



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

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*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.

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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 tumor-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.

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