Drug-eluting beads transarterial chemoembolization for hepatocellular carcinoma: Current state of the art

Antonio Facciorusso

Antonio Facciorusso, Gastroenterology Unit, Department of Medical Sciences, University of Foggia, Foggia 71122, Italy

ORCID number: Antonio Facciorusso (0000-0002-2017-2156).

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Correspondence to: Antonio Facciorusso, MD, PhD, Assistant Professor, Gastroenterology Unit, Department of Medical Sciences, University of Foggia, Viale L.Pinto 1, Foggia 71100, Italy. antonio.facciorusso@virgilio.it
Telephone: +39-88-1732154
Fax: +39-88-1732135

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Abstract

Transarterial chemoembolization (TACE) represents the current gold standard for hepatocellular carcinoma (HCC) patients in intermediate stage. Conventional TACE (cTACE) is performed with the injection of an emulsion of a chemotherapeutic drug with lipiodol into the artery feeding the tumoral nodules, followed by embolization of the same vessel to obtain a synergistic effect of drug cytotoxic activity and ischemia. Aim of this review is to summarize the main characteristics of drug-eluting beads (DEB)-TACE and the clinical results reported so far in the literature. In order to overcome the drawbacks of cTACE, namely lack of standardization and unpredictability of outcomes, non-absorbable embolic microspheres charged with cytotoxic agents (DEBs) have been developed. DEBs are able to simultaneously exert both the therapeutic components of TACE, either drug-carrier function and embolization, unlike cTACE in which applying the embolic agent is a second moment after drug injection. This way, risk of systemic drug release is minimal due to both high-affinity carrier activity of DEBs and absence of a time interval between injection and embolization. However, despite promising results of preliminary studies, clear evidence of superiority of DEB-TACE over cTACE is still lacking. A number of novel technical devices are actually in development in the field of loco-regional treatments for HCC, but only a few of them have entered the clinical arena. In absence of well-designed randomized-controlled trials, the decision on whether use DEB-TACE or cTACE is still controversial.

Key words: Embolization; Doxorubicin; Conventional; Hepatocarcinoma; Liver cancer; Survival

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Core tip: Aim of this review is to summarize the main characteristics and the clinical results of drug-eluting beads (DEB)-transarterial chemoembolization (TACE). To obviate to the limitations of cTACE, non-absorbable embolic microspheres charged with cytotoxic agents (DEBs) have been developed. DEBs are able to simultaneously exert both the therapeutic components of TACE, either drug-carrier function and embolization. This way, risk of systemic drug release is minimal. However, despite promising results of preliminary studies, clear evidence of superiority of DEB-TACE over cTACE is still lacking. In absence of well-designed randomized-controlled trials, the decision on whether use DEB-TACE or cTACE is still controversial.

INTRODUCTION

Transarterial chemoembolization (TACE) constitutes the gold standard for patients in intermediate stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system, specifically those presenting with large or multifocal hepatocellular carcinoma (HCC) with preserved liver function, deteriorated performance status, and neoplastic portal vein thrombosis (PVT) or extrahepatic metastases[1,2]. By the way, TACE may constitute a valuable therapy also in early stage patients unsuitable to curative treatments, such as hepatic resection, liver transplantation (LT) or ablative therapy[3]. TACE is performed through the injection of a chemotherapeutic drug (mainly doxorubicin or cisplatin) selectively into the artery feeding the target tumoral nodules, followed by embolization of the same vessel to obtain a synergistic effect of either cytotoxic activity and ischemia[4]. Injection should be continued until the contrast column clears within 2-5 heartbeats (so called “near stasis”) and a number of different embolic agents may be used (see below) to avoid drug release into the systemic circulation[5].

The different post-treatment outcomes are probably due to the fact that TACE is a not well standardized procedure widely varying as for chemotherapeutic agents injected, treatment devices used and therapeutic schedule. In fact, overall survival (OS) of patients treated with TACE ranges from 3.4 up to beyond 40 mo (median 16.5 mo)[6]. The best survival median reported is 48 mo in a series recently published by the Barcelona group[7].

INDICATIONS AND SAFETY

Current guidelines consider as optimal candidates to TACE patients with preserved liver function, namely under or equal to Child-Pugh (CP) B7 stage without ascites in accordance with European Association for the Study of the Liver (EASL) guidelines[2] or CP A stage according to American Association for the Study of Liver Diseases (AASLD) guidelines[1].

Table 1 reports main absolute and relative contraindications to TACE.

Despite decompensated cirrhosis is commonly considered an absolute contraindication to TACE, some authors still consider chemoembolization as an option in cases of impaired portal blood flow[3].

Indeed, both EASL and AASLD guidelines strongly stand against use of TACE in PVT patients (defined as “advanced” according to BCLC staging system) because of the considerably increased risk of liver failure and consider sorafenib as the only validated option in attendance of definitive results of transarterial radioembolization (TARE) in such patients[8-10]. However, survival benefit of TACE over Best Supportive Care (BSC) has been observed in some small Asian RCTs and in a recent meta-analysis of 8 studies (of which 3 prospective) conducted in advanced HCC patients with PVT[11-13]. However, these results should be interpreted with caution since subjects with better liver function were preferably recruited in the TACE group while decompensated patients tended to be treated with BSC. The only published head-to-head comparison between TACE and sorafenib is a retrospective Austrian study which reported similar survival outcomes with a very competitive role of TACE in selected advanced patients (CP A and segmental PVT), as further confirmed in other observational studies[14,15]. By the way, the same selection bias can be detected in the Austrian study since thrombosis of the main trunk of portal vein (at more dismal prognosis) was more frequently observed in patients treated with sorafenib than in those who underwent TACE (25% vs 3%), thus claiming for great caution in interpreting this finding, and significantly higher severe adverse event (SAE) rate was experienced by TACE patients[14].

