. Ann Surg 2015;261:947-55.
8. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
9. 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.
10. Llovet JM, Montal R, Sia D, et al. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol 2018;15:599-616.
11. Valle JW, Lamarca A, Goyal L, et al. New horizons for precision medicine in biliary tract cancers. Cancer Discov 2017;7:943-62.
12. Zhu AX, Baron AD, Malfertheiner P, et al. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma: analysis of REACH Trial Results by child-pugh score. JAMA Oncol 2017;3:235-43.
13. Mandal R, Samstein RM, Lee KW, et al. Genetic diversity of tumors with mismatch repair deficiency influences anti-PD-1 immunotherapy response. Science 2019;364:485-91.
14. Teufel M, Seidel H, Köchert K, et al. Biomarkers associated with response to regorafenib in patients with hepatocellular carcinoma. Gastroenterology 2019;156:1731-41.
15. Wei X, Jiang Y, Zhang X, et al. Neoadjuvant three-dimensional conformal radiotherapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: a randomized, open-label, multicenter controlled study. J Clin Oncol 2019;37:2141-51.

Cite this article as: Lin J, Zhao H. Systemic management for patients with hepatobiliary tumors in a multi-dimensional view. Hepatobiliary Surg Nutr 2019;8(6):626-628. doi: 10.21037/hbsn.2019.07.21

