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

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KEYWORDS
Liver; Carcinoma; Transarterial chemoembolization; Therapeutic

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\textsuperscript{®}. 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\textsuperscript{®} 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.
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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
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
addition, embolization of feeder arteries to the HCC adds to the efficacy of the procedure, producing tumor necrosis as a result of ischemia.

Efficacy and toxicity

Since the first clinical study in 1983 which reported a significant reduction in alphafetoprotein concentrations and tumor size in patients suffering from HCC [6], more than 100 randomized or cohort studies have been published on the efficacy of TACE on HCC [7].

In 2002–2003, two randomized studies and two meta-analyses demonstrated that TACE significantly increased the survival of patients with inoperable non-metastatic HCC compared to supportive care or intravenous chemotherapy [8–11]. Based on these positive studies, TACE is deemed in 2015 to be the reference treatment in patients suffering from intermediary B stage HCC, i.e. patients with preserved liver function (Child-Pugh A or up to B7), and a large or multifocal tumor without vascular invasion or metastases and in the absence of symptoms (recommendation grade 1A) [3,12,13]. In 2011, a meta-analysis showed no benefit in terms of survival for TACE/embolization alone in patients with inoperable HCC [14] although the selection of studies included in the meta-analysis has been criticized. Beyond these clear recommendations it should be understood that intermediary B stage represents a heterogeneous group of patients in terms of features of their tumor (etiology, size, number of nodules) and liver function (Child-Pugh A/B). Not all of these patients gain the same benefit from TACE. A subclassification of B stage was therefore proposed in order to select patients most likely to benefit from TACE treatment [15]. The best candidates are uni- or pucinodular disease without vascular invasion or metastases, who are asymptomatic and have a Child-Pugh stage of ≤ B7 [15–18]. TACE achieved a median survival of over two years in these patients. Finally, an expert panel has defined absolute contraindications to TACE as being decompensated cirrhosis (Child-Pugh ≥ B8), severely reduced portal venous flow (with or without tumor obstruction, flow outside of the liver), a tumor entirely involving both lobes of the liver, technical contraindication to IA treatment and renal impairment (serum creatinine ≥ 2 mg/dL or creatinine clearance < 30 mL/min) [19].

In terms of toxicity, the TACE related mortality one month after the procedure was 4% in the Precision V study (2/93 in the microspheres arm and 6/108 in the Lipiodol® arm) [20]. The most common reasons for death from the TACE were acute hepatocellular failure (>60% of cases), hemorrhage due to portal hypertension, tumor rupture, liver abscess and sepsis. When the patient selection criteria are followed (cf. above) and the technical procedure is carried out rigorously (see below practical details), TACE is considered to be a procedure which has a positive benefit-risk balance. The post-embolization syndrome which involves transient abdominal pain, nausea and fever, occurs in over 25% of patients [20]. This syndrome is often associated with a rise in transaminases which rarely lasts for more than 72 hours. The adverse effects of TACE are mostly due to the ischemia of non-malignant liver parenchyma caused by the procedure: ischemia causes or worsens hepatic impairment in cirrhotic patients; a rise in serum bilirubin, encephalopathy, ascites, reduced prothrombin ratio and rupture of varices. The actual incidence of hepatic decompensation due to TACE is difficult to assess because of the wide variety of definitions used in the studies but is between 22 and 67% of cases [21]. The other rarer but potentially fatal complications of TACE are perforated duodenal ulcer, perforated small bowel or colon, gallbladder complications due to injection into the cystic artery (cholecystitis, gallbladder ischemia), biliary tract ischemia (biliomas, stenosis and dilatations), extra-hepatic embolizations (pulmonary, pancreatic, gastrointestinal or splenic) and renal impairment [21]. The hematological and cardiac toxicity of TACE is generally mild because of the low doses of anticancer agent used compared to those used in intravenous therapy.

Optimization of TACE

Whilst TACE has been performed worldwide for many years, there are major differences in practices depending on the center, particularly in terms of the anticancer agent, dose, vector, embolization agent, means of preparation and administration and the frequency and number of courses. The survival of patients treated with TACE is still low (<30% at three years) and there is no consensus on the optimal procedure. The TACE technique is very empirical and can certainly be improved.

