

Review

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Technical update on transcatheter arterial chemoembolization

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Abstract

Transcatheter arterial chemoembolization has become an established drug delivery system for palliative or bridging treatment of hepatocellular carcinoma. Over the last two decades, various research and developments have taken place to improve the transcatheter arterial chemoembolization procedure from both a clinical and a technical perspective. This review article aims to provide an update on the technical developments over the last decade.

Keywords: Transcatheter arterial chemoembolization, Doxorubicin, bead, cisplatin

INTRODUCTION

Since its first introduction in the late 1970s, transcatheter arterial chemoembolization (TACE) has become an established drug delivery system for palliative or bridging treatment of hepatocellular carcinoma (HCC)^[1,2]. Randomized controlled trials have shown a survival benefit in patients treated with TACE, compared to transcatheter arterial embolization (TAE) using bland agents with no additional chemotherapy^[3-5]. TACE has also replaced trans-arterial chemotherapy (TAC), which delivered chemotherapy in isolation without vessel occlusion.

The liver has a dual blood supply via both the hepatic artery and the portal vein; TACE takes advantage of this dual blood supply. As 80%-90% of HCCs derive their blood supply from the hepatic artery, it therefore, becomes an ideal vessel to access and deliver both an embolic and a chemotherapeutic agent,



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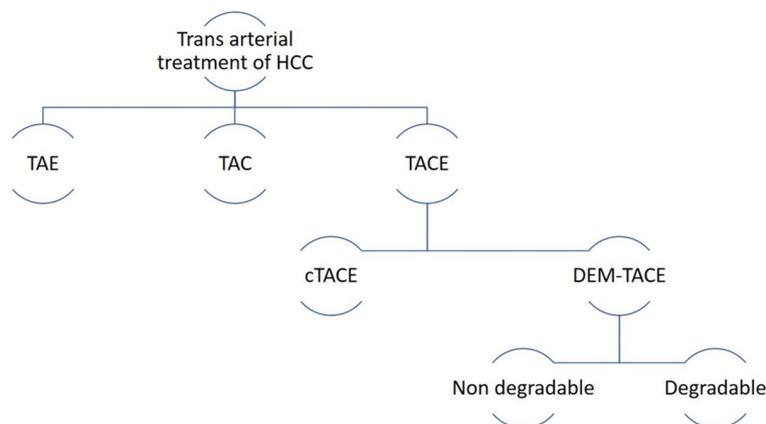


Figure 1. A simplified classification of various transarterial image-guided treatment options for HCC. TAE is a bland embolization that is rarely used unless in an emergency for treating ruptured HCC. TAC is currently not used. TACE is the most commonly used technique with cisplatin or doxorubicin. HCC: hepatocellular carcinoma; TAE: transarterial embolization; TAC: transarterial chemotherapy; TACE: transcatheter arterial chemoembolization; cTACE: conventional transcatheter arterial chemoembolization; DEM-TACE: drug-eluting microsphere-transcatheter arterial chemoembolization

leading to tumor ischemia, necrosis, and growth control^[6]. As most normal hepatocytes are supplied by the portal vein, embolizing via the hepatic artery minimizes collateral ischemic damage and reduction in liver function, and the chemotherapy agent is not affected by the first-pass metabolism, as it would be if administered orally or intravenously.

TACE can be technically classified as conventional (cTACE), which can be selective or less than selective, and drug-eluting microsphere (DEM-TACE), where the treatment is delivered as close to the tumor as possible by super-selective catheterization of the feeding arteries. DEM-TACE can be further subdivided based on the degradable nature of the microsphere [Figure 1].

cTACE is undertaken with lipiodol, a poppy seed oil-based contrast medium, causing transient ischemia, in which chemotherapy agents such as cisplatin, doxorubicin, or mitomycin are suspended as an emulsion. Due to the lack of Kupffer cells in the tumor, lipiodol has the benefit of being retained in the tumor for weeks, thus enabling post-procedural computed tomography (CT) evaluation of the tumor load. However, lipiodol can lead to severe pain requiring strong opioid analgesia. cTACE lacks the benefit of a sustained high drug level in the tumor and can also lead to systemic elevation of the drug levels. Post-embolization syndrome is more common with cTACE^[7,8]. Due to the above disadvantages, DEM-TACE was introduced in 2006, which produced sustained tumor-selective drug delivery, limited systemic elevation of drug levels, and permanent feeding vessel embolization^[9]. Fewer courses of TACE are required with DEM-TACE compared to cTACE^[10]. There is no Level 1 evidence demonstrating superiority in efficacy between the two techniques; however, there are many single-center prospective cohort studies demonstrating a higher complete response and lower rate of progressive disease with DEM-TACE^[11].

