Liver resection is always a good choice for hepatocellular carcinoma (HCC) patients regardless of Barcelona Clinic Liver Cancer (BCLC) stage: the therapeutic hierarchy

Maria Guarino, Nicola Caporaso, Filomena Morisco

Department of Clinical Medicine and Surgery, Gastroenterology Unit, University of Napoli Federico II, Napoli, Italy

Correspondence to: Filomena Morisco. Department of Clinical Medicine and Surgery, Gastroenterology Unit, University of Naples Federico II, Napoli, Italy. Email: filomena.morisco@unina.it.

Comment on: Zhao S, Zhang X, Wang M, et al. Identifying optimal candidates for liver resection or transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma. Ann Transl Med 2020;8:586.

Submitted Aug 24, 2020. Accepted for publication Sep 01, 2020.
doi: 10.21037/atm-20-6004
View this article at: http://dx.doi.org/10.21037/atm-20-6004

The treatment of hepatocellular carcinoma (HCC) is changing over time and it is turning to a personalized approach taking into account the tumor morphology, the entity of liver function impairment, patients’ comorbidities and the presence of cancer-related symptoms [ECOG Performance Status (PS)]. In particular, for the advanced stage, defined by the presence of vascular invasion or extrahepatic spread and/or mild cancer-related symptoms (PS 1–2), the first-line treatment should be the systemic therapy according to Barcelona Clinic Liver Cancer (BCLC) classification. However, as for the intermediate stage (1), also the advanced stage includes a considerably heterogeneous set of patients (2). For all these reasons, the BCLC “stage hierarchy” approach (3), linking each HCC stage to a specific treatment, has been exceeded firstly by the concept of “treatment stage migration” strategy (4), which allows moving to another treatment in a bidirectional way (the previous or the subsequent one in BCLC classification, according to each single case), and more recently by the theory of “therapeutic hierarchy” (5), historically endorsed by the Asia-Pacific guidelines (6) as well as by Italian guidelines (7).

Accordingly, Zhao et al. recently published a study in Ann Transl Med entitled “Identifying optimal candidates for liver resection or TACE in patients with unresectable hepatocellular carcinoma” (8). This study aimed to compare the post-treatment outcomes after liver resection (LR) or transarterial chemoembolization (TACE) to recognize prognostic factors related to overall survival (OS) for BCLC stage C patients with PS 1 having single tumor and without vascular invasion or extrahepatic spread. The results by Zhao et al. confirmed that LR is superior to TACE in terms of prognosis and it should be considered rather than TACE for BCLC stage C patients with PS 1 having single tumor and without vascular invasion or extrahepatic spread.

The definition of unresectable HCC clearly implies that LR should be considered the first treatment option in these patients. In particular, unresectable HCC was defined as a liver neoplasia not suitable for surgery because of the disease burden (multinodular disease, portal vein invasion or extrahepatic spread), for location of nodule(s) in the liver or tumor characteristics, or because of their PS, the residual liver function (Child-Pugh B-C), comorbidities (9). As a matter of fact, in the last version of BCLC (4), monofocal HCC without vascular or extrahepatic involvement is classified in the early stage (BCLC A), irrespective of the tumor size, because they benefit from LR as first line treatment (10,11). Liver surgery in cirrhotic patients should be taken into account two aims: to be curative and to preserve as much liver parenchyma as possible to avoid post-hepatectomy liver failure (PHLF). For assessing the feasibility of LR, the main prognostic factors of PHLF are liver functional reserve, degree of portal hypertension and extension/complexity of LR (12). Recently, a higher survival benefit with a definite therapeutic hierarchy, starting from LR through progressively less radical treatments, has been
demonstrated for single tumor HCC, irrespective of the tumor size (13). On the other hand, the efficacy of TACE in large HCC is still debatable and should be limited to patients unsuitable for LR (14-17). In this context the study by Zhao et al. confirmed data already presents in literature.

The peculiarity of the study by Zhao et al. is the enrolment of patients with PS 1, the only characteristic putting these patients in advanced stage instead of early one. The PS scale sets how the daily life capability is influenced by the ongoing tumoral disease. But it is well known that patients with cirrhosis (without HCC) suffer from physical debility that can interfere with activities and impair quality of life. So, in this setting (patients with HCC and cirrhosis) it is very difficult to discriminate tumour-related symptoms from symptoms due to cirrhosis. As a matter of fact, patients with decompensated cirrhosis show a significant decline of their PS, despite of tumor burden. In this context, Orman et al. focus their attention on PS in cirrhotic patients by defining the independent impact of the PS on mortality or transplantation in 79,092 waitlisted liver transplant candidates followed between 2005 and 2015 (18). In competing risk analysis, only the relationship between PS and mortality maintained significance and it was most pronounced in patients without HCC, suggesting that PS may be more informative or relevant in patients without HCC. What is important for the study by Zhao et al. is to understand if the PS of the enrolled patients was tumor—or cirrhosis—related. Probably, since the full population has a Child-Pugh A5–A6, we supposed it was only tumor-related and accordingly, it had less impact on treatment access and survival.

