Viewpoint

Hepatocellular carcinoma with portal invasion, still a place for liver surgery in the era of immunotherapy?

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Comment on: Lau WY, Wang K, Zhang XP, *et al.* A new staging system for hepatocellular carcinoma associated with portal vein tumor thrombus. Hepatobiliary Surg Nutr 2021;10:782-95.

Submitted Aug 16, 2022. Accepted for publication Sep 07, 2022.
doi: 10.21037/hbsn-22-373
View this article at: https://dx.doi.org/10.21037/hbsn-22-373

Hepatocellular carcinoma (HCC) is a leading cause of cancer death worldwide and is associated with a 5-year overall survival (OS) of 10–15% all stages combined. However, 5-year OS reaches 50–70% when patients are in an early stage and can access curative treatments such as liver transplantation, liver resection (LR) or ablation. Currently, LR is reserved to very selected patients with adequate performance status, preserved liver function, to be matched with grade of portal hypertension (PHT), sufficient volume of the future liver remnant and acceptable tumor burden (1,2). Worldwide, the definitions of "tumor burden" and vascular invasion vary as illustrated in *Tables 1*,*2*, and the impact of portal vein tumoral thrombosis (PVTT) on the choice for HCC treatment is not consensual (1,2).

European Association for the Study of the Liver (EASL) guidelines consider through the Barcelona Clinic Liver Cancer (BCLC) classification that macrovascular invasion is a contraindication to curative treatment and that systemic therapy is currently the reference treatment for these patients. Atezolizumab-bevacizumab should now be proposed as first-line treatment instead of the previously used sorafenib, as median OS was 19 months with atezolizumab-bevacizumab *vs.* 13 months with sorafenib (P<0.001). To note, in this study only 40% of the patients had macrovascular invasion (3).

Conversely, the American Association for Study of Liver Diseases (AASLD) and Asian Pacific Association for the Study of the Liver (APASL) guidelines may consider LR for resectable tumor regardless PVTT (1,2). That is why LR for lesions with macrovascular invasion is therefore performed in international centers, especially in Asia, and is associated with competitive results in terms of OS compared to the standard of care [transarterial chemoembolization (TACE) or systemic treatment with tyrosine kinase inhibitors (TKIs)]. Indeed, 5-year OS of BCLC stage C was 20.0% after LR in a systematic review that included 74 articles (4). In a large Japanese nationwide survey, including 6,474 HCC patients with PVTT (Child-Pugh A), the median OS in the LR group was 1.77 years longer than that in the non-LR group (TACE or TKIs), but the survival benefit was not observed in patients with PVTT 4 (5). Therefore, these data confirm the potential benefit of LR in well selected patients with HCC and PVTT and suggest the importance of a new staging system incorporating the presence or not of PVTT and its extension. This was the purpose of the study published by Lau *et al.* (6) in which the authors set up a new staging system by incorporating liver function, resectability of tumor, performance status, extrahepatic metastasis and extent of PVTT to better discriminate patients with HCC associated with PVTT and their prognosis in order to not exclude them systematically from LR. Even if this is not the first staging system published incorporating PVTT and other prognosis factors, this staging system shows an interesting OS prediction on the time-dependent receiver operating characteristic (ROC) analysis. Nevertheless, in the validation cohort, this new algorithm does not seem to perform better than the already published staging systems Chinese University Prognostic Index (CUPI) and Cancer

Table 1 Portal vein tumor thrombosis classification according to guidelines

Cheng classification	Liver cancer study group of Japan classification	Xu classification
PVTT 0 (microscopic vascular invasion)	NA	NA
PVTT 1 (thrombus located in the second order segmental branches)	Vp 1: thrombus located beyond second order branches	Type B: thrombus in either right or left portal vein
PVTT 2 (thrombus located in the right or left portal vein)	Vp 2: thrombus located in the second order branches	
PVTT 3 (thrombus located in the main portal vein)	Vp 3: thrombus located in the first order branches	Type A: thrombus in the main portal vein or both left and right portal veins
PVTT 4 (thrombus located in the superior mesenteric vein)	Vp 4: thrombus located in the main portal vein	

PVTT, portal vein tumor thrombosis; NA, not available; Vp, vein portal.

