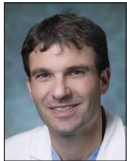


# HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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## Locoregional Therapy for Patients With Hepatocellular Carcinoma



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### **G&H** What are the most common types of locoregional therapy used in hepatocellular carcinoma?

**JFG** There are 2 major types of locoregional therapy used in hepatocellular carcinoma (HCC): percutaneous ablation (either chemical or thermal) and intraarterial chemoembolotherapy. Percutaneous ablation consists of inserting a needle directly into the tumor under image guidance (either ultrasound or computed tomography) to destroy the tumor through heating, freezing, or the application of alcohol. Although percutaneous ethanol ablation is still being performed in some parts of the world, such as Asia, it has largely disappeared from the United States. In this country, percutaneous ethanol ablation has been replaced by thermal-based ablations, such as radiofrequency ablation, microwave ablation, and cryoablation. Percutaneous ablation is typically reserved for early-stage HCC (Barcelona Clinic Liver Cancer [BCLC] stage A) and is therefore limited to tumors 3 to 4 cm or smaller and less than 3 in number. In these conditions, ablation is considered curative and therefore nearly, if not completely, equivalent to other surgical therapies. In fact, percutaneous ablative therapies have been included in all the guidelines for HCC as curative treatments, along with transplantation and surgical resection.

The other type of locoregional therapy is intraarterial-based and consists of utilizing the hepatic artery to deliver highly concentrated doses of chemotherapy or radiation directly to the tumor, sparing the healthy liver tissue in the process. This approach stems from the fact that the liver has a dual blood supply, with most of the blood coming from the portal vein that brings all the nutrients to the liver from the gut to be processed, and only a small fraction coming from the hepatic artery. However, liver tumors draw their blood supply almost exclusively from the hepatic artery, thereby providing a unique roadway to the tumors. In

this way, catheters can be manipulated deeply within the arterial liver circulation in close proximity to the tumors. After this step, toxic doses of chemotherapy (in the case of chemoembolotherapy, also called transcatheter arterial chemoembolization [TACE]) or high doses of radiation (in the case of radioembolization) can be delivered directly to tumors. Because the healthy liver is mostly supplied by the portal vein, it is largely spared, minimizing toxicities. These procedures also are performed under image guidance, using fluoroscopy, and have been perfected over the past 20 years. In fact, chemoembolization has become the mainstay of therapy for patients with unresectable HCC, and is considered the standard of care. Indeed, chemoembolization is by far the most commonly performed procedure in the world for patients with HCC. Its track record as an effective therapy is no longer in question, as it too has been incorporated in all the treatment guidelines for HCC, albeit limited to patients with intermediate-stage disease (BCLC stage B). The standard of practice is slightly different, however, because patients with even more advanced disease—that is, those with early BCLC stage C disease, who have limited macrovascular invasion, preserved liver function, and a good performance status (ECOG 0-1 using the Eastern Cooperative Oncology Group scale)—also would be considered for treatment with chemoembolization and possibly radioembolization.

### **G&H** How effective is locoregional therapy in patients with HCC?

**JFG** It clearly depends on the stage of the disease. As mentioned earlier, ablation can be considered curative when performed for patients with early-stage HCC (BCLC stage A), whereas TACE is largely palliative because it is used for patients with unresectable HCC. The only exception is when TACE is used as a bridge to transplant. In such cases, TACE

allows patients to remain on the transplant list, thereby offering a chance for curative treatment. However, in the vast majority of cases—that is, patients with intermediate- to advanced-stage HCC—TACE has been shown to improve survival in a number of randomized trials and prospective studies, from 16 months when best supportive care is provided to 20 and even possibly 24 months. Some studies with drug-eluting beads, a new drug delivery system, have even reported median survival of 47 months for BCLC stage B patients. It is therefore clear that TACE improves patient survival, which is why it is now included in all treatment guidelines. In addition, there has been a tremendous degree of technical improvement related to the actual technique of TACE. The advent of cone-beam computed tomography imaging during the procedure has improved the ability to visualize, target, and treat tumors in the liver, thereby improving the potency of TACE while minimizing further its potential toxicity to the healthy liver. However, controversy remains for patients who demonstrate more advanced disease—that is, those considered BCLC stage C. Whereas the standard of practice in most Asian countries and in the United States would include TACE to treat such patients, no prospective randomized trials have demonstrated a substantial benefit of TACE. For those patients, the guidelines recommend treatment with sorafenib (Nexavar, Bayer/Onyx). Yet, because many studies have reported survival rates with TACE superior to those established with sorafenib, many experts in the field support using TACE as the first line of therapy for BCLC stage C patients. Recent data from Hong Kong, which led to the creation of a new staging system for HCC, would support such an approach.

Data on radioembolization are scarcer, and no prospective study to date has shown radioembolization to be superior to TACE in terms of patient survival. This explains why radioembolization has yet to be formally included in treatment guidelines.

### **G&H** What are the most common adverse events and limitations associated with these treatments?

**JFG** Adverse events for ablation are limited, and the procedure generally is very well tolerated. One potential problem with ablative technique is the need to access the tumor through the skin, which can be difficult in cases in which the tumor is located in close proximity to another organ or major blood vessel. Technological improvements that have come to light in the past few years, such as hydrodissection to push bowel or organs away from the planned needle track, have largely remedied such problems. Although rare, another potential problem with percutaneous ablation is tumor seeding, which could have devastating consequences because it would preclude a patient from being eligible for transplantation. There too, advances in needle insertion kits have reduced this potential risk to almost zero.