Hence, TACE may represent a valuable option for a specific subset of BCLC C patients (segmental PVT and CP A) who do not have access or are intolerant/unsuitable to sorafenib or TARE, however safety could represent an issue in these subjects and this therapeutic opportunity should be limited to highly-experienced centers[3].

Experts suggest also high tumor burden with massive replacing of both hepatic lobes as other absolute contraindication, whereas huge tumor nodule ≥ 10 cm, bile-duct occlusion, and untreated high-risk varices constitute relative contraindication rather than
absolute ones\textsuperscript{[6]}. A considerable number of patients treated with conventional TACE (cTACE) experience a transient episode of post-embolization syndrome (characterized by abdominal pain, fever and nausea), reported in 35% up to 100% of cases\textsuperscript{[16,17]}. Treatment-related deaths are observed in ≤ 2% of cases if proper selection of candidates is adopted\textsuperscript{[3,18]}. Hence, according to current guidelines, TACE represents a safe treatment in selected subjects.

**TREATMENT SCHEDULE**

A single cycle of TACE is usually insufficient for effective treatment of intermediate-stage HCC and repeating TACE is widely recognized to prolong OS; however, guidelines do not specify the criteria for treatment repetition and current clinical practice relies only on expert opinions which suggest “on-demand” TACE (i.e., number of sessions on the basis of tumor response after each TACE cycle) up to 3 to 4 times per year and switching to other therapeutic options in absence of response to at least 2 sessions\textsuperscript{[6,19]}. As a consequence of the sturdy and definitive data, there is great heterogeneity in applying TACE repetition in the common clinical practice, although a systematic review of observational and randomized trials reported a mean number of TACE sessions worldwide of 2.5 ± 1.5 per patient\textsuperscript{[20]}. Many prognostic systems have been proposed to help the clinician in selecting appropriate candidates for starting or repeating TACE, but none of them achieved an universal validation mainly due to overfitting\textsuperscript{[21-23]}.

**USEFULNESS OF DRUG INJECTION**

Robust data in favor of a clear superiority of TACE (with chemotherapy injection) over TAE (bland embolization) is still lacking\textsuperscript{[24]}. In fact, while the well-known hypervascularization of HCC nodules provides the rationale for the occlusion by embolic particles which results in tumour hypoxia and necrosis, on the other hand whether adding a local chemotherapeutic agent could determine a synergistic anti-tumor effect is still matter of debate\textsuperscript{[3,24]}.

A landmark RCT conducted in early 2000s comparing cTACE, TAE and BSC was prematurely terminated because such was the superiority of cTACE over BSC that keeping enrolling patients resulted unethical\textsuperscript{[25]}. Unfortunately, this prevented the possibility to verify the competitive efficacy of TAE and only a comparable trend in OS with respect to TACE could be observed\textsuperscript{[25]}. Similarly, no difference in terms of survival rates and safety was reported in another important multicentric American RCT published this year\textsuperscript{[26]}. However, positive results by adding doxorubicin to drug-eluting bead (DEB)-TACE over bland embolization has been recently found in a Greek trial\textsuperscript{[27]} and in a retrospective Italian report assessing as primary endpoint the degree of necrosis in explanted livers during OLT\textsuperscript{[28]}.

To make even more complicated this matter, there is no univocal agreement on the optimal chemotherapy to use in TACE. Worldwide, the most commonly used agent is doxorubicin administered at a dose ranging from 30 to 75 mg/m\textsuperscript{2} (to a maximum of 150 mg)\textsuperscript{[3,5]}. However, robust data provided by properly conducted RCTs are needed in order to deliver definitive indications in this regard.

**DEVELOPMENT OF DEB-TACE AND TECHNICAL ASPECTS**

Despite its well-proved efficacy and superiority over BSC, cTACE presents several unsolved issues. In fact, although lipiodol acts as a carrier of doxorubicin to the target nodules, release of the injected drug into systemic circulation has been demonstrated maybe due to the non-concomitant embolization, thus allowing release of a certain amount of doxorubicin in the interval time between injection and embolization\textsuperscript{[29]}. Other important limitation of cTACE is the lack of standardization as the injected particles are prepared extemporaneously, therefore is operator-dependent (not standardized) and unstable\textsuperscript{[3,20]}.

The optimal procedure should be able to selectively deliver the injected chemotherapeutic into the target tumor where the drug should be retained with no passage into blood stream to avoid systemic toxicity\textsuperscript{[3]}. In order to obviate to the aforementioned limitations of conventional TACE, non-absorbable embolic microspheres charged with cytotoxic agents (DEBs) have been developed.