CURRENT INDICATIONS AND PATIENT SELECTION

Patient selection for TACE continues to depend on the tumor size, number, extrahepatic spread, liver function, portal vein involvement, and the patient's general performance status. Childs-Pugh score and Barcelona clinic liver criteria are used to select patients for the appropriate treatment^[12]. A multidisciplinary team approach to consider a patient for TACE and pre-procedure patient counseling are important to ensure ideal patient selection. Table 1 summarizes the indications for TACE. Decompensated liver function, infiltrative HCC, untreatable AV fistula, renal dysfunction, and chemotherapy-related

Table 1. Indications for transcatheter arterial chemoembolization

Intermediate stage patients, BCLC-B (asymptomatic, multinodular tumors without vascular invasion or extrahepatic spread)
Patients tumor suitable for curative treatment but not eligible due to performance status
Disease recurrence after curative treatment by surgery or ablation
Bridging or downstaging while patient fulfills criteria for liver transplantation or donor becomes available
Downsizing tumor or reducing circulation to meet criteria for ablation

BCLC: barcelona clinic liver cancer



Figure 2. A: an oblique axial CTA multiple intensity projections reformat, showing the vascular path from the coeliac axis to the left lobe tumor; B, C: intraprocedural images pre- and post-embolization. Given the prior delineation of vascular anatomy, only two arterial angiograms were done, reducing contrast load and radiation exposure

contraindication are absolute contraindications. HCC size above 10 cm, portal hypertension with or without untreated varices, portal vein thrombosis, and biliary involvement are relative contraindications. The more infiltrative the tumor is into the vessels and bile ducts, the higher is the risk of complications. Cardiac failure is a contraindication for cTACE but not for DEM-TACE.

TACE and liver transplantation

Unlike TACE, liver transplantation is curative in a select group of patients with HCC. TACE can be used as a bridging treatment to inhibit tumor progression in patients who are candidates for transplant while awaiting a suitable donor or fulfillment of transplant criteria^[13,14].

TACE as an adjunct to other therapies

Increasingly, TACE is being used as an adjunct to reduce tumor size and vascularity to facilitate ablation techniques, such as radiofrequency, microwave, and cryotherapy. These ablation techniques can also be used after TACE for residual disease even if a patient was originally deemed suitable only for TACE^[15-17].

PRE-PROCEDURE PATIENT MANAGEMENT

The preparation of a patient for TACE includes high-quality triple-phase post-contrast CT or magnetic resonance imaging to delineate the arterial anatomy and circulation to the tumor [Figure 2]. Besides, 4D CT can help reduce intra procedural volume of contrast and risk of nephrotoxicity. CIN (contrast-induced nephrotoxicity) is more common in larger tumors measuring above 5 cm in size^[18-20].

A review of the patient by the operator ahead of the procedure ensures the patient is being informed of the palliative, curative, or bridging nature of the procedure and its complications. For example, accidental damage to the main hepatic artery during TACE is a rare risk, which can make transplant challenging and rarely impossible.

