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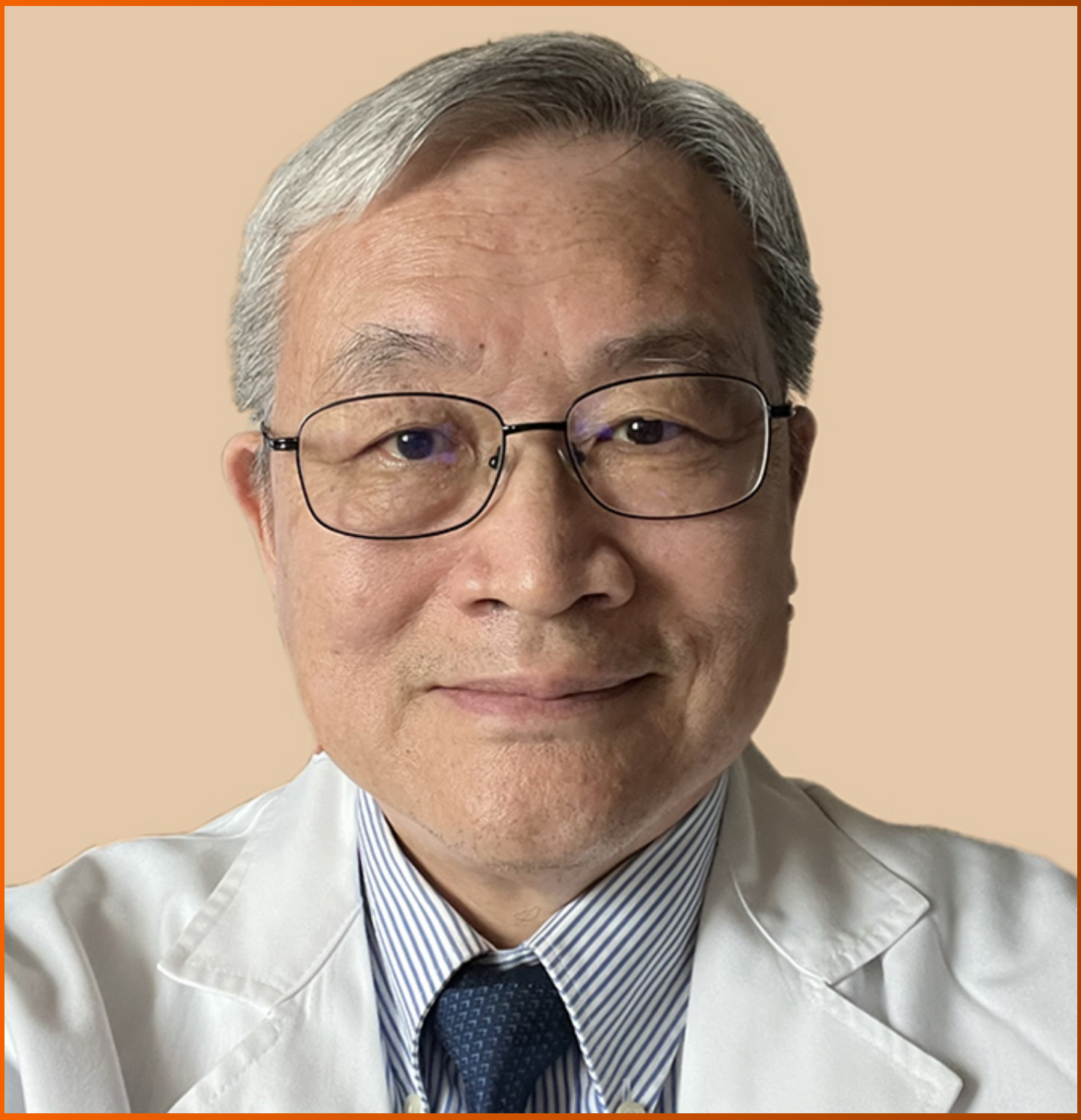

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Editorial Board Member of *World Journal of Gastroenterology*, Dar-In Tai, MD, PhD, Senior Attending Doctor, Professor, Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Taipei 105, Taiwan. tai48978@cgmh.org.tw