DEBs are composed of a hydrophilic, ionic polymer that can bind anthracyclines via an ion exchange mechanism. The drug is usually loaded into DEBs prior to the TACE procedure creating a solution at a pre-defined concentration and then merging it into a vial with a slurry of DC Bead from which the packing solution has been removed\textsuperscript{[30]}. The drug takes from 30 min to 2 h (depending on bead size) to be loaded

**Table 1 Absolute and relative contraindications to transarterial chemoembolization**

| Contraindications |
|-------------------|
| Absolute contraindications |
| Decompensated cirrhosis (Child-Pugh ≥ 8) |
| Extensive tumor with massive replacement of both entire lobes |
| Severely reduced portal vein flow |
| Technical impediments to hepatic intra-arterial treatment |
| Kidney failure |
| **Relative contraindications** |
| Severe cardiopulmonary comorbidities |
| Tumor size ≥ 10 cm |
| Untreated varices at high risk of bleeding |
| Bile-duct occlusion |

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with small beads loading faster because of surface area effects. The maximum drug loading capacity is determined by the quantity of drug-binding sites in the beads, thus being the maximum dose dependent on drug molecular mass\(^{[30,31]}\). This is why a group of experts in the field has suggested in a recent review a dosage of 75 mg doxorubicin loaded into one vial of DC Bead for disease within the Milan criteria and up to 150 mg doxorubicin loaded into two vials of DC Bead in the case of Milan-out patients\(^{[35]}\).

DEBs are able to simultaneously exert both the therapeutic components of TACE, either drug-carrier function and embolization, unlike CTACE in which applying the embolic agent is a second moment after drug injection. This way, risk of systemic drug release is minimal due to both high-affinity carrier activity of DEBs and absence of a time interval between injection and embolization.

An in vitro analysis showed that DEB spheres could be easily loaded with doxorubicin way better than other commercial embolic microspheres\(^{[32]}\). Furthermore, drug loading led to a decrease in the average size of the beads in function of the bead size and drug dose \(^{[32]}\). Interestingly, the same study calculated half-lives of drug-elution of 150 h for the 100-300-mc range to a maximum of 1730 h for the 700-900-mc size range while there was a fast release of the chemotherapeutic agent from the unstable Lipiodol emulsion with a half-life of approximately 1 h\(^{[32]}\). Authors then concluded that DEBs lead to an accurate dosage of drug per unit volume of beads and drug release is predictable and sustained, unlike Lipiodol. In addition to all of these advantages, beads are easy to handle and to deliver thus making them a valuable option for selective TACE\(^{[33]}\).

Plasma concentration of doxorubicin resulted very low (0.009-0.05 mmol/L at different consecutive time-points) after DEB-TACE in an in-animal study conducted in a rabbit model, suggesting considerable doxorubicin retention into the tumor\(^{[33]}\). This was significantly lower (70%-85% decrease in plasma concentration) than control animals treated with doxorubicin intra-arterially\(^{[33]}\). Of note, doxorubicin concentration into the nodule had a peak at 3 d (413.5 nmol/g), remaining high to 7 d (116.7 nmol/g) and then declining at 14 d (41.76 nmol/g), indicating continuous release of the drug from the microparticles\(^{[33]}\). As a consequence of this slower release of doxorubicin, maximal tumor necrosis was observed at 7 d, with limited local complications\(^{[33]}\).

In vivo demonstration of the aforementioned strengths of DEBs has been provided by a French study conducted in 6 HCC patients who had undergone DEB-TACE before OLT\(^{[34]}\). Doxorubicin was detected on the explanted livers in an area of at least 1.2 mm in diameter around the occluded vessel. The tissue concentration of drug ranged from 5 µmol/L at 8 h to 0.65 µmol/L at 1 mo\(^{[30]}\). Necrotic tissue was characterized by a more profound penetration and a higher concentration of the drug than non necrotized areas. Authors concluded that DEBs provide a sustained delivery of drug for a period of 1 mo and local tissue concentrations above cytotoxic into the target nodules\(^{[34]}\).

The first clinical study reporting the efficacy of DEB-TACE was a phase II study by the Barcelona group\(^{[35]}\). In this pivotal paper conducted on 27 CP A HCC treated with DEB-TACE (500-700 µm particles), objective response rate (ORR) was 66.6% (of which 26% complete responses) after two consecutive sessions performed 2 mo apart\(^{[35]}\). Doxorubicin maximal concentration (Cmax) and area under the curve were considerable inferior in DEB-TACE patients in comparison with a previous cohort of CTACE patients (\(P = 0.00002\) and \(P = 0.001\), respectively)\(^{[35]}\). Moreover, SAE rate was very low with only two cases of liver abscesses experienced by treated patients\(^{[35]}\). These findings were reproduced by Poon et al\(^{[36]}\) with the maximal dose of doxorubicin (150 mg). Noteworthy, no patients in both studies experienced doxorubicin-related systemic adverse events (alopecia, bone marrow toxicity, dyspnea or pulmonary embolism)\(^{[35,36]}\).

In light of the aforementioned in-animal studies\(^{[32,37]}\), 100-300 µm beads became the most frequently used particles and are still actually recommended\(^{[3]}\).

In early 2010s, two retrospective European studies reported striking survival results in unresectable HCC patients treated with 100-300 µm DEB-TACE, particularly 43.8 mo in a Greek series\(^{[38]}\) and 48 mo of median OS in the Barcelona group’s article\(^{[37]}\). These findings, really of note considering that TACE represents only a palliative therapy, paved the way to a wide use of DEB-TACE in the clinical practice.