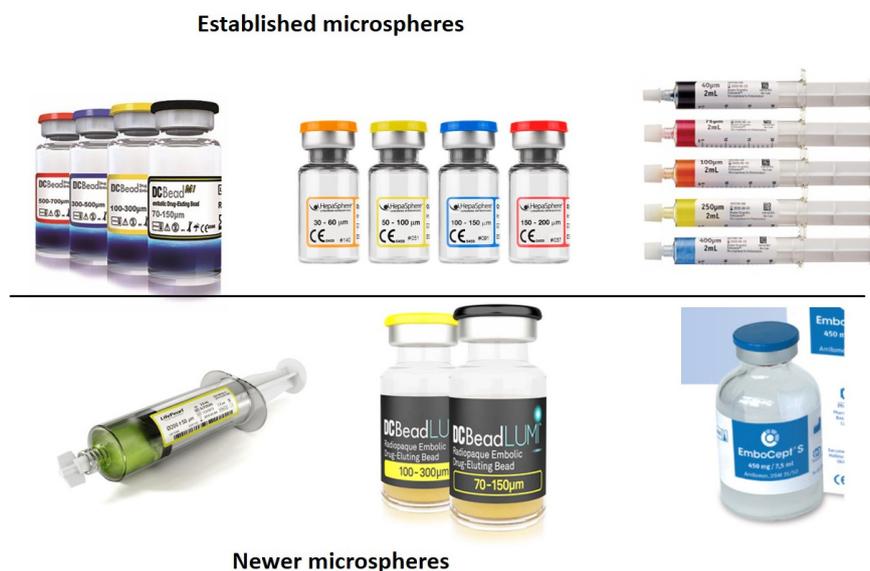


Figure 3. The top row shows the established spheres. The bottom row shows the newer spheres currently coming into clinical use. Image courtesy of Biocompatibles UK Limited, Merit Medical USA and Terumo UK. Images of Embozene and Embocept obtained from free brochures on the Internet

Before the procedure, patients should be well hydrated. This is to reduce the risk of nephrotoxicity from iodinated contrast medium, tumor lysis syndrome, and dehydration due to a lack of fluid intake from post-procedure nausea or vomiting^[19,20]. Due to the risk of infection and abscess formation, antibiotics for prophylaxis is a routine practice based on the local departmental or hospital rules^[21,22]. Antibiotics, when used, should cover both Gram-positive, Gram-negative and anaerobic organisms and are recommended for all high-risk patient groups such as diabetics, immunosuppressed, *etc.* A mandatory up to date liver function test should be performed within a week of the TACE given the risk of liver ischemia and failure from the procedure. An echocardiogram of the heart is performed to assess the left ventricular function and to facilitate both patient selection and assess the impact of cytotoxins on the myocardium, especially if multiple episodes of treatment are being considered.

CHEMOTHERAPY AND EMBOLIC AGENTS UPDATE

Chemotherapy agents

Cisplatin and doxorubicin remain the routinely used chemotherapy agents for HCC. Other agents such as epirubicin and combinations have been tried with limited advantage^[23,24].

Embolitic agents

*c*TACE

Lipiodol is the agent used for *c*TACE. Lipiodol has a limited embolic property and causes transient ischemia. Further bland embolization with gel foam or Polyvinyl alcohol (PVA) is used to bring arterial flow to stasis. There has been no further development and a clinical alternative to lipiodol is not available. Cisplatin and doxorubicin are the routine chemotherapy agents used with lipiodol.

DEM-TACE

DEM-TACE uses a drug-eluting microsphere as embolic agents. The various spheres available and their advantages are listed in [Table 2](#) and depicted in [Figure 3](#). DC bead, HepaSphere, and Embozenes are polyvinyl alcohol-based. Life pearl is polyethylene glycol-based.

Table 2. Various drug-eluting microspheres currently available in the market and their advantages

Types	Company	Structure	Available sizes (μm)	Advantages
DC Bead (EU) LC Bead (USA) M1 version is smaller size	BTG, London, UK (Now Boston Scientific)	Polyvinyl alcohol hydrogel modified with sulfonate groups	70-150 100-300 300-500 500-700	Largest data available, can be loaded before embolization and as a secondary action, will elute a local, controlled and sustained dose to the tumor after embolization
DC bead LUMI	BTG, London, UK (Now Boston Scientific)	As above and also, covalently bound radio-opaque moiety	70-150 100-300	Visibility on fluoroscopy and on table cone-beam CT
HepaSphere or QuadraSphere	Merit Medical, South Jordan, UT, USA	Poly (vinyl alcohol-co-sodium acrylate) hydrogel	Dry state 30-60 50-100 100-150 Hydrated state 120-240 200-400 400-600 600-800	Compresses by 80% but returns to shape and size becoming predictable and conformable. Entire sphere loads
Embozene TANDEM Oncozene	Varian Medical Systems, Inc. 3100 Hansen Way, USA	Hydrogel core made of sodium poly (methacrylate) and outer biocompatible shell of poly bis [trifluoroethoxy] phosphazene	Oncozene 40 \pm 10 75 \pm 15 100 \pm 25 Embozene 40- 75 100 250 400 500 700 900	Tightly calibrated to enable more choices for embolization. Less than 5% size change on eluting
LifePearl	Terumo European Interventional Systems, Leuven, Belgium	Hydrogel network of poly ethylene glycol and 3-sulfopropyl acrylate	100 \pm 25 200 \pm 50 400 \pm 50	Wide range of drug loading options Enhanced suspension characteristic. Tight calibration and longer suspension time
DSM - TACE EMBOCEPTc	PharmaCept GmbH, Berlin, Germany	Active ingredient - Amilomer DSM 35/50. Partly hydrolyzed starch, cross-linked and substituted with glycerol ether groups	50	Biodegradable. Tolerated better as less post embolization syndrome. Nonimmunogenic