Another interesting result showed by Zhao et al. is the relationship between patients with poorer prognosis and higher bilirubin level, while high albumin level was considered as a mark of better OS at univariate and multivariate analyses. This data confirmed the well-known impact of residual liver function on OS (both serum bilirubin and albumin are defined as liver function tests) more than the tumor burden per se, as demonstrated by the development of several scoring systems for patients with HCC, like the Albumin-Bilirubin (ALBI) grade (19) or the new Child-Turcotte-Pugh class 0 (20).

The study by Zhao et al. is important for the diffusion of the new concept of “therapeutic hierarchy” in patients with HCC, for which is always necessary a surgical evaluation before any treatment approach since it is the mainstay of HCC therapy, with the best outcomes when compared to any treatment available in well-selected patients after a multidisciplinary discussion.

**Acknowledgments**

**Funding:** None.

**Footnote**

**Provenance and Peer Review:** This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-6004). 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.

**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. Bolondi L, Burroughs A, Dufour JF, et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012;32:348–59.
2. Giannini EG, Bucci L, Garuti F, et al. Patients with advanced hepatocellular carcinoma need a personalized management: A lesson from clinical practice. Hepatology 2018;67:1784–96.
3. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329–38.
4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
5. Vitale A, Trevisani F, Farinati F, et al. Treatment of hepatocellular carcinoma in the Precision Medicine era: from treatment stage migration to therapeutic hierarchy. Hepatology 2020. [Epub ahead of print].

6. 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.

7. Raccomandazioni Multisocietarie Italiane (AISF, AIOM, IT-IHPBA, SIC, SIRM, SITO) per la gestione clinica integrata del paziente con epatocarcinoma. Available online: https://www.webaisf.org/aisf-guidelines-e-position-papers/page/3/

8. Zhao S, Zhang X, Wang M, et al. Identifying optimal candidates for liver resection or transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma. Ann Transl Med 2020;8:586.

9. Bruix J, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. Gastroenterology 2016;150:835-53.

10. Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. Gut 2014;63:844-55.

11. Vitale A, Burra P, Frigo AC, et al. Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: a multicentre study. J Hepatol 2015;62:617-24.

12. Roayaie S, Jibara G, Tabrizian P, et al. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 2015;62:440-51.

13. Vitale A, Farinati F, Pawlik TM, et al. The concept of therapeutic hierarchy for patients with hepatocellular carcinoma: A multicenter cohort study. Liver Int 2019;39:1478-89.

14. Pecorelli A, Lenzì B, Gramenzi A, et al. Curative therapies are superior to standard of care (transarterial chemoeMBOLization) for intermediate stage hepatocellular carcinoma. Liver Int 2017;37:423-33.

15. Morisco F, Camera S, Guarino M, et al. Laser ablation is superior to TACE in large-sized hepatocellular carcinoma: a pilot case-control study. Oncotarget 2018;9:17483-90.

16. Yin L, Li H, Li AJ, et al. Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan Criteria: a RCT. J Hepatol 2014;61:82-8.

17. Sangiovanni A, Triolo M, Iavarone M, et al. Multimodality treatment of hepatocellular carcinoma: How field practice complies with international recommendations. Liver Int 2018;38:1624-34.

18. Orman ES, Ghabril M, Chalasani N. Poor Performance Status Is Associated With Increased Mortality in Patients With Cirrhosis. Clin Gastroenterol Hepatol 2016;14:1189-95.e1.

19. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. J Clin Oncol 2015;33:550-8.

20. Lee YH, Hsu CY, Chu CW, et al. A new Child-Turcotte-Pugh class 0 for patients with hepatocellular carcinoma: determinants, prognostic impact and ability to improve the current staging systems. PLoS One 2014;9:e99115.

Cite this article as: Guarino M, Caporaso N, Morisco F. Liver resection is always a good choice for hepatocellular carcinoma (HCC) patients regardless of Barcelona Clinic Liver Cancer (BCLC) stage: the therapeutic hierarchy. Ann Transl Med 2020;8(20):1282. doi: 10.21037/atm-20-6004