



Combining loco-regional treatments in early hepatocellular carcinoma: new achievements overcoming old limitations

Nelci Antunes de Moura, Fernando Gomes Romeiro

Department of Internal Medicine, Botucatu Medical School, UNESP – Univ Estadual Paulista, Botucatu, Brazil

Correspondence to: Prof. Fernando Gomes Romeiro, PhD. Distrito de Rubião Jr., Zip Code 18 608 917, Botucatu, São Paulo State, Brazil.

Email: fgromeiro@fmb.unesp.br.

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Hepatocellular carcinoma (HCC) is the most common primary liver tumor and one of the few malignant diseases that is still increasing around the world. Countless patients are stricken by HCC worldwide, and the tumor incidence is notably linked to the prevalence of other liver diseases such as hepatitis B, hepatitis C, alcohol abuse, non-alcoholic steatohepatitis and any other disease that can cause liver cirrhosis. In the Western countries, it is estimated that more than one million people die due to HCC each year (1). The impact of HCC has led to the development of numerous treatment modalities and algorithms in order to provide better strategies to the patients. However, curative treatments are only proposed for a restricted group of cases that had the tumor diagnosed in the early stage, before the emergence of any type of local or systemic complications (2,3).

Current recommendations regarding curative strategies comprise tumor ablation [such as radiofrequency ablation (RFA)] and surgical procedures (such as liver resection or transplantation) (2,3). As a rule, the increasing number of HCC cases and the shortage of liver donations make resections and ablations a growing necessity. Consequently, the use of these procedures has been encouraging for more and more patients, including those waiting for liver transplantation (LT). Thus, if a given patient with HCC is supposed to spend more than 6 months on the LT list, the current recommendation is to perform a local treatment as a bridge therapy, such as partial resection, transarterial chemoembolization (TACE) or RFA (4). The strategy of using loco-regional procedures for HCC treatment has also been a reason to exceed the parameters stated by the

guidelines by offering a curative treatment even when the tumor cannot be included within the limits proposed for a surgical treatment. For instance, many studies have accomplished good results by combining treatment modalities that could never be used together for a given patient, because they are recommended for different tumor stages.

This is the case when TACE, a procedure applied for patients with intermediate tumors, is combined with treatment modalities used for advanced or early tumors. Many articles have been written about the success rates achieved by combined treatments for patients with intermediate and/or advanced tumor stages, because the amount of patients with such conditions has been higher than the number of cases with early stage HCC (5-9). However, the spreading of surveillance programs around the world has been increasing the number of tumors diagnosed in the early stage. As a result, many trials have combined two treatment modalities for patients with small tumors, which are very useful because these tumors have a better prognosis and can be submitted to curative therapies, even when surgical procedures cannot be offered.

In an interesting work, Vasnani *et al.* compared two modalities of tumor ablation performed after TACE (10). The subjects were submitted to RFA from 2005 to 2009, and microwave ablation (MWA) from 2009 to 2015. One day before the ablation therapy, all the patients were submitted to a drug-eluting bead TACE (DEB-TACE). The results obtained were assessed by multi-phase computed tomography (CT) before and at three-month intervals for

the first year, and then at six-month intervals until LT. To assess local response, the authors applied the European Association for the Study of the Liver (EASL) criteria (11). After LT, all the explanted livers were evaluated to calculate the percentage of tumor coagulation. A remarkable finding is that even patients with three or more tumors obtained good results, particularly in the RFA group. Comparing their results with trials using only RFA, the authors showed a striking achievement by combining DEB-TACE with RFA or MWA.

Although the article aimed to compare the results obtained by the two strategies, other findings must be highlighted. First, the authors showed that the ablation techniques performed after DEB-TACE achieved outstanding radiological results, with most subjects attaining complete response. Second, they had excellent histopathological results regardless of the ablation technique. The mean tumor coagulation was around 90% in the explanted livers, showing a strong agreement between radiological and histopathological results. The correlation between the EASL criteria and the tumors examined in the explanted livers was also registered in a similar study performed by Gordic *et al.* (12), which was somewhat different from the one published by Vasnani *et al.* For instance, this latter study included some patients with advanced cirrhosis and used MRI instead of CT, because the aim was to compare the performance of various MRI-based response criteria. Even so, the agreement between the EASL criteria and the tumors evaluated in the explanted livers was similar.

Combining loco-regional therapies is a promising strategy to work around the shortage of organ donations, thereby avoiding the tumor growth while LT is not available. It can also be a means for treating tumor recurrence or new lesions after a putatively curative treatment such as resection. At best, it can achieve tumor coagulation of 100%, which can be viewed as a temporary curative procedure. However, the risk of recurrence and/or the occurrence of new lesions must be always kept in mind. Worth mentioning, in all these settings the loco-regional therapies are still limited to patients submitted to strict surveillance programs to diagnose tumors in the early stage. The study performed by Vasnani *et al.* included only two patients with intermediate-stage HCC (3% of the DEB-TACE/MWA group). Unfortunately, the results of TACE and RFA procedures for intermediate stage HCC are very different (13-17).

In spite of the methods applied, HCC treatment is

highly dependent on specific patients' conditions. For instance, patients with HCC graded as B1 or B2 according to the subclassification of the intermediate stage (18) are more likely to achieve better survival rates after RFA, even without TACE, but this outcome is not attained by those with tumors graded as B3 or B4 (13). In the future, other strategies can also be combined to accomplish better results, such as adjuvant therapy. Since RFA and TACE induce transient devascularization followed by neo-angiogenic stimuli (19), some authors have investigated whether using additional drugs for patients submitted to loco-regional procedures would be valuable (19-21). Some studies achieved good results while other seemed disappointing, but this matter still requires a deep analysis after many more clinical trials. For now, the message of Vasnani and collaborators is that treating HCC can attain outstanding successful rates by combining early diagnosis with the best treatment strategy according to each patient's condition.

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