

The problem of the most appropriate curative treatment for hepatocellular carcinoma. When to embolize? When to operate?

To the Editor:

In the *Journal of Hepatology*, Kim and colleagues [1] recently published an interesting and timely observation on the prognostic significance of treatment responses following transarterial chemoembolization (TACE) for patients with hepatocellular carcinoma (HCC).

We congratulate the authors for their paper, which was read with great interest because of the special need of published, specific analyses on this matter. Actually, the implications of their findings can be of significant value in clinical practice, especially considering potential predictive applications. However, with regard to methodology, some aspects require further consideration as we are concerned that the selection criteria used may impair the power of the analysis and the possibility to draw definitive conclusions from their outcomes.

As exclusion criteria the authors considered five thorough features: inadequate target lesion (infiltrative pattern or largest lesion being smaller than one centimetre), other primary or secondary malignancies, presence of extrahepatic tumour lesions and/or invasion to main portal vein, Child-Pugh class different from A and presence of uncontrolled functional or metabolic disease. Some perplexities arise.

The clinical and radiological conditions evaluated by the inclusion protocol are likely to admit a number of patients which may represent optimal candidates to surgical resection. In this regard, it would be extremely interesting to know how many included patients had very early (0), early (A) and intermediate (B) stage according to the Barcelona Clinic Liver Cancer (BCLC) classification at preprocedural assessment. Likewise, it would be interesting to know on the basis of which criteria unresectability was assessed, by considering that the median tumour size was reported to be 3.1 centimetres, with the number of lesions being <4 for the largest majority of cases. Of note, large and multiple tumours were finally independently associated with failure to achieve complete response after the initial TACE treatment. Thus, better responses were observed in patients with small, single or few intrahepatic lesions, preserved liver function and, potentially, low co-morbidity. In fact, the outcomes should be more appropriately analysed in comparison with those of surgical resection given that the subgroup of patients who experienced better results was likely to include a number of excellent candidates to liver resection.

In this regard, in a recent, extremely interesting multicentric study published by Vitale *et al.* [2], including more than 2000 patients with HCC and preserved liver function, resection was confirmed to be associated with significant survival benefit over loco-regional therapies, regardless of BCLC stages. Furthermore, it has been demonstrated that radical therapies such as surgical resection and liver transplantation achieve better results and are increasingly employed even in HCC patients with intermediate and advanced diseases [3,4].

The problem of offering HCC patients the most appropriate therapy is not new. Indeed, although it is largely known that in patients with preserved hepatic function and resectable

malignancies, the best chance for a cure is surgical extirpation [2,5]. It has already been demonstrated that the recommendation whether to receive surgery is largely influenced by the type of specialist by whom patients are seen initially [6].

In this regard, what several authors lately observed [6,7] sharply indicates the need for further evidence on treatment strategies and stronger collaboration among specialists, especially considering how much has changed through the last decades in the rapidly maturing field of hepatic surgery.

First, liver resection indications for HCC have been implemented with new surgical treatments: the Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) procedure may increase the rate of curative resections for tumours previously considered unresectable for major vascular invasion or tumour thrombosis [8].

Second, it must be considered that with the diffusion of modern technologies, the significant rate of morbidity and mortality historically associated with hepatic surgery has decreased dramatically. Advanced laparoscopy as well as robotics now permit oncologically adequate and safe surgery with the advantages of the minimally invasive method and respected principles of parenchyma-sparing surgery [9,10].

Given the significant rise in prevalence of predisposing conditions, in coming years hepatologists will be increasingly confronted with the question of the most appropriate therapy for HCC patients. Currently, a substantive mismatch exists between the possibility of receiving curative surgery and its application [7].

While we agree with the successful nonoperative management of HCC patients with TACE, we further commend that all patients with potentially resectable HCC should be routinely evaluated in dedicated centres with large experience of liver surgery, possibly where the technological progress is part of daily surgical practice. Otherwise, we are possibly missing a valuable opportunity to significantly improve the patients' survival and quality of life.