The anticancer agent

In 2007, a systematic literature review which assessed the different anticancer agents used in 52 studies of TACE for HCC did not show any drug to be superior to the others [7]. The most widely used drugs throughout the world for TACE in HCC are doxorubicin (36%), cisplatin (31%), epirubicin (12%), mitoxantrone (8%), mitomycin C (8%) and SMANCS (5%). The use of these drugs is based mostly on the results of clinical studies on intravenous chemotherapy carried out in the 1970–1980s, which showed objective responses in patients with inoperable HCC. A recent preclinical study showed that idarubicin, an anthracycline used to treat acute leukemias was the most cytotoxic on three lines of HCC of the 11 compounds tested, including those widely used for TACE [22]. The maximum tolerated dose of 10 mg of idarubicin was established during a phase I study with loadable microspheres [23]. Its efficacy and tolerability have since been demonstrated at this dose for Lipiodol® conventional TACE [24,25] or with other loaded microspheres [26] in patients with inoperable HCC. Once phase II multicenter study is currently ongoing to assess the long term efficacy-tolerability profile of TACE using microspheres loaded with idarubicin in patients with inoperable HCC (study FFCD1307-IDASPHHERE II).

In terms of the doses used for each anticancer agent these are often fixed and independent of the patient’s body surface area because of the locoregional nature of the treatment. They are, however, very variable depending on the center, ranging from 50 mg to 150 mg per procedure, for example for doxorubicin. No study has shown the relationship between the toxicity of TACE and dose of anticancer agent used although some centres adjust the dose of drug according to the patient’s serum bilirubin, particularly for
anticancer agents, which are metabolized in the liver, such as the anthracyclines.

**The vector**

**Conventional TACE or Lipiodol® TACE**

In the 1980s, Lipiodol® was used as the main vector in TACE for HCC in order to increase intra hepatocyte tumor penetration of the anticancer agent [6]. Lipiodol® is a lipophilic iodinated contrast medium made up of a mixture of ethyl esters of carnation oil fatty acids, which has been marketed in France since 1901 by laboratoire Guerbet under the name Lipiodol® Ultra Fluide®, packaged in 10 mL injectable vials containing 48% iodine (i.e. 4.8 g/vial). It has multiple roles in TACE [27]. Firstly, when it is injected into the hepatic artery it is maintained in contact with the tumor tissue and hepatic tissue around the tumor for several weeks or even months, whereas it is removed from healthy liver parenchyma within seven days after being injected. By labeling Lipiodol® with 131 iodine, Raoul et al. showed that over 80% of the compound remained highly selectively within the liver tumor (tumor/non-malignant liver ratio over 5) for a long period of time [28]. The reasons why Lipiodol® persists within the tumor are not fully understood although are believed to be to a large extent due to embolization of tumor microvasculature characterized by their slow blood flow and abnormalities of electrostatic wall charges. Secondly, in addition to its radio-opacity which enables the injection of the emulsion to be visualized and monitored, its binding to HCC nodules at the end of the procedure is associated with improved patient response and/or survival (Fig. 2a–b) [29]. Thirdly, the Lipiodol® droplets conform the size of the vessel in which they are circulating and can reach portal venules through arterio-portal anastomoses, which is believed to increase the response to treatment on the periphery of the HCC and in satellite nodules [27]. Finally, the only two randomized phase III studies which have shown TACE to have benefit in terms of survival in patients suffering from inoperable HCC used Lipiodol® as the vector with cisplatin [8] or doxorubicin [9].

**TACE with microspheres**

TACE with microspheres loaded with an anticancer agent was developed during the 2000s. The particles are derived directly from the non-loaded embolization microspheres used in various therapeutic embolization procedures since the 1990s. The loaded embolization microspheres are sterile class IIB and III medical devices which are biocompatible hydrogel microspheres with are deformable and non-resorbable. Their ideal features are shown in Table 1.

Three of these have a specific indication for embolization of HCC or other hypervascularized tumors in France in 2015 (Table 2). These are formed from polymers bonded onto negatively charged groups, which enable the anticancer agents to be loaded provided that they are positively charged. This applies for example to the anthracyclines, which have a proton-carrying amine group. The theoretical advantage of loaded embolization microspheres is that they firstly combine local ischemia, which contributes to their anti-tumor efficacy and secondly a local action with progressive release of the anticancer agent and minimal systemic absorption.

