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Review article

# Embolization therapy with microspheres for the treatment of liver cancer: State-of-the-art of clinical translation

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ABSTRACT

Embolization with microspheres is a therapeutic strategy based on the selective occlusion of the blood vessels feeding a tumor. This procedure is intraarterially performed in the clinical setting for the treatment of liver cancer. The practice has evolved over the last decade through the incorporation of drug loading ability, biodegradability and imageability with the subsequent added functionality for the physicians and improved clinical outcomes for the patients.

This review highlights the evolution of the embolization systems developed through the analysis of the marketed embolic microspheres for the treatment of malignant hepatocellular carcinoma, namely the most predominant form of liver cancer. Embolic microspheres for the distinct modalities of embolization (i.e., bland embolization, chemoembolization and radioembolization) are here comprehensively compiled with emphasis on material characteristics and their impact on microsphere performance. Moreover, the future application of the embolics under clinical investigation is discussed along with the scientific and regulatory challenges ahead in the field.

**Statement of significance**

Embolization therapy with microspheres is currently used in the clinical setting for the treatment of most liver cancer conditions. The progressive development of added functionalities on embolic microspheres (such as biodegradability, imageability or drug and radiopharmaceutical loading capability) provides further benefit to patients and widens the therapeutic armamentarium for physicians towards truly personalized therapies. Therefore, it is important to analyze the possibilities that advanced biomaterials offer in the field from a clinical translational perspective to outline the future trends in therapeutic embolization.



## 1. Introduction

According to data from the World Health Organization (WHO) for 2020, it is estimated that the incidence of liver cancer worldwide is of 905,677 new cases, being the 6th in terms of incidence. However, when taking into account the number of deaths due to liver cancer, it rises to the 3rd place, having been the cause of 830,180 estimated deaths worldwide in 2020 [1,2]. As a result, liver cancer ranks 2nd in terms of annual deaths with respect to new cases, only after pancreas cancer (Fig. 1a). Alarmingly, the WHO estimates that 1276,679 patients will die from liver cancer in 2040 [3].

Liver cancer can be a primary cancer itself or secondary, metastasized from a primary tumor (mostly colorectal liver metastases). There are different types of primary liver cancer (Fig. 1b): hepatocellular carcinoma (HCC) is the predominant form of liver cancer as it represents about 90% of the cases, followed by intrahepatic cholangiocarcinoma or bile duct cancer [4]. Other less frequent primary liver cancers are hepatic angiosarcoma (<2%), fibrolamellar carcinoma (1%) and hepatic epithelioid hemangioendothelioma (0.1%) [5–7]. Risk factors for HCC are highly heterogeneous among patients and geographic regions, including chronic hepatitis B, hep-

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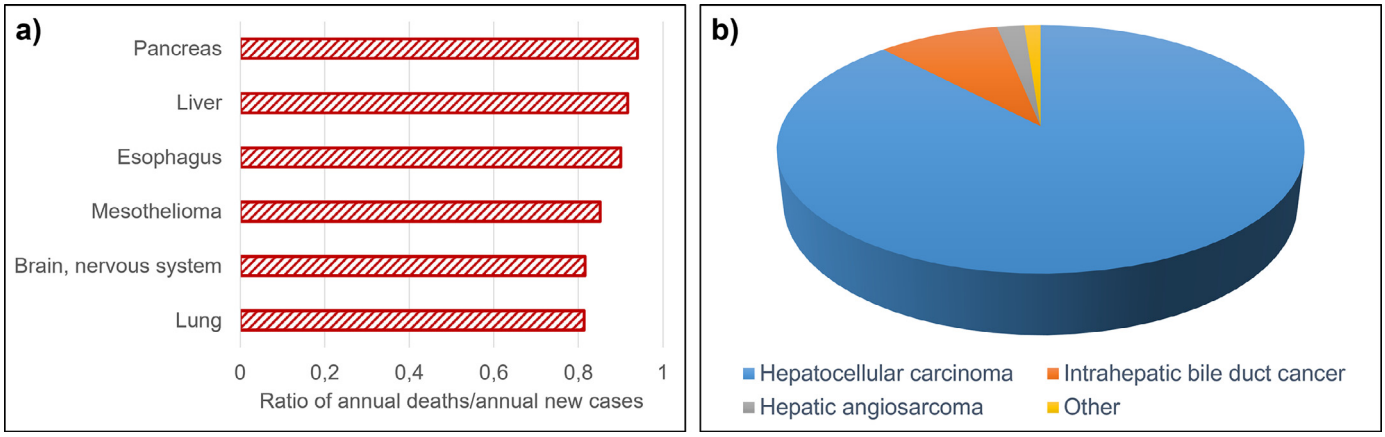


**Fig. 1.** a) Ratio of annual deaths per estimated new cases by cancer type in 2020 according to WHO estimates. b) Percentage of primary liver cancer subtypes.

atitis C , alcoholic cirrhosis, obesity, diabetes, non-alcoholic fatty liver disease or non-alcoholic steatohepatitis [8,9].

Depending on the degree of liver injury and the stage in which the tumor is detected, the treatment options will be different [10]. In early stages (I or II), partial hepatectomy or transplantation represents the first-line treatment supplemented with neoadjuvant locoregional therapies as embolization, radiofrequency or microwave ablation. However, surgical treatment can only be used in 20% of cases, as most liver cancer patients have no symptoms until the tumor is at an advanced stage [11]. When tumours are detected in more advanced stages (III or IV), the treatments of choice are, in addition to ablation and embolization, immunotherapy, radiotherapy and chemotherapy [12,13].

Transarterial embolization (TAE), also referred to as bland embolization, involves the selective occlusion of blood vessels feeding a tumor through the arterial administration of micrometric systems [14]. In this sense, the liver is the ideal target for this type of therapy since it has two fundamental blood sources: the portal vein and the hepatic artery. The portal vein is mostly responsible for the blood supply of healthy liver parenchyma, while the hepatic artery is predominantly responsible for the tumor blood supply [15]. Thus, embolization of the branches of this artery would prevent the cancer cells from receiving nutrients since they would not be irrigated whereas the normal cells of the liver would not be affected. This technique has been used in clinical practice since the early 1980s, when it was discovered that this therapeutic strategy improved the survival rate of patients, with almost no side effects [16,17]. Since then, these systems have evolved to deliver sequentially or concurrently chemotherapeutics (procedure termed as transarterial chemoembolization, TACE) or radiopharmaceuticals (procedure termed as transarterial radioembolization, TARE) (Fig. 2). In all cases, the intraarterial embolization procedure is usually performed by an interventional radiologist.

The most common complication of bland, chemo and radioembolization is the post-embolization syndrome, which is hypothesised to be caused by an inflammatory response to tissue infarction and necrosis. This syndrome consists of pain in the right upper quadrant, fever, nausea, vomiting and fatigue [18]. The post-embolization syndrome usually occurs within the first 72 h after embolization and tends to be self-limiting with complete resolution in 7 to 10 days but can also be alleviated with medication [19]. Other possible complications after embolization include infection in the liver, appearance of blood clots in the main blood vessels of the liver, non-target embolization of extrahepatic vascular supply and worsening of liver function depending on the extent of healthy liver tissue that is affected by embolization. Side effects of radioembolization also include radiation-induced liver disease and, in case of significant hepatopulmonary shunting, radiation pneumonitis due to unintended radiation to the lungs [20,21].

Overall, the introduction of embolic microspheres to conduct the distinct forms of embolization for HCC enables fewer systemic adverse effects in comparison with standard chemotherapy or radiotherapy because microspheres are selectively delivered through the hepatic artery to the tumor while sparing most of the healthy liver tissue. Indeed, conventional radiotherapy has a limited role in the treatment of liver cancer on these grounds [12].

The marketed embolic material needs to be suspended prior to its administration through an appropriately positioned microcatheter. An adequate suspension is required to minimize catheter occlusion. Overall, viscous suspension media reduce the sedimentation over time and prolong time to loss of suspension within a syringe. Altogether, suspension of embolic microspheres is typically conducted with viscous radiopaque contrast agents for image-guided administration.

The aim of this review is to highlight the evolution of the embolization systems developed through the analysis of the distinct commercially available embolic microspheres for the treatment of malignant HCC. Moreover, the future application of the embolics currently under clinical investigation will be evaluated along with the challenges ahead in the field.

## 2. Commercially available embolic microspheres for the treatment of liver cancer

### *2.1. Commercially available embolic microspheres for trans-arterial embolization (TAE)*

There are multiple microspheres commercially available to be used as embolization devices for TAE both in the USA and Europe (Table 1). In this article, the approved embolic devices are classified first as a function of the type of embolization (either permanent or transient) that they allow. A third subcategory of evolved embolic microspheres for TAE with imaging capability is included. In all cases, the composition and characteristics of the distinct microspheres as well as the influence of these on their clinical outcome are detailed.

#### *2.1.1. Microspheres for permanent embolization*

Permanent embolization is the complete and non-transient blockage of blood vessels. This long-lasting blockage of the tumor blood supply is achieved using microspheres manufactured with non-degradable materials capable of being permanently lodged in the tumor-feeding vessels. Permanent embolization may be of substantial benefit before surgery decreasing the size of the tumor and

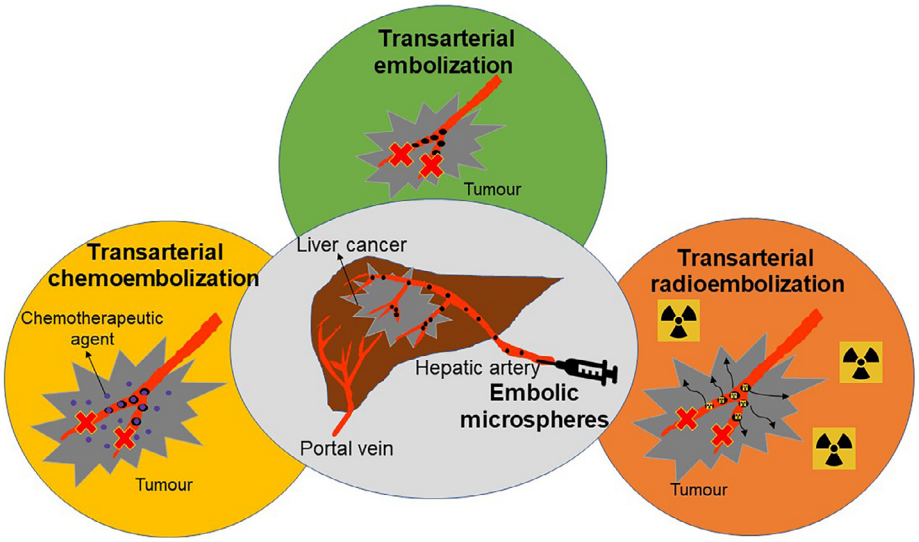


**Fig. 2.** Distinct therapeutic strategies for hepatocellular carcinoma (HCC) using embolic microspheres: a) Transarterial embolization (TAE, green); b) Transarterial chemoembolization (TACE, yellow); c) Transarterial radioembolization (TARE, orange). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reducing the intraoperative bleeding, which is a significant concern during surgery of hypervascular tumours [22]. Nonetheless, the possibility of producing the obstruction of non-target blood vessels or producing certain side effects such as post-embolization syndrome should be carefully considered [23,24].

Although several types of microspheres have been authorized to perform permanent embolization, the selection of the most appropriate device is not trivial. The most relevant factors that affect the clinical performance of embolic microspheres are particle size, shape, density, and mechanical properties. Overall, larger microspheres are prone to become lodged proximally to the site of administration occluding larger caliber vessels, whereas smaller particles result in more distal penetration from the catheter within arteries ultimately occluding smaller caliber vessels. Besides, irregularly shaped microspheres have more probability to clump together, therefore making the occlusion extent less predictable [25]. Finally, mechanical properties such as the ability to deform and resilience also dictate the occlusive behavior of embolic microspheres. On the one hand, the ability to deform of the microspheres dictates the force required for their delivery through the catheter lumen. On the other hand, the resilience or elasticity, defined in terms of extent of recovery of the initial size after compression, dictates that non-elastic microspheres may cause more distal penetration than expected due to their irreversible shrinkage during catheter delivery [26]. Taken together, the development of spherical and calibrated microspheres through control of all these parameters has been prioritized to achieve a more efficient embolization with fewer side effects [27].

There are six non-degradable, spherical, and calibrated types of microspheres authorized as medical devices for TAE. All of them are available in various calibrated sizes. First, Embosphere® received authorization in 1997 and 2000 to be commercialized in Europe and in the USA, respectively. Embosphere® microspheres are made of a copolymer of acrylamide-derived monomers reticulated with gelatine [28]. These trisacryl gelatine microspheres have a hydrogel structure that transiently deforms to facilitate smooth catheter passage but are also very elastic, returning to their original spherical shape after delivery for consistent and durable occlusion. Secondly, Contour SE® was approved in 2002 and 2003 in Europe and in the USA, respectively. Contour SE® are sponge-like microspheres composed of cross-linked polyvinyl alcohol (PVA); i.e. their internal structure is highly microporous unlike hydrogel-like microspheres [29]. However, the pore size progressively increases from the surface to the sphere core as these PVA embolic microspheres have a smooth surface [30]. Thanks to the properties of PVA, these microspheres also show a good deformability but do not recover their original size after catheter delivery, which results in causing more distal embolization than expected from the original particle size.

As an evolution of Embosphere® and Contour SE®, a third type of microspheres reached the market in 2004. BeadBlock® are microspheres composed of a PVA hydrogel cross-linked with an acrylic polymer that imparts hydrophilicity and anionic character to the hydrogel. These microspheres are deformable to approximately 30% by diameter for catheter delivery. With a similar composition to that of Bead Block®, but synthesized using a higher content of acrylic polymer, LC Bead® are PVA hydrogel microspheres authorized in 2003 [28]. The higher content of acrylic polymer in LC Bead® lowers their ability to deform in comparison with Bead Block® and for this reason are manufactured at lower size ranges.

