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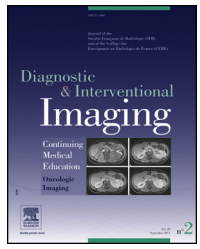

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Transarterial chemoembolization for hepatocellular carcinoma: An old method, now flavor of the day

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Abstract Transarterial chemoembolization (TACE) is the recommended treatment for patients suffering from intermediate, B stage, hepatocellular carcinoma. Despite an undisputed pharmacokinetic advantage, TACE with microspheres has not been shown to be superior in terms of survival compared to conventional TACE using Lipiodol®. The best guarantee to reduce toxicity and maximize the efficacy of TACE is to strictly observe the contraindications for the procedure (Child-Pugh > B8, reduced portal flow, very large tumor, any technical contraindication and renal impairment), and rigorous application of the administration requirements for the Lipiodol® emulsion or loaded microspheres (assessment of hepatic vascularization investigating for accessory vascularization, injection methods). Tumor response should be assessed after four weeks by CT or MRI using the modified RECIST criteria.

With approximately 700,000 deaths annually, hepatocellular carcinoma (HCC) is the 3rd leading worldwide cause of cancers deaths after colorectal and lung cancers [1]. A positive diagnosis of HCC is based on its vascularization, studied in dynamic views after enhanced CT or MRI [2]. The use of the Barcelona Clinic Liver Cancer (BCLC) treatment algorithm is currently recommended by the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) societies to treat patients suffering from HCC [3]. The latest version of the algorithm was published in 2012 (Fig. 1).

Approximately 30% of patients are diagnosed in the early stage A of the BCLC classification. These patients are in good general health (WHO 0) and have a single nodule or up

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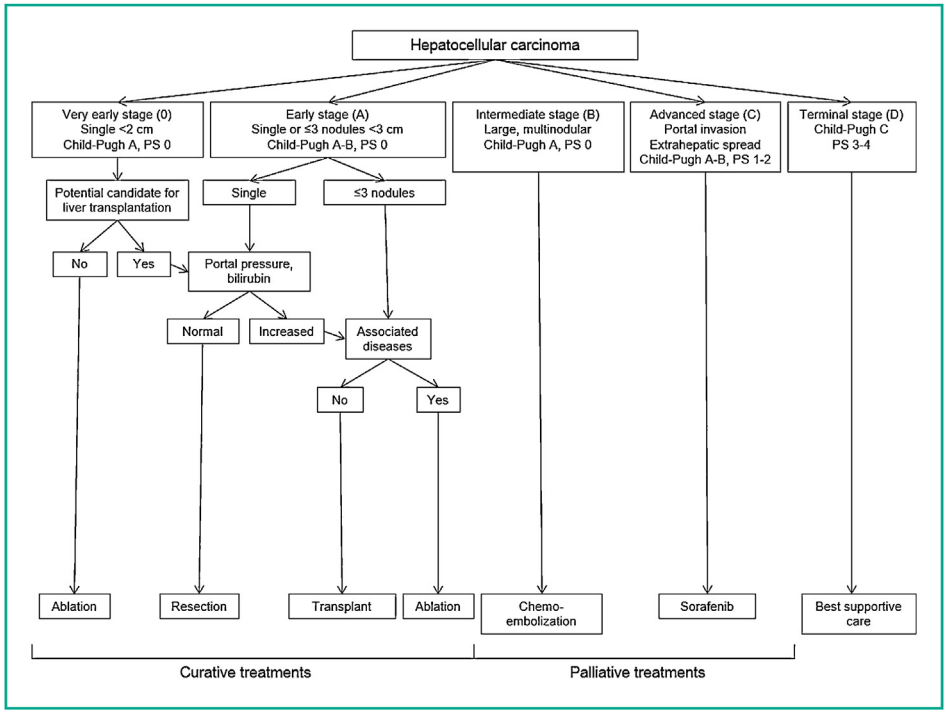

Figure 1. BCLC treatment algorithm.
Adapted from [13].

to three nodules each measuring under 3 cm in size. The curative treatments indicated at this stage, i.e. resection, transplantation and percutaneous destruction achieve a 5-year survival rate of over 50% in these patients who have preserved liver function. Resection is preferred if the liver is healthy (non-cirrhotic) and a single nodule is present, although this limits its use. Liver transplantation is limited by a lack of transplants. Percutaneous destruction (alcoholization and in particular radiofrequency ablation) is the most widely used curative treatment because of its similar efficacy to resection. Its limitations are the size and site of the tumor.

The BCLC classification intermediary B stage includes all patients who cannot be treated curatively (whose tumor is too large and/or is multifocal), but who are still asymptomatic, in very good general health and have preserved liver function (Child-Pugh up to B7). TACE is the recommended treatment for these patients. In patients with advanced (stage C) HCC, sorafenib (Nexavar®) is the treatment which is currently recommended and is the only drug to have been shown to significantly increase survival in these patients.

TACE

History

A French radiologist, Dominique Doyon, was the first to use arterial embolization to treat patients with HCC in 1974, using gelatin as the embolization agent [4]. The rationale for this was that HCC received most of their blood supply from the hepatic artery [5] and the hepatic artery could be occluded without causing complete necrosis of the organ as it continued to be supplied by the portal venous system.

The Japanese surgeon Konno subsequently discovered that if Lipiodol® was injected into the hepatic artery of patients suffering from HCC, it bound selectively to the tumor and accumulated there for long periods of time, up to several months. Konno et al. were the first to report the results of a pivot study on the use of an anticancer agent, styrene-maleic acid neocarzinostatin (SMANCS) mixed with Lipiodol® and injected IA into patients suffering from HCC [6].

Definition

TACE is a locoregional interventional radiology technique which uses the combination of IA injection of an anticancer agent with a vector (Lipiodol® or embolization microspheres) combined with arterial occlusion using resorbable (e.g. gelatin) or non-resorbable (e.g. sized particles) embolization agents when the Lipiodol® is used as a vector. In this latter situation, the term conventional TACE is used. When loadable microspheres are used they act both as a vector and as an embolization agent and the term TACE with microspheres is used. The technique was often limited in the past to arterial embolization alone or to IA chemotherapy with or without Lipiodol®. These are no longer recommended to treat HCC [3].

Compared to the intravenous administration conventionally used for chemotherapies, TACE has a dual theoretical advantage: it increases local concentration and the remanence time of the anticancer agent in the tumor tissue, increasing its therapeutic effects and reducing its diffusion outside of the liver and therefore its systemic toxicity. In