



## Downstaging strategies for unresectable hepatocellular carcinoma

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### Abstract

A significant number of patients with hepatocellular carcinoma (HCC) are usually diagnosed in advanced stages, that leads to inability to achieve cure. Palliative options are focusing on downstaging a locally advanced disease. It is well-supported in the literature that patients with HCC who undergo successful conversion therapy followed by curative-intent surgery may achieve a significant survival benefit compared to those who receive chemotherapy alone or those who are successfully downstaged with conversion therapy but not treated with surgery. Hepatic artery infusion chemotherapy can be a potential downstaging strategy, since recent studies have demonstrated excellent outcomes in patients with colorectal liver metastatic disease as well as primary liver malignancies.

**Key Words:** Unresectable hepatocellular carcinoma; Hepatic arterial infusion chemotherapy; Downstaging; Hepatocellular carcinoma

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**Core Tip:** Patients with hepatocellular carcinoma who undergo successful conversion therapy followed by curative-intent surgery may achieve a significant survival benefit compared to those who receive chemotherapy only without surgery. Hepatic artery infusion chemotherapy can be a potential downstaging strategy, since recent studies have demonstrated excellent outcomes in patients with colorectal liver metastatic disease as well as primary liver malignancies.

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## TO THE EDITOR

We read with great interest the meta-analysis from Cao *et al*[1] showing that triple therapy, including hepatic artery infusion chemotherapy (HAIC) combined with angiogenesis inhibitors and programmed cell death protein 1/programmed death ligand 1 blockers (AIPB) were able to increase the survival in cases of unresectable hepatocellular carcinoma (uHCC) more than AIPB regimens. This meta-analysis strongly suggested that HAIC-based treatments are likely to be the best choice for uHCC.

We agree with the conclusions of the authors and the urge for analyses at the cellular level and additional large-scale randomized controlled trials[1]. It is well known that HCC is the most common primary liver cancer[2]. Even though treatment of early HCC seems to achieve cure in most patients, unfortunately, a significant number of patients with HCC are diagnosed in advanced stages[3]. This fact leads to inability to achieve cure. Palliative options are focusing on downstaging a locally advanced disease. In their meta-analysis, the authors did not present strong data about the rate of conversion to resectability, if any, in the group of patients with unresectable, liver confined, disease for both the triple therapy and the AIPB groups. We suspect that some patients could become eligible for locoregional therapies after downstaging, that will revolutionize and liberalize treatment options for this category of HCC patients. It is well-supported in the literature that patients with HCC who undergo successful downstaging therapy followed by curative-intent surgery may achieve a significant survival advantage compared to those who receive chemotherapy only or those who are successfully downstaged without being followed by surgery. As the authors highlighted, even if the success rate of conversion varies greatly, ranging from 0.8% to 60% and depending on the therapeutic protocols, combined locoregional and systemic downstaging treatment shows significant benefit, with a downstaging rate of up to 60% and a disease stability rate of up to 100%[4].

Moreover, the authors omitted to acknowledge the difficulties starting and maintaining a HAI-pump program. Popularization and development of HAI pump chemotherapy programs has been limited by logistic and feasibility concerns. Despite recent studies demonstrating excellent outcomes in patients with colorectal liver metastatic disease as well as primary liver malignancies[5], many challenges are encountered when building that mainly have to do with lack of multidisciplinary care, lack of access to device/equipment access and chemotherapeutic drugs[6]. Another concern about the popularity of HAIC is the fact that its safety and efficacy has been limited to centers of excellence increasing number of new HAI programs emerging across the world. In the same vein, as HAI programs continue to develop and evolve and consider pump as an available downstaging modality, it is of paramount importance to develop a quality frame for HAI utilization that could lead to optimization regarding safety of patients and minimization of toxicity.

## FOOTNOTES

**Author contributions:** Karachaliou GS and Moris DP designed the research study; Dimitrokallis N and Moris DP performed the research; Karachaliou GS and Moris DP analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

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