Next, Embozene®, poly (methylacrylic acid) microspheres coated with the inorganic perfluorinated polymer Polyzene-F, were authorized in the USA in 2008 [31]. Embozene® has a higher in vivo deformation, which results in a more distal occlusion within the vascular network compared with Embosphere® [32]. Finally, HydroPearl® was introduced in 2015 as pioneering microspheres manufactured with a copolymer of polyethylene glycol (PEG) and diacrylamide. The use of PEG ensures good ability to deform and elasticity while maximizing the time in suspension thanks to the low density of hydrated PEG hydrogel. Taken together, it improves catheter deliverability [30]. After catheter delivery, HydroPearl® recovers the original spherical shape.

A comparison of the mechanical properties of these embolic microspheres revealed that Contour SE®, due to their macroporous structure, exhibited the highest ability to deform, while Embosphere®, due to their hydrogel-like structure, showed the highest elasticity. Moreover, thanks to their hydrophilicity, BeadBlock® remained suspended in saline for longer [33,34].

**Table 1**
Authorized microspheres for TAE in the treatment of HCC. N.d.: not disclosed.

| Trade name | Manufacturer | First authorization | Material | Type of embolization | Degradation time | X-ray imageability | Radiopacity material | Size (μm) |
|---|---|---|---|---|---|---|---|---|
| Embosphere® | Merit Medical | 1997 | tris-acryl gelatin | permanent | – | no | – | 40–120, 50–100, 100–300, 300–500, 500–700, 700–900, 900–1200 |
| Contour SE® | Boston Scientific | 2002 | PVA | permanent | – | no | – | 70–150; 100–300; 300–500 |
| BeadBlock® | Boston Scientific | 2004 | PVA hydrogel cross-linked with acrylic polymer | permanent | – | no | – | 100–300, 300–500, 500–700, 700–900, 900–1200 |
| LC Bead® | Boston Scientific | 2003 | acrylamido sulfonate-PVA hydrogel | permanent | – | no | – | 70–150, 100–300, 300–500, 500–700 |
| Embozene® | Varian Medical Systems | 2008 | poly(methylacrylic acid) coated with Polyzene-F | permanent | – | no | – | 40, 75, 100, 250, 400, 500, 700, 900, 1100, 1300 |
| HydroPearl® | Terumo | 2015 | copolymer of PEG and diacrylamide | permanent | – | no | – | 75, 200, 400, 600, 800, 1100 |
| Embocept® | Pharmacept | n.d. | starch | transient | 35–40 min | no | – | 50 |
| Spherex® | Magle Life Sciences | n.d. | starch | transient | 35–40 min | no | – | 50 |
| Gel-Bead® | Teleflex | 2014 | gelatin | transient | 4–12 weeks | no | – | 100–300, 300–500, 500–700, 700–1000 |
| Occlusin500® | IMBiotechnologies | 2010 | collagen-coated PLGA | transient | 12–24 weeks | no | – | 150– 210 |
| EmboGold® | Merit Medical | 2001 | acrylic polymer | permanent | – | no | – | 40–120; 100–300; 300–500; 500–700; 700–900; 900–1200 |
| X-Spheres® | Interface Biomaterials | 2015 | triiodobenzyl-modified acrylic polymer | permanent | – | yes | iodinated moiety | 400–600; 600–710; 710–850 |
| LC Bead LUMI™ | Boston Scientific | 2018 | triiodobenzyl-modified acrylamido-sulfonate PVA hydrogel | permanent | – | yes | iodinated moiety | 75–150; 100–300; 300–500 |

*2.1.2. Biodegradable microspheres for TAE*

Alternatively, biodegradable microspheres with predictable degradation rates that cause the transient embolization of tumor blood vessels ranging from minutes to months have been marketed. These devices can be subclassified according to whether they cause shorter or longer embolization and, consequently, their clinical use will be different. First, biodegradable microspheres that produce transient embolization over 30–60 min are used in patients with decreased hepatic function to protect normal liver parenchyma from ischaemia following TAE. To this end, they are injected into non-tumor-supplying arteries immediately before permanent embolic microspheres [35]. Moreover, this shorter transient embolization may clinically prove advantageous for other hypervascular tumours that do not necessarily have dual blood supplies as occurs in HCC. Secondly, those that produce transient embolization over weeks-months may be useful in TAE procedures where retreatment is required after several weeks, while limiting the duration of tumor hypoxia that drives angiogenesis, which eventually accounts for the high relapse rates after permanent embolization. The degradation rate of microspheres should be tailored to balance the desired duration of tissue ischemia with vessel recanalization.

On the one hand, Spherex® and EmboCept® are the main representatives of short-term transient embolics. Both are degradable starch microspheres capable of providing vessel occlusion for 35–40 min. The hydrolysed starch is degraded by serum alpha-amylases into oligo and monosaccharides that eventually enter the physiological metabolic cycle [36,37]. Both starch microspheres have a considerably smaller diameter than most other TAE embolics, averaging 50 $\mu$m.

On the other hand, Occlusin-500® and Gel-Bead® are the most representative marketed microspheres among the long-term temporary embolics. Oclussin-500® was introduced in the market in 2010 and consists of poly (lactic co-glycolic acid) (PLGA) microspheres coated with type I bovine fibrillar collagen. Their degradation mechanism is through hydrolysis of the ester linkage of PLGA into lactic acid and glycolic acid, with a degradation time of 12–24 weeks [22]. The collagen coating of Occlusin 500® serves to bind platelets effectively increasing the nominal size of the embolic microspheres. Gel-Bead® was introduced in the market in 2014. They are biodegradable gelatin microspheres pre-filled in a 20 mL syringe with a specific degradation time of 4–12 weeks.

*2.1.3. Imageable microspheres for TAE*

As a first attempt to develop imageable microspheres, a coloured version of Embosphere® was authorized under the trade name of EmboGold® in 2001 and 2002 in the USA and Europe, respectively. These microspheres are impregnated with 2% of elementary gold so that their visualization during handling and administration is improved. However, EmboGold® does not offer real-time visualization of the microspheres within the body.

The capacity of real-time visualization is a mainstay of embolization procedures, as it would allow the accurate tracking of spatial distribution of the embolic material to be assessed both intra- and post-procedurally as a subrogate of the extent of the target embolization to early detect undertreated regions. Unfortunately, most microspheres approved for TAE do not offer possibility of visualization, so that they are usually mixed with soluble contrast medium before administration and are indirectly monitored using fluoroscopic angiography. However, the co-localization of the microspheres and the contrast agent is not ensured, hindering therefore their applications in long-term monitoring. For this reason, the clinical need of improving the visualization of microspheres compared with soluble contrast medium alone has prompted the development and authorization of various radiopaque embolic microspheres [38,39]. Micro-

spheres have been tailored to produce radiopacity through the encapsulation, attachment, or polymerization of inorganic or organic radiopaque moieties such as tantalum, barium, or iodine species into the microsphere structure, allowing therefore its X-ray imageability [40].

Two radiopaque microspheres have been authorized for TAE; namely, X-Spheres™ and LC Bead LUMI™. In X-Spheres™, radiopacity is introduced by using a methacrylate monomer that contains a covalently bound iodine-derivative. Due to their three-dimensional macromolecular poly(methacrylate) network, X-Spheres™ are non-resorbable microspheres [41–43]. LC Bead LUMI™ entered the market in 2018 as the imageable counterpart of LC Bead®. The difference between these two microspheres is that in LC Bead LUMI™ an iodine moiety (i.e., 2,3,5-triiodobenzaldehyde) is covalently bounded into the PVA hydrogel structure to gain radiopacity [44,45]. However, the iodination of the microsphere structures increases their density, which reduces the suspension time and ultimately hampers handling and administration of the embolics [46]. As a result, for X-ray imageable microspheres, the sedimentation effect must be reduced by using more viscous suspension media.

### *2.2. Commercially available embolic microspheres for trans-arterial chemoembolization (TACE)*

Alternatively, TAE can be supplemented with local chemotherapy for synergism, a procedure known as trans-arterial chemoembolization (TACE). TACE delivers through the same catheter the embolic device in combination with a chemotherapeutic agent, to locally deliver and retain drug therapeutic levels into the tumor [47]. Currently, there are two modalities of this procedure: conventional TACE (cTACE) [48] and TACE using drug-eluting microspheres (DEMs) [18]. The first modality involves the delivery of a mixture of a chemotherapeutic drug and Lipiodol® followed by the administration of the embolic microspheres. Lipiodol® is an ethiodized oil derived from *Papaver somniferum* approved in 1954 by the FDA as contrast agent for imaging tumours in adults with HCC [49,50]. However, to increase chemotherapeutics retention at the tumor site and reduce systemic drug exposure, the second modality of TACE utilizes DEMs that can act both as a embolic agent and as a drug carrier with the capability of slowly releasing chemotherapeutics locoregionally [51,52]. Pharmacokinetic studies have evidenced that DEM-TACE, in comparison with conventional TACE, significantly reduced both peak plasma drug concentrations and area under the curve, as a subrogate of limited systemic exposure with subsequent reduced systemic side effects [53,54]. Nevertheless, in terms of efficacy, the superiority of DEM-TACE over conventional TACE remains controversial [55,56]. In general, indications of cTACE and DEM-TACE are almost the same. However, DEM-TACE should be preferable over cTACE for patients with more advanced disease, poor heart function and impaired liver function [53,57]. Conversely, given the higher association of DEM-TACE with hepatic locoregional toxicities, cTACE is deemed to be more appropriate for patients with less advanced cirrhosis [58].

In general, drug loading may affect the mechanical properties of the microspheres and therefore affect clinical outcome. For example, the presence of drugs might alter the surface characteristics and affect the tendency of the microspheres to aggregate. Besides, drug loading usually reduces the water content of the microspheres, which can affect the density and hence time in suspension of the product [59,60]. This reduction in the water content comes together with a decrease in particle size, which tends to be offset by the fact that drug loading also increases the elasticity of the DEMs so that the penetration potential remains largely unaltered in comparison with their unloaded counterparts [61].

#### *2.2.1. Drug-eluting microspheres (DEMs) for permanent embolization*

Over the last 20 years, four DEMs have been approved for use in permanent embolizing therapies in Europe (Table 2), although unlike embolizing agents for TAE, drug-loading microspheres have not been approved by the FDA. Doxorubicin and irinotecan are the most frequent drugs authorized for its extemporary incorporation into DEMs prior to administration. However, there are embolic microspheres that exceptionally are authorized to be loaded with idarubicin and epirubicin in addition to doxorubicin and irinotecan [14].

Among the four permanent DEMs approved for TACE, two of them were approved in the 2000s and two in the 2010s. On the one hand, DC (Drug Capable) Bead® and HepaSphere® received authorization in Europe in 2003 and 2005, respectively. DC Bead® stems from LC Bead®, so both are composed of PVA hydrogel cross-linked with acrylic polymer. The higher content of acrylic polymer with negatively charged sulfonate groups in LC Bead® in comparison with Bead Block® enables the loading of positively charged chemotherapeutics via ion-exchange upon submersion of the microspheres in a solution of the drug to obtain DC Bead® [62–64]. Conversely, HepaSphere® are superabsorbent microspheres composed of a copolymer of vinyl alcohol and methyl acrylate with negatively charged carboxylic groups. They are supplied dry and swell 4-fold upon hydration. Indeed, unlike DC Bead®, the drug loading mechanism of HepaSphere® is swelling, so that when the dry microsphere gets in contact with an aqueous solution containing the drug of interest, it quickly swells up and drags the drug together with water into it. Then, electrostatic interactions between the drug and the carboxylic groups maintain the drug within the microsphere [65]. As a result, both microspheres are authorized for loading with the cationic drugs doxorubicin or irinotecan. Both microspheres show similar loading profiles in terms of encapsulation efficiencies, i.e., 98 and 100% for doxorubicin and 93 and 90% for irinotecan in DC Bead® and Hepasphere®, respectively [61]. According to the technical recommendations for DC Bead®, its maximum drug loading capability is 25–37.5 mg/mL for doxorubicin and 50 mg/mL for irinotecan [66]. In the case of Hepasphere®, the maximum loadable amount of drug is referred to the dry amount of microspheres per vial as provided by the manufacturer (namely, 75 mg of doxorubicin/25 mg of dry microspheres or 100 mg of irinotecan/25 mg of dry microspheres). Nonetheless, the in vitro drug release profiles in saline by using a pharmacopeia flow-through apparatus were different for both drugs: whereas irinotecan, with little interaction with the microspheres rapidly achieved complete release from both DC Bead® and Hepasphere® within 2–3 h, doxorubicin, with higher affinity for the negatively-charged microspheres, took longer to achieve a partial release of only 20–25% of the dose over 1 week from both DC Bead® and Hepasphere® [61]. Moreover, in the case of doxorubicin-loaded DC Bead®, it has been evidenced that smaller microspheres display faster release rates in comparison with larger microspheres due to their higher surface area [67].

On the other hand, two additional permanent DEMs were authorized in the European Union for TACE in the 2010 decade: Embozene Tandem® and LifePearl®, marketed in 2012 and 2015, respectively.

