



Comment on: “A review on radiofrequency, microwave and high-intensity focused ultrasound ablations for hepatocellular carcinoma with cirrhosis”

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We read with great interest the published article of Cheung *et al.* (1) on *Hepatobiliary Surgery and Nutrition*.

The authors provided a comprehensive review and critical evaluation of the three main locoregional ablation (LRA) techniques for liver cancer: radiofrequency (RFA), microwave (MWA), and high-intensity focused ultrasound ablations (HIFU). The focus of the paper is on their application to patients affected by hepatocellular carcinoma (HCC) in the context of end-stage liver disease.

The topic is extremely important as it is in constant development. HCC accounts for more than 80% of liver tumors, usually arising in the context of liver dysfunction and cirrhosis, where the energy dispersion of the LRA is completely different compared to a non-cirrhotic liver due to fibrosis.

If chronic viral hepatitis and alcohol-related liver disease are still the main risk factors for chronic liver disease and HCC, in high-income countries nonalcoholic fatty liver disease (NAFLD) is a growing risk factor for HCC. In Asia and North America, in less than 30 years, the prevalence of NAFLD increased from 20% to 30%, with an estimated prevalence of liver fibrosis in 3.2% and 10.3% of the patients, reaching 17% in some Asiatic studies (2).

In this picture and especially with the expansion of the NAFLD disease, the correct diagnosis and treatment for HCC are essential.

However, HCC treatment is complex and requires a multidisciplinary evaluation (hepatologists, hepatobiliary and transplant surgeons, radiologists, anesthesiologists), especially for cirrhotic patients. Unlike other tumors, the HCC prognosis is not only related to the tumor behavior, but also to the underlying liver disease.

Cheung *et al.* described in detail the pro and cons of each technique (RFA, MWA, and HIFU), pointing out their different efficacy and safety based on the tumor characteristics (size, position, numbers) and timing of use [i.e., bridge therapy, combination with transarterial chemoembolization (TACE) in advance liver dysfunction] (1).

However, in daily practice, the patient should be the starting point, not the therapeutic tool, and the physicians should address the question: which is the best treatment for that patient? How that treatment will affect the underlying liver disease?

The efficacy of these procedures is related not only to the techniques themselves but mainly to the patient's selection and who will benefit the most from each of the procedures.

Furthermore, these procedures have to be evaluated in the context of other therapeutic options: liver resection (LR), liver transplant (LT), and the promising results of the systemic therapies based on multi-kinase inhibitors (sorafenib and regorafenib), vascular endothelial growth factor receptor inhibitors (lenvatinib and cabozantinib),

and immunotherapy (nivolumab and pembrolizumab) (3).

The decision of the therapeutic options should be tailored to the patient (personalized medicine) evaluating three main factors that can affect the HCC prognosis: the stage of the tumor, the liver function, and the general health status of the patient.

In this context, multiple score systems have been proposed to guide the physician to choose the best treatment option.

The most known and common algorithm used to guide treatment decisions, thanks to its ease of use and the therapeutic indications for each stage, is the Barcelona Clinic Liver Cancer (BCLC) staging system. It is based on prognostic variables and the stage of the disease, validated from randomized controlled studies, and endorsed by many guidelines (AASLD, EASL-EORTC, and ESMO-ESDO). LT, LR, and LRA are considered potential curative tools in the early stage (BCLC 0 and A), while in the intermediate stage (BCLC B) TACE is considered the standard of care. Stage C and D are usually covered by medical therapy and the best supportive care is considered palliative treatments. However, the BCLC algorithm is considered too rigid by many authors (especially in stage B) because each stage is too strictly related to the therapeutic option. The BCLC has been upgraded in 2022, including in the discussion of the concept of treatment stage migration (TSM) and the untreatable progression (UTP), pointing out the need for a multidisciplinary, and individual approach to the patient. This is true, especially in the BCLC B stage, which includes a heterogeneous group of patients, where many authors considered LRA applicable (4).

Furthermore, new staging systems are rising, with a better ability to predict the prognosis in HCC patients, such as the HKLC and ITA.LI.CA staging scores (5,6). In particular, in the ITA.LI.CA staging score, the treatment is not guided by the stage of the disease (stage hierarchy), but by the most effective therapy beneficial for that patient (therapeutic hierarchy) (7). In this score, LRA can be applied in a highly selected patient with HCC on BCLC stage B (8).

In conclusion, HCC treatment in the context of cirrhosis is demanding, not only for the underlying chronic disease and the complexity of the patients at high risk of clinical decompensation, but also for the choice of the best treatments. HCC can be treated by several tools: LT, LR, systemic therapy, and as described by Cheung *et al.*, LRA (RFA, MWA, and HIFU). The main point is to correctly

choose the therapeutic options, to reach the lowest recurrence rate and the best overall survival for that patient.

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