Table 2 Optimal liver surgery candidate according to guidelines

Characteristics	EASL guidelines	AASLD guidelines	APASL guidelines
Tumor burden	No extrahepatic spread	No extrahepatic spread	No extrahepatic spread
	No macrovascular invasion	Solitary tumor <5 cm	Resectable tumor regardless
	Solitary nodule	With/without vascular invasion	Vascular invasion
	Regardless tumor size	Mulifocal tumor, none >5 cm	Number and tumor size
Liver function	Child-Pugh A, MELD <10	Child-Pugh A	Child-Pugh A and B
Volume of the future liver remnant	>25–30% in the absence of severe fibrosis and >40% in case of cirrhosis		
PHT	CSPH is not an absolute contraindication for LR but must be balanced with the extension of the resection and the liver function		

PHT, portal hypertension; EASL, European Association for the Study of the Liver; MELD, model for end-stage liver disease; CSPH, clinically significant portal hypertension; LR, liver resection; AASLD, American Association for Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver.

of the Liver Italian Program (CLIP). The discrepancies observed between the derivation and validation cohort are probably linked to significant differences between patients (significantly more cirrhosis and tumor size >5 cm, and less multiple tumors in training than validation cohort).

However, some concerns can be raised about the applicability of this new staging system. The first one is that 90% of patients included suffer from hepatitis B while no data regarding morbi-mortality related to LR are available. Patients with metabolic liver disease are prone to develop more complications after LR, which questions the applicability of this study to out of the context of viral-related liver disease, as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are growing causes of chronic liver disease worldwide. The second one is the absence of progression-free survival (PFS) analysis while 57% of patients underwent LR. Even though OS data are displayed, only deaths due to HCC progression or recurrence were considered while PFS remains one of the best outcome surrogates for curative treatment. The third concern points out the definition of "resectability" which remains vague although taking a major part in the algorithm. Although liver surgery tends towards more standardization, LR feasibility remains surgeon-dependent, operative technique dependent (laparoscopic *vs.* open approach) or patient-dependent (cirrhosis stage and PHT) and may greatly vary among centers and countries. The last but not the least concern is that patients with a-posteriori diagnosed HCC with microvascular invasion were included in the cohort, although these patients would have undergone LR in any case. Including this population questions the methodological validity of the algorithm.

In our opinion, early-stage or stage I patients with HCC and PVTT are the key population in which LR benefit is

controversial and should be debated. In this study, median OS in stage IA was 14 months (macrovascular invasion without involving main portal vein) and 6 months in stage IB (main portal vein involved) in training cohort *vs.* 31 months for stage IA and 15 months for stage IB in validation cohort. To note, the median OS in PVTT patients treated with atezolizumab-bevacizumab was 14.2 and 9.7 months in patients treated with sorafenib. In these patients with resectable HCC and PVTT, these results question the justification to perform LR instead of atezolizumab-bevacizumab which is the new standard of care for this specific population according to EASL recommendations. Further studies comparing LR *vs.* immunotherapy *vs.* combined treatment in patients with PVTT that included or not the main portal vein appear as a major requirement to improve the outcome of this specific population of patients.

In conclusion, offering curative treatment to some very selected patients with HCC and PVTT seems justified. However, the results of immunotherapy studies show competitive OS data in this setting and the place of LR in the era of immunotherapy for advanced HCC need to be defined using a specific staging system as proposed by the authors. The next step would probably be a combination of treatments (with neo-adjuvant or adjuvant immunotherapy for instance) as it has already been explored with radiotherapy in a recent randomized multicentric controlled trial in which OS was improved by neoadjuvant 3D radiotherapy in patients with resectable HCC and PVTT (7).

Acknowledgments

Funding: None.

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: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-373/coif). 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.

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Cite this article as: Giudicelli H, Goumard C, Allaire M. Hepatocellular carcinoma with portal invasion, still a place for liver surgery in the era of immunotherapy? HepatoBiliary Surg Nutr 2022;11(5):782-784. doi: 10.21037/hbsn-22-373