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LETTER TO THE EDITOR

Impact of neoadjuvant multimodal therapy in the setting of locally advanced hepatocellular carcinoma

Daniele Ferraro, Federica Falaschi, Luca Nazzaro, Giovanni Vennarecci

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Daniele Ferraro, Federica Falaschi, Luca Nazzaro, Giovanni Vennarecci, Hepato-biliary and Liver Transplant Centre, Department of General Surgery and Woman's Health, AORN Antonio Cardarelli, Naples 80131, Italy

Corresponding author: Daniele Ferraro, MD, Consultant in HPB Surgery and Liver Transplantation, Hepato-biliary and Liver Transplant Centre, Department of General Surgery and Woman's Health, AORN Antonio Cardarelli, Naples 80131, Italy.
daniele.ferraro@aocardarelli.it

Abstract

Immunotherapy and the implementation of more aggressive treatment schemes for locally advanced hepatocellular carcinomas have expanded the boundaries of curative options. Because of these advancements, patients who were once considered beyond the aim of a cure are now eligible for liver transplantation and resection.

Key Words: Hepatocellular carcinoma; Immunotherapy; Radioembolization; Chemoembolization; Liver transplantation; Liver resection

Core Tip: The field of treatment for hepatocellular carcinoma is constantly evolving due to the advances in highly effective chemotherapeutic regimens. The possible use of drugs in the neoadjuvant setting as a powerful downstaging tool opens up the possibility of liver transplantation or liver resection for patients once deemed incurable. The use of these drugs in the adjuvant therapy setting could reinforce the results of surgery in the treatment of hepatocellular carcinoma.

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TO THE EDITOR

We read with great interest the paper by Wu *et al*[1], who presented a retrospective study comparing the oncological outcomes of two arms of patients affected by hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) with or without distant metastasis, who underwent either triple therapy with transarterial chemoembolization (TACE) combined with PD-1 inhibitors and lenvatinib or TACE plus lenvatinib alone.

Despite the limits of the study (*i.e.*, its retrospective nature, limited study population, and different proportions of patients with metastatic disease in the two study groups), we agree with the authors of the study that multimodal therapy for locally advanced HCC shows superior results in terms of local control of the disease, downstaging ability, and prolonged time to progression.

We have already published a case of a patient with locally advanced HCC of segment IX with satellite nodules, alpha-fetoprotein > 3000 ng/mL, left portal vein tumor thrombosis with partial response to TACE, and complete and persistent radiological and biological responses to neoadjuvant therapy with lenvatinib[2]. However, since this publication, treatment options have advanced and expanded. The application of immunotherapy with a PD-1 inhibitor and anti-CTLA-4 has been proven as an effective tool to downstage locally-advanced HCC patients, allowing curative treatments such as salvage liver transplantation and liver resection[3].

Patients who achieve a partial response after conversion therapy benefit from liver resection or liver transplantation as the only curative option remaining. Indeed, it has been shown that surgery after locoregional treatment with a partial response improves overall survival (OS)[4]. Performing surgery after conversion therapy that leads to a complete response, however, remains a matter of debate. The gold standard therapeutic approach is still questionable, and solid scientific evidence is lacking. There is evidence, though, that a watch-and-wait approach might be safe and feasible for these patients[5]. Arguments in favor of surgical resection after complete radiological response include the possibility of persistent microscopic residue only evident on resected specimens and the possibility of *in situ* recurrence after a complete response. Future research on circulating molecular markers could provide an implementation strategy for a watch-and-wait approach in well-selected cases. In our case, the patient remained cancer-free for more than 2 years and was ineligible for liver transplantation as liver function remained stable and the disease did not recur.

When HCC involves the major portal vein branches, we believe radioembolization performs better for local control. There is a better possibility of complete regression of neoplastic thrombosis[6], better control of microvascular invasion [7], and improvement of time-to-progression compared to other transarterial locoregional therapies[8]. Stable and durable response to radioembolization could serve as a tool to test HCC biology in the setting of downstaging prior to liver transplantation. Many groups[7,8], including ours[6], have shown acceptable oncological outcomes of liver transplantation in patients affected by HCC complicated by PVTT.