CT: computed tomography; DSM: degradable starch microsphere; TACE: transcatheter arterial chemoembolization

These microspheres or beads are available in various sizes. A very small size bead usage in a large HCC stands the risk of shunting. Large size bead, on the other hand, can cause proximal occlusion without enough beads reaching the middle of the tumor. The size of the microsphere should be chosen based on tumor circulation^[25,26]. Routinely, a non-degradable DC bead at 100-300 μm is our preferred size, which shrinks by 20% upon standing.

DC bead

Consists of polymeric microspheres with the ability to encapsulate chemotherapeutic agents such as doxorubicin, irinotecan, and epirubicin with hydrogen ions, by electron attraction. It is manufactured by free radical polymerization of PVA with modification of sulfonate sodium to enable it to encapsulate the chemotherapeutic agent. DC beads have the most available clinical data and provide a sustained release of the drug. Patients with DC bead DEM-TACE treatments can receive a higher dose of doxorubicin without the undesired systematic circulation of injected drugs in comparison with cTACE^[27]. Ninety percent of patients with unresectable HCC receiving DEM-TACE do not have hepatic artery damage with one- and two-year survival rates around 70% and 60%, respectively^[23].

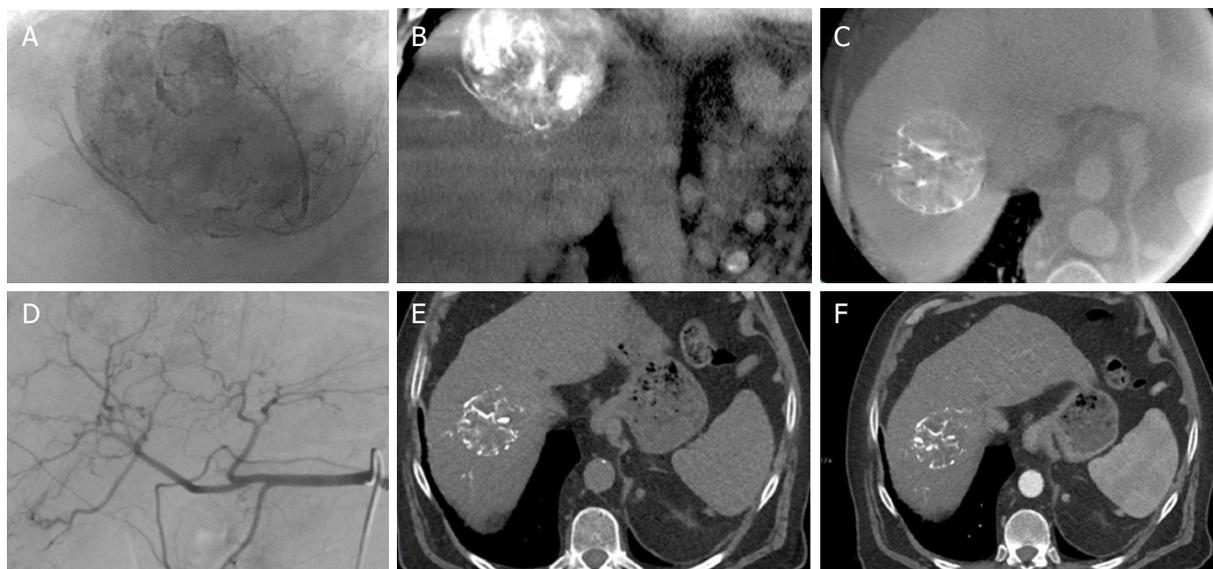


Figure 4. A-C: fluoroscopy and non-contrast CBCT immediately and first LUMI-TACE demonstrate excellent uptake within the lesion with minimal non-target embolization; D: second LUMI-TACE Angiography showing feeding vessels supplying small areas of residual disease; E, F: unenhanced and arterial-phase axial computed tomography images one month following the second LUMI-TACE, demonstrating a complete response. Comparison with the unenhanced imaging is vital. Image courtesy of Dr. Peter Littler - consultant interventional radiologist, Freeman Hospital, Newcastle upon Tyne, UK