Embozene Tandem® are polymethacrylate hydrogel microspheres coated with Polyzene-F pioneeringly manufactured with tighter size distributions and smaller particle sizes than their TAE counterparts (i.e., Embozene®) to achieve more distal intratumoral embolization. Remarkably, as a result, Embozene Tandem® is only available in three distinct size ranges in comparison to the ten sizes in which its TAE counterpart is available. Analogously to the aforementioned DEMs, Embozene Tandem® has been authorised for loading doxorubicin and irinotecan. The mechanism of drug loading in Embozene Tandem® is ionic interaction between the

**Table 2**
Authorized DEMs for TACE in the treatment of HCC. N.d.: not disclosed.

| Trade name | Manufacturer | First authorization | Material | Type of embolization | Degradation time | Drug loading mechanism | Type of drug (maximum drug loading) | X-ray imageability | Radiopacity material | Size (μm) |
|---|---|---|---|---|---|---|---|---|---|---|
| DC Bead® | Boston Scientific | 2003 | PVA crosslinked with acrylate sulfonate | permanent | – | ion exchange | Doxorubicin (25–37.5 mg/mL)<br>Irinotecan (50 mg/mL) | no | – | 70–150, 100–300, 300–500, 500–700 |
| Hephasphere® | Merit Medical | 2005 | sodium acrylate PVA | permanent | – | swelling | Doxorubicin (3 mg/mg of microspheres)<br>Irinotecan (4 mg/mg of microspheres) | no | – | 30–60, 50–100, 100–150, 150–200 |
| Embozene Tandem® | Varian Medical Systems | 2012 | polymethacrylate hydrogel | permanent | – | ion exchange | Doxorubicin (50 mg/mL)<br>Irinotecan (50 mg/mL) | no | – | 40, 75, 100 |
| LifePearl® | Terumo | 2015 | PEG crosslinked with acrylate sulfonate | permanent | – | ion exchange | Doxorubicin (37.5 mg/mL)<br>Irinotecan (50 mg/mL)<br>Idarubicin (5 mg/mL)<br>Epirubicin (25 mg/mL) | no | – | 100, 200, 400 |
| BioPearl® | Terumo | 2020 | n.d. | transient | n.d. | n.d. | Doxorubicin (n.d.)<br>Idarubicin (n.d.)<br>Epirubicin (n.d.) | no | – | undisclosed |
| DC Bead LUMI™ | Boston Scientific | 2015 | triiodobenzyl-modified acrylamido-sulfonate PVA hydrogel | permanent | – | ion exchange | Doxorubicin (25–37.5 mg/mL)<br>Irinotecan (50 mg/mL) | yes | iodinated moiety | 40–90, 70–150 |

negatively charged carboxylate binding groups on its hydrogel matrix and the positively charged drugs. Embozene Tandem® can be loaded with up to 50 mg/ml of microspheres for each of the drugs [68].

In vitro data have evidenced that Embozene Tandem® shows a sustained release of doxorubicin and a more prolonged release of irinotecan in comparison with DC Bead® [68].

LifePearl®, which stems from HydroPearl®, consists of a hydrogel network of PEG and 3-sulfopropyl acrylate. LifePearl® is currently the only non-biodegradable DEM-TACE approved for loading of not only doxorubicin and irinotecan, but also idarubicin and epirubicin. The loading mechanism of LifePearl® is the same as that of DC Bead® (i.e., ion interaction of negatively charged sulfonate groups with positively charged drugs). In vitro doxorubicin release from LifePearl® occurred more rapidly than the elution rate observed for DC Bead®, Hepasphere® and Embozene Tandem® with 30% of the loaded doxorubicin eluted over 24 h [69]. In the case of irinotecan, near complete elution from LifePearl® was achieved within the first hour with a similar release rate as that observed for DC Bead®, whereas the release profile of irinotecan from Embozene Tandem® was significantly more prolonged, which could be accounted for by the distinct interaction of irinotecan with the sulfonate and carboxylate groups in their hydrogel matrixes, respectively [70]. In vitro idarubicin release from LifePearl® reached a plateau after 2 h with around 75% of the loaded idarubicin eluted from LifePearl® [71]. The more hydrophilic material allows the irinotecan-loaded LifePearl® to stay in suspension for longer than DC Bead® and Hepasphere® as well as their catheter deliverability to be improved, decreasing the chances of catheter clogging [70].

One study compared loading times and changes in the microsphere diameter and time in suspension of the four commercially available DEMs for permanent TACE upon doxorubicin loading. The four microspheres loaded doxorubicin in less than one hour. In all cases in which doxorubicin loading is driven by ion-exchange, drug loading decreased the average diameter of the microsphere due to water displacement from the microsphere as a result of the loading process. Noticeably, Embozene Tandem® showed minimal size change upon drug loading in comparison with DC Bead® and LifePearl®. Finally, the study showed that doxorubicin-loaded Embozene Tandem® remained the longest time in suspension, which is partially explained because these microspheres had the smallest diameters of the four embolization devices in the study [69].

The PRECISION V study demonstrated a significant reduction in hepatotoxicity and drug-related systemic side effects with DC Bead® than with cTACE [53]. These results highly correlated with pharmacokinetic profiles, where the maximum plasma concentration was dramatically lower in patients in the DC Bead® group compared with the cTACE group (78.97 ± 38.3 ng/mL versus 895.66 ± 653.1 ng/mL, respectively) and so was the area under the curve (662.6 ± 417.6 ng/mL min versus 1532.98 ± 295.2 ng/mL min) even though the dose of doxorubicin was higher in the DC Bead® group (106.4 ± 37.2 mg versus 70.0 ± 11.2 mg for the cTACE group) [54]. Similar results have been observed for Hepasphere® with both doxorubicin maximum plasma concentration and area under the curve significantly lower in Hepasphere® patients than in cTACE group [72]. Analogous maximum plasma concentration values have been observed in other pharmacokinetic studies that evaluated irinotecan-loaded DC Bead® and LifePearl® [73,74]. Altogether, this ultimately facilitates the potential combination of DEM-TACE with other systemic therapies given the reduced risk of interactions.

Other preliminary clinical studies have also demonstrated that Hepasphere®, Embozene Tandem® and LifePearl® loaded with doxorubicin provide positive clinical outcomes for HCC [72,75,76].

*2.2.2. Biodegradable drug-eluting microspheres for TACE*

The development of biodegradable microspheres for TAE (see Section 2.1.2) represented an important milestone. As a result of this, the possibility of developing the same type of microspheres with drug-loading capacity was proposed [77,78]. The rationale is that all the advantages of temporary embolization (such as reduced liver damage and avoidance of ischemia-induced neovascularization) and of DEMs (such as increased drug concentrations at the tumor site and fewer systemic side effects) could be merged in one pioneering system to improve clinical outcome and patient's quality of life. When developing biodegradable DEMs. it should be considered that drug release times must occur within the timeframe of microsphere degradation times to avoid unexpected drug bursts [79]. In 2020, BioPearl® was introduced in the market of the European Union as the first biodegradable DEM authorized for the treatment of HCC. According to manufacturer's information, BioPearl® is loadable with three distinct chemotherapeutic drugs (i.e., doxorubicin, idarubicin and epirubicin) Unfortunately, no further information is available to date except that a post market follow-up study (BioPearl-FIRST) has just been launched to confirm the safety and efficacy of doxorubicin-loaded BioPearl® microspheres (NCT04231929).

*2.2.3. Imageable drug-eluting microspheres for TACE*

In the same vein as microspheres authorized for TAE, one of the drawbacks of the previous DEMs is that they are radiolucent and thus their distribution cannot be directly tracked. To address this issue, the formulation of DEMs has been tailored to produce intrinsically X-ray imageable DEMs by incorporating radiopaque moieties together with chemotherapeutics. Altogether, radiopaque DEMs allows real-time tracking of the extent of vessel occlusion to early identify undertreated regions of a tumor as microsphere imaging has been demonstrated to serve as a surrogate for drug levels. Indeed, in a study with doxorubicin-loaded radiopaque DEMs, Mikhail et al., pioneeringly demonstrated the positive linear correlation (0.950) existing between microsphere volume measured on computed tomography images and doxorubicin content measured through fluorescence microscopy in rabbit VX2 liver tumours 1 hour after embolization [80]. DC Bead LUMI™ is the only radiopaque DEM available in the market [45,81]. It was authorized in 2015 and has the same composition as DC Bead® (i.e., it causes permanent embolization) except that part of the hydroxyl functional groups are conjugated with an iodine derivative to gain X-ray imageability. Analogously to DC Bead®, DC Bead LUMI™ is authorized to be loaded with doxorubicin and irinotecan. Remarkably, unlike DC Bead®, DC Bead LUMI™ does not shrink upon loading of either doxorubicin or irinotecan at their maximum recommended levels [45]. However, this fact may be due to the smaller original size of DC Bead LUMI™ in comparison with DC Bead®, where the actual shrinkage in the average microsphere diameter was more pronounced for larger sizes and less significant for 100–300 $\mu$m-sized DC Bead® [63]. With the same mechanism for drug loading as DC Bead® based on ion-exchange between sulfonic acid groups on the matrix and positively charged amine groups of doxorubicin and irinotecan, release profiles for both drugs from DC Bead LUMI™ showed complete doxorubicin release over approximately 2 weeks and much faster irinotecan release within just few hours. However, for equally sized microspheres, because of the increased hydrophobicity of the DC Bead LUMI™ hydrogel matrix, elution profiles for both doxorubicin and irinotecan were slightly delayed in comparison with those from DC Bead®. [45]. DC Bead LUMI™ shows appropriate catheter deliverability and imageability both on intraprocedural fluoroscopy, and on follow-up computed tomography [82,83]. There are still few clinical trials that have studied the safety and efficacy of these radiopaque microspheres but those that exist have shown promising efficacy and tolerability with side effects of mild intensity [82,84].

*2.3. Commercially available embolic microspheres for trans-arterial radioembolization (TARE)*

Trans-arterial radioembolization (TARE), also known as radioembolization or as selective internal-radiation therapy, is an intra-arterial procedure performed by the interventional radiologist for the treatment of primary and secondary hepatic cancers, including HCC, associated with high therapeutic efficacy and low rate of adverse events [85,86]. It essentially consists of the intra-arterial injection of micron-sized embolic particles loaded with a radioisotope to locally increase the dose of radiation in the tumor with minor radiation-induced hepatic damage. Unlike the DEMs approved for TACE, in these microspheres the radioisotope is already supplied incorporated in the microsphere itself. This fact provides two important advantages over DEMs for TACE. Firstly, the extemporaneous loading phase of the therapeutic agent prior to administration, characteristic of DEMs, is eliminated providing therefore rapid intraprocedural access to loaded microspheres. Secondly, the regulatory discrepancies that exist for DEMs, where extemporaneous drug loading is only authorized in some European and Asian countries, disappear.

Several clinical trials support that TARE may provide some clinical benefits over TACE in the treatment of HCC. One clinical trial compared 123 patients assigned to TARE and 122 patients receiving TACE. Results showed longer time to progression (13.3 months vs 8.4 months) and less incidence of complications in patients after treatment with TARE, although no difference in overall survival was reported [87]. However, the potential irradiation of nontarget liver tissues, the complexity of the procedure and high costs are obstacles that impede the widespread use of TARE [88].

There are various microspheres loaded with radioisotopes authorized for the treatment of HCC (Table 3). Among the different radioisotopes available, Yttrium$^{90}$ ($Y^{90}$), which is the most used for radioembolization, emits $\beta$-radiation with a tissue penetration that ranges from 2.5 mm to 11 mm. Differently, other radioisotopes such as Holmium$^{166}$ ($^{166}$Ho) are showing promising potential. $^{166}$Ho emits $\beta$ and $\gamma$ -radiation with a tissue penetration that ranges from 2.5 mm to 8.7 mm. $Y^{90}$ and $Ho^{166}$ have a half-life of 2.7 and 1.2 days, respectively [89].

*2.3.1. Radiolabeled microspheres for permanent embolization*

Currently, there are two commercially available radioembolic agents approved for permanent TARE and both are loaded with $^{90}$Y (Table 3). The first one is TheraSphere®, authorized since 1999 by the FDA as a humanitarian exemption device- based on proven safety and potential clinical benefit and since 2014 in Europe. In 2021, the FDA has finally granted TheraSphere premarket approval for HCC. The second one is SIR-Spheres®, authorized in 2002 both in the USA and Europe. Both microspheres can deliver high doses of radiation, resulting in cell death and tumor necrosis [89,90].

On the one hand, TheraSphere® consist of radioactive $^{90}$Y integrated within an oxide-aluminosilicate non-biodegradable glass matrix [91,92]. Their mean sphere diameter ranges from 20 to 30 $\mu$m. The final product has a specific activity of 2500 Bq per sphere and is supplied in six activity sizes (3, 5, 7, 10, 15, and 20 GBq). As a result, the number of microspheres supplied in each vial is proportional to the activity size (i.e., 3 and 20 GBq vials contain approximately 1.2 and 8 million microspheres, respectively [93].

On the other hand, SIR-spheres® are cation exchange resin microspheres with $^{90}$Y adsorbed in the resin matrix [94]. In this case, the mean sphere diameter ranges between 20 and 60 $\mu$m. Each vial contains approximately 45 million microspheres [95]. Traditionally, the final product was provided with a maximum specific

**Table 3**
Authorized radiolabelled microspheres for TARE in the treatment of HCC. SPECT/CT: Single-photon emission computed tomography/ computed tomography; MRI: magnetic resonance imaging.

| Trade name | Manufacturer | First authorization | Material | Type of embolization | Degradation time | Size ($\mu$m) | Imaging technique |
|---|---|---|---|---|---|---|---|
| TheraSpheres® | Boston Scientific | 1999 | glass | permanent | – | 20–30 | SPECT/CT |
| SIR-Spheres® | SIRTeX | 2002 | resin | permanent | – | 20–60 | SPECT/CT |
| QuiremSpheres® | Terumo | 2015 | polylactic acid | transient | > 1 year | 15–60 | SPECT/CT, MRI |

activity of 75 Bq per microsphere supplied as a single 3 GBq dose. Nonetheless, the manufacturing company has recently enabled the FLEXdose delivery program which introduces three delivery options supplied with 7.3, 5.6 or 4.3 GBq (i.e., 3-, 2- or 1-day pre-calibration, respectively) to deliver the same activity with more or less spheres [96].