A mindset change is needed for the issue of treating HCC with PVTT. PVTT can partially or completely respond to radiotherapy (stereotactic body radiation therapy/external beam radiation therapy/selective internal radiation therapy), TACE, proton beam therapy, or systemic therapy, used alone or in combination, thus improving progression-free survival and OS. Soin *et al*[9] showed 5-year OS and recurrence-free survival rates of 53% and 52%, respectively, in patients who successfully downstaged to stable disease. These rates are far superior to the 10% OS at 3-year expected by the Barcelona Clinic Liver Cancer (BCLC) staging and treatment algorithm. These data translate into a huge transplant benefit measured for these categories of HCC patients.

Similar results have been achieved by Serenari *et al*[10] and Assalino *et al*[11] who showed a 5-year OS of 60% in patients who were successfully downstaged and received a liver transplantation. Careful selection of patients with HCC with favorable biology (small tumor sizes, low alpha-fetoprotein level, low tumor grade, low avidity on fluorodeoxy-glucose-positron emission tomography) is warranted to obtain adequate oncological results. In this scenario, a living donor donation may be advantageous because it is favorable for a planned and timely transplant and it avoids depletion of the already scarce pool of deceased donors.

Under these premises, however, it could be postulated that brand new scenarios might be faced in the foreseeable future. With the advent of highly active locoregional and biological therapies, after an appropriate test of time, two questions arise: (1) Would it be possible to label patients within BCLC stage B and C who achieve complete response biologically and radiologically as cured? or (2) Should we proceed to liver transplantation anyway, having achieved just a very good downstaging? The vast majority of HCC patients seen in our clinics nowadays belong to BCLC stage B and C, which is by definition biologically very aggressive. Offering a pre-emptive liver transplant, *i.e.*, without radiologic or biologic evidence of residual/recurrent disease, after an appropriate test of time, might represent the only potentially curative option for these categories of HCC patients. However, as far as allocation policies are concerned, it remains unclear whether these patients that might not have MELD scores sufficient to be listed for transplantation should be prioritized or not and in what measure in a system that provides patients with untreatable HCC or with partial response to bridge therapy with exception points in the waiting list. Regardless of what the right answer will be proven to be, we should start looking at patients with locally advanced HCC or portal neoplastic thrombosis as a focus for our best efforts in order to rescue a portion of them so that they are candidates for curative options, although those are few, according to the principles of treatment stage migration and therapeutic hierarchy.

The results of the IMbrave050 trial[12] demonstrated the ability of the combination of atezolizumab-bevacizumab to improve the recurrence-free survival of patients with resected or ablated HCC. It is advisable to enroll patients with HCC with a high risk of recurrence in prospective and randomized studies to further investigate the role in the adjuvant setting of other lines of immunotherapy, such as durvalumab/tremelimumab. The latter combination of drugs, available in Italy since last April and with areas of application similar to atezolizumab/bevacizumab and lenvatinib, showed promising results in terms of overall survival compared to sorafenib in patients with unresectable HCC, in a recent phase-3 trial[13].

In conclusion, we are facing a rapidly growing body of neoadjuvant systemic treatment schemes that may in the future be used as adjuvant therapies. Robust data on which therapies will stand the test of time and represent the standardized treatment for locally advanced HCC in the neoadjuvant and adjuvant settings are much needed. Undoubtedly, liver transplantation and resection still represent curative options. Their utility is bound to increase as the abovementioned therapies allow locally advanced HCC patients to become eligible for these treatments. Approximately 1700 liver transplants were performed in Italy in 2023. Among those, more than half listed HCC as the main indication. The steady decline of viral etiologies as main indications, along with the implementation of the highly active biologic therapies, will continue to increase the number of liver transplantations performed for HCC.

FOOTNOTES

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Country/Territory of origin: Italy

ORCID number: Daniele Ferraro 0000-0002-1022-8864; Giovanni Vennarecci 0000-0001-9727-4304.

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