The initial animal studies were promising and they were demonstrated to have pharmacokinetic advantages over Lipiodol® in 2007 [31]. The authors showed that in TACE in patients suffering from HCC, doxorubicin was released more slowly from the microspheres than from a Lipiodol® emulsion. Clinical studies which have assessed the efficacy and tolerability of TACE using loaded microspheres in patients suffering from HCC are encouraging, although the only phase II randomized study which has been published as yet and which compared Lipiodol® TACE to TACE with loaded microspheres did not find any significant difference in terms of response rate (at six months) between the two techniques [20]. The response rate according to EASL criteria in this study was 52% in the TACE with loaded microspheres group compared to 44% in the Lipiodol® TACE group (P=0.11) and the specific toxicity of doxorubicin (hematological toxicity, alopecia, mucositis and skin discoloration) was significantly less in the TACE with loaded microspheres group. Microspheres have advantages over Lipiodol®: loading is standardized in pharmacies whereas extemporaneous

![Figure 2](image-url)  
**Figure 2.** a: Lipiodol® uptake at the end of TACE; b: associated with tumor necrosis at 1 month.
The preparation of a Lipiodol® emulsion is still very empirical; the particles are poorly deformable and the calibrated size enables the operator to select the size of vessels to be embolized. Very recent studies have shown small microspheres (≤ 100 μm) to be of particular benefit as they cause more distal embolization [26,32–34]. More severe hepatic and biliary toxicity, however, has also been found for the microspheres compared to Lipiodol® [35,36]. An economic study has recently shown that TACE with loaded microspheres was globally financially viable despite

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Ideal features of microspheres for TACE.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microspheres</strong></td>
<td>Monitoring extent of obstruction and distribution in the vascular system</td>
</tr>
<tr>
<td>Calibration</td>
<td>Passes into microcatheters</td>
</tr>
<tr>
<td>Compressibility</td>
<td>Returns to initial spherical form after leading the catheter</td>
</tr>
<tr>
<td>Elasticity</td>
<td>No adhesion of microspheres to the catheter (hydrophobic) or formation of clumps</td>
</tr>
<tr>
<td>Hydrophilic nature</td>
<td>Easy to suspend in injectable solutions (physiological saline, contrast medium, etc.)</td>
</tr>
<tr>
<td>Biocompatibility</td>
<td>Avoids a chronic inflammatory reaction or immunization against the microsphere</td>
</tr>
<tr>
<td><strong>Microspheres—an active substance compatibility</strong></td>
<td>Active substance stable when loaded and released</td>
</tr>
<tr>
<td><strong>Active substance</strong></td>
<td>No damage to the microsphere from the presence of the active substance</td>
</tr>
<tr>
<td>Type of active substance</td>
<td>Local therapeutic effect</td>
</tr>
<tr>
<td>Dose of active substance</td>
<td>Action if possible on a target cell population</td>
</tr>
<tr>
<td>Release profile of the active substance</td>
<td>Therapeutic concentrations for the desired effect</td>
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</tbody>
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<thead>
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<th>Table 2</th>
<th>Regulatory details for loadable embolization microspheres in France.</th>
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</thead>
<tbody>
<tr>
<td><strong>Company</strong></td>
<td>Biocompatibles</td>
</tr>
<tr>
<td><strong>Composition</strong></td>
<td>Macromere of polyvinyl alcohol with an acryl group replacement and a sulfate monomer</td>
</tr>
<tr>
<td><strong>Granule size (μm)</strong></td>
<td>Dry particles</td>
</tr>
<tr>
<td>70–150&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30–60</td>
</tr>
<tr>
<td>100–300&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50–100</td>
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<tr>
<td>300–500&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100–150</td>
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<td>500–700&lt;sup&gt;b&lt;/sup&gt;</td>
<td>150–200</td>
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<tr>
<td>700–900&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Loadable molecule</strong></td>
<td>Doxorubicin/irinotecan</td>
</tr>
<tr>
<td><strong>Indications</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hypervascularized tumors (doxorubicin) or liver metastases from a colorectal cancer (irinotecan)</td>
</tr>
</tbody>
</table>

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<sup>a</sup> For the exact indications, refer to the company data sheet; only the indications for microspheres for tumor embolization are shown here.