Due to their physical differences, these microspheres will have different clinical performance [93]. For instance, as SIR-Spheres® have high embolic power compared to TheraSphere® (45 million vs up to 8 million of microspheres), it is possible to achieve a higher and more homogeneous coverage of the tumor with SIR-Spheres® when compared with TheraSphere®. Nonetheless, performing TARE with a limited number of microspheres may be less toxic, preventing the microspheres from reaching healthy liver tissue [97–99]. Indeed, although strong evidence from phase III trials comparing the efficacy of both $^{90}$Y microspheres is not yet available, results from 31 observational studies that compared TheraSpheres® and SIR-Spheres® showed that more patients treated with SIR-Spheres® reported gastrointestinal and pulmonary adverse events. However, in terms of post-embolization syndrome, both $^{90}$Y microspheres showed a similar safety profile [97].

The safety of TARE must also control the exposure dose to the medical staff and family members as following treatment with radiolabeled microspheres, patients become a source of radiation that could potentially affect people around them. Although during the week following radioembolization, patients are encouraged to limit social contact to maintain the exposure to other individuals as low as possible, it has been evidenced that patients treated with $^{90}$Y glass and resin microspheres were within current US Nuclear Regulatory Commission regulations for release without instructions [100]. Likewise, after adequate training, medical staff (i.e., radiopharmacists, nuclear medicine physicians and interventional radiologists) are exposed to safe levels of radiation during preparation and administration of radiolabelled embolic microspheres. Importantly, their exposure to radiation was lower with radiolabelled microspheres than with treatments using iodinated-lipiodol [101].

#### *2.3.2. Biodegradable and imageable radiolabeled microspheres for TARE*

Alternatively, a new type of microspheres labelled with $^{166}$Ho entered the European market in 2015. They are authorized under the trade name of QuiremSpheres® and are the first microspheres made of poly-L-lactic acid. For the process of labeling with $^{166}$Ho, a chemical complex is first formed between $^{166}$Ho and acetyl-acetonate, which acts as a chelating agent. Then, the complex is mixed with the poly-L-lactic acid dissolved in chloroform and added to an aqueous solution of 1% polyvinyl alcohol to prepare the final microspheres by the solvent displacement technique [102].

Poly-L-lactic acid is a biodegradable polymer. However, it has been evidenced that no significant degradation occurs within the first year, which is a considerable low degradation rate to be considered truly biodegradable microspheres [103,104]. Their mean sphere diameter ranges from 15 to 60 $\mu$m. The final product has a maximum specific activity of 450 Bq per microsphere and the number of microspheres is 30 million per vial.

More importantly, QuiremSpheres® present a significant advantage over the $^{90}$Y microspheres in terms of radiopacity. Certainly, imaging properties are of highly importance for evaluating the distribution in the targeted tissues and for a quantitative assessment of the dose deposition. Both isotopes ($^{90}$Y and $^{166}$Ho) emit $\beta$-radiation that can be visualised by imaging techniques such as single-photon emission computed tomography (SPECT)/computed tomography (CT) [105]. However, $^{166}$Ho additionally emits $\gamma$ radiation and has paramagnetic properties, which allows it to be imaged both by SPECT and magnetic resonance imaging (MRI). For this reason, the visualization capacity provided by $^{166}$Ho in QuiremSpheres® is of higher quality and accuracy compared to $^{90}$Y microspheres [106].

## 3. Embolic microspheres for the treatment of liver cancer under clinical investigation

Given the versatility of DEMs for TACE, which can be loaded with distinct drugs extemporaneously, most of the new active clinical investigations have mostly focused on embolic microspheres for TACE over those for TAE or TARE [30]. Only clinical trials with embolic microspheres in different combinations than those already authorized and that are registered in the clinical trials.gov database are here discussed (Table 4).

Among CE-marked embolic microspheres, optimization of TACE in HCC has largely focused heretofore on the development of distinct DEMs almost exclusively loaded with doxorubicin or irinotecan, although their superiority over other drugs remains elusive. In this regard, DC Bead® has entered clinical trials to evaluate its efficacy with chemotherapeutics other than those that have been CE-marked for chemoembolization.

Idarubicin can be efficiently loaded into DC Bead® through the ionic interaction between the positively charged protonated amine group of idarubicin and the negatively charged sulphonate group of the microspheres. Two single-arm clinical trials evaluating idarubicin-loaded DC Bead® have been registered on clinicaltrials.gov, namely the phase I trial IDASPHERE (NCT01040559) and the phase II study IDASPHERE II (NCT02185768).

In both cases, microspheres were loaded with idarubicin for 60 min in aseptic conditions at the hospital pharmacy prior to TACE. The IDASPHERE trial was conducted in cirrhotic patients with unresectable nonmetastatic hepatocellular carcinoma ($n = 21$) with a single administration of idarubicin-loaded 300–500 µm-sized DC Bead® [107]. The maximum tolerated dose of idarubicin was 10 mg. The 2-month objective response rate was 52%, which equated the rate reported for patients from the doxorubicin-loaded DC bead® arm of the PRECISION V trial, namely the largest phase II study published to date comparing DEM-TACE with conventional TACE [53]. Moreover, the median time to progression and the overall survival in the IDASPHERE trial were 12.1 and 24.5 months, respectively, which was encouraging as 2-year survival is rarely observed in TACE trials.

Given the promising clinical results of the IDASPHERE trial, the IDASPHERE II trial was subsequently conducted in patients with unresectable hepatocellular carcinoma ($n = 44$) through chemoembolization with idarubicin-loaded 100–300 µm-sized DC Bead® ev-

**Table 4**
Embolic microspheres for the treatment of liver cancer in NCT-numbered clinical studies.

| Embolic microsphere | Drug | Condition | NCT number | Status |
|---|---|---|---|---|
| DC Bead | Idarubicin | Unresectable hepatocellular carcinoma | NCT01040559 (IDASPHERE) | Completed |
| DC Bead | Idarubicin | Unresectable hepatocellular carcinoma | NCT02185768 (IDASPHERE II) | Completed |
| Callispheres | Doxorubicin or irinotecan | Hepatocellular carcinoma, intrahepatic cholangiocarcinoma, secondary liver cancer | NCT03317483 (CTILC) | Completed |
| Callispheres | Oxaliplatin | Inoperable neuroendocrine neoplasm liver metastases | NCT03881306 | Recruiting |

ery 4–8 weeks [108]. In the IDASPHERE II trial, smaller drug-eluting DC Bead® was used as smaller sized microspheres allow for more distal embolization with an improved safety profile [109,110]. In this study, the 6-month objective response rate was maintained at 52% with a median time to progression and a median overall survival of 9.5 and 18.6 months, respectively. The IDASPHERE II trial was stopped for efficacy at the interim analysis because 23 patients had an objective response at 6 months. In conclusion, idarubicin-eluting DC Bead® confirmed a promising clinical response when used as a TACE regimen for unresectable hepatocellular carcinoma.

Initial clinical experience is also being gained with CalliSpheres® in recent years. Callispheres® are non-resorbable embolic microspheres made of a macromer derived from PVA that are available in a range of sizes (from 100 to 1200 µm). These microspheres are negatively charged, so that they can be loaded with positively charged chemotherapeutic drugs. In the CTILC cohort prospective study (NCT03317483), 300–500 µm-sized CalliSpheres loaded with doxorubicin or irinotecan were evaluated for TACE in patients with liver cancer including hepatocellular carcinoma ($n = 275$), intrahepatic cholangiocarcinoma ($n = 37$) and secondary liver cancer ($n = 55$). After 1–3 months, treatment response was assessed resulting in an objective response rate of 79.6%. This objective response rate was slightly higher in primary HCC patients (83.6%) compared with primary intrahepatic cholangiocarcinoma (67.6%) and secondary liver cancer patients (67.3%), suggesting that primary HCC patients could benefit more from DEM-TACE than the other groups. However, no differences in overall survival (384 days) were observed among the distinct liver cancer conditions [111].

A new phase 2 clinical trial which uses CalliSpheres loaded with oxaliplatin (DEBOXA) for TACE is currently recruiting patients to study their safety and effectiveness in treating inoperable neuroendocrine neoplasm liver metastases (NCT03881306).

## 4. Combination therapies with embolic microspheres for the treatment of liver cancer under clinical investigation

Embolization therapies with microspheres have also started being tested in clinical trials in conjunction with systemic therapies for HCC. Tyrosine kinase inhibitors (TKIs) currently constitute the first-line systemic treatment for HCC. Among them, sorafenib is considered the standard of care for advanced-stage HCC since 2008 [112,113]. As sorafenib and TACE are both recommended therapies for HCC, the combination of both has been hypothesized to be synergistic. The rationale for this combination is supported by the fact that liver embolization generates hypoxia and triggers the release of angiogenic factors, increasing therefore the risk of revascularization and recurrence, while TKIs are multikinase inhibitors with anti-angiogenic effects [114,115].

For this reason, various phase III clinical trials have studied the combination of both therapeutic strategies. First, Kudo et al. reported a phase III multi-center randomized study that included 458 patients which were treated with sorafenib after cTACE [116]. Unfortunately, neither the primary nor the secondary endpoint (i.e., time to progression and overall survival, respectively) were met, as results showed that sorafenib did not significantly prolong any of those over placebo. Subsequently, Meyer et al. investigated in another phase III clinical trial whether the combination of DEM-TACE with sorafenib suppresses tumor progression and extends progression-free survival in 313 patients [117]. However, also in this case no statistical difference in progression-free survival was observed over placebo, concluding therefore that the combination of DEM-TACE and sorafenib did not improve patients' outcome compared with DEM-TACE alone. Noticeably, in the phase III STAH trial, it was also observed in 339 patients with advanced HCC that the combination of cTACE with sorafenib did not improve the overall survival compared with sorafenib alone, but this combination did improve time to progression, progression-free survival and tumor response rate [118].

Combination of TACE with lenvatinib (namely, the second TKI approved as first-line treatment for HCC [119]) has likewise been explored in the phase III LAUNCH trial in 338 patients with advanced HCC, with encouraging data from interim analysis recently presented [120]. The combination of lenvatinib plus TACE significantly improved clinical outcomes in terms of overall survival, progression-free survival and objective response rate compared with lenvatinib alone. Of note, TACE with either cTACE or DEB-TACE were allowed in the LAUNCH trial, depending on the condition of each center. In particular, 69% of patients received DEM-TACE, while the remainder received cTACE.

Additionally, the combination of TACE with alternative TKIs such as brivanib and oranitib has been investigated separately in the BRISK-TA and ORIENTAL phase III clinical trials [121,122]. These trials were intended to evaluate the efficacy of brivanib and oranitib after performing TACE in 502 and 889 patients, respectively. In the case of the BRISK-TA trial, both DEM-TACE and cTACE were allowed in the study protocol, whereas only cTACE was allowed in the ORIENTAL trial. Nonetheless, no improvement in overall survival was observed combining TACE neither with brivanib nor with oranitib.

Alternatively, immune checkpoints inhibitors (ICIs) such as nivolumab, camrelizumab, pembrolizumab or ipilimumab have recently been introduced as second-line systemic treatment in advanced HCC [123,124]. They are inhibitory drugs able to restore or enhance the killing effect of immune cells on tumor cells. On this basis, the combination of these immune agents with locoregional treatments such as embolization therapy is being assessed under clinical trials. In this regard, the phase III TACE-3 trial evaluating nivolumab in combination with TAE/TACE for intermediate stage HCC is still ongoing (NCT04268888), so it is still too early to evaluate whether this combinatory regimen offers a significant improvement in safety and efficacy for patients with HCC.

Further efforts to enhance the efficacy of embolization therapies include their combination with two or more different kinds of systemic therapies (i.e., TKIs + ICIs -NCT04246177 [125], NCT0505633, NCT05301842, NCT05320692-; the FDA-approved combination treatment for HCC consisting of atezolizumab plus bevacizumab -NCT04246177- or alternative combinations - NCT0377895-). However, results from all these phase III trials are still pending as they are currently ongoing.

In comparison with TACE, the combination of TARE with systemic therapy is lagging behind as it has not reached phase III tri-

als yet. Only the phase II SORAMIC trial has been completed evaluating the combination of sorafenib with SIR-Spheres in 424 patients with advanced HCC. However, results did not show a significant improvement in overall survival in comparison with sorafenib alone [126].

Altogether, despite the positive outcomes obtained with the use of TKIs/ICIs in monotherapy for HCC, most of the clinical trials evaluating the combination of TACE/TARE with TKIs have failed to meet their primary endpoints in terms of overall survival. However, there are many phase III trials still ongoing that will enable the efficacy of the combination of embolization therapies with ICIs and alternative TKIs to be evaluated in the future. In this regard, the interim analysis from the latest trial has shown promising results stemming from the combination of TACE with lenvatinib. Moreover, subgroup analyses of existing trials may also give indications to support the design of future studies using the combination of locoregional embolization and systemic therapies.

## 5. Outlook

TACE is currently the recommended first-line therapy for patients with intermediate-stage HCC [127,128], although, according to a recent survey, 40% of TACEs in daily clinical practice are performed also in patients with early-stage HCC as a bridge to liver transplantation or, more rarely, in patients with advanced-stage HCC [129]. The use of DEM-TACE has shown similar benefit to cTACE, although in terms of systemic side effects DEM-TACE is preferred over cTACE [53,56]. Several cost-effectiveness studies have consistently demonstrated the lower overall treatment costs per patient in favor of DEM-TACE compared with cTACE [130–132]. For example, Vadot et al. reported a significantly shorter mean hospital duration for patients who received DEM-TACE [130]. Cuchetti et al. concluded that cTACE patients more frequently experienced postembolization syndrome, had a longer hospitalization and a shorter life expectancy than patients treated with DEM-TACE (3.3 years vs. 4 years) [131]. Finally, Fateen et al. observed that patients undergoing DEM-TACE required fewer procedures over the studied period [132]. Altogether, DEM-TACE should be the TACE technique of choice at least in clinical trials, due to the higher standardized and reproducible methodology and the lower systemic drug levels in comparison with cTACE [133].