Conflict of interest

Francesco Guerra and Giovanni Battista Levi Sandri have no conflict of interests related to the present paper and declare no financial relationships with any pharmaceutical or device company.

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Reply to “The problem of the most appropriate curative treatment for hepatocellular carcinoma. When to embolize? When to operate?”

To the Editor:

We appreciate the valuable comments by Guerra *et al.* on our recently published article [1]. They raised some issues.

We recognize that surgical resection should be considered first, provided that patients are clinically eligible for this approach when considering liver function, portal pressure, remnant liver volume after surgical resection, and performance status. Vitale *et al.* [2] indicated that surgical resection can prolong survival compared with loco-regional therapy in patients with hepatocellular carcinoma (HCC), regardless of the Barcelona Clinic Liver Cancer (BCLC) stage, provided that liver dysfunction (Child-Pugh Class B or Model for End-stage Liver Disease score >9) and poor performance status (Eastern Cooperative Oncology Group >1) are absent. Indeed, it is more important to identify optimal candidates who will benefit from multi-disciplinary approaches rather than offering a formulaic treatment modality. Accordingly, nonsurgical approaches can also be considered in a patient with early stage HCC to avoid the risk of postoperative complications, including hepatic insufficiency and mortality, particularly for those with a morphologically cirrhotic liver on a pre-operative radiological assessment. In this clinical setting, orthotopic liver transplantation (OLT) is a better option than surgical resection as it manages the underlying cirrhotic liver and HCC simultaneously. However, OLT is often ineligible due to the shortage of appropriate donors in South Korea.

Approximately, one-third of our study participants had a tumor burden within the Milan criteria [3], i.e., BCLC early stage, in which surgical resection or OLT may be recommended according to the degree of underlying liver disease. Surgical resection should be performed with caution in highly selected patients with BCLC early stage HCC and a morphologically cirrhotic liver, if they do not receive a suitable graft quickly. Furthermore, although patients who show BCLC early stage HCC and morphologically non-cirrhotic liver may be obviously good candidates for

surgical resection, nonsurgical approaches can be considered in clinical practices for several reasons, such as patient refusal to undergo surgical resection, old age, relatively poor performance status, accompanying co-morbidities, evidence of portal hypertension, high indocyanine green retention test at 15 min, high liver stiffness value assessed using transient elastography [4,5], and inappropriate location for surgical resection based on the remnant liver volume.

The major aim of our study was to assess the impact of achieving a complete response (CR) at an early time point among patients with HCC treated with transarterial chemoembolization (TACE), not to compare the clinical outcomes between treatment modalities. When we stratified the 298 patients without tumor invasion of the peripheral portal vein branches into three groups; patients within the Milan criteria [3], patients beyond the Milan criteria, but within the up-to-seven criteria [6], and patients beyond the up-to-seven criteria, the patients within the Milan criteria had the highest CR rate (initial response, 82.9%), followed by those beyond the Milan criteria, but within the up-to-seven criteria (59.2%) ($p < 0.001$ vs. those within the Milan criteria), and those beyond the up-to-seven criteria (13.7%) ($p < 0.001$ vs. those beyond the Milan criteria, but within the up-to-seven criteria). Similarly, in the view of achieving a CR as the best response, patients within the Milan Criteria had the highest CR rate of 88.6%, followed by those beyond the Milan criteria, but within the up-to-seven criteria with 74.5% ($p = 0.009$ vs. those within the Milan criteria) and those beyond the up-to-seven criteria with 40.0% ($p < 0.001$ vs. those beyond the Milan, but within the up-to-seven criteria) (Table 1). We agree that better clinical outcomes are anticipated after TACE in patients with a smaller tumor burden, but the prognostic significance of achieving a CR as the initial and best response was also observed in all three subgroups. Patients who achieved a CR (both initial and best response) had a longer median overall survival than the others