Expert Opinion

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Drug delivery embolization systems: a physician's perspective

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Introduction: The number of patients suffering from primary and secondary liver tumoral diseases is on the increase worldwide. The development of new technologies and drugs requires an increasingly multidisciplinary approach in the management of these diseases. Therapies should be based on scientifically supported guidelines and at the same time should be designed to suit the individual patient. In this decision-making process, an understanding of the advantages and disadvantages of every treatment is very important. The efficacy of transarterial chemoembolization (TACE) in improving survival and its role in the management of hepatocellular carcinoma (HCC) have been demonstrated in several clinical trials. The introduction of drug-eluting beads seems to have overcome some of the limitations of conventional TACE.
Areas covered: This review provides an overview of the spread of primary and secondary liver cancers, then it explains the basis for the use of conventional TACE and its potential benefits and, finally, outlines its clinical application and possible future uses.
Expert opinion: The management of the treatment of focal liver lesions is a difficult process, which must involve various specialists such as the interventional radiologist. The use of drug-eluting microspheres seems to improve the results of TACE both in HCC and in colorectal liver metastases.

Keywords: DEBIRI, drug-eluting beads, hepatocellular carcinoma, transarterial chemoembolization

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1. Introduction

Although surgery is the first choice of treatment for primary and secondary liver lesions, the diagnosis of most cases at a very advanced stage has led to the development of many alternative strategies over the years. These strategies mainly consist of systemic chemotherapy or locoregional therapies alone or in combination with each other.

Locoregional therapies, such as the intra-arterial administration of chemotherapeutic drugs, have a well-defined role in the management of hepatocellular carcinoma (HCC) and have good prospects in the treatment of colorectal liver metastases.

Colorectal cancer is the third most common cancer in men and the second most common cancer in women, with 12,300,000 new cases diagnosed per year. About 608,000 deaths are estimated to be due to colorectal cancer worldwide, making it the fourth most common cause of cancer death [1]. Colorectal metastatic disease most frequently affects the liver. It is estimated that at the time of diagnosis about 14.5% of patients present with synchronous liver metastases [2] and 14.5% will develop metachronous liver metastases during 5 years of follow-up [2], whereas the overall incidence varies from 19 to 23% [2,3]. The prognosis of untreated patients is very poor: < 30% of patients are alive at 1 year follow-up and < 5% at 5 years [2]; the median survival in metastatic

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Article highlights.

- DEB-TACE is performed using precisely calibrated, permanent embolic agents that are able to bind, deliver and elute chemotherapeutic drugs within the tumor.
- DEB-TACE provides a higher drug concentration within the tumor and lower systemic concentration than c-TACE.
- DEB-TACE is performed using more standardized techniques than c-TACE, both during preparation and during administration of beads. Patient data obtained after DEB-TACE are more homogeneous and better comparable in RCTs.
- DEB-TACE has better survival rates than c-TACE in the mid-term (2 years). Five-year survival data are not available at the moment.
- At present, there are no statistically significant data on patient survival in the treatment of colorectal liver metastases (DEBIRI), but there are promising results on tumor response.

This box summarizes key points contained in the article.

cancer patients who are untreated by any modality is 5 – 10 months according to some retrospective studies, whereas metastasectomy results in a median survival of 46 months. Despite surgery being widely considered the first choice of treatment, it is estimated that only 20% of patients with predominant liver disease are eligible for hepatic resection [4]. Based on a consensus statement, the contraindications are unresectable extrahepatic metastases, > 70% of liver involvement, hepatic failure and advanced comorbidities [5]. Other than these, the main reason for not referring patients for surgery is age: patients older than 75 years are often excluded, which could be a major problem, considering that the medium age at diagnosis is 68 years [4]. Recently, transarterial chemoembolization (TACE) with irinotecan-loaded beads, after unsuccessful systemic chemotherapy, has been proposed as a treatment option, with promising results.

HCC is the sixth most common cancer. About 630,000 new cases are diagnosed every year and 600,000 deaths are recorded every year, making HCC the third most common cause of cancer death [6]. The 5-year survival rate is < 8.6% in Europe. The major risk factor is underlying cirrhosis (95% of HCC cases develop in cirrhotic livers). It is estimated that 3 – 8% of cirrhotic patients develop HCC nodules every year [7]. The hepatitis B virus (HBV) accounts for 53 – 80% of all HCC cases, as it is more common than the hepatitis C virus (HCV) worldwide. According to the literature, the annual incidence of HCC in patients with HBV-related cirrhosis varies between 1.5 and 8%, being higher in Asia than in other countries. HCV-related cirrhosis tends to develop HCC nodules more frequently than HBV-related cirrhosis (about 3% every year), and it is estimated that 30% of patients with HCV-related cirrhosis will develop HCC during their lifetime. The management of patients affected by HCC is more challenging compared with the management of metastatic patients, because the underlying liver disease often limits the treatment choices and affects the prognosis as much as tumor extension. Therefore, besides TNM (where T describes the size of the tumor, N describes regional lymph nodes that are involved and M describes distant metastasis), other classifications have been proposed by different associations (e.g., Barcelona Clinic Liver Cancer (BCLC), Cancer of the Liver Italian Program (CLIP), Chinese University Prognostic Index (CUPI)), adding a prognostic factor to the treatment flow chart. In the last few years, the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD) have recommended the use of the BCLC system, proposed by the Barcelona Group, because it is the only one combining tumor stage, liver disease stage and therapeutic indications (**Figure 1**). According to the BCLC system, patients who are in very early (0) and early stage (A) are suitable for curative therapies, such as surgical resection, liver transplantation and radiofrequency or microwave thermoablation. Only a few patients are eligible for such treatments: about 20 – 35% of patients can be treated using surgical therapies [9-11]. Patients at the intermediate stage (B) are treated using TACE, as it is not considered a radical therapy. In fact, this heterogeneous population of unresectable patients includes different entities in terms of tumor burden, liver function and disease etiology (i.e., patients with unique but large tumors, plurinodular disease or vascular invasion, which retrospective studies have shown to have a better survival when treated surgically, and patients with larger liver involvement or a degree of compromised liver function). Therefore, it can be expected that not all patients at the intermediate stage will derive similar benefits from TACE. These differences could account for the controversial opinion regarding whether chemoembolization could improve survival or not. In fact, although TACE was introduced as early as in 1977, it was only in 2002 that Llovet demonstrated a benefit in terms of survival in patients treated with conventional TACE (c-TACE) compared with support therapies in a randomized controlled trial (RCT) [12]. Until then, tumor response was considered a good surrogate parameter for survival.

2. Assessment of tumor response

The assessment of tumor response is a critical issue: objective response is used as a surrogate marker of survival in many studies on cancer therapies.

Several criteria have been proposed by different associations to allow a uniform evaluation and comparison of data. In 1979, the WHO published its objective tumor response criteria, which became the most used criteria by investigators. However, these criteria resulted in several problems related to interpretation.