Even though overall survival and progression free survival observed for both TAE and TACE are not statistically different [18] the truth is that very few institutions perform TAE as their standard of care for intermediate-stage HCC patients.

TARE using microspheres is indicated for the treatment of patients with locally advanced HCC, although its performance is more demanding than TACE and is therefore less available [128]. A cost-effectiveness study comparing TARE with cTACE revealed that radioembolization costs seem to be justified for patients with more advanced stages of HCC. In fact, as the overall cost of treatment strongly depend on the total number of procedures, the treatment of advanced HCC is more likely to involve multiple TARE or cTACE procedures, ultimately leading to higher costs in both treatments but with higher survival benefit after radioembolization [134].

Altogether, as a proof of their translational potential, the distinct modalities of particle embolization reviewed herein are currently used in the clinical setting. In both DEM-TACE and TARE, microspheres serve both as an embolic and a locoregional drug or radiopharmaceutical delivery vehicle to the tumor feeding vessels. Currently, there are 13 microspheres commercially available for TAE (59.1% of marketed embolic microspheres), 6 for TACE (27.3%) and 3 for TARE (13.6%). Whereas all of them have been granted CE marking, no DEM has been approved by the FDA. The ever-increasing functionality incorporated to embolic microspheres over the last decades such as degradability and X-ray imageability has not distributed uniformly among the distinct type of embolotherapies. On the one hand, biodegradable microspheres account for 30.8%, 16.7% and 33.3% (considering QuiremSpheres® as biodegradable despite their prolonged degradation times) of the microspheres marketed for TAE, TACE and TARE, respectively. On the other hand, radiopaque microspheres for post-procedural follow-up represent 15.4%, 16.6% and 100% of the microspheres marketed for TAE, TACE and TARE, respectively.

Marketed embolic microspheres vary in material composition and mechanical properties (such as size, ability to deform, resilience, density, or flow behavior), which ultimately affect their clinical outcome as they dictate the extent and the duration of occlusion. For this reason, upon modification with the introduction of imaging or drug/radiopharmaceutical loading capabilities, the mechanical properties of microspheres must always be compared with their approved counterparts-to verify that the additional functionalities do not adversely alter their embolic features [26].

Comparing in broad terms the embolic potential of the distinct locoregional embolization strategies, it is worth highlighting that DEM-TACE is usually used for more distal penetration of HCC to deliver the drug dose within the tumor feeding vessels [26]. This is the reason why microspheres for DEM-TACE are overall manufactured in smaller sizes than their TAE counterparts.

Concerning the microspheres for TARE, their size is the smallest (20–60 $\mu$m range) among the three types of locoregional therapy, which explains why this procedure provides most of its therapeutic effect via radiation rather than via embolization [19]. Indeed, due to their minimal level of embolic effect, TARE is highly dependent on hemodynamics. As a result of this lower embolic effect, TARE is particularly indicated for HCC patients with portal vein thrombosis, although, in return, TARE is contraindicated in case of hepatopulmonary or hepato-enteric shunts due to the higher likelihood of unintended non-target embolization given the small microsphere size.

The future directions in the development of novel embolic microspheres are likely to be determined not only by the unmet clinical needs but also to a great extent by the distinct regulatory requirements based on their material composition and intended use.

Given that their principal intended action is physical occlusion of a blood vessel feeding a tumor, embolic microspheres are considered medical devices. Microspheres intended for permanent bland embolization are regulated in Europe as implantable class IIb devices under the Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (MDR) requiring a conformity assessment by a notified body, whereas in the USA they are regulated as class II medical devices requiring a Premarket Notification 510(k) by the FDA that demonstrate that the device is substantially equivalent to a previous one (i.e., predicate device) legally in commercial distribution. The addition of biodegradable features to embolic microspheres intended for bland embolization puts them at the highest risk class possible (class III devices) according to the European MDR because they are implantable devices to be absorbed with the subsequent obligation to demonstrate that biodegradability does not raise additional safety concerns. These additional requirements may well account for the fact that current marketed biodegradable microspheres for TAE are fewer in number than those marketed for permanent TAE (30.8% versus 69.2%, respectively). To palliate this hurdle, manufactures often opt to use biodegradable materials with solid track of use with well-known breakdown products such as polylactide-co-glycolide derivatives.

Medical devices can be assisted in their principal intended actions by medicinal substances on an ancillary basis. Indeed, the incorporation of medicinal substances in medical devices to support their action is an ever-growing trend [135]. This is also the case for drug- and radiopharmaceuticals-eluting embolic micro-

spheres intended for TACE and TARE, respectively. In these cases, even though the medicinal substance contributes to the therapeutic effect through pharmacological means upon local release, the principal intended action is still achieved by physical occlusion of the blood vessel. Taken together, embolic microspheres (intended either for permanent or transient embolization) including an ancillary medicinal substance, are regulated in Europe as class III medical devices in virtue of the MDR. Moreover, a favorable scientific opinion must be provided by a medicinal products authority before a notified body can issue an EU certificate for the device. On the contrary, in the USA, drug-eluting microspheres have not been granted FDA approval yet, whereas microspheres intended for TARE are regulated as class III devices requiring a Premarket Approval.

The level of clinical evidence required to gain regulatory approvals depends on the type of product. In broad terms, the Premarket Approval process is more involved and includes the submission of clinical data to support claims made for the device, whereas for microspheres intended for bland embolization, clinical investigations may not be needed. Given the extensive and costly nature of clinical studies for manufacturers, this can explain why DEMs have not been granted FDA approval yet. Analogously, it can explain why previous clinical investigations have been required for approval of the distinct microspheres for TARE (i.e., DOSISPHERE-01 [136], LEGACY [137], HEPAR I [138] or HEPAR II [139] studies) whereas the first clinical investigation registered in clinicaltrials.gov for the latest approved DEMs for TACE such as BioPearl is a postmarket follow-up study (BioPearl FIRST, NCT0423129). However, the situation is likely to change in Europe since the full application of the MDR on 26th May 2021, as for the first time the MDR states that clinical investigations shall be performed for all implantable devices and class III devices to prove clinical benefit [140] not only for being issued an EU certificate, but also for their post-market clinical follow-up, which will need to be updated annually for such devices.

Altogether, this strengthening of the requirements for approval of new embolic microspheres will lead to a considerable increase in clinical investigations, which will likely result in additional costs and more prolonged times for certification that may discourage manufactures from continuing with some of their market access strategies for these products. Although the actual impact is yet difficult to measure, this can ultimately lead to stifle innovation in the field.

In this context, future innovations in the remit of embolic microspheres may well be oriented to exploit new combinations of chemotherapeutics and already marketed DEMs to enhance the efficacy of TACE. In fact, unlike microspheres for TARE, which are marketed with the radiopharmaceutical already incorporated, all currently marketed DEMs for TACE are extemporaneously loaded immediately before use in the hospital pharmacy by mixing the microspheres with a solution of the drug. This gives higher versability for inclusion of alternative chemotherapeutics with distinct mechanisms of action to screen the optimal drug for delivery with DEMs. A major drawback of currently marketed DEM-TACE is that they can only be loaded with positively charged chemotherapeutics due to the anionic character of their polymeric matrixes. As a proof of it, doxorubicin remains the most used drug for DEM-TACE despite its abandonment as a systemic therapy for HCC and in vitro evidence suggesting that other drugs may have greater efficacy [79]. This limitation has spurred investigational advances on the development of alternative microspheres for DEM-TACE including other drugs such as sorafenib, a hydrophobic non-ionizable drug, to reduce the incidence of adverse effects in comparison with its oral administration [141]. To this end, biodegradable PLGA microspheres have been used as an alternative to commercially available DEM-TACE hydrogel-based platforms [142–144]. ICIs loaded into embolic microspheres are also currently under investigation, although in this case, given their ionizable nature, loading has been achieved into commercial LC Bead LUMI® microspheres [145].

Noticeably, new combinations of radiopharmaceuticals and microspheres are also under investigation for TARE. In this context, microspheres loaded with $^{131}$I have been developed for investigational TARE [146–148]. Some of these microspheres are made of new biodegradable polymers (i.e., silk fibroin or chitosan-collagen composite) that degrade within a much shorter timeframe in comparison with Quiremspheres® (8–12 weeks versus at least 1 year), overcoming thereby some of its limitations to eventually enable multiple administrations and prevent ischemia-induced angiogenesis [146,148].

Moreover, in parallel to the trend observed in clinical trials for combination therapies, the combination of distinct therapies within embolic microspheres is currently under investigation. This can be achieved either by co-encapsulating two distinct drugs to combat postembolization hypoxia and prevent neovascularization [149–151] or by supplementing embolization with a distinct type of therapy such as photothermal therapy [152] or magnetic ablation [153]. In the same vein, the pioneering combination of TACE and TARE (under the name of TARCE) in embolic microparticles loaded with both doxorubicin and $^{131}$I has recently been evaluated with promising results [147]. However, in these cases, the microspheres sizes were adapted for animal embolization, which makes them yet too small for translation into clinical practice with a true embolic effect in humans.

Given the suitability of embolotherapy for hypervascularized tumors, manufacturers have also started diversifying their applications to hypervascular tumors other than hepatocellular carcinoma. In this respect, the development of biodegradable microspheres has expanded therapeutic options to tumors that do not necessarily have dual blood supply. This is the case, for example, of Embocept®, that is also indicated for lung cancer to perform transpulmonal embolization. Moreover, some of the currently available permanent TAE microspheres are also indicated for the treatment of uterine fibroids and, more recently, for embolization of prostatic arteries for symptomatic benign prostatic hyperplasia (Embosphere®, BeadBlock®, Embozene® or HydroPearl®).

Altogether, embolic microspheres have provided added functionality for the physician and improved clinical outcomes for the patients with the incorporation of biodegradability and imageability to the embolic material over the last decades. In the same vein, embolic microspheres are expected to become more sophisticated to ultimately fulfill the promise of truly personalized therapies through multi-drug loading and real-time multi-parametric image follow-up in the decades to come.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

[1] International Agency for Research on Cancer: Cancer Today, World Health Organization, 2022 Available from: https://gco.iarc.fr/today (Accessed 06/06/2022).