As for intraarterial therapy, the adverse events and limitations depend on whether chemotherapy or radiation is used. One clear advantage of radioembolization over TACE is the fact that it is extremely well tolerated, with minimal side effects. In fact, the procedure can be performed on an entirely outpatient basis. Bone marrow suppression is exceedingly rare, and patient quality of life after treatment is generally excellent. Typical side effects include fatigue or loss of appetite, but these are usually short-lived.

Although TACE tends to be fairly well tolerated, toxicities and side effects are more commonly encountered than after radioembolization. Patients may experience postembolization syndrome, a constellation of nausea, vomiting, abdominal pain, fatigue, profound asthenia, and alopecia. Although typically transient (symptoms may last 1-2 weeks after TACE), they should not be ignored or trivialized. It is estimated that 20% to 40% of patients will experience such side effects, with a variable range of severity after TACE. Patients must therefore be followed closely to mitigate these symptoms. Nontarget embolization also can be a problem. This occurs when chemotherapy or radiation beads are deployed in undesired areas; that is, far from where the tumors are located. The gallbladder is one such possibility. Fortunately, nontarget embolization of the gallbladder rarely results in the need for a surgical cholecystectomy. In radioembolization, it is critical to ensure that no radioactive beads end up in the stomach or proximal small bowel. The consequences of this could be quite dire. Ulcers and even perforation can take place, leading to death if not recognized early. It is fairly common for patients to be treated with prophylactic measures, such as sucralfate and proton pump inhibitors, to prevent such occurrences.

Finally, it is almost certain that marked elevation of liver enzymes will take place after TACE. Again, as with other toxicities after TACE, such elevation is typically a transient effect. Nonetheless, clinicians should be aware that it may occur and should monitor the patient carefully to ensure that the levels come down to respectable numbers by the time the patient returns to the clinic for imaging to evaluate tumor response.

### **G&H** Is there a consensus on the definitions of locoregional therapy failures and ineligible patients?

**JFG** This question is a very difficult one to answer. The short answer is that there is no clear consensus, but we are making progress. A group of internationally recognized experts in HCC, including myself, has met on a number of occasions to address this issue specifically. I am pleased to say that we have come a long way and that a consensus is indeed emerging. First, TACE is the gold standard for unresectable HCC, and radioembolization probably should not be used as first-line therapy in HCC. Second, at least

2 TACE treatments to the same tumor area should be performed before considering another option. Third, the goal of TACE should be to produce at least a partial response using the modified Response Evaluation Criteria in Solid Tumors guidelines. If patients still do not respond after these recommendations have been followed, then another therapy—considered second-line—should be considered.

In terms of ineligibility, the answer is a little more straightforward. For ablation, as already mentioned, patients who present with tumors greater than 3 to 4 cm in size and more than 3 in number would be considered ineligible. For TACE, patients presenting with very advanced HCC (BCLC stage C) along with a high performance status (ECOG  $\geq 2$ ), compromised liver function, and the presence of macrovascular invasion and/or extrahepatic metastases should not be treated, as the likelihood of a benefit would probably be nonexistent.

### G&H How often does treatment failure occur?

**JFG** I do not like to use the term *treatment failure* when dealing with locoregional therapies because we know that when treating patients with cancer, the treatment almost always invariably fails. Only in rare instances have we been able to cure patients with cancer. In the case of HCC, we have made considerable progress. For every stage of the disease, we now have a treatment that clearly benefits patients: for early-stage disease, surgery or ablation; for intermediate-stage disease, TACE; and for advanced-stage disease, sorafenib and possibly TACE or radioembolization. However, we still have a long way to go.

To answer the above question in terms of TACE, we can safely say that lack of response after at least 2 to 3 treatments to the same tumor area would result in considering another treatment option, and could be called treatment failure. However, it is critically important to distinguish lack of response from tumor recurrence. We know that tumor recurrence is quite common and when it occurs, retreatment with ablation or TACE is recommended.

### G&H If a patient's disease fails to respond to locoregional therapy, what are the next steps?

**JFG** As mentioned earlier, if the treatment did not elicit a significant response in the treated tumor, then another locoregional approach should be considered. This is where radioembolization can play an important role, as a second-line treatment following TACE. When the option of locoregional therapy is no longer available, systemic treat-

ment with sorafenib should be considered. If this is not an option either, a phase 1 clinical trial should be proposed.

### G&H Is there any benefit to using sorafenib in combination with locoregional therapy?

**JFG** We performed the initial study in the United States using the combination of sorafenib and TACE, with a primary endpoint of toxicity. We found that it was safe to administer sorafenib and TACE at the same time throughout all of the planned TACE sessions and that the combination therapy was effective provided that the patients stayed on sorafenib for at least 6 months. In such cases, the survival benefit was quite demonstrable, especially for patients with advanced-stage HCC (BCLC stage C). The rationale for combining TACE and sorafenib is scientifically sound because sorafenib mostly has antiangiogenic effects. These counteract the proangiogenic effects of TACE, which are likely the main driver of tumor recurrence after TACE. What was especially interesting in our study, and confirmed by others since, is the fact that the treatment duration with sorafenib may play a very important role in keeping the HCC tumor in check. If these findings are confirmed in prospective randomized trials, the combination of TACE and sorafenib could indeed be considered as first-line treatment for both intermediate- and advanced-stage HCC patients (BCLC stages B and C).

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