HepaSpheres or QuadraSphere

These microspheres are hydrophilic, calibrated, and can be compressed by 80%, facilitating a smooth transit in a microcatheter. They are small, soft, and easily conform to the vessel lumen for complete occlusion, enabling greater tumor necrosis^[28,29].

LifePearl

LifePearl is made from polyethylene glycol unlike the preceding three microspheres, which are made from polyvinyl alcohol. Polyethylene glycol offers a longer time in suspension than DC Bead and HepaSphere when loaded with doxorubicin and DC Bead and Tandem when loaded with irinotecan. Longer time in suspension enables a smoother embolization procedure without the need for any interruption to resuspend the microspheres^[30].

Radio-opaque microspheres - DC or LC bead LUMI

Classically, the microspheres or beads, after loading with the chemotherapy agent, are mixed with non-ionic contrast for direct fluoroscopic visualization. These beads do not retain contrast in tumor vessels and are washed out within minutes of the procedure. DC or LC Bead LUMI™ microspheres contain covalently bound iodine making them radio-opaque and enabling real-time assessment of the bead deposition in the HCC. The density and distribution of the radio-opaque beads can help accurately identify the embolization endpoint and the degree of flow stasis. Additionally, one can also visualize non-target reflux. Performing an on-table cone-beam non-contrast enhanced CT scan, immediately after embolization with LUMI beads, may provide important information about the completeness of treatment based on contrast retention^[31]. During follow up imaging, it is essential to compare unenhanced with contrast-enhanced CT images to ensure accurate assessment of response, as shown in [Figure 4](#).

Degradable starch microsphere-TACE

Degradable starch microsphere (DSM) has an active ingredient called Amilomer, DSM 35/50. The starch microspheres are derived from partly hydrolyzed starch, which is cross-linked and substituted with