In 2000, the National Cancer Institute proposed a simplified set of standardized criteria, the Response

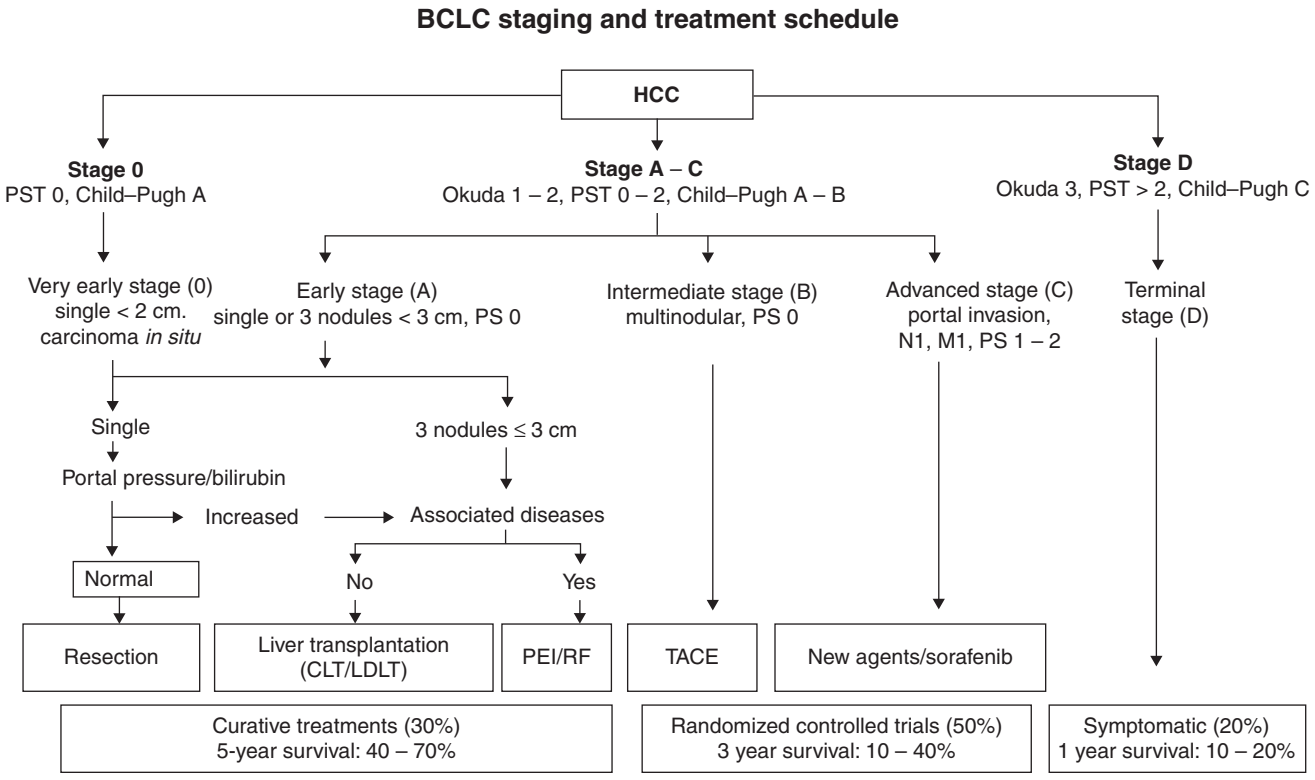

Figure 1. The BCLC classification system correlating liver function, tumor extension and treatment strategy [65].
BCLC: Barcelona Clinic Liver Cancer; CDL: Cadaveric liver transplantation; HCC: Hepatocellular carcinoma; LDLT: Live liver donor transplantation; PEI: Percutaneous ethanol injection; PS:Performance status; PST: Performance status test; RF: Radiofrequency ablation; TACE: Transarterial chemoembolization.

Evaluation Criteria in Solid Tumours (RECIST), to unify evaluation criteria [13].

RECIST criteria are based on the measurement of the sum of largest diameter of target lesions (up to 10) before and during treatment, on CT, MR or conventional radiograms. The objective response is categorized into complete response (CR; complete disappearance of all target lesions), partial response (PR; > 30% decrease in the sum of the diameter of target lesions), progressive disease (PD; > 20% increase in the sum of the diameter of target lesions and/or appearance of new lesions and/or unequivocal progression of non-target lesions) and stable disease (SD; neither PR nor PD).

Initially, RECIST criteria were widely adopted, but several problems arose, the main issues being the improvement of the imaging technique and the development of new treatment strategies and drugs. According to RECIST criteria, tumor shrinkage on axial images is the only factor related to tumor response, but it can be misleading when applied to non-cytotoxic drugs and locoregional therapies. In 2001, a panel of experts published the EASL's conclusions: they reported that simple determination of the bi-dimensional diameter is not accurate enough, because extensive tumor necrosis due to treatment may not be accompanied by a reduction in tumor diameter. Hence, estimation of the reduction of viable tumor (recognized as the non-enhancing areas on a CT scan) should be considered as the optimal method to assess local response [14]. Response is divided into CR (complete disappearance of all known lesions and no new lesions in two observations not less than 4 weeks apart), PR (> 50% reduction in total tumor load of all measurable lesions in two observations not less than 4 weeks apart), SD (neither CR nor PR) and PD (> 25% increase in the size of one or more measurable lesions or the appearance of new lesions). The objective response includes CR and PR.

Some recent studies have found poor correlations between the extent of tumor necrosis induced by molecular targeted drugs (such as sorafenib) or locoregional therapies (such as radiofrequency and chemoembolization) and conventional methods of response assessment (i.e., WHO and RECIST 1.0) in terms of survival. On the other hand, different studies demonstrated an association between complete tumor necrosis and improvement of survival: in a multivariate analysis of a group of patients treated with radiofrequency thermal ablation (RFTA), Sala *et al.* [15] found that initial achievement of complete necrosis was associated with better survival. Similar results were reported by Camma *et al.* [16].

In 2009, Forner *et al.* [17] compared the agreement of RECIST and EASL criteria in a cohort of patients with HCC treated with either RFTA/PEI (percutaneous ethanol injection) or drug-eluting beads (DEB)-TACE. According to

the EASL criteria, they found an objective response in 87.1, 75 and 81.8% in the RFTA/PEI group, the DEB-TACE group and all patients, respectively, with a significantly higher CR in the RFTA/PEI group, as they are curative treatments. Based on the RECIST criteria, in the RFTA/PEI group, no objective responses (neither CR nor PR) were observed, SD was observed in 61.3% of patients and PD in 38.7%. In the DEB-TACE group, again no CRs were observed. PR was observed in 50% of patients, SD in 29.2% and PD in 20.8%. Therefore, despite DEB-TACE having no curative capacity, it has a better objective response than RFTA/PEI according to the RECIST criteria.

The same limitations could be found by analyzing the results of new molecular targeted drugs, which are expected to have a cytostatic rather than cytotoxic effect.

In 2008, a modified version of the RECIST criteria – RECIST 1.0 – was published, which includes the amendments proposed by Llovet *et al.* [18] to measure only the solid portion of the tumor (i.e., the enhancing portion), to evaluate tumor response in HCC.

Similar conclusions could be reached for the assessment of tumor response after chemoembolization of colorectal liver metastases using irinotecan-eluting beads (DEBIRI).

3. From cTACE and transarterial embolization to DEB-TACE

Intra-arterial therapies consist of a group of techniques based on the injection of chemotherapeutic drugs or embolic agents through a catheter directly into the arterial vessel supplying a target tumor. In the late 1970s, Yamada first introduced intra-arterial therapy for liver treatment [19] using a gelatin sponge, while Matsui proposed the use of 5-fluorouracil (5-FU) [20], based on the observation that most hepatic primary or secondary malignant lesions derived their blood supply from arterial vessels, unlike normal parenchyma, which has mainly a portal blood supply. The aim was to perform focalized therapy on the target lesion, thereby minimizing systemic toxic effects.

In the early 1980s, lipiodol (an iodinated ester from poppy seed oil) was added to the cocktail, based on the observation that it is taken up and retained in HCCs as well as colon and neuroendocrine tumor metastases [21,22], to reduce the washout of drugs and induce arterial embolization.

The TACE technique involves the injection of an emulsion of a chemotherapeutic drug and lipiodol into the lobar, segmental or subsegmental branches of the hepatic artery, often followed by artery embolization with a gelatin sponge or polyvinyl alcohol (PVA) particles. There are different variants of this technique, with regard to the choice of the chemotherapeutic drug, the site of embolization (proximal or distal) and the embolizing material (gelatin sponge or PVA). These differences make it difficult to compare the results from different research institutions.

There has been considerable debate about whether the antitumoral effect of TACE is due to the ischemic damage of embolization or due to the cytotoxic effect of the chemotherapeutic drug. Currently, there is no agreement on which is the most effective chemotherapeutic drug. Doxorubicin is the most widely used as a sole agent, whereas the combination of cisplatin, doxorubicin and mitomycin C is the most widely used for HCC. Although these agents achieve high intratumoral concentrations, their advantage over bland embolization has not been clearly proved in RCTs.

In 2002, Cammà *et al.* [23] reviewed 18 RCTs, comparing transarterial chemotherapy (TAC), transarterial embolization (TAE) and TACE versus non-active treatment. In these trials, lipiodol and gelatin sponge were used as the embolizing materials. The meta-regression analysis showed a lower overall mortality for TAC, TAE and TACE compared with non-active treatment. Moreover, the authors found a significant lower odds ratio for both the TAE and the TACE groups compared with the TAC group, although they found no statistically significant difference between the TAE and the TACE groups, suggesting that the treatment does not benefit from the addition of chemotherapeutic drugs.

A more recent meta-analysis by Marelli *et al.* of the outcome for patients treated with TACE or embolization alone (TAE) failed to demonstrate an advantage for the TACE group in three studies [24]. Many authors have suggested that more effective anticancer drugs should be tested. Besides HCC resistance to lipiodol and doxorubicin, there is no true chemical bond between them, leading to a rapid washout of the drug, as demonstrated by the systemic concentration curve after TACE.

The precise effect of embolization on tumor cells is still largely unknown. The addition of embolizing material combines ischemic necrosis with the cytotoxic effects of drugs. Recent studies suggest that hypoxia induced by embolization can activate different genes, such as VEGF (vascular endothelial growth factor), leading to neoangiogenesis and tumor growth stimulation [25].

Until 2002, the use of TACE was based on data from Phase II trials, which showed effectiveness in terms of tumor response, but no data about survival were collected until then. In 1998, a meta-analysis of six RCTs failed to demonstrate benefits from TACE at 1-year survival [23]. After that, other RCTs found controversial results. In 2000, the EASL argued that TACE was not recommended for the treatment of intermediate-stage HCC, as benefits were not clearly proved, even in patients with local response to treatment.

In 2002, the results of two RCTs carried out by Llovet *et al.* [12] and Lo *et al.* [26] were published, which provided statistically significant evidence of survival improvement in patients treated with TACE versus best supportive care (BSC). In their study, Llovet *et al.* compared TACE, TAE and BSC. They found that TACE prolonged survival compared with BSC (28.7 vs 17.9 months, p=0.009), while no statistically significant differences between TACE and TAE (28.7 vs 25.3 months) were found although TACE reduced the probability of portal vein invasion. Similar results were found by Lo *et al.* who compared TACE and BSC (survival

at 1, 2 and 3 years was 57, 31 and 26% in the TACE group, respectively, and 32, 11 and 3% in the control group, respectively). Lo *et al.* also indicated fever, abdominal pain and vomiting as the most common side effects for TACE. Since then, several studies reported the benefits of TACE in unresectable HCC. The largest study from Japan, comprising 8510 patients, reported a median survival of 34 months and a 2-year survival rate of 63% [27]. A recent review by Raoul et al [28] analyzed results from different randomized controlled studies and meta-analyses. They identified seven studies only two of which (by Llovet and Lo) showed an increase in overall survival. They also found many differences in terms of the patient population, which comprised unresectable HCC cases that did not correspond with the intermediate BCLC stage, and the TACE technique, which may account for these different results. In the Llovet trial, bilirubin levels were lower in the TACE group, and in the Lo cohort, extrahepatic tumor spread, portal vein thrombosis (PVT) and poor hepatic function were the reasons for exclusion. All this underlines the need for careful patient selection. Raoul *et al.* also examined two meta-analyses, both of which confirmed an improvement in the overall survival, although they concluded that other locoregional therapies such as TAE and PEI yielded similar or better results.

Based on these observations, the Barcelona Group proposed TACE as the standard treatment for intermediate-stage HCC.

The contraindications for TACE are portal vein occlusion, hepatofugal blood flow, severe hepatic disease (Child–Pugh score > B8), recent variceal bleeding, surgical portocaval anastomosis, encephalopathy, refractory ascites, spontaneous portosystemic shunt or extrahepatic spread. Most of them are related to decompensated cirrhosis. Some authors claim that PVT should not be considered an absolute contraindication. Georgiades *et al.* [29] evaluated the safety of TACE in 32 patients with PVT. The Child–Pugh score was the most important factor related to survival. They found no evidence of TACE-related liver dysfunction. The median overall survival was 9.5 months. Therefore, as the prognosis of patients with PVT is very poor, it may not be appropriate to treat them.

In 1999, a new tris-acryl gelatin microparticle was proposed as permanent embolizing material (Embosphere, BioSphere Medical, Rockland, MA, USA). Compared with PVA and round PVA particles, which have a semispherical or irregular shape, these new microparticles are spherical flexible beads, do not aggregate in clots, are available in predefined sizes (40 – 120, 100 – 300, 500 – 700 μm, etc.) and allow a quite predictable penetration. They were used in combination with the chemotherapeutic drug for TACE or as a sole agent for TAE, to induce a more sustained ischemic effect. As Embospheres are permanent embolic beads, embolization is performed only superselectively, until the blood flow is completely stopped.

There are a few papers that discuss the use of Embospheres. Gomes *et al.* [30] compared TACE performed using triple-drug therapy plus non-permanent embolic agents with triple-drug plus Embospheres. They found a significantly better survival in the Embospheres group. This benefit was present up to 30 months, when the survival curves of the two groups crossed. Four more papers reported the use of Embospheres for TAE [31-34]. They are based on the prospective study by Llovet and the review by Cammà , which found no advantages in the use of chemotherapeutic drug over bland embolization. In our institution, we treated a series of 18 patients, including 15 with unresectable HCC and 3 patients on a liver transplant waiting list, and obtained CR in 89% of cases, which is much higher than that for TACE (which is reported to have CR in 10 – 60% of cases according to the literature). About 62% of patients developed local recurrence within a mean follow-up of 21 months, whereas RFTA and PEI are reported to have early recurrence in 10 – 30% of cases, suggesting that TAE cannot be considered a radical treatment. The high recurrence rate could be due to an overestimation of CR by CT and due to treatment-induced hypoxia, which stimulated neoangiogenesis in residual tumoral cells. None of the patients showed deterioration of liver function, probably due to both the site of embolization (superselective) and the avoidance of the chemotherapeutic drug. Covey *et al.* reviewed a series of 45 patients treated by bland embolization for disease recurrence after surgery. Similar to a previous study, they found a median survival time of 46 months, which is significantly higher than in patients with recurrence but who are not eligible for TAE. The two-year survival rates were 87 and 0%, respectively. As in our study, they did not find elevated liver enzymes. Amesur *et al.* compared different sizes of Embospheres, suggesting a slightly better response with 100 – 300 μm beads.

The experience with Embospheres, although evidence-based, makes physicians confident about the use of this type of permanent embolizing beads and their potential use in HCC treatment.

The key points for transarterial treatments at the time were how to reduce early recurrence, which is the best site for embolization, what is the optimum particle size and how useful is the chemotherapeutic drug.

4. Drug-eluting bead-TACE

4.1 Technical aspects

Drug delivery systems consist of non-degradable polymers, characterized by tissue/blood compatibility, durability, robust structure and mechanical strength during *in vivo* applications [35], which can bind specific substances and release them for a prolonged time. Their advantage over systemic chemotherapy and bland embolization is that they add the potential cytotoxic effect of drugs to bland embolization, thereby minimizing the systemic toxic effects. The aim is to achieve high drug concentration within the tumor and low systemic concentration. This is achieved by a sustained release of the drug locally into the tumor.

DEBs have an inert coating material that acts like a rate-controlling membrane. They were first used in Europe in 2004 for the treatment of HCC in combination with anthracycline drugs. Some of them can load camptothecin derivates, which can be used for the treatment of colon liver metastases.

Two types of DEBs are available: DC Bead® (Biocompatible UK Limited, Surrey, UK) and HepaSphere™ (BioSphere Medical, Roissy CDG Cedex, France); they differ in terms of materials, characteristics and preparation.

4.1.1 DC Bead

DC Bead is composed of a PVA hydrogel hybrid polymer with 2-acrylamido-2-methylpropanesulfonate sodium salt (AMPS). AMPS provides a number of sulfonic acid groups that are capable of effecting ion exchange between the sodium ions and positively charged drugs, such as anthracycline and camptothecin derivates. DC Beads are blue colored. They are provided in a saline suspension, which must be replaced by the chemotherapeutic solution. Drug uptake is very efficient (> 99%) when no other competitive ions are present in the solution. Within 20 min, up to 90% of the drug is loaded into the beads. The maximum loading capacity is 37.5 mg/mL of beads for doxorubicin and 50 mg/mL for irinotecan. These amounts of drugs are high enough to be therapeutically active, when delivered locally.

After doxorubicin loading, the beads turn red in color, while the solution tends to become pale red. Once loaded, the drug has an adequate stability for at least 28 days. Drug uptake is accompanied by a decrease in water content and bead diameter and a concomitant increase in resistance to compression. Pharmacokinetic studies have demonstrated a lower systemic burst and overall exposure compared with intra-arterial administration of the drug alone and c-TACE. Varela *et al.* [36] compared the serum profile of doxorubicin after c-TACE and DEB-TACE. C_{max} is reached within 5 min after injection, but it is much higher for c-TACE than DEB-TACE (895.66 ± 653.1 vs 78.97 ± 38.3 mg/mL). Moreover, C_{max} had a greater variability for c-TACE, with no relation to doxorubicin dose. Total systemic exposure was higher in the c-TACE group, although the doxorubicin dose was much higher in the DEB-TACE group (up to 150 mg). In the tumor, the doxorubicin concentration shows an initial surge, then it decreases until the IC_{50} is reached and stays stable for weeks. The drug diffuses to a distance of up to 600 µm from the beads [37].

When irinotecan is loaded, the beads turn green–turquoise in color [38]. The loading of low doses (10 mg) is very rapid (> 98% within 10 min), while the loading of the optimum 50 mg dose requires about 2 h for all sizes. The beads tend to become smaller even when loaded with irinotecan, but this change is almost insignificant for the most frequently used size (100 – 300 µm). Unlike doxorubicin-loaded beads, irinotecan loading does not change the compressibility of the microspheres, thus facilitating their delivery through the microcatheter. Drug elution from the beads is more rapid for irinotecan than for doxorubicin. It requires the presence of an ionic medium and depends on bead size (it is faster for smaller beads). Plasma C_{max} is lower after DEBIRI than after an intra-arterial bolus of irinotecan. DEBIRI is very well tolerated by the liver, with minimal damage in the surrounding liver tissue, whereas DEB-DOX can cause extensive pan-necrosis [39].

Beads are mixed with contrast medium for an X-ray-controlled injection. During the initial stages of their use, the suggested dilution was 1:1, but now most centers prefer a more diluted suspension, generally 1:4, which allows a higher dose injection, thereby avoiding early vessel occlusion. For the same reason, the most frequently used size is 100 – 300 µm. The importance of bead penetration into the small vessels within the tumor has been recently emphasized: hypoxia is thought to be the most important factor that induces VEGF-mediated neoangiogenesis. Distal embolization is supposed to enhance tumor necrosis, thus reducing tumor hypoxia.

4.1.2 HepaSphere

HepaSphere is a superabsorbent microsphere composed of PVA-co-sodium acrylate. They are biocompatible, hydrophilic and non-reabsorbable. They are available in dry form and in different calibrated sizes (50 – 100 µm, 100 – 150 µm and 150 – 200 µm), with the most frequently used size being 50 – 100 µm. They should be reconstituted before use by adding the chemotherapeutic solution. Their diameter increases 4 times and they swell to 64 times their initial volume, if suspended in saline solution, blood or non-ionic contrast media within 10 min. Therefore, unlike DC Beads, which decrease in diameter, HepaSpheres increase in size from 50 – 100 to 200 – 400 µm. This allows HepaSpheres to absorb up to 64 times their volume of drug solutions. HepaSpheres load drugs in two different ways: by a reservoir effect, which consists of the reconstitution process not present in DC Beads, and by an ionic effect due to the negative charges on the particle surface, which reversibly bind positive drugs such as doxorubicin. The first process takes 10 min, but the second process is slower. This is the reason for the faster loading profile for HepaSpheres than DC Beads. After 20 min, 90 – 95% of a 50 mg solution of doxorubicin is loaded, similar to DC Beads.

HepaSpheres are highly compressible and elastic (**Figure 2**): they act like a gel in the embolization process, conforming to the vessel lumen.

In 2008, Lee *et al.* [40] evaluated the *in vivo* drug release of HepaSpheres in a rabbit model. They found that after an early increase the doxorubicin plasma levels, decrease rapidly and stay stably low. Doxorubicin levels in the tumor are much higher than systemic levels and stay high for days after embolization (they stopped observation after 7 days), suggesting a prolonged release. Finally, after 3 and 7 days, the death rate

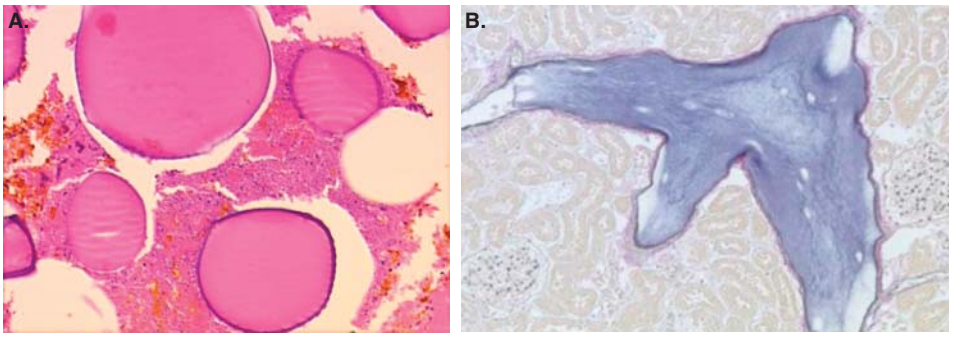

Figure 2. DC Beads (A) and HepaSpheres **(B)** in a histological sample. DC Beads are round shaped, whereas HepaSpheres act like a gel, conforming to the vessel lumen.

of tumor cells was higher in the doxorubicin-loaded group than in the bland embolization group.

Jordan *et al.* [41] recently compared DC Beads and HepaSpheres. Both types of microspheres are able to load doxorubicin very efficiently (almost 100%), while HepaSpheres tend to load a lower amount of irinotecan (91%). Once loaded, DC Beads stay separated, while HepaSpheres tend to aggregate, leading to an inhomogeneous uptake of drug in the center of the clumps. The release kinetics are similar for both beads, but final levels of the eluting drug are lower for HepaSpheres. Both microspheres retain a certain percentage of doxorubicin, while all irinotecan is eluted, indicating a weaker interaction with the beads. Moreover, irinotecan elution from HepaSpheres is very rapid (within few minutes).

Sottani *et al.* [42] found a low systemic exposure for HepaSpheres compared with DC Beads (range 9.6 – 155.6 and 6.6 – 42.2 μg/L, respectively), with a statistically significant lower peak for HepaSpheres, while the overall exposure, although lower for HepaSpheres, was not statistically significant ($p > 0.05$).

4.2 Clinical aspects

4.2.1 DEB-TACE in the treatment of HCC

The use of c-TACE in a well-defined class of HCC patients has been justified by different randomized studies and meta-analyses, but many trials comparing c-TACE with bland embolization have failed to demonstrate any benefit in terms of survival from the addition of chemotherapeutic drugs. However, some issues should be pointed out: c-TACE is a non-standardized procedure that differs in technique (selective or superselective) and materials (different embolizing agents and drugs) from institution to institution and from patient to patient. As beads are permanent embolic agents, DEB-TACE requires the superselective catheterization of subsegmental branches of the hepatic artery, to avoid ischemic damage to non-tumoral tissue; this means that it has a percentage of technical non-feasibility, due to an unfavorable vascular anatomy, but on the other hand, it has better reproducibility, as it is performed using similar materials (microcatheter, beads and drug), with predetermined proportions of drug and beads and using a similar technique (superselective). Furthermore, there is no true chemical bond between lipiodol and doxorubicin, which results in a rapid systemic release of the drug after c-TACE. Varela *et al.* demonstrated that systemic levels of doxorubicin are much higher after c-TACE than after DEB-TACE, indicating a more sustained release and a higher drug concentration within the tumor for DEB-TACE (which means prolonged contact of the tumor with high dose of drugs). These features allow a better evaluation of the role of chemotherapeutic drugs in TACE treatments.

Preclinical studies on a rabbit model performed by Hong *et al.* [43] investigated the impact of a permanent and calibrated embolic agent on drug concentrations: they found higher drug concentrations in the tumor using a permanent embolic agent, than using lipiodol, regardless of the type of microspheres (PVA or Embosphere). They also found higher drug concentration within the tumor with Embospheres (117 vs 31 μg/g). Interestingly, they investigated drug distribution within the tumor and found a higher concentration (two to eight times) in the core than at the periphery; in the peripheral zone of the tumor, which is a critical area for all locoregional therapies because it's the site where most of the recurrences develop, they found four times higher concentration of the drug when using Embospheres than when using PVA or intra-arterial drugs.

Most of literature concerns the use of DC Beads, while there are only a few papers on the use of HepaSpheres.

Lewis *et al.* [39] compared the effects of DC Beads of different sizes and bland embolization in a porcine model. They found that histopathological changes were different: loaded beads induced various degrees of necrosis, while unloaded beads led to non-necrotic changes. Moreover, smaller beads (e.g., 100 – 300 μm) induce more extensive pan-necrosis than larger beads. This could be due to deeper penetration of smaller beads into small tumoral vessels. In 2008, Lee *et al.* [44] investigated microsphere distribution using iron oxide-coated microspheres and reported that smaller beads (100 – 300 μm) lodge inside the tumor and along its rim, while larger beads remain outside. Therefore, if the purpose

is to deliver embolic agents within the lesion, smaller beads should be preferred.

Different clinical trials have investigated the efficacy of DEB-TACE on HCC.

Malagari *et al.* [45] investigated the efficacy of DC Beads, finding 80.7% of objective response, sustained at 9 months, with 12.2% of cumulative CR (versus a CR rate of 6% reported in literature for c-TACE).

A large multicenter study, including 212 patients, compared c-TACE with DEB-TACE [46]. The overall response rate was 51.6% in the DEB-TACE group versus 43.5% in the c-TACE group ($p = 0.11$). Although this difference is not statistically significant, a trend toward better response rate in all subcategories (CR, PR and SD) was observed for DEB-TACE, with lower liver toxicity, despite the higher dose of doxorubicin administered. Improved tolerability allows patients with more advanced disease (Child–Pugh B or ECOG 1, with recurrent HCC or bilobar involvement) to be treated. In this subgroup, DEB-TACE showed significantly higher objective response ($p = 0.038$), which was sustained in a higher number of patients ($p = 0.026$).

In 2010, our group published a retrospective study, comparing DEB-TACE with bland embolization, performed with Embospheres [47]. Although the sample was quite small, it was an interesting study, as all patients subsequently underwent orthotopic liver transplantation and the explanted livers were analyzed to determine the histological response to DEB-TACE or TAE. Despite CT evaluation showing no statistically significant difference between the two groups, histological examination found a significantly higher complete necrosis in the DEB-TACE group (77 vs 27.2%). Moreover, necrosis affected liver tissue around the HCC nodule in some patients of the DEB-TACE group. This could be desirable to obtain a sort of 'safety margin' at the periphery of the lesions.

In 2010, Malagari *et al.* [48] compared DEB-TACE with bland embolization (performed with BeadBlock). They found higher CR and SD rates in patients treated with DEB-TACE, with a statistically significant difference for SD at 12 months (25.7 vs 2.7%). Moreover, PD rate at 12 months was significantly lower in the DEB-TACE group (48.6 vs 78.4%), as well as overall recurrence (45.7 vs 78.3%). Time to progression was longer in the DEB-TACE group (42.6 vs 36.2 weeks). They analyzed survival rate within 12 months, but they did not observe any significant difference between DEB-TACE and bland embolization.

The use of HepaSphere (superabsorbent polymer microspheres) was less extensively investigated. In 2004, Khankan *et al.* [49] published a preclinical study in a rabbit renal model, comparing superabsorbent polymer microspheres, Embosphere and PVA. They found that Embospheres and HepaSpheres migrate distally up to the interlobular artery, while PVA particles aggregate in the proximal vessels. Embospheres maintain a spherical shape, while HepaSphere conformed to the vessel lumen. In 2008, Grosso *et al.* published the only clinical trial on HepaSphere [50]. They obtained a high objective response at 1-month CT (84%), comparable with that reported in the literature for DC Beads, which was sustained in 77% of patients at 6-month follow-up (**Table 1**).

Early recurrence is a major problem with every locoregional therapy (ablation and TACE): molecular studies have shown that local recurrence and new nodules that develop within 2 years can be attributed to the spread of the original tumor [51]. To improve the local efficacy, some centers combined RFTA and TACE. DEB-TACE is performed just before, during or just after RFTA. When performed before RFTA, the embolization is used to reduce the heat washout and enlarge the thermally induced necrosis. If performed during or after RFTA, the hypervascular reaction at the periphery of the necrotic area is used to increase the number of beads, which can release chemotherapeutic drugs in high concentrations in this critical zone. Lencioni *et al.* [52] treated 21 patients with a single HCC of 5 cm mean diameter and obtained a significant enlargement of the necrotic volume (up to 60%). Despite the large diameter of the lesions, they obtained a high CR rate (60%), but no data about disease-free survival were reported. Other studies used lipiodol instead of DEBs. In a recent meta-analysis, Wang *et al.* [53] found a better 1-, 2- and 3-year survival in patients with large HCC treated with combined therapy, but not in patients with small HCC; moreover, the combined therapy was found to significantly reduce tumor recurrence.

For patients with multiple nodules, TACE is the treatment of choice, but without curative intention. Tumor recurrence after TACE is accompanied by increased VEGF production [54]. This increased expression of VEGF and other angiogenic factors (e.g., hypoxia-inducible factor 1α) is also found in the residual tumoral tissue after incomplete response to TACE. This is the rationale for the combination of TACE and sorafenib, a multi-kinase inhibitor that is actually used in advanced HCC. A multicenter randomized trial is ongoing, comparing DEB-TACE plus placebo with DEB-TACE plus sorafenib. The results are not available at the moment.

Locoregional therapies are also used as bridge treatments to liver transplantation. DEB-TACE has been used to prevent patients dropping out from transplantation lists and sometimes for downstaging. Apart from this latter application, which is currently still being discussed, the treatment of HCC while patients are on a waiting list has been found to reduce tumor recurrence after transplantation. Lao *et al.* reviewed 124 patients who had undergone liver transplantation and found using multivariate regression that the lack of pretransplant treatment was a risk factor for HCC recurrence [55].

4.2.2 *DEB-TACE in colorectal liver metastases*

While c-TACE and DEB-TACE have a well-established role in the treatment of HCC, their use in the treatment of colorectal metastases has not been investigated in extensive RCT s, but are limited to small series of patients in different centers.

Table 1. The main characteristics (outcome and side effects) of some significant works cited in the text.

Authors		DEB-TACE	c-TACE	TAE
Malagari *et al.* 48	No. of patients	41		43
	Survival	1-year 85.3%		1-year 86%
	Local response	CR 12 months 20%		CR 12 months 16.2%
		OR 12 months 25.7%		OR 12 months 18.9%
	Complications	Liver failure 4.8%		Liver failure 4.6%
		Liver abscess 4.8%		Liver abscess 2.3%
		Cholecystitis 4.8%		Cholecystitis 0
		Pleural effusion 9.7%		Pleural effusion 9.3%
		PES 80.4%		PES 81.4%
		Skin erythema 2.4%		Skin erythema 0
Lammer *et al.* 46	No. of patients	93	108	
	Survival	NA	NA	
	Local response	CR 6 months 26.9%	CR 6 months 22.2%	
		OR 6 months 51.6%	OR 6 months 43.5%	
	Complications	SAE 20.4%	SAE 19.4%	
		PES 24.7%	PES 25.9%	
		Toxicity 11.8%	Toxicity 19.4%	
Lo *et al.* 26	No. of patients		40	
	Survival		1-year 57%	
			2-year 31%	
			3-year 26%	
	Local response		CR 0%	
			OR 39%	
	Complications		Fever 32.8%	
			Abdominal pain 26%	
			Vomiting 16.7%	
			Ascites 5.2%	
			GI bleeding 4.2%	
			Ruptured tumor 1%	
			Pleural effusion 1%	
			Liver abscess 0.5%	
Llovet *et al.* 12	No. of patients		40	37
	Survival		1-year 82%	1-year 75%
			2-year 63%	2-year 50%
			3-year 29%	3-year 29%
	Local response		OR 6 months 35%	OR 6 months 43.2%
	Complications		Cholecystitis 5%	Cholecystitis 5.4%
			Leucopenia 5%	Liver abscess 2.7%
			Hepatic infarct 2.5%	Pulmonary embolism 2.7%
			SBP 2.5%	Liver failure 2.7%
			Septic shock 2.5%	GI bleeding 2.7%
			Alopecia 2.5%	
Varela *et al.* 36	No. of patients	27		
	Survival	1-year 92.5%		
		2-year 88.9%		
	Local response	CR 26%		
		OR 66.6%		
	Complications	PES 37%		
		Liver abscess 7.4% (2/27, 1 fatal)		

CR: Complete response; c-TACE: Conventional transarterial chemoembolization; DEB: Drug-eluting bead; GI: Gastrointestinal; NA: Data not available; OR: Objective response; PES: Post embolization syndrome; SAE: Severe adverse events; SBP: Spontaneous bacterial peritonitis; TAE: Transarterial embolization.

Transarterial therapies (from intra-arterial infusion of chemotherapeutic drugs to TACE) are well known. Unlike HCC, most liver metastases are not hypervascular, but they derive their blood supply mainly from the hepatic artery, similar to HCC. Like other locoregional therapies, transarterial therapies are used in patients with liver predominant disease, when surgical resection is not possible and after chemotherapy has failed or is known to be ineffective. In 1994, Fordy *et al.* compared intra-arterial infusion of 5-FU with palliative care and found a survival benefit and an improvement in the quality of life [56]. Some papers compared systemic chemotherapy with intra-arterial infusion of 5-FU and reported an increase in response (40 – 50%), but without survival benefit. However, these studies were performed before the

introduction of drug combinations such as FOLFIRI (folinic acid, 5-FU and irinotecan) and FOLFOX (folinic acid, 5-FU and oxaliplatin).

Similar to HCC, the addition of embolizing material would induce tumor necrosis through ischemia and prevent washout of drugs from the liver. TACE is performed in many different ways by combining different chemotherapeutic drugs (5-FU, cisplatin, adriamycin, mitomycin, epirubicin) with different embolizing materials (lipiodol, gelfoam, PVA, collagen, degradable starch microspheres); thus the treatment regimen is extremely variable. In 1998, Tellez *et al.* reviewed 19 studies with 324 patients [57] and found that all of studies showed an objective response to treatment, while most studies reported an improved survival (range 6 – 46 vs 6 months for untreated patients in the literature). Some studies suggested that response to treatment was correlated with tumor vascularity. Careful patient selection is crucial, as demonstrated by Stuart who found a correlation between performance status at the onset of therapy and survival [58].

DEBIRI-TACE has the potential advantages to be a precisely directed treatment with minimal systemic side effects. In their series, Martin *et al.* [59] found no irinotecan systemic adverse events, but only hepatic-related adverse events.

Technically, DEBIRI is similar to DEB-DOX. It involves the release of irinotecan-loaded DC Beads through a microcatheter. The most frequently used size is 100 – 300 µm. During DEBIRI, injection is performed into the left or the right hepatic artery, sometimes after an initial distal release, while during DEB-DOX the embolization is always segmental or subsegmental. This proximal embolization allows the administration of a larger number of beads and higher amounts of drug.

The clinical experience with DEBIRI is limited. There are no well-established guidelines for patient selection. Generally, the patients have failed first-line chemotherapy and sometimes second-line chemotherapy as well. In these patients, the response rate to standard chemotherapy decreases by 12%.

After initial reports of small series by Aliberti *et al.* [60] and Fiorentini *et al.* [61], who described 100 and 80% of objective response, the largest DEBIRI series was reported by Martin *et al.* [59,62-63]. In different papers, they describe a 3-month overall response of 65% with 12% CR, a 6-month overall survival of 50% with 12% CR and a 12-month overall response of 40% with 15% of CR. They concluded that the response obtained in 6 months is sustained until 12 months. Better results have been found in patients who failed first-line therapy, with no more than six lesions < 3 cm in size, receiving more than two treatments. In this subgroup, the median overall survival was 19 months. In another paper, a multivariate analysis found that only the presence of extrahepatic disease and the extent of prior chemotherapy were predictors of overall survival. Moreover, after a good control of hepatic disease, extrahepatic progression is often observed, thus suggesting the association of systemic chemotherapy.

Less encouraging results have been reported by Bower *et al.* [64]. They found that 20% of patients demonstrated significant response and downstage of their disease or SD without extrahepatic spread. In some cases, resection or ablation could be performed.

5. Expert opinion

Treatment of focal liver lesions represents a renovated challenge for interventional radiologists. It is now accepted that the management of patients affected by HCC requires a multidisciplinary approach. From this viewpoint, the interventional radiologist plays a co-leading role. In particular, after the trails by Llovet and Lo, which demonstrated the potential ability of TACE to improve survival in patients with intermediate-stage HCC, there has been a renewed interest in transarterial therapies, which has further increased owing to the introduction of new emerging technologies based on the intra-arterial release of macromolecules or microspheres.