<sup>b</sup> Possible variation of 20% in size of microspheres (loaded with 25 mg/mL of doxorubicin).

<sup>c</sup> 20% reduction in size after loading with doxorubicin.

<sup>d</sup> Variation in microsphere size < 5%.
the higher basic costs of these devices compared to Lipiodol® and that a ratio of 1.3 sessions (conventional TACE/TACE with microspheres) would enable the new technique to be funded [37]. In practice, conventional TACE is still widely used [38] and the stability of an idarubicin-Lipiodol® emulsion which has a release profile for the anticancer agent similar to that of the microspheres could lead to a resurgence in the use of the conventional technique [25].

Practical considerations

TACE is always performed in an interventional radiology suite. A routine imaging assessment (MRI or gastrointestinal artery CT angiography) should always be performed in order to identify the main arterial anatomical variations and accessory arteries [39]. After catheterizing the femoral artery and a full vascular explanation (assessment of hepatic vascularization and looking for accessory vascularization), the anticancer agent-Lipiodol® emulsion needs to be injected rapidly to promote its entry into the tumor arteries. Conversely, the loaded microspheres need to be injected slowly (in order to avoid clumping and reflux), ideally as selectively as possible into one of the segmental or sub-segmental branches supplying the largest part of the tumor mass using a microcatheter (Fig. 3a–b). 3D images (cone beam CT) are recommended in order to optimally identify the feeder arteries for the nodule(s) (Fig. 4a) and to confirm post-procedure that the tumor has been correctly targeted and saturated (Fig. 4b) [40].

The Lipiodol® emulsion (a maximum of 15 mL of Lipiodol® is recommended) is prepared extemporaneously using the pumping method. After connecting a syringe of Lipiodol® (oily phase) to the syringe containing the anticancer agent (aqueous phase), a minimum of ten consecutive forward backward pumping movements are required through a three way tap (Fig. 5). After injection, the procedure is combined by injecting an embolizing agent, usually gelatin cut into cubes of ≈1 mm³ or unloaded embolization microspheres until substasis is obtained (defined as washout in 3–5 systolic beats) [41].

For TACE with microspheres, particular attention needs to be paid to investigating for arterio-portal or hepatic venous shunts. It is recommended that a shunt be embolized with gelatin coils or large particles (depending on the shunt size) before injecting the loaded microspheres. Also before being injected the loaded microspheres should be mixed slowly with a non-ionic contrast medium (approximately 5 to 10 mL per mL of microspheres) by turning upside down and back in succession. It is essential that the contrast medium was either non-ionic because of the risk of removing the

Figure 3. a: microcatheterization for TACE; b: to be used with caution.

Figure 4. Cone-beam CT (a) optimal identification of feeder arteries to the nodule(s); b: post-TACE confirmation of correct targeting and saturation of the tumor.
load from the microspheres and it is also always essential to ensure that the loaded microspheres remain well suspended in the syringe. The loaded microspheres-non-ionic contrast medium should be injected slowly at a flow rate of approximately 1 mL/min until subaortic is achieved in the artery supplying the tumor. If subaortic is not seen at the end of the injection, either unloaded microspheres should be injected (until subaortic is obtained) (an option which is very contentious) or a further session should be planned if necessary depending on the imaging response [41,42].

Assessment of response, time interval and frequency of courses

The joint recommendation from EASL and EORTC is to assess response four weeks after a TACE session by CT or MRI using the modified RECIST criteria [3]. Two options are available after this assessment: to re-treat the patient at fixed intervals or "on demand". There is no good evidence to recommend an "on demand" strategy although it appears that toxicity is greater with repeated TACE sessions at fixed intervals [19]. In practice, an "on demand" strategy with re-treatment of patients if viable tumor tissue remains (partial response, stabilization or progression) is usually carried out depending on the patient’s liver function and general health. Three monthly imaging follow up is recommended for patients who no longer have viable tumor tissue (complete response). Finally, the criteria for stopping TACE (and considering subsequent treatments) do not have a clear consensus. In this context, the ART (Assessment for Re-treatment with TACE) score has been developed to optimally select patients who will benefit from a 2nd or 3rd session [43]. The concept of progression which cannot be treated by CE has also recently emerged [44]. The criteria for TACE untreated progression include: failure of objective response from the target lesions on at least two occasions, clinical or functional deterioration of the patient (WHO >2 and/or liver decompensation), in addition to the usual factors which contraindicate TACE.

Treatments combined with TACE

There are no recommendations in 2015 for a treatment combined with TACE. The results obtained with adjuvant or concomitant sorafenib have been negative. A number of groups use TACE either to enable a patient to meet the transplantation criteria (down staging) or as a holding treatment prior to transplantation (to remain within transplantation criteria, or bridging). Good evidence, however, is lacking to justify one or other of these two practices [45].

Conclusion

In conclusion, the recommendation to use TACE as the reference treatment in patients with intermediate B stage HCC is based on a high level of scientific evidence. There is, however, no consensus as to an optimal treatment modality, which explains the wide range of TACE practices between centers. Many areas for improvement and standardization are currently being studied, in particular with the use of more effective anticancer agents, new generation microspheres or combinations or other curative and palliative treatments. These changes will need to undergo phase II and particularly phase III studies in order to provide evidence of improved survival in this disease, which carries a very poor prognosis.

Take-home messages
- TACE is the recommended treatment for patients with intermediate B stage HCC (embolization alone or intra-arterial chemotherapy with or without Lipiodol® are not recommended).
- TACE increases survival in these patients.
- TACE is contraindicated in case of decompensated cirrhosis (Child-Pugh > B), severely reduced portal flow (tumor occlusion, flow outside of the liver), tumors involving the majority of both lobes of the liver, any technical contraindication to intra-arterial treatment and renal impairment with a serum creatinine of ≥2 mg/dL or a creatinine clearance of <30 mL/min.
- It is recommended that response be assessed 4 weeks after a TACE session by CT or MRI using the modified RECIST criteria.
- An “on demand” strategy with retreatment of patients if viable tumor tissue remains after a 1st session is recommended.
- There are no recommendations about treatments combined with TACE.

Clinical case

A 68-year-old man with HCC developed on alcoholic cirrhosis, resected three years ago presents tumor recurrence as a single 5 cm nodule. The patient is asymptomatic (no ascites, jaundice or encephalopathy), Child-Pugh stage A6 with no vascular invasion or metastases. TACE treatment is decided in a multidisciplinary meeting (Fig. 6).

Figure 5. Preparation of an emulsion for lipid or TACE. A homogeneous emulsion is obtained extemporaneously by the intervention radiologist by passing the aqueous phase (anticancer agent)—oily phase (Lipiodol®) from one syringe to another round ten times (pumping method) through a 3-way tap.
Questions

1. Comment on the treatment decision?
2. What are the absolute contraindications to TACE?
3. As the patient has received TACE with microspheres, what are the administration requirements, which should be followed?
4. When and how should the response to the treatment be assessed?
5. In view of the appearances, what is your practical approach for this patient?

Answers

1. According to the description the patient presents an intermediate B stage. TACE is the recommended treatment is indeed TACE.
2. Decompensated cirrhosis (Child-Pugh > B), severely restricted portal flow (tumor occlusion, flow outside of the liver), a tumor involving the majority of both lobes of the liver, any technical contraindication to intra-arterial treatment and renal impairment with a serum creatinine of >2 mg/dL or creatinine clearance of <30 mL/min.
3. Investigate for an arterio-portal or hepatic venous shunt and embolize this if possible:
   • before injection, slowly mix the microspheres loaded with a non-ionic contrast medium (approximately 5 to 10 mL per mL of microspheres) by turning upside down and backwards and ensure that the loaded microspheres remain well suspended in the syringe with the non-ionic contrast medium;
   • slowly inject (1 mL/min) the mixture of loaded microspheres—non-ionic contrast medium until sub-stasis is achieved in the hepatic artery supplying the tumor. If sub-stasis is not achieved at the end of the injection of the loaded microspheres—non-ionic contrast medium, unloaded microspheres can be injected (very contentious) until sub-stasis is obtained.
4. 4 weeks after a TACE session by CT or MRI according to the modified RECIST criteria.
5. Patients in complete response (major tumor necrosis), quarterly monitoring with imaging.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

Transarterial chemoembolization for hepatocellular carcinoma: an old method