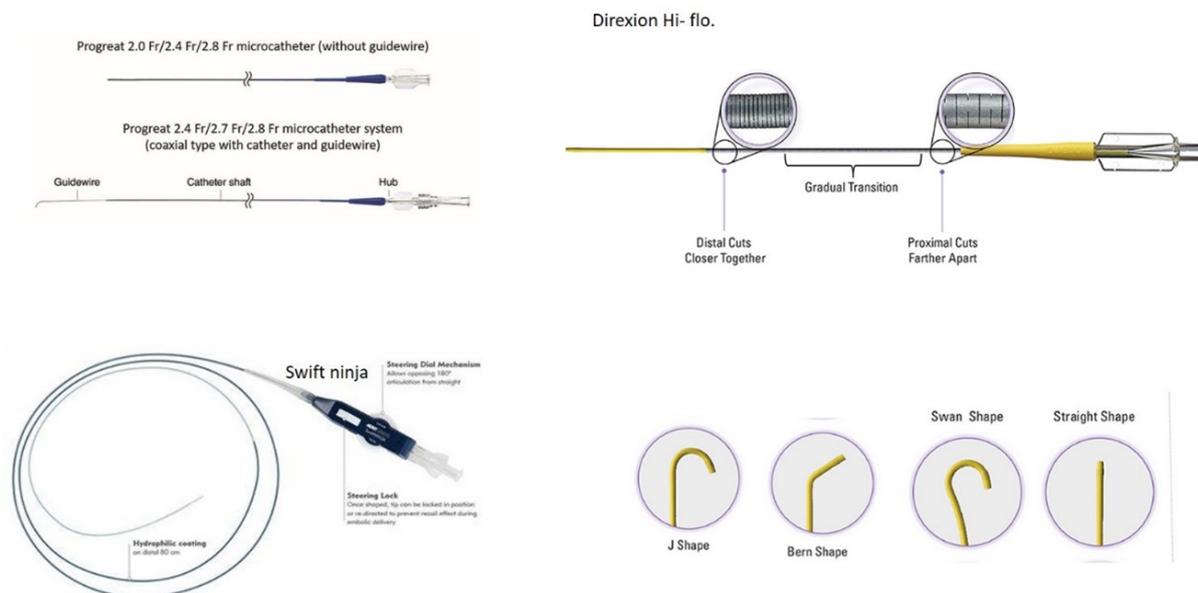


Figure 5. Various microcatheters with advanced properties such as coaxial wires, shapes, torque ability, and steerability. Image courtesy of Pro great - Terumo UK, Direxion Boston Scientific UK, Swift Ninja Merit Medical USA

glycerol ether groups. The microsphere is non-immunogenic and is prepared in a highly pure form of starch, which undergoes enzymatic degradation by α -amylase. The degraded material is completely water-soluble. The DSM sphere is small at 50 μm with a half-life of 35 min. There is reduced post-embolization syndrome with less pain and ischemic damage to the tumor-bearing organ. This makes it ideal for large tumors enabling therapeutic benefits for patients with repeated cycles and better tolerance^[32,33].

NEWER INTRAPROCEDURAL ACCESSORIES

Interventional kit

Compared to the 1980s and 1990s, super-selective catheterization techniques and catheter skills have evolved and become a routine for various transcatheter procedures. Selective catheterization with microcatheters is routine, with the use of a 2.7 French and 2.4 French micro-catheter. More recently, 2.0 French, angled and steerable micro-catheters with or without coaxial wire systems have become readily available. As shown in [Figure 5](#). Novel techniques of catheterization have also evolved such as side hole access via a balloon occlusion catheter^[34,35].

On-table CT

Development of the hybrid CT/angiography system and C-arm cone-beam CT technology provides cross-sectional imaging as an adjunct to catheter angiography with or without intra-arterial contrast. This can be used with image fusion or co-registration with catheter angiogram to help localize and perform selective TACE^[36-38].

The LUMI beads are radio-opaque, enabling fluoroscopic visualization of bead deposition in the tumor, and are ideally suited to be visualized on the cone-beam on-table CT to assess for endpoints and plan further courses of TACE^[31].

Radial access TACE

This approach is gaining popularity as an option for patients to choose between femoral and radial access, as shown in [Figure 6](#). In the past, radial and brachial access TACE were used as alternative access sites in



Figure 6. Catheter angiogram before (A) and after (B) transcatheter arterial chemoembolization performed via radial access due to steep downward angulation of the coeliac axis and upward of the hepatic artery

patients with a steeply angled coeliac axis, challenging or occluded iliac and femoral arteries, or due to an unstable catheter position via the femoral access.

More recently, the benefits of early mobilization and superior patient satisfaction via radial artery access have made radial access a routine rather than an alternative^[39]. Radial access has been studied extensively for coronary intervention with additional benefits in an acute setting^[40]. The medical device industry also responded by developing longer shaft length catheter systems to reach the tumors in the liver^[41]. A small risk of posterior fossa stroke and hand ischemia exists, and this should be clearly explained to the patients as part of the informed consent. A Barbeau test is a modification of Allen's test and is a requirement to ensure enough collateral flow via the ulnar artery to the hand. Vasodilators are used to prevent spasm of the radial artery but can be beneficial in the hepatic circulation during catheter manipulation.

COMPLICATIONS

The incidence of post-TACE complications is unchanged and liver ischemia; infarction and failure continue to be the major risks. However, in comparison to cTACE, the severity of post-embolization syndrome can be less with DEM-TACE due to the highly selective technique of embolization. The newer starch microspheres (DSM-TACE) are biodegradable and better-tolerated, making them ideal in unresectable large HCCs and patients requiring multiple episodes of TACE.

CONCLUSION

TACE continues to be an important treatment option to improve survival for a chosen group of patients with HCC who are unsuitable for other modern image-guided techniques or are unfit for surgery. It is largely a palliative procedure and to a lesser extent curative. The advances in catheters, embolic technology, and catheter skills over the last two decades have made it a safe, effective, and well-tolerated procedure. Standardization of type of TACE, size of bead, and the type and volume of a chemotherapy agent is not yet available. Magnetic nanoparticle as a carrier is ongoing research^[42].

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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