**COMPARATIVE EFFECTIVENESS OF DEB-TACE AND CTACE**

In spite of the interesting findings of the aforementioned studies\(^{[35,36]}\), data on comparative efficacy between CTACE and DEB TACE is still matter of debate. In fact, the 4 comparative RCTs and several retrospective studies report conflicting results.

The PRECISION V trial, a broad multicentric RCT published in 2010, enrolled 212 patients (75% BCLC B, 25% A; 80% CP A, 20% B) treated at 2-monthly intervals according a pre-defined schedule up to a maximum of three sessions\(^{[39,40]}\). Higher complete response, objective response, and disease control rates were registered in the DEB-TACE group (300-500 and 500-700 µm) as compared to CTACE (27% vs 22%, 52% vs 44%, and 63% vs 52%, respectively) but the hypothesis of superiority was not supported (one-sided \(P = 0.11\))\(^{[40]}\). Primary endpoint (tumor response) was reached only in the subgroup of more advanced patients, namely those CP B, Eastern Cooperative Oncology Group (ECOG), bilobar and recurrent disease,
where DEB-TACE outperformed cTACE\(^{[40]}\). The sole result clearly in favor of DEB-TACE was a better safety profile with significant decrease in serious liver-related adverse events (\(P < 0.001\)) and systemic side effects (particularly alopecia) (\(P = 0.0001\)), while the incidence of post embolization syndrome was comparable in the treatment groups\(^{[40]}\). Unfortunately, the short follow-up time prevented assessment of OS and Time-to-Progression (TTP).

Two Italian RCTs failed to find any significant difference in tumor response and survival between the two TACE regimens\(^{[41,42]}\). In particular, the broad PRECISION ITALIA trial, a multicentre, RCT comparing “on demand” cTACE (with epirubicin injection) and DEB-TACE (100-300 µm loaded with 50 mg of doxorubicin), was stopped for futility at the second interim analysis when only 83% of the original planned sample size had been enrolled\(^{[42]}\). Of note, 46 (26%) patients were classified as BCLC C due to ECOG-1 status. Tumor response was similar between the two groups with the only difference registered as for complete response at 1 mo which resulted significantly higher after cTACE likely due to the lipiodol “staining” effect on CT-scan. In fact, at successive response assessments in concomitance with lipiodol discharge from the target nodule, this difference disappeared\(^{[42]}\).

No difference neither in median TTP (9 mo in both treatment groups, \(P = 0.766\)) nor in 2-year survival rate (primary endpoint: 55.4% after cTACE and 56.8% after DEB-TACE, \(P = 0.949\)) was observed, hence the decision to prematurely stop the trial because the primary endpoint would have not been met\(^{[42]}\). Unlike the PRECISION trial, there was no significant difference in the incidence of AEs\(^{[42]}\).

Retrospective studies reported discordant results, with only a single outlier Korean series clearly in favor of DEB-TACE\(^{[43]}\).

A recent meta-analysis of 12 studies (4 RCTs and 8 observational) performed by my group reported similar pooled odds ratios of survival rate at 1, 2 and 3 years with a decreasing trend in favor of DEB-TACE (0.76, 0.68 and 0.57, respectively)\(^{[55]}\). This result was mainly determined by the difference in follow-up length between the two treatment groups in the retrospective reports since DEB-TACE patients, being DEBs recently introduced in the clinical practice, reported more frequent censored data and more limited absolute number of deaths\(^{[55]}\). In order to partially obviate to this bias, we plotted relative hazard ratios which are less sensitive to follow-up time bias and final result was a ratio close to 1 with no difference between the
two groups and low evidence of heterogeneity\textsuperscript{[55]} In particular, when restricting the analysis to only RCTs, the efficacy between the two techniques was absolutely comparable\textsuperscript{[55]}. Our findings updated those of previous meta-analyses which had concluded that DEB-TACE is superior to cTACE as for objective response; by the way, these systematic reviews included a limited number of studies and were underpowered to properly explore the sources of the high heterogeneity found in their results\textsuperscript{[56,57]}. Instead, no difference concerning neither tumor response nor safety profile was found in our meta-analysis which is in keeping with another recent systematic review\textsuperscript{[58]}.

In conclusion, as clearly stated in the editorial to this paper, no evidence enough to support the current extensive use of DEB-TACE exists\textsuperscript{[59]}. The same editorial, commenting a cost-effective analysis published by the Bologna group\textsuperscript{[60]}, stated that the suggested cost-effectiveness advantage of DEB-TACE requires further trials conducted in countries other than Italy and with standardized procedures and clinical settings\textsuperscript{[59]}.

LATEST ADVANCEMENTS IN THE FIELD OF TRANSARTERIAL CHEMOEMBOLIZATION

Although a clear evidence of the superiority of DEB-TACE is still lacking, novel beads have been recently developed and clinically tested. As previously described, small microparticles have been found to determine necrosis of the target lesion as they lead to a more distal embolization, thus also obstructing collateral vessels\textsuperscript{[61-63]}. Some concerns have been initially raised on the potential extrahepatic toxicity of these micro-particles due to the theoretical risk of their extrahepatic passage via collateral small vessels\textsuperscript{[64,65]}. In fact, larger particles results in more proximal embolization and consequently in broader area of ischemia, thus increasing the risk of liver damage.

An Italian prospective series from Milan showed interesting results with DEBs 70-150 $\mu$m (M1 and BTG, United Kingdom)\textsuperscript{[66]}. In this study conducted on 45 HCC early/intermediate patients, complete response was achieved in one third of them (33.3%) whereas other 20 (44.4%) reached partial response, accounting for a 77.7% ORR\textsuperscript{[66]}. The histological analysis of 28 nodules in 13 explanted livers showed 100% necrosis (complete pathologic necrosis) in 7 cases and 90%-99% necrosis in 3 cases\textsuperscript{[66]}. Noteworthy, only one SAE (grade 5) was reported, namely a case of bleeding from esophageal varices caused by the worsening of the portal hypertension\textsuperscript{[66]}. These findings have been later confirmed in other retrospective studies\textsuperscript{[64,65]}.

HepaSphere microspheres 30-60 $\mu$m (Biosphere®, Merit, United States) constitute another promising device. HepaSphere 30-60 $\mu$m/L is a new size of a loadable microsphere that has a dry caliber of 30-60 $\mu$m/L that expands to 166-242 (197 ± 31) $\mu$m/L in saline and 145-213 (148 ± 45) $\mu$m/L after loading with doxorubicin\textsuperscript{[67]}. In addition, doxorubicin was found to be released by the beads over 1 mo after TACE. Moreover, the concentration of doxorubicin in the treated tissue was high with very low plasma levels of the drug\textsuperscript{[67,68]}. A recent Greek study enrolling 45 patients treated with HepaSphere microspheres 30-60 $\mu$m/L found a complete response rate of 22.2% for the target lesions and ORR of 68.9%\textsuperscript{[69]}. No patient died in the first year after TACE and no SAE was registered\textsuperscript{[69]}.

By the way, in absence of RCTs comparing these novel microspheres, no definitive indication can be released on which DEB should be used in the common clinical practice, and the decision still relies on local expertise or availability of device.

CONCLUSION

A number of novel technical devices are actually in development in the field of loco-regional treatments for HCC\textsuperscript{[70,71]}, but only a few of them have entered the clinical arena. Beside the lack of RCTs, many other issues remain unsolved, such as understanding the real balance between the two components of the therapy (i.e., ischemia and cytotoxicity), further defining the several steps of hepatocarcinogenesis which could be targeted by combined pharmacological and interventional therapy\textsuperscript{[72-75]}, and identifying reliable prognostic markers in order to deliver a more precise oncology in patients really amenable of loco-regional treatments\textsuperscript{[76-77]}.

REFERENCES

1 Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; 67: 358-380 [PMID: 28130646 DOI: 10.1002/hep.29086]

2 European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; 56: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]

3 Facciorusso A, Licino R, Muscatello N, Di Leo A, Barone M. Transarterial chemoembolization: Evidences from the literature and applications in hepatocellular carcinoma patients. *World J Hepatol* 2015; 7: 2009-2019 [PMID: 26261690 DOI: 10.4254/wjh. v7.i16.2009]

4 Lencioni R, Petruzzi P, Crocetti L. Chemoembolization of hepatocellular carcinoma. *Semin Intervent Radiol* 2013; 30: 3-11 [PMID: 24436512 DOI: 10.1055/s-0033-1333648]

5 Lencioni R, de Baere T, Burrel M, Cardi JG, Lammer J, Malagari K, Martin RC, O’Grady E, Real MI, Vogl TJ, Watkinson A, Geschwind JF. Transcatheter therapy of hepatocellular carcinoma with Doxorubicin-loaded DC Bead (DEBDOG) technical recommendations. *Cardiovasc Intervention Radiol* 2012; 35: 980-985 [PMID: 22009576 DOI: 10.1007/s00270-011-0287-7]
for a subclassification to facilitate treatment decisions. *Semin Liver Dis* 2012; 32: 348-359 [PMID: 23397536 DOI: 10.1055/s-0032-1329906]

20 Forner A, Agudo A, Varela M, Rimola J, Hessheimer AJ, de Lope CR, Reig M, Bianchi L, Llovet JM, Bruix J. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? *Cancer* 2009; 115: 616-623 [PMID: 19117042 DOI: 10.1002/cncr.245050]

21 Sieghart W, Huckle P, Pinzler M, Gaziadei I, Vogel W, Müller C, Heinzl H, Trauner M, Peck-Radosavljevic M. The ART of decision making: retrieval with transarterial chemoembolization in patients with hepatocellular carcinoma. *Hepatology* 2013; 57: 2261-2273 [PMID: 23316013 DOI: 10.1002/hep.26256]

22 Adhoute X, Penandara G, Naude S, Raoul JL, Perrier H, Bayle O, Monnet O, Beaureaun P, Bazin C, Pol B, Folgoc GL, Castellani P, Bronowicki JP, Bourlière M. Retrieval with TACE: the ABCR SCORE, an aid to the decision-making process. *J Hepatol* 2015; 62: 855-862 [PMID: 25463541 DOI: 10.1016/j.jhep.2014.11.014]

23 Facciorusso A, Bhoori S, Papposito C, Mazzaferro V. Repeated transarterial chemoembolization: An overfitting effort? *J Hepatol* 2015; 62: 1440-1442 [PMID: 25678386 DOI: 10.1016/j.jhep.2015.01.033]

24 Facciorusso A, Bellantini F, Villani R, Salvatore V, Muscatiello N, Piscaglia F, Vendemiale G, Serviddio G. Transarterial chemoembolization vs bland embolization in hepatocellular carcinoma: A meta-analysis of randomized trials. *United European Gastroeneterology J* 2015; 7: 511-518 [PMID: 28588882 DOI: 10.1177/205064161763516]

25 Llovet JM, Real ML, Montaña X, Planas R, Coll S, Aponte J, Reig M, Forner A, Burrel M, de Lope CR, Balkanci F, Kayhan B, Uzunaloglu B, Gokoz D, RK, Gonen M, Covey AM, Getrajdman GI, 2016; 57: 1984-1992 [PMID: 27673268 DOI: 10.1007/s00270-016-2702-1]

26 Brown KT, Do RK, Gonen M, Covey AM, Getrajdman GI, 2016; 57: 1984-1992 [PMID: 27673268 DOI: 10.1007/s00270-016-2702-1]

27 Malagari K, Ponmoni A, Kelekis A, Ponmoni A, Dourakis S, Spyridopoulos T, Moschours H, Emmanouil E, Rizos S, Kelekis D. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma. *Cardiovasc Interv Radiol* 2016; 39: 489-499 [PMID: 26834067 DOI: 10.1007/JCO.2015.64.0821]

28 Nicolini A, Martinetti L, Crespi S, Maggioni M, Sangiovanni A. Transarterial chemoembolization with epirubicin-eluting beads versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. *Lancet* 2002; 359: 1734-1739 [PMID: 12049862 DOI: 10.1016/S0140-6736(02)08649-X]

29 da Baere T, Aray L, Yencioni R, Geschwind JF, Rilling W, Salem R, Matsui O, Soulen MC. Treatment of Liver Tumors with Lipiodol Block for hepatocellular carcinoma. *Cardiovasc Interv Radiol* 2010; 33: 541-551 [PMID: 19937027 DOI: 10.1002/civm.20057]

30 Nicolini A, Martinetti L, Crespi S, Maggioni M, Sangiovanni A. Transarterial chemoembolization with epirubicin-eluting beads versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. *Lancet* 2002; 359: 1734-1739 [PMID: 12049862 DOI: 10.1016/S0140-6736(02)08649-X]

31 de Baere T, Aray L, Yencioni R, Geschwind JF, Rilling W, Salem R, Matsui O, Soulen MC. Treatment of Liver Tumors with Lipiodol Block: Technical Recommendations from Experts Opinion. *Cardiovasc Interv Radiol* 2016; 39: 334-343 [PMID: 26390875 DOI: 10.1002/civm.2012-015-1208-y]

32 Hecq JD, Lewis AL, Vanbeekbergen D, Athanassopoulos A, Galanti I, Jamart J, Czuczmar PN, Chau J. Doxorubicin-loaded drug-eluting beads (DC Bead®) for use in transarterial chemoembolization: a stability assessment. *Int J Oncol Pharm Pract* 2016; 14: 123-129 [PMID: 26390875 DOI: 10.1002/civm.2012-015-1208-y]
Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. J Vasc Interv Radiol 2006; 17: 1335-1343 [PMID: 16923981 DOI: 10.1016/j.jvir.20050828.16.21560.77]

Hong K, KGeorge CS, Liapi E, Torbenson MS, Georgiades CS, Geschwind JF. New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer. Clin Cancer Res 2006; 12: 2563-2567 [PMID: 16638866 DOI: 10.1158/1078-0432.CCR-05-2225]

Namur J, Citron SJ, Sellers MT, Dupuis MH, Wassef M, Manfait M, Laurent A. Embolization of hepatic carcinoma with drug-eluting beads: doxorubicin tissue concentration and distribution in patient liver explants. J Hepat 2011; 55: 1332-1338 [PMID: 21703910 DOI: 10.1016/j.jhep.2011.03.024]

Varella M, Real MI, Burrell M, Forment F, la Parra C, Esteban E, Vaño M, Tumino E, Ginanni B, Federici G, Cioni R, Metrangolo S, Tumino E, Ginanni B, Federici G, Cioni R, Metrangolo S, 2012; 43: 47-54 [PMID: 17627902 DOI: 10.1016/j.jvir.2008.02.023]

Malgarei K, Pomoni M, Moschouris H, Bouma E, Koskinas J, Stefaniotou A, Malagari K, V ogl T, Pilleul F, Denys A, Watkinson A, Denys A, Watkinson A, Pilleul F, Renard G, Schell F, Platek Z, Wawrynzyk W, Stroszczyński C. Transarterial Chemoembolization of Child-A hepatocellular carcinoma: drug-eluting bead TACE (DEB TACE) vs. TACE with cisplatin/lipiodol (cTACE). Med Sci Monit 2011; 17: CR189-1915 [PMID: 21455104 DOI: 10.12659/MSM.881714]

40 Recchia F, Passalacqua G, Filauri P, Dodici P, Boscarato P, Candeloro G, Necoioze S, Desideri G, Rea S. Chemoembolization of unresectable hepatocellular carcinoma: Decreased toxicity with slow-release doxorubicin-eluting beads compared with lipiodol. Oncol Rep 2012; 27: 1377-1383 [PMID: 22940368 DOI: 10.3892/or.2012.1651]

Facciorusso A, Mariani L, Sposito C, Spreafico F, Bongini M, Morosi C, Cascella T, Marchiàno A, Camerini T, Bhooi S, Brunero F, Barone M, Mazzaferrro V. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma. J Gastroenterol Hepatol 2016; 31: 645-653 [PMID: 26331807 DOI: 10.1111/jgh.13147]

42 Arabi M, BenMousa A, Baezzi K, Garad F, Ahmed I, Al-Otaibi M. Doxorubicin-loaded drug-eluting beads versus conventional transarterial chemoembolization for nonresectable hepatocellular carcinoma. Saudi J Gastroenterol 2015; 21: 175-180 [PMID: 26021777 DOI: 10.4103/1519-3767.157571]

Kloockner R, Weinmann A, Prinz F, Pinto dos Santos D, Ruckes C, Duher C, Pitton MB. Conventional transarterial chemoembolization versus drug-eluting bead transarterial chemoembolization for the treatment of hepatocellular carcinoma. BMC Cancer 2015; 15: 465 [PMID: 26059447 DOI: 10.1186/s12885-015-1480-x]

44 Megias Vericat JE, García Marcos R, López Briz E, Gómez Muñoz F, Ramos Ruiz J, Martinez Rodrigo JJ, Poveda Andrés JL. Trans-arterial chemoembolization with doxorubicin-eluting particles versus conventional trans-arterial chemoembolization in unresectable hepatocellular carcinoma: A study of effectiveness, safety and costs. Radiologia 2015; 57: 496-504 [PMID: 25857250 DOI: 10.1016/j.rx.2015.01.008]

45 Liu YS, Ou MC, Tsai YS, Lin XZ, Wang CK, Tsai HM, Chuang MT. Transarterial chemoembolization using gelatin sponges or microspheres plus lipiodol-doxorubicin versus doxorubicin-loaded beads for the treatment of hepatocellular carcinoma. Korean J Radiol 2015; 16: 125-132 [PMID: 25598680 DOI: 10.3348/jkra.2015.06.2.125]

46 Scartozzi M, Baroni GS, Faloppi L, Paolo MD, Pierantonio C, Candelari R, Berardi R, Antognoli S, Mincarello C, Risaliti A, Marmarola C, Antico E, Benedetti A, Cascini S. Trans-arterial chemoembolization (TACE), with either lipiodol (traditional TACE) or drug-eluting microspheres (precision TACE, pTACE) in the treatment of hepatocellular carcinoma: efficacy and safety results from a large mono-institutional analysis. J Exp Clin Cancer Res 2010; 29: 164 [PMID: 21159184 DOI: 10.1186/1756-9966-29-164]
55 Facciorusso A, Di Maso M, Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: A meta-analysis. *Dig Liver Dis* 2016; 48: 571-577 [PMID: 26965785 DOI: 10.1016/j.dld.2016.02.005]

56 Huang K, Zhou Q, Wang R, Cheng D, Ma Y. Doxorubicin-eluting beads versus conventional transarterial chemoembolization for the treatment of hepatocellular carcinoma. *J Gastroenterol Hepatol* 2014; 29: 920-925 [PMID: 24224722 DOI: 10.1111/jgh.12439]

57 Han S, Zhang X, Zou L, Lu C, Zhang J, Li J, Li M. Does drug-eluting bead transarterial arterial chemotheroembolism improve the management of patients with hepatocellular carcinoma? A meta-analysis. *PLoS One* 2014; 9: e102686 [PMID: 25083860 DOI: 10.1371/journal.pone.0102686]

58 Xie ZB, Wang XB, Peng YC, Zhu SL, Ma L, Xiang BD, Gong WF, Chen J, You XM, Jiang JH, Li LQ, Zhong JH. Systematic reviewing comparing the safety and efficacy of conventional and drug-eluting bead transarterial chemoembolization for inoperable hepatocellular carcinoma. *Hepatol Res* 2015; 45: 190-200 [PMID: 25388603 DOI: 10.1111/hepr.12450]

59 Angelico M. TACE vs DEB-TACE: Who wins? *Dig Liver Dis* 2016; 48: 796-797 [PMID: 27257050 DOI: 10.1016/j.dld.2016.05.009]

60 Cucchiatti A, Trevisani F, Cappelli A, Mosconi C, Renzulli M, Pinna AD, Golferri R. Cost-effectiveness of doxorubicin-eluting beads versus conventional trans-arterial chemo-embolization for hepatocellular carcinoma. *Dig Liver Dis* 2016; 48: 798-805 [PMID: 27263056 DOI: 10.1016/j.dld.2016.03.031]

61 Nishikawa H, Kita R, Kimura T, Osaki Y. Transarterial arterial embolic therapies for hepatocellular carcinoma: a literature review. *Anticancer Res* 2014; 34: 6877-6886 [PMID: 25503113]

62 Minocha J, Salem R, Lewandowski RJ. Transarterial chemoembolization and yttrium-90 for liver cancer and other lesions. *Clin Liver Dis* 2014; 18: 877-890 [PMID: 25438288 DOI: 10.1016/j.cld.2014.07.007]

63 Gholamrezaeehad A, Mirpour S, Geschwind JF, Rao P, Loffroy R, Pellerin O, Liapi EA. Evaluation of 70-150 µm doxorubicin-eluting beads for transarterial arterial chemoembolization in the rabbit liver VX2 tumour model. *Eur Radiol* 2016; 26: 3474-3482 [PMID: 26780638 DOI: 10.1007/s00330-015-4197-y]

64 Odisio BC, Ashton A, Yan Y, Wei W, Kasheb A, Wallace MJ, Vauthery JN, Gupta S, Tam AL. Transarterial hepatic chemoembolization with 70-150 µm drug-eluting beads: assessment of clinical safety and liver toxicity profile. *J Vasc Interv Radiol* 2015; 26: 965-971 [PMID: 25979305 DOI: 10.1016/j.jvir.2015.03.020]

65 Deipolyi AR, Oklu R, Al-Ansari S, Zhu AX, Goyal L, Ganguli S. Safety and efficacy of 70-150 µm and 100-300 µm drug-eluting bead transarterial chemoembolization for hepatocellular carcinoma. *J Vasc Interv Radiol* 2015; 26: 516-522 [PMID: 25704226 DOI: 10.1016/j.jvir.2014.12.020]

66 Spreafico C, Cascella T, Facciorusso A, Sposito C, Rodolfo L, Morosi C, Civelli EM, Vaiani M, Bhoori S, Pellegrinelli A, Marchiani A, Mazzaffero V. Transarterial chemoembolization for hepatocellular carcinoma with a new generation of beads: clinical-radiological outcomes and safety profile. *Cardiovasc Intervent Radiol* 2015; 38: 129-134 [PMID: 24870698 DOI: 10.1007/s00270-014-0907-0]

67 Dinca H, Pelage JP, Baylarly MT, Ghedigian SH, Pascale F, Manfait M. Why do small size doxorubicin-eluting microspheres induce more tissue necrosis than larger ones? A comparative study in healthy pig liver (oral communication 2206-2). CIRSE Annual meeting, Lisbon 2012

68 Liu DM, Kos S, Buczowski A, Kee S, Munk PL, Klass D, Wasan E. Optimization of doxorubicin loading for superabsorbent polymer microspheres: in vitro analysis. *Cardiov Intervent Radiol* 2012; 35: 391-398 [PMID: 21567274 DOI: 10.1007/s00270-011-0168-0]

69 Malagari K, Ponomi M, Moschouris H, Kelekis A, Charokopakis A, Bouma E, Spyridopoulos T, Chatziioannou A, Sotichos V, Karampelas T, Tamvakopoulos C, Filipiadjas D, Karagiannis E, Marinis A, Koskinas J, Kelekis DA. Chemoembolization of hepatocellular carcinoma with HepaSphere 30-60 µm. Safety and efficacy study. *Cardiovasc Intervent Radiol* 2014; 37: 165-175 [PMID: 24243774 DOI: 10.1007/s00270-013-0777-x]

70 Kumar Y, Sharma P, Bhatt N, Hooda K. Transarterial Therapies for Hepatocellular Carcinoma: A Comprehensive Review with Current Updates and Future Directions. *Asian Pac J Cancer Prev* 2016; 17: 473-478 [PMID: 26925530 DOI: 10.7314/APJCP.2016.17.2.473]

71 Greco G, Cascella T, Facciorusso A, Nani R, Lanoceira R, Morosi C, Vaiani M, Calareso G, Greco FG, Ragnanese A, Bongini MA, Marchiano A, Mazzafzerro V, Sprefaco C. Transarterial chemoembolization using 40 µm drug eluting beads for hepatocellular carcinoma. *World J Radiol* 2017; 9: 245-252 [PMID: 28634515 DOI: 10.4329/wjr.v9.i5.245]

72 Facciorusso A, Villani R, Bellanti F, Mitarotonda D, Vendemiale G, Servidido G. Mitochondrial Signaling and Hepatocellular Carcinoma: Molecular Mechanisms and Therapeutic Implications. *Curr Pharm Des* 2016; 22: 2689-2696 [PMID: 26861645 DOI: 10.2174/1381612822666160209153624]

73 Facciorusso A, Antonino M, Del Prete V, Neve V, Scavo MP, Barone M. Are hematopoietic stem cells involved in hepatocarcinogenesis? *Hepatobiliary Surg Nutr* 2014; 3: 199-206 [PMID: 25202697 DOI: 10.3978/j.issn.2304-3881.2014.06.02]

74 Facciorusso A. The influence of diabetes in the pathogenesis and the clinical course of hepatocellular carcinoma: recent findings and new perspectives. *Curr Diabetes Rev* 2013; 9: 382-386 [PMID: 23845075 DOI: 10.2174/15733998113090900068]

75 Lencioni R, Llovet JM, Han G, Tak WY, Yang J, Gugglielm A, Paik SW, Reig M, Kim DY, Chau GY, Luca A, Del Arbol LR, Leberre MA, Niu W, Nicholson K, Meinhardt G, Bruix J. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. *J Hepatol* 2016; 64: 1090-1098 [PMID: 26809111 DOI: 10.1016/j.jhep.2016.01.012]

76 Facciorusso A, Del Prete V, Antonino M, Crucini N, Neve V, Di Leo A, Carr BI, Barone M. Post-recurrence survival in hepatocellular carcinoma after percutaneous radiofrequency ablation. *Dig Liver Dis* 2014; 46: 1014-1019 [PMID: 25085684 DOI: 10.1016/j.dld.2014.07.012]

77 Facciorusso A, Del Prete V, Antonino M, Crucini N, Neve V, Di Leo A, Carr BI, Barone M. Serum ferritin as a new prognostic factor in hepatocellular carcinoma patients treated with radiofrequency ablation. *J Gastroenterol Hepatol* 2014; 29: 1905-1910 [PMID: 24731153 DOI: 10.1111/jgh.12618]

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