Different intra-arterial therapies (such as TACE, TAE, radioembolization, intra-arterial chemotherapy) have been used for many years in the treatment of focal liver lesions, primary HCC and, more recently, secondary hepatic lesions. In the latter case, there is no well-codified role, leading to a "case-by-case" use after the failure of chemotherapy. On the contrary, it is mandatory to identify the effective impact of these treatment strategies on patient survival, which is the primary goal, in both primary and secondary tumoral hepatic diseases. It is important to remember that local tumor response is only a surrogate parameter to evaluate survival, but only a few trials on locoregional therapies report survival data. Thus, the assessment of local response is still a critical issue. The WHO and RECIST criteria have been demonstrated to be quite inadequate for locoregional therapies [17]; different staging systems have been proposed, such as the EASL and modified RECIST criteria, which are actually recommended to be used in such therapies.

In intermediate-stage HCC (BCLC B), c-TACE is the main palliative treatment, as validated by two important meta-analyses [12,26] that showed improved survival in these patients. Many studies failed to demonstrate a clear advantage of c-TACE over TAE and conflicting data have been reported. This disagreement is probably due to multiple factors such as the great heterogeneity within the BCLC B group, which includes patients with a single lesion > 5 cm in diameter, patients with three lesions > 3 cm in diameter and patients with an unspecified number of nodules. It would be desirable to divide BCLC B into subgroups and validate TACE within every subgroup, to identify patients receiving a true benefit from this technique. As different ablation therapies, such as microwaves, that are able to produce larger necrosis and mini-invasive resection techniques are now available, different groups are trying to expand the indications for such curative treatments, but there are no randomized trials or data proving a survival benefit. c-TACE has been used as palliative

treatment in patients with metastatic liver disease from colorectal cancer, breast cancer and neuroendocrine tumors, showing preliminary but promising results. However, c-TACE has not been included in a well-codified protocol, but was used episodically.

c-TACE components (lipiodol, gelfoam, chemotherapeutic drugs) present important intrinsic limits: lipiodol does not bind chemotherapeutic drugs permanently, leading to low intratumoral concentration and rapid washout, as indicated by high systemic levels; gelfoam is a temporary embolizing material, used in fragments of different sizes, which occlude hepatic vessels at a different level. These limits and the different techniques used (selective or superselective) can explain the unclear role of the drug.

Recently, the molecular engineering industry has developed new carriers, to improve the embolizing effects of intra-arterial techniques, such as liposomes, magnetic beads and microspheres, which can be loaded with chemotherapeutic drugs or yttrium. These carriers are able to enhance the embolic effect of TACE and increase the length of tumor exposure to high concentrations of the drug.

TACE performed with doxorubicin-loaded beads represents the overcoming of the limitations of c-TACE, as beads have a precise diameter (which means that they permanently occlude the vessel at a well-defined level). Moreover, their capability to absorb a drug and release it for a sustained time increases the intratumoral drug concentration and prolongs the exposure of tumoral cells, dramatically reducing systemic toxicity, as many studies (e.g., Varela *et al.*) have shown. The technical features are positively correlated in clinical trials, which report a higher objective response rate with less systemic side effects than c-TACE. In addition, DEB-TACE requires a certain preparation and a more standardized technique to avoid non-target tissue embolization, providing better uniformity and usability of data.

Recently, some authors pointed out the potential benefit of using smaller beads (50 μm) to obtain a larger contact surface with tumoral cells and deeper penetration into small peripheral tumoral vessels. However, these smaller beads should be used carefully, as their small diameter could allow them to pass into small sinusoids, increasing the risk of necrotic damage to non-target tissue.

In TACE with drug-eluting microspheres, there is an increased interest in the role of chemotherapeutic drugs, and this feature is stressed in the treatment of metastatic lesions, where the pharmacologic aspect of TACE becomes more important than the embolizing aspect. Different drugs have been used both in combination and as a sole agent, and new drugs will be available in the coming years. In particular, new molecules that modify cell membrane permeability or have an antiangiogenic effect have shown promising results.

The real advantages of DEB-TACE or DEBIRI must be validated by well-designed randomized controlled studies and in meta-analysis, both in terms of local tumor response assessed by imaging (CT, MR, contrast-enhanced ultrasound sonography) and, more importantly, in terms of patient survival.

We think that the use of carriers to deliver and release drugs, cells or other compounds is one of the most interesting and promising techniques for the immediate future. Using new biological markers, we should be able to stratify patients much more accurately to obtain more specifically targeted treatments. In fact, the technical improvements in locoregional therapies will result in a higher necrosis percentage and their action being confined to the treated lesion, without affecting the remaining liver tissue and the possibility of recurrence. Thus, it could be desirable to have both more radical locoregional therapies and all-liver targeted therapies to delay the onset of new lesions and recurrences.

Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008. Cancer incidence and mortality worldwide: IARC CancerBase No. 10. 2010. Lyon, France: International Agency for Research on Cancer. Available from: http://globocan.iarc.fr
2. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 2006;244:254-9
3. Gatta G, Capocaccia R, Sant M, et al. Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high resolution study. Gut 2000;47:533-8
4. Ksienski D, Woods R, Speers C, et al. Patterns of referral and resection among patients with liver-only metastatic colorectal cancer (MCRC, Ann Surg Oncol 2010;8:3085-93
5. Poston G, Adam R, Alberts S, et al. OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer. J Clin Oncol 2005;23:7125-34
6. Parkin DM, Bray F, Ferlay J, et al. Global Cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108
7. Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127:S35-50
8. Chu CM, Liaw YF. Hepatitis B virus-related cirrhosis: natural history and treatment. Semin Liver Dis 2006;26:142-52
9. Kassahun WT, Fangmann J, Harms J, et al. Liver resection and transplantation in the management of hepatocellular carcinoma: a review. Exp Clin Tranplant 2006;4:549-58
10. Guan YS, Liu Y. Interventional treatments for hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2006;5:495-500
11. Sotiropoulus GC, Lang H, Frilling A, et al. Resectability of hepatocellular carcinoma: evaluation of 333 consecutive cases at a single hepatobiliary speciality center and systematic review of the literature. Hepatogastroenterology 2006;53:322-9
12. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734-9

• **One of the first randomized controlled trials that demonstrated a better survival in patients treated with TACE than in untreated patients.**

13. van Persijin van Meerten E, Gelderbrom H, Bloem JL. RECIST revised: implications fort he radiologist. A review article on the modified RECIST guidelines. Eur Radiol 2010;20:1456-67
14. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL Conference. J Hepatol 2001;35:421-30
15. Sala M, Llovet JM, Vilana R, et al. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology 2004;40:1352-60
16. Camma C, Di Marco V, Orlando A, et al. Treatment of hepatocellular carcinoma in compensated cirrhosis with radiofrequency thermal ablation: a prospective study. J Hepatol 2005;42:535-40
17. Forner A, Ayuso C, Varela M, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma. Cancer 2009;115:616-23
18. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698-711
19. Yamada R, Sato M, Kawabata M, et al. Hepatic artery embolisation in 120 patients with unresectable hepatoma. Radiology 1983;148:397-401
20. Matsui K, tomoe T, Teragima S et al. Clinical study on continuous 5-FU infusion for the treatment of primary liver cancer. Gan No Rinsho 1970;16:43-7
21. Nakakuma K, Tashiro S, Hiraoka T, et al. Studies on anticancer treatment with an oily anticancer drug injected into the ligated feeding hepatic artery for liver cancer. Cancer 1983;52:2193-200
22. Nakakuma K, Tashiro S, Hiraoka T, et al. Hepatocellular carcinoma and metastatic cancer detected by iodized oil. Radiology 1985;154:15-17
23. Camma C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology 2002;224:47-54
24. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol 2007;30(1):6-25

• **A detailed systematic review of transarterial therapy for hepatocellular carcinoma.**

25. Li X, Feng GS, Zheng CS, et al. Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effects of transcatheter arterial chemoembolisation therapy on plasma vascular endothelial growth factor level. World J Gastroenterol 2004;10:2878-82
26. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolisation for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-71
27. Takayasu K, Arii S, Ikai I, et al. Prospective cohort study of transarterial chemoembolisation for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006;131:461-9
28. Raoul JL, Sangro B, Forner A, et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev 2011;37:212-20
29. Georgiades CS, Hong K, D'Angelo M, et al. Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis. J Vasc Interv Radiol 2005;16:1653-9
30. Gomes AS, Rosove MH, Rosen PJ, et al. Triple-drug transcatheter arterial chemoembolisation in unresectable hepatocellular carcinoma: assessment of

survival in 124 consecutive patients. AJR 2009;193:1665-71

31. Covey AM, Maluccio MA, Schubert J, et al. Particle embolisation of recurrent hepatocellular carcinoma after hepatectomy. Cancer 2006;106:2181-9
32. Amesur NB, Zajko AB, Carr BI. Chemo-embolisation for unresectable hepatocellular carcinoma with different sizes of embolisation particles. Dig Dis Sci 2008;53:1400-4
33. Nicolini A, Fasani P, Manini M, et al. Transarterial embolisation with microspheres in the treatment of monofocal HCC. Dig Liv Dis 2009;41:143-9
34. Bruix J, Llovet JM, Castells A, et al. Transarterial embolisation versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. Hepatology 1998;27:1578-83
35. Fu Y, Kao WJ. Drug release kinetics and transport mechanisms and degradable polymeric delivery systems. Expert Opin drug Deliv 2010;7:429-44
36. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007;46:474-81

• **One of the first clinical studies reported with DC Bead including pharmacokinetic analysis.**

37. Namur J, Wassef M, Millot JM, et al. Drug-eluting beads for liver embolization. Concentration of doxorubicin in tissue and in beads in a pig model. JVIR 2010;4:259-67
38. Taylor RR, Tang Y, Gonzalez MV, et al. Irinotecan drug eluting beads for use in chemoembolization: in vitro and in vivo evaluation of drug release properties. Eur J Pharm Sci 2007;30:7-14
39. Lewis AL, Taylor RR, Hall B, et al. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolisation. J Vasc Interv Radiol 2006;17:1335-43
40. Lee KH, Liapi E, Cornell C, et al. Doxorubicin-loaded Quadrasphere microspheres: plasma pharmacokinetics and intratumoral drug concentration in an animal model of liver cancer. Cardiovasc Intervent Radiol 2010;33:576-82
41. Jordan O, Denys A, De Baere T, et al. Comparative study of chemoembolization loadable beads: in vitro drug release and physical properties of DC-Bead and Hepasphere loaded with doxorubicin and irinotecan. JVIR 2010;21:1084-90
42. Sottani C, Leoni E, Porro B, et al. Validation of an LC-MS/MS method for the determination of epirubicin in human serum of patients undergoing drug eluting microsphere-transarterial chemoembolization (DEM-TACE). J Chromatogr B Analyt Technol Biomed Life Sci 2009;877:3543-8
43. Hong K, Kobeiter H, Georgiades CS, et al. Effects of the type of embolisation particles on carboplatin concentration in liver tumors after transcatheter arterial chemoembolization in a rabbit model of liver cancer. J Vasc Interv Radiol 2005;16:1711-17
44. Lee KH, Liapi E, Vossen JA, et al. Distribution of iron oxide-containing embosphere particles after transcatheter arterial embolization in an animal model of liver cancer: evaluation with MR imaging and implication for therapy. JVIR 2008;19:1490-6
45. Malagari K, Chatzimichael K, Alexopoulou E, et al. Transarterial chemoembolisation of unresectable hepatocellular carcinoma with drug eluting beads: result of an open-label study of 62 patients. Cardiovasc Intervent Radiol 2008;31:269-80
46. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33:41-52

•• **Randomised multicenter controlled trial for a drug delivery embolisation system.**

47. Nicolini A, Martinetti L, Crespi S, et al. Transarterial chemoembolisation with epirubicin-eluting beads versus transarterial embolisation before liver transplantation for hepatocellular carcinoma. J Vasc Interv Radiol 2010;21:327-32

• **One of the first clinical studies that compare the histological results between TAE with microspheres and DEB-TACE.**

48. Malagari K, Pomoni M, Keleki A, et al. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma. Cardiovasc Intervent Radiol 2010;33:541-51
49. Khankan AA, Osuga K, Hori S, et al. Embolic effects of superabsorbent polymer microspheres in rabbit renal model: comparison with tris-acryl gelatin microspheres and polyvinyl alcohol. Radiat Med 2004;22:384-90
50. Grosso M, Vignali C, Quaretti P, et al. Transarterial chemoembolization for hepatocellular carcinoma with drug-eluting microspheres: preliminary results from an Italian multicenter study. Cardiovasc Intervent Radiol 2008;31:1141-9

• **One of the few published papers that analyzed results with DEB-TACE using HepaSpheres.**

51. Poon RT. Differentiating early and late recurrence after resection of HCC in cirrhotic patients: implications on surveillance, prevention, and treatment strategies. Ann Surg Onc 2009;16:792-4
52. Lencioni R, Crocetti L, Petruzzi P, et al. Doxorubicin-eluting beads enhanced radiofrequency ablation of hepatocellular carcinoma: a pilot clinical study. J Hepatol 2008;49:217-22
53. Wang W, Shi J, Xie WF. Transarterial chemoembolization in combination with percutaneous ablation therapy in unresectable hepatocellular carcinoma: a meta-analysis. Liver Int 2010;30:741-9
54. Wang B, Xu H, Gao ZQ, et al. Increased expression of vascular endothelial growth factor in hepatocellular carcinoma after transcatheter chemoembolisation. Acta Radiol 2008;49:523
55. Lao OB, Weissman J, Perkins JD. Pre-transplant therapy for hepatocellular carcinoma is associated with a lower recurrence after liver transplantation. Clin Transplant 2009;23:874-81
56. Fordy C, Burke D, Earlam S, et al. Quality of life and survival with continuous hepatic artery floxuridine infusion for colorectal liver metastases. Lancet 1994;344:1255-60

57. Tellez C, Benson AB III, Lyster MT, et al. Phase II trial of chemoembolization for the treatment of metastatic colorectal carcinoma to the liver and review of the literature. Cancer 1998;82:1250-9

58. Stuart K. Chemoembolization in the management of liver tumors. Oncologist 2003;8:425-37

59. Martin RCG, Robbins K, Tomalty D, et al. Transarterial chemoembolisation (TACE) using irinotecan-loaded beads for the treatment of unresectable metastases to the liver in patients with colorectal cancer: an interim report. World J Surg Oncol 2009;7:80-91

60. Aliberti C, Tilli M, Benea G, et al. Transarterial chemoembolisation (TACE) of liver metastases from colorectal cancer using irinotecan-eluting beads: preliminary results. Anticancer Res 2006;26:3793-5

• **The first reported clinical use of DC Bead loaded with irinotecan for treatment of colorectal metastases of the liver.**

61. Fiorentini G, Aliberti C, Turrisi G, et al. Intra-arterial hepatic chemoembolization of liver metastases from colorectal cancer adopting irinotecan-eluting beads: results of a phase II clinical study. In Vivo 2007;21:1085-91

62. Martin RCG, Joshi J, Robbins K, et al. Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unresectable colorectal liver metastases refractory to systemic chemotherapy: results of multi-institutional study. Ann Sur Oncol 2011;18:192-8

63. Martin RCG, Joshi J, Robbins K, et al. Transarterial chemoembolization of metastatic colorectal carcinoma with drug-eluting beads, irinotecan (DEBIRI): multiinstitutional registry. J Oncol 2009;2009:539795

64. Bower M, Metzger T, Robbins K, et al. Surgical downstaging and neo-adjuvant therapy in metastatic colorectal carcinoma with irinotecan drug-eluting beads: a multi-institutional study. HBP 2010;12:31-6

65. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907-17

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