[2] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA-Cancer J. Clin. 71 (3) (2021) 209–249.
[3] M. Feng, Y. Pan, R. Kong, S. Shu, Therapy of Primary Liver Cancer, Innovation (New York, N.Y.) 1(2) (2020) 100032.
[4] E. Gigante, V. Paradis, M. Ronot, F. Cauchy, O. Soubrane, N. Ganne-Carrie, J.C. Nault, New insights into the pathophysiology and clinical care of rare primary liver cancers, JHEP Rep. 3 (1) (2021) 14.
[5] N. Rujeerapaiboon, P. Wetwittayakhlang, Primary hepatic angiosarcoma: a rare liver malignancy - varying manifestations but grave prognosis, case reports in gastroenterology 14(1) (2020) 137–149.
[6] C.C. Lin, H.M. Yang, Fibrolamellar Carcinoma A Concise Review, Arch. Pathol. Lab. Med. 142 (9) (2018) 1141–1145.
[7] S.K. Kamarajah, D. Robinson, P. Littler, S.A. White, Small, incidental hepatic epithelioid haemangioendothelioma the role of ablative therapy in borderline patients, J. Surg. Case Rep. (8) (2018) 3.
[8] S. Heinrich, A.J. Craig, L.C. Ma, B. Heinrich, T.F. Greten, X.W. Wang, Understanding tumour cell heterogeneity and its implication for immunotherapy in liver cancer using single-cell analysis, J. Hepatol. 74 (3) (2021) 700–715.
[9] S. He, S.L. Tang, WNT/beta-catenin signaling in the development of liver cancers, Biomed. Pharmacother. 132 (2020) 8.
[10] R. Mohr, B. Ozdirik, J. Lambrecht, M. Demir, J. Eschrich, L. Geisler, T. Hellberg, S.H. Loosen, T. Luedde, F. Tacke, L. Hammerich, C. Roderburg, From liver cirrhosis to cancer: the role of micro-RNAs in hepatocarcinogenesis, Int. J. Mol. Sci. 22 (3) (2021) 17.
[11] W.Q. Chen, C.L. Chiang, L.A. Dawson, Efficacy and safety of radiotherapy for primary liver cancer, Chin, Clin. Oncol. 10 (1) (2021) 11.
[12] H. Petrowsky, R. Fritsch, M. Guckenberger, M.L. De Oliveira, P. Dutkowski, P.A. Clavien, Modern therapeutic approaches for the treatment of malignant liver tumours, Nat. Rev. Gastroenterol. Hepatol. 17 (12) (2020) 755–772.
[13] B. Zhou, T. Yuan, M.G. Liu, H.M. Liu, J. Xie, Y.B. Shen, P. Chen, Overexpression of the structural maintenance of chromosome 4 protein is associated with tumor de-differentiation, advanced stage and vascular invasion of primary liver cancer, Oncol. Rep. 28 (4) (2012) 1263–1268.
[14] A. Perez-Lopez, C. Martin-Sabroso, A.I. Torres-Suarez, J. Aparicio-Blanco, Timeline of translational formulation technologies for cancer therapy: successes, failures, and lessons learned therefrom, Pharmaceutics 12 (11) (2020) 35.
[15] Z. Kan, D.C. Madoff, Liver anatomy: microcirculation of the liver, Semin. Intervent. Radiol. 25 (2) (2008) 77–85.
[16] H.C. Nam, B. Jang, M.J. Song, Transarterial chemoembolization with drug-eluting beads in hepatocellular carcinoma, World J. Gastroenterol. 22 (40) (2016) 8853–8861.
[17] J.M. Llovet, M.I. Real, X. Montana, R. Planas, S. Coll, J. Aponte, C. Ayuso, M. Sala, J. Muchart, R. Sola, J. Rodes, J. Bruix, G. Barcelona Clin Liver Canc, Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial, Lancet 359 (9319) (2002) 1734–1739.
[18] K.T. Brown, R.K. Do, M. Gonen, A.M. Covey, G.I. Getrajdman, C.T. Sofocleous, W.R. Jarnagin, M.I. D'Angelica, P.J. Allen, J.P. Erinjeri, L.A. Brody, G.P. O'Neill, K.N. Johnson, A.R. Garcia, C. Beattie, B.S. Zhao, S.B. Solomon, L.H. Schwartz, R. DeMatteo, G.K. Abou-Alfa, Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone, J. Clin. Oncol. 34 (17) (2016) 2046–+.
[19] M.S. Makary, U. Khandpur, J.M. Cloyd, K. Mumtaz, J.D. Dowell, Locoregional therapy approaches for hepatocellular carcinoma: recent advances and management strategies, Cancers (Basel) 12 (7) (2020) 19.
[20] A. Kennedy, D.B. Brown, J. Feilchenfeldt, J. Marshall, H. Wasan, M. Fakih, P. Gibbs, A. Knuth, B. Sangro, M.C. Soulen, G. Pittari, R.A. Sharma, Safety of selective internal radiation therapy (SIRT) with yttrium-90 microspheres combined with systemic anticancer agents: expert consensus, J. Gastrointest. Oncol. 8 (6) (2017) 1079–1099.
[21] M.J. Powerski, C. Erxleben, C. Scheurig-Munkler, D. Geisel, U. Heimann, B. Hamm, B. Gebauer, Hepatopulmonary shunting in patients with primary and secondary liver tumors scheduled for radioembolization, Eur. J. Radiol. 84 (2) (2015) 201–207.
[22] J.J. Hu, H. Albadawi, B.W. Chong, A.R. Deipolyi, R.A. Sheth, A. Khademhosseini, R. Oklu, Advances in Biomaterials and Technologies for Vascular Embolization, Adv. Mater. 31 (33) (2019) 52.
[23] T.J. Vogl, T. Gruber-Rouh, HCC: transarterial Therapies-What the Interventional Radiologist Can Offer, Dig. Dis. Sci. 64 (4) (2019) 959–967.
[24] H. Blackburn, S. West, Management of postembolization syndrome following hepatic transarterial chemoembolization for primary or metastatic liver cancer, Cancer Nurs. 39 (5) (2016) E1–E18.
[25] A. Yamamoto, S. Imai, M. Kobatake, T. Yamashita, T. Tamada, K. Umetani, Evaluation of tris-acryl gelatin microsphere embolization with monochromatic x rays: comparison with polyvinyl alcohol particles, J. Vasc. Interv. Radiol. 17 (11) (2006) 1797–1802.
[26] M. Caine, D. Carugo, X.L. Zhang, M. Hill, M.R. Dreher, A.L. Lewis, Review of the development of methods for characterization of microspheres for use in embolotherapy: translating bench to cathlab, Adv. Healthc. Mater. 6 (9) (2017) 21.
[27] K. Osuga, N. Maeda, H. Higashihara, S. Hori, T. Nakazawa, K. Tanaka, M. Nakamura, K. Kishimoto, Y. Ono, N. Tomiyama, Current status of embolic agents for liver tumor embolization, Int. J. Clin. Oncol. 17 (4) (2012) 306–315.
[28] A. Poursaid, M.M. Jensen, E. Huo, H. Ghandehari, Polymeric materials for embolic and chemoembolic applications, J. Control. Release 240 (2016) 414–433.
[29] A. Laurent, Microspheres and nonspherical particles for embolization, Tech. Vasc. Interv. Radiol. 10 (4) (2007) 248–256.
[30] G.R. Jia, J. Van Valkenburgh, A.Z. Chen, Q. Chen, J.D. Li, C.J. Zuo, K. Chen, Recent advances and applications of microspheres and nanoparticles in transarterial chemoembolization for hepatocellular carcinoma, Wiley Interdiscip. Rev.-Nanomed. Nanobiotechnol. (2021) 29.
[31] S. Vaidya, K.R. Tozer, J. Chen, An overview of embolic agents, Semin. Intervent. Radiol. 25 (3) (2008) 204–215.
[32] V. Verret, S.H. Ghegediban, M. Wassef, J.P. Pelage, J. Golzarian, A. Laurent, The arterial distribution of embozene and embosphere microspheres in sheep kidney and uterus embolization models, J. Vasc. Interv. Radiol. 22 (2) (2011) 220–228.
[33] K. Hidaka, L. Moine, G. Collin, D. Labarre, J.L. Grossiord, N. Huang, K. Osuga, S. Wada, A. Laurent, Elasticity and viscoelasticity of embolization microspheres, J. Mech. Behav. Biomed. Mater. 4 (8) (2011) 2161–2167.
[34] A.L. Lewis, C. Adams, W. Busby, S.A. Jones, L.C. Wolfenden, S.W. Leppard, R.R. Palmer, S. Small, Comparative in vitro evaluation of microspherical embolisation agents, J. Mater. Sci.-Mater. Med. 17 (12) (2006) 1193–1204.
[35] A. Schwarz, H.M. Zhang, A. Metcalfe, I. Salazkin, J. Raymond, Transcatheter embolization using degradable crosslinked hydrogels, Biomaterials 25 (21) (2004) 5209–5215.
[36] A. Schicho, P.L. Pereira, M. Putzler, K. Michalik, T. Albrecht, C. Nolte-Ernsting, C. Stroszczynski, P. Wiggermann, Degradable Starch Microspheres Transcatheter Arterial Chemoembolization (DSM-TACE) in Intrahepatic Cholangiocellular Carcinoma (ICC): results from a National Multi-Center Study on Safety and Efficacy, Med. Sci. Monitor 23 (2017) 796–800.
[37] A. Schicho, P.L. Pereira, K. Michalik, L.P. Beyer, C. Stroszczynski, P. Wiggermann, Safety and efficacy of transarterial chemoembolization with degradable starch microspheres (DSM-TACEACE) in the treatment of secondary liver malignancies, OncoTargets Ther. 11 (2018) 345–350.
[38] K.V. Sharma, M.R. Dreher, Y.Q. Tang, W. Pritchard, O.A. Chiesa, J. Karanian, J. Peregoy, B. Orandi, D. Woods, D. Donahue, J. Esparza, G. Jones, S.L. Willis, A.L. Lewis, B.J. Wood, Development of "Imageable" Beads for Transcatheter Embolotherapy, J. Vasc. Interv. Radiol. 21 (6) (2010) 865–876.
[39] A.L. Lewis, S.L. Willis, M.R. Dreher, Y.Q. Tang, K. Ashrafi, B.J. Wood, E.B. Levy, K.V. Sharma, A.H. Negussie, A.S. Mikhail, Bench-to-clinic development of imageable drug-eluting embolization beads: finding the balance, Future Oncol. 14 (26) (2018) 2741–2760.
[40] K.V. Sharma, Z. Bascal, H. Kilpatrick, K. Ashrafi, S.L. Willis, M.R. Dreher, A.L. Lewis, Long-term biocompatibility, imaging appearance and tissue effects associated with delivery of a novel radiopaque embolization bead for image-guided therapy, Biomaterials 103 (2016) 293–304.
[41] C.S.J. van Hooy-Corstjens, K. Saralidze, M.L.W. Knetsch, P.J. Emans, M.W. de Haan, P. Magusin, B. Mezari, L.H. Koole, New intrinsically radiopaque hydrophilic microspheres for embolization: synthesis and characterization, Biomacromolecules 9 (1) (2008) 84–90.
[42] A. Benzina, A. Yb, R.J.J. Heijboer, L.H. Koole, Translational Development of Biocompatible X-Ray Visible Microspheres for Use in Transcatheter Embolization Procedures, J. Mater. Sci. Eng. 5 (2016) 1–5.
[43] K. Saralidze, M.L.W. Knetsch, R.G.M. van Berkel, C. Mostert, L.H. Koole, Radiopaque microspheres for improved transarterial chemical embolization (TACE), J. Control. Release 152 (2011) E74–E75.
[44] E.B. Levy, V.P. Krishnasamy, A.L. Lewis, S. Willis, C. Macfarlane, V. Anderson, I.M.J. van der Bom, A. Radaelli, M.R. Dreher, K.V. Sharma, A. Negussie, A.S. Mikhail, J.F.H. Geschwind, B.J. Wood, First Human Experience with Directly Image-able Iodinated Embolization Microbeads, Cardiovasc. Interv. Radiol. 39 (8) (2016) 1177–1186.
[45] K. Ashrafi, Y.Q. Tang, H. Britton, O. Domenge, D. Blino, A.J. Bushby, K. Shuturminska, M. den Hartog, A. Radaelli, A.H. Negussie, A.S. Mikhail, D.L. Woods, V. Krishnasamy, E.B. Levy, B.J. Wood, S.L. Willis, M.R. Dreher, A.L. Lewis, Characterization of a novel intrinsically radiopaque Drug-eluting Bead for image-guided therapy: DC Bead LUMITM, J. Control. Release 250 (2017) 36–47.
[46] R. Duran, K. Sharma, M.R. Dreher, K. Ashrafi, S. Mirpour, M.D. Lin, R.E. Schernthaner, T.R. Schlachter, V. Tacher, A.L. Lewis, S. Willis, M. den Hartog, A. Radaelli, A.H. Negussie, B.J. Wood, J.F.H. Geschwind, A Novel Inherently Radiopaque Bead for Transarterial Embolization to Treat Liver Cancer - A Preclinical Study, Theranostics 6 (1) (2016) 28–39.
[47] J.M. Idee, B. Guiu, Use of Lipiodol as a drug-delivery system for transcatheter arterial chemoembolization of hepatocellular carcinoma: a review, Crit. Rev. Oncol./Hematol. 88 (3) (2013) 530–549.
[48] S.M. Yoon, B.Y. Ryoo, S.J. Lee, J.H. Kim, J.H. Shin, J.H. An, H.C. Lee, Y.S. Lim, Efficacy and Safety of Transarterial Chemoembolization Plus External Beam Radiotherapy vs Sorafenib in Hepatocellular Carcinoma With Macroscopic Vascular Invasion A Randomized Clinical Trial, JAMA Oncol. 4 (5) (2018) 661–669.
[49] T. de Baere, Y. Arai, R. Lencioni, J.F. Geschwind, W. Rilling, R. Salem, O. Matsui, M.C. Soulen, Treatment of Liver Tumors with Lipiodol TACE: technical Recommendations from Experts Opinion, Cardiovasc. Interv. Radiol. 39 (3) (2016) 334–343.
[50] E. Ahnfelt, O. Degerstedt, E. Lilienberg, E. Sjogren, P. Hansson, H. Lennernas, Lipiodol-based emulsions used for transarterial chemoembolization and drug delivery: effects of composition on stability and product quality, J. Drug Deliv. Sci. Technol. 53 (2019) 11.

[51] Y.M. Nouri, J.H. Kim, H.K. Yoon, H.K. Ko, J.H. Shin, D.I. Gwon, Update on Transarterial Chemoembolization with Drug-Eluting Microspheres for Hepatocellular Carcinoma, Korean J. Radiol. 20 (1) (2019) 34–49.
[52] Y.P. Chen, J.L. Zhang, Y.H. Zou, Y.L. Wu, Recent Advances on Polymeric Beads or Hydrogels as Embolization Agents for Improved Transcatheter Arterial Chemoembolization (TACE), Front. Chem. 7 (2019) 11.
[53] J. Lammer, K. Malagari, T. Vogl, F. Pilleul, A. Denys, A. Watkinson, M. Pitton, G. Sergent, T. Pfammatter, S. Terraz, Y. Benhamou, Y. Avajon, T. Gruenberger, M. Pomoni, H. Langenberger, M. Schuchmann, J. Dumortier, C. Mueller, P. Chevallier, R. Lencioni, P.V. Investigators, Prospective Randomized Study of Doxorubicin-Eluting-Bead Embolization in the Treatment of Hepatocellular Carcinoma: results of the PRECISION V Study, Cardiovasc. Interv. Radiol. 33 (1) (2010) 41–52.
[54] M. Varela, M.I. Real, M. Burrel, A. Forner, M. Sala, M. Brunet, C. Ayuso, L. Castells, X. Montana, J.M. Llovet, J. Bruix, Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics, J. Hepatol. 46 (3) (2007) 474–481.
[55] Z.S. Zhang, H.Z. Li, C. Ma, Y.D. Xiao, Conventional versus drug-eluting beads chemoembolization for infiltrative hepatocellular carcinoma: a comparison of efficacy and safety, BMC Cancer 19 (1) (2019) 10.
[56] R. Golfieri, E. Giampalma, M. Renzulli, R. Cioni, I. Bargellini, C. Bartolozzi, A.D. Breatta, G. Gandini, R. Nani, D. Gasparini, A. Cucchetti, L. Bolondi, F. Trevisani, G.R.P. Precision Italia Study, Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma, Br. J. Cancer 111 (2) (2014) 255–264.
[57] W.C. Chang, H.H. Hsu, S.H. Chiu, W.Y. Huang, C.H. Lo, H.H. Lin, P.C. Huang, Y.L. Shih, Y.L. Wan, Transcatheter Arterial Chemoembolization with Drug-Eluting Beads for the Treatment of Hepatocellular Carcinoma: recommended Selection for Small-Caliber (<100 mu m) Beads, J. Hepatocell. Carcinoma 8 (2021) 937–949.
[58] A. Monier, B. Guiu, R. Duran, S. Aho, P. Bize, P. Deltenre, V. Dunet, A. Denys, Liver and biliary damages following transarterial chemoembolization of hepatocellular carcinoma: comparison between drug-eluting beads and lipiodol emulsion, Eur. Radiol. 27 (4) (2017) 1431–1439.
[59] A.L. Lewis, M.V. Gonzalez, S.W. Leppard, J.E. Brown, P.W. Stratford, G.J. Phillips, A.W. Lloyd, Doxorubicin eluting beads-1: effects of drug loading on bead characteristics and drug distribution, J. Mater. Sci.-Mater. Med. 18 (9) (2007) 1691–1699.
[60] R.R. Taylor, Y.Q. Tang, M.V. Gonzalez, P.W. Stratford, A.L. Lewis, Irinotecan drug eluting beads for use in chemoembolization: in vitro and in vivo evaluation of drug release properties, Eur. J. Pharm. Sci. 30 (1) (2007) 7–14.
[61] O. Jordan, A. Denys, T. De Baere, N. Boulens, E. Doelker, Comparative Study of Chemoembolization Loadable Beads: in vitro Drug Release and Physical Properties of DC Bead and Hepasphere Loaded with Doxorubicin and Irinotecan, J. Vasc. Interv. Radiol. 21 (7) (2010) 1084–1090.
[62] A.L. Lewis, R.R. Holden, DC Bead embolic drug-eluting bead: clinical application in the locoregional treatment of tumours, Expert Opin. Drug Deliv. 8 (2) (2011) 153–169.
[63] A.L. Lewis, M.V. Gonzalez, A.W. Lloyd, B. Hall, Y.Q. Tang, S.L. Willis, S.W. Leppard, L.C. Wolfenden, R.R. Palmer, P.W. Stratford, DC bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization, J. Vasc. Interv. Radiol. 17 (2) (2006) 335–342.
[64] A.L. Lewis, B. Hall, Toward a better understanding of the mechanism of action for intra-arterial delivery of irinotecan from DC Bead((TM)) (DEBIRI), Future Oncol. 15 (17) (2019) 2053–2068.
[65] K. Malagari, A. Pomoni, D. Filippiadis, D. Kelekis, Chemoembolization of hepatocellular carcinoma with HepaSphere (TM), Hepat. Oncol. 2 (2) (2015) 147–157.
[66] R. Lencioni, T. de Baere, M. Burrel, J.G. Caridi, J. Lammer, K. Malagari, R.C.G. Martin, E. O'Grady, M.I. Real, T.J. Vogl, A. Watkinson, J.F.H. Geschwind, Transcatheter Treatment of Hepatocellular Carcinoma with Doxorubicin-loaded DC Bead (DEBDOX): technical Recommendations, Cardiovasc. Interv. Radiol. 35 (5) (2012) 980–985.
[67] E. Ahnfelt, E. Sjogren, P. Hansson, H. Lennernas, In vitro release mechanisms of doxorubicin from a clinical bead drug-delivery system, J. Pharm. Sci. 105 (11) (2016) 3387–3398.
[68] J. Delicque, B. Guiu, M. Boulin, H. Schwanz, L. Piron, C. Cassinotto, Liver chemoembolization of hepatocellular carcinoma using TANDEM((R)) microspheres, Future Oncol. 14 (26) (2018) 2761–2772.
[69] T. de Baere, S. Plotkin, R. Yu, A. Sutter, Y. Wu, G.M. Cruise, An in vitro evaluation of four types of drug-eluting microspheres loaded with doxorubicin, J. Vasc. Interv. Radiol. 27 (9) (2016) 1425–1431.
[70] P.L. Pereira, S. Plotkin, R. Yu, A. Sutter, Y. Wu, C.M. Sommer, G.M. Cruise, An in-vitro evaluation of three types of drug-eluting microspheres loaded with irinotecan, Anticancer Drugs 27 (9) (2016) 873–878.
[71] B. Guiu, G. Hincapie, L. Thompson, Y. Wu, M. Boulin, C. Cassinotto, G.M. Cruise, An in vitro evaluation of four types of drug-eluting embolics loaded with idarubicin, J. Vasc. Interv. Radiol. 30 (8) (2019) 1303–1309.
[72] K. Malagari, M. Pomoni, H. Moschouris, A. Kelekis, A. Charokopakis, E. Bouma, T. Spyridopoulos, A. Chatziioannou, V. Sotirchos, T. Karampelas, C. Tamvakopoulos, D. Filippiadis, E. Karagiannis, A. Marinis, J. Koskinas, D.A. Kelekis, Chemoembolization of Hepatocellular Carcinoma with Hepasphere 30-60 um. Safety and Efficacy Study, Cardiovasc. Interv. Radiol. 37 (1) (2014) 165–175.
[73] K. Eichler, S. Zangos, M.G. Mack, R. Hammerstingl, T. Gruber-Rouh, C. Gallus, T.J. Vogl, First human study in treatment of unresectable liver metastases from colorectal cancer with irinotecan-loaded beads (DEBIRI), Int. J. Oncol. 41 (4) (2012) 1213–1220.
[74] G. Maleux, H. Prenen, T. Helmberger, I. Spriet, T. Isailovic, P. Pereira, Life-Pearl microspheres loaded with irinotecan in the treatment of Liver-dominant metastatic colorectal carcinoma: feasibility, safety and pharmacokinetic study, Anticancer Drugs 31 (10) (2020) 1084–1090.
[75] G. Richter, B. Radeleff, C. Stroszczynski, P. Pereira, T. Helmberger, M. Barakat, P. Huppert, Safety and feasibility of chemoembolization with doxorubicin-loaded small calibrated microspheres in patients with hepatocellular carcinoma: results of the MIRACLE I prospective multicenter study, Cardiovasc. Interv. Radiol. 41 (4) (2018) 587–593.
[76] G. Tovar-Felice, A. Garcia-Gamez, V. Benito-Santamaria, D. Balaguer-Paniagua, J. Villalba-Aunon, J. Sampere-Moragues, Unresectable hepatocellular carcinoma treatment with doxorubicin-eluting polyethylene glycol microspheres: a single-center experience, Hepat. Oncol. 8 (3) (2021) 9.
[77] L.H. Weng, P. Rostamzadeh, N. Nooryshokry, H.C. Le, J. Golzarian, In vitro and in vivo evaluation of biodegradable embolic microspheres with tunable anticancer drug release, Acta Biomater. 9 (6) (2013) 6823–6833.
[78] L.H. Weng, H.J. Tseng, P. Rostamzadeh, J. Golzarian, In vitro comparative study of drug loading and delivery properties of bioresorbable microspheres and LC bead, J. Mater. Sci.-Mater. Med. 27 (12) (2016) 9.
[79] A.S. Mikhail, A.H. Negussie, M. Mauda-Havakuk, J.W. Owen, W.F. Pritchard, A.L. Lewis, B.J. Wood, Drug-eluting embolic microspheres: state-of-the-art and emerging clinical applications, Expert Opin. Drug Deliv. 18 (3) (2021) 383–398.
[80] A.S. Mikhail, W.F. Pritchard, A.H. Negussie, V.P. Krishnasamy, D.B. Amchin, J.G. Thompson, P.G. Wakim, D. Woods, I. Bakhutashvili, J.A. Esparza-Trujillo, J.W. Karanian, S.L. Willis, A.L. Lewis, E.B. Levy, B.J. Wood, Mapping drug dose distribution on CT images following transarterial chemoembolization with radiopaque drug-eluting beads in a rabbit tumor model, Radiology 289 (2) (2018) 396–404.
[81] A.L. Lewis, M. Caine, P. Garcia, K. Ashrafi, Y.Q. Tang, L. Hinchcliffe, W. Guo, Z. Bascal, H. Kilpatrick, S.L. Willis, Handling and performance characteristics of a new small caliber radiopaque embolic microsphere, J. Biomed. Mater. Res. Part B 108 (7) (2020) 2878–2888.
[82] C. Aliberti, R. Carandina, D. Sarti, E. Pizzirani, G. Ramondo, U. Cillo, S. Guadagni, G. Fiorentini, Transarterial chemoembolization with DC Bead LUMI (TM) radiopaque beads for primary liver cancer treatment: preliminary experience, Future Oncol. 13 (25) (2017) 2243–2252.
[83] M. Caine, X.L. Zhang, M. Hill, W. Guo, K. Ashrafi, Z. Bascal, H. Kilpatrick, A. Dunn, D. Grey, R. Bushby, A. Bushby, S.L. Willis, M.R. Dreher, A.L. Lewis, Comparison of microsphere penetration with LC Bead LUMP (TM) versus other commercial microspheres, J. Mech. Behav. Biomed. Mater. 78 (2018) 46–55.
[84] J. Reicher, S. Mafeld, G. Priona, H.L. Reeves, D.M. Manas, R. Jackson, P. Littler, Early experience of trans-arterial chemo-embolisation for hepatocellular carcinoma with a novel radiopaque bead, Cardiovasc. Interv. Radiol. 42 (11) (2019) 1563–1570.
[85] L.E. Moreno-Luna, J.D. Yang, W. Sanchez, R. Paz-Fumagalli, D.M. Harnois, T.A. Mettler, D.N. Gansen, P.C. de Groen, K.N. Lazaridis, K.V.N. Menon, N.F. LaRusso, S.R. Alberts, G.J. Gores, C.J. Fleming, S.W. Slettedahl, W.S. Harmsen, T.M. Therneau, G.A. Wiseman, J.C. Andrews, L.R. Roberts, Efficacy and safety of transarterial radioembolization versus chemoembolization in patients with hepatocellular carcinoma, Cardiovasc. Interv. Radiol. 36 (3) (2013) 714–723.
[86] D.Y. Kim, K.H. Han, Transarterial chemoembolization versus transarterial radioembolization in hepatocellular carcinoma: optimization of selecting treatment modality, Hepatol. Int. 10 (6) (2016) 883–892.
[87] R. Salem, R.J. Lewandowski, L. Kulik, E. Wang, A. Riaz, R.K. Ryu, K.T. Sato, R. Gupta, P. Nikolaidis, F.H. Miller, V. Yaghmai, S.M. Ibrahim, S. Senthilnathan, T. Baker, V.L. Gates, B. Atassi, S. Newman, K. Memon, R. Chen, R.L. Vogelzang, A.A. Nemcek, S.A. Resnick, H.B. Chrisman, J. Carr, R.A. Omary, M. Abecassis, A.B. Benson, M.F. Mulcahy, Radioembolization Results in Longer Time-to-Progression and Reduced Toxicity Compared With Chemoembolization in Patients With Hepatocellular Carcinoma, Gastroenterology 140 (2) (2011) 497–U205.
[88] R. Sacco, C. Conte, E. Tumino, G. Parisi, S. Marceglia, S. Metrangolo, R. Eggenhoffner, G. Bresci, G. Cabibbo, L. Giacomelli, Transarterial radioembolization for hepatocellular carcinoma: a review, J. Hepatocell. Carcinoma 3 (2016) 25–29.
[89] B. Sangro, M. Inarrairaegui, J.I. Bilbao, Radioembolization for hepatocellular carcinoma, J. Hepatol. 56 (2) (2012) 464–473.
[90] J.R. Kallini, A. Gabr, R. Salem, R.J. Lewandowski, Transarterial Radioembolization with Yttrium-90 for the Treatment of Hepatocellular Carcinoma, Adv. Ther. 33 (5) (2016) 699–714.
[91] R. Salem, A. Gabr, A. Riaz, R. Mora, R. Ali, M. Abecassis, R. Hickey, L. Kulik, D. Ganger, S. Flamm, R. Atassi, B. Atassi, K. Sato, A. Benson, M.F. Mulcahy, N. Abouchaleh, A. Al Asadi, K. Desai, B. Thornburg, M. Vouche, A. Habib, J. Caicedo, F.H. Miller, V. Yaghmai, J.R. Kallini, S. Mouli, R.J. Lewandowski, Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience, Hepatology 68 (4) (2018) 1429–1440.
[92] D. Manas, J.K. Bell, S. Mealing, H. Davies, H. Baker, H. Holmes, R.A. Hubner, The cost-effectiveness of TheraSphere in patients with hepatocellular carcinoma who are eligible for transarterial embolization, Ejso 47 (2) (2021) 401–408.

[93] M.A. Westcott, D.M. Coldwell, D.M. Liu, J.F. Zikria, The development, commercialization, and clinical context of yttrium-90 radiolabeled resin and glass microspheres, Adv. Radiation Oncol. 1 (4) (2016) 351–364.
[94] T. Helmberger, R. Golfieri, M. Pech, T. Pfammatter, D. Arnold, R. Cianni, G. Maleux, G. Munneke, O. Pellerin, B. Peynircioglu, B. Sangro, N. Schaefer, N. de Jong, J.I. Bilbao, C.S. Comm, C.P. Investigators, Clinical Application of Trans-Arterial Radioembolization in Hepatic Malignancies in Europe: first Results from the Prospective Multicentre Observational Study CIRSE Registry for SIR-Spheres Therapy (CIRT), Cardiovasc. Interv. Radiol. 44 (1) (2021) 21–35.
[95] A.S. Kennedy, C. Nutting, D. Coldwell, J. Gaiser, C. Drachenberg, Pathologic response and microdosimetry of Y-90 microspheres in man: review of four explanted whole livers, Int. J. Radiat. Oncol. Biol. Phys. 60 (5) (2004) 1552–1563.
[96] A. Mahvash, S. Chartier, M. Turco, P. Habib, S. Griffith, S. Brown, S.C. Kappadath, A prospective, multicenter, open-label, single-arm clinical trial design to evaluate the safety and efficacy of Y-90 resin microspheres for the treatment of unresectable HCC: the DOORwaY90 (Duration Of Objective Response with arterial Ytrrium-90) study, BMC Gastroenterol. 22 (1) (2022) 10.
[97] J.R. Kallini, A. Gabr, K. Thorlund, C. Balijepalli, D. Ayres, S. Kanters, S. Ebrahim, E. Mills, R.J. Lewandowski, R. Salem, Comparison of the Adverse Event Profile of TheraSphere (R) with SIR-Spheres (R) for the Treatment of Unresectable Hepatocellular Carcinoma: a Systematic Review, Cardiovasc. Interv. Radiol. 40 (7) (2017) 1033–1043.
[98] M.D. Li, K.F. Chu, A. DePietro, V. Wu, E. Wehrenberg-Klee, O. Zurkiya, R.W. Liu, S. Ganguli, Same-Day Yttrium-90 Radioembolization: feasibility with Resin Microspheres, J. Vasc. Interv. Radiol. 30 (3) (2019) 314–319.
[99] P. Hilgard, M. Hamami, A. El Fouly, A. Scherag, S. Muller, J. Ertle, T. Heusner, V.R. Cicinnati, A. Paul, A. Bockisch, G. Gerken, G. Antoch, Radioembolization with Yttrium-90 Glass Microspheres in Hepatocellular Carcinoma: european Experience on Safety and Long-Term Survival, Hepatology 52 (5) (2010) 1741–1749.
[100] J.W. McCann, A.M. Larkin, L.J. Martino, D.J. Eschelman, C.F. Gonsalves, D.B. Brown, Radiation Emission from Patients Treated with Selective Hepatic Radioembolization Using Yttrium-90 Microspheres: are Contact Restrictions Necessary? J. Vasc. Interv. Radiol. 23 (5) (2012) 661–667.
[101] S. Laffont, Y. Rolland, V. Ardisson, J. Edeline, M. Pracht, S.Le Sourd, T. Rohou, L. Lenoir, N. Lepareur, E. Garin, Occupational radiation exposure of medical staff performing Y-90-loaded microsphere radioembolization, Eur. J. Nucl. Med. Mol. Imaging 43 (5) (2016) 824–831.
[102] R.J. Mumper, U.Y. Ryo, M. Jay, Neutron-activated Holmium-166-Poly (L-lactic acid) microspheres - a potential agent for the internal radiation-therapy of hepatic tumors, J. Nucl. Med. 32 (11) (1991) 2139–2143.
[103] S.W. Zielhuis, J.F.W. Nijsen, G.C. Krijger, A.D. van het Schip, W.E. Hennink, Holmium-loaded poly(L-lactic acid) microspheres: in vitro degradation study, Biomacromolecules 7 (7) (2006) 2217–2223.
[104] S.W. Zielhuis, J.F.W. Nijsen, J.H. Seppenwoolde, C.J.G. Bakker, G.C. Krijger, H.F.J. Dullens, B.A. Zonnenberg, P.P. van Rijk, W.E. Hennink, A.D.V. Schip, Long-term toxicity of holmium-loaded poly(L-lactic acid) microspheres in rats, Biomaterials 28 (31) (2007) 4591–4599.
[105] M. Elschot, B.J. Vermolen, M. Lam, B. de Keizer, M. van den Bosch, H. de Jong, Quantitative Comparison of PET and Bremsstrahlung SPECT for Imaging the In Vivo Yttrium-90 Microsphere Distribution after Liver Radioembolization, PLoS One 8 (2) (2013) 10.
[106] P. d'Abadie, M. Hesse, A. Louppe, R. Lhommel, S. Walrand, F. Jamar, Microspheres Used in Liver Radioembolization: from Conception to Clinical Effects, Molecules 26 (13) (2021) 14.
[107] M. Boulin, P. Hillon, J.P. Cercueil, F. Bonnetain, S. Dabakuyo, A. Minello, J.L. Jouve, C. Lepage, M. Bardou, M. Wendremaire, P. Guerard, A. Denys, A. Grandvuillemin, B. Chauffert, L. Bedenne, B. Guiu, Idarubicin-loaded beads for chemoembolisation of hepatocellular carcinoma: results of the IDASPHERE phase I trial, Aliment. Pharmacol. Ther. 39 (11) (2014) 1301–1313.
[108] B. Guiu, P. Chevallier, E. Assenat, E. Barbier, P. Merle, A. Bouvier, J. Dumortier, E. Nguyen-Khac, J. Gugenheim, A. Rode, F. Oberti, P.J. Valette, T. Yzet, O. Chevallier, J.C. Barbare, M. Latournerie, M. Boulin, Idarubicin-loaded Beads for Chemoembolization of Hepatocellular Carcinoma: the IDASPHERE II Single-Arm Phase II Trial, Radiology 291 (3) (2019) 801–808.
[109] R. Martin, J. Irurzun, J. Munchart, I. Trofimov, A. Scupchenko, C. Tatum, G. Narayanan, Optimal technique and response of doxorubicin beads in hepatocellular cancer: bead size and dose, Korean J. Hepatol. 17 (1) (2011) 51–60.
[110] H.J. Prajapati, M.Z. Xing, J.R. Spivey, S.I. Hanish, B.F. El-Rayes, J.S. Kauh, Z.J. Chen, H.S. Kim, Survival, Efficacy, and Safety of Small Versus Large Doxorubicin Drug-Eluting Beads TACE Chemoembolization in Patients With Unresectable HCC, Am. J. Roentgenol. 203 (6) (2014) W706–W714.
[111] Z.Y. Peng, G.H. Cao, Q.M. Hou, L. Li, S.H. Ying, J.H. Sun, G.H. Zhou, J. Zhou, X. Zhang, W.B. Ji, Z.H. Yu, T.F. Li, D.D. Zhu, W.H. Hu, J.S. Ji, H.J. Du, C.S. Shi, X.H. Guo, J. Fang, J. Han, W.J. Gu, X.X. Xie, Z.C. Sun, H.H. Xu, X. Wu, T.Y. Hu, J. Huang, H.J. Hu, J.P. Zheng, J. Luo, Y.T. Chen, W.Q. Yu, G.L. Shao, The Comprehensive Analysis of Efficacy and Safety of CalliSpheres (R) Drug-Eluting Beads Transarterial Chemoembolization in 367 Liver Cancer Patients: a Multiple–Center, Cohort Study, Oncol. Res. 28 (3) (2020) 249–271.
[112] J.M. Llovet, S. Ricci, V. Mazzaferro, P. Hilgard, E. Gane, J.F. Blanc, A.C. de Oliveira, A. Santoro, J.L. Raoul, A. Forner, M. Schwartz, C. Porta, S. Zeuzem, L. Bolondi, T.F. Greten, P.R. Galle, J.F. Seitz, I. Borbath, D. Haussinger, T. Giannaris, M. Shan, M. Moscovici, D. Voliotis, J. Bruix, S.I.S. Grp, Sorafenib in advanced hepatocellular carcinoma, N. Engl. J. Med. 359 (4) (2008) 378–390.
[113] A.L. Cheng, Y.K. Kang, Z.D. Chen, C.J. Tsao, S.K. Qin, J.S. Kim, R.C. Luo, J.F. Feng, S.L. Ye, T.S. Yang, J.M. Xu, Y. Sun, H.J. Liang, J.W. Liu, J.J. Wang, W.Y. Tak, H.M. Pan, K. Burock, J. Zou, D. Voliotis, Z.Z. Guan, Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial, Lancet Oncol. 10 (1) (2009) 25–34.
[114] S.J. Schoenleber, D.M. Kurtz, J.A. Talwalker, L.R. Roberts, G.J. Gores, Prognostic role of vascular endothelial growth factor in hepatocellular carcinoma: systematic review and meta-analysis, Br. J. Cancer 100 (9) (2009) 1385–1392.
[115] J.H. Shim, J.W. Park, J.H. Kim, M. An, S.Y. Kong, B.H. Nam, J.I. Choi, H.B. Kim, W.J. Lee, C.M. Kim, Association between increment of serum VEGF level and prognosis after transcatheter arterial chemoembolization in hepatocellular carcinoma patients, Cancer Sci. 99 (10) (2008) 2037–2044.
[116] M. Kudo, K. Imanaka, N. Chida, K. Nakachi, W.Y. Tak, T. Takayama, J.H. Yoon, T. Hori, H. Kumada, N. Hayashi, S. Kaneko, H. Tsubouchi, D.J. Suh, J. Furuse, T. Okusaka, K. Tanaka, O. Matsui, M. Wada, I. Yamaguchi, T. Ohya, G. Meinhardt, K. Okita, Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma, Eur. J. Cancer 47 (14) (2011) 2117–2127.
[117] T. Meyer, R. Fox, Y.T. Ma, P.J. Ross, M.W. James, R. Sturgess, C. Stubbs, D.D. Stocken, L. Wall, A. Watkinson, N. Hacking, T.R.J. Evans, P. Collins, R.A. Hubner, D. Cunningham, J.N. Primrose, P.J. Johnson, D.H. Palmer, Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial, Lancet Gastroenterol. Hepatol. 2 (8) (2017) 565–575.
[118] J.W. Park, Y.J. Kim, D.Y. Kim, S.H. Bae, S.W. Paik, Y.J. Lee, H.Y. Kim, H.C. Lee, S.Y. Han, J.Y. Cheong, O.S. Kwon, J.E. Yeon, B.H. Kim, J. Hwang, Sorafenib with or without concurrent transarterial chemoembolization in patients with advanced hepatocellular carcinoma: the phase III STAH trial, J. Hepatol. 70 (4) (2019) 684–691.
[119] A. Huang, X.R. Yang, W.Y. Chung, A.R. Dennison, J. Zhou, Targeted therapy for hepatocellular carcinoma, Signal Transduct. Target. Ther. 5 (1) (2020) 13.
[120] Z. Peng, W. Fan, B. Zhu, J. Li, M. Kuang, Lenvatinib combined with transarterial chemoembolization as first-line treatment of advanced hepatocellular carcinoma: a phase 3, multicenter, randomized controlled trial, J. Clin. Oncol. 40 (4_suppl) (2022) 380 -380.
[121] M. Kudo, G.H. Han, R.S. Finn, R.T.P. Poon, J.F. Blanc, L.N. Yan, J.J. Yang, L.G. Lu, W.Y. Tak, X.P. Yu, J.H. Lee, S.M. Lin, C.P. Wu, T. Tanwandee, G.L. Shao, I.B. Walters, C. Dela Cruz, V. Poulart, J.H. Wang, Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial, Hepatology 60 (5) (2014) 1697–1707.
[122] M. Kudo, A.L. Cheng, J.W. Park, J.H. Park, P.C. Liang, H. Hidaka, N. Izumi, J. Heo, Y.J. Lee, I.S. Sheen, C.F. Chiu, H. Arioka, S. Morita, Y. Arai, Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study, Lancet Gastroenterol. Hepatol. 3 (1) (2018) 37–46.
[123] B. Scheiner, M.M. Kirstein, F. Hucke, F. Finkelmeier, K. Schulze, J. von Felden, S. Koch, P. Schwabl, J.B. Hinrichs, F. Waneck, O. Waidmann, T. Reiberger, C. Muller, W. Sieghart, M. Trauner, A. Weinmann, H. Wege, J. Trojan, M. Peck-Radosavljevic, A. Vogel, M. Pinter, Programmed cell death protein-1 (PD-1)-targeted immunotherapy in advanced hepatocellular carcinoma: efficacy and safety data from an international multicentrereal- world cohort, Aliment. Pharmacol. Ther. 49 (10) (2019) 1323–1333.
[124] C. Donisi, M. Puzzoni, P. Ziranu, E. Lai, S. Mariani, G. Saba, V. Impera, M. Dubois, M. Persano, M. Migliari, A. Pretta, N. Liscia, G. Astara, M. Scartozzi, Immune Checkpoint Inhibitors in the Treatment of HCC, Front. Oncol. 10 (2021) 15.
[125] J.M. Llovet, A. Vogel, D.C. Madoff, R.S. Finn, S. Ogasawara, Z.G. Ren, K. Mody, J.J. Li, A.B. Siegel, L. Dubrovsky, M. Kudo, Randomized Phase 3 LEAP-012 Study: transarterial Chemoembolization With or Without Lenvatinib Plus Pembrolizumab for Intermediate-Stage Hepatocellular Carcinoma Not Amenable to Curative Treatment, Cardiovasc. Interv. Radiol. 45 (4) (2022) 405–412.
[126] J. Ricke, H.J. Klumpen, H. Amthauer, I. Bargellini, P. Bartenstein, E.N. de Toni, A. Gasbarrini, M. Pech, M. Peck-Radosavljevic, P. Popovic, O. Rosmorduc, E. Schott, M. Seidensticker, C. Verslype, B. Sangro, P. Malfertheiner, Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma, J. Hepatol. 71 (6) (2019) 1164–1174.
[127] A. Forner, M. Reig, J. Bruix, Hepatocellular carcinoma, Lancet 391 (10127) (2018) 1301–1314.
[128] L. European, Assoc Study, EASL Clinical Practice Guidelines: management of hepatocellular carcinoma, J. Hepatol. 69 (1) (2018) 182–236.
[129] J.W. Park, M.S. Chen, M. Colombo, L.R. Roberts, M. Schwartz, P.J. Chen, M. Kudo, P. Johnson, S. Wagner, L.S. Orsini, M. Sherman, Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study, Liver Int. 35 (9) (2015) 2155–2166.
[130] L. Vadot, M. Boulin, B. Guiu, L.S. Aho, M. Vourc'h, A. Musat, P. Hillon, C. Lepage, M.H. Guignard, P. Fagnoni, Clinical and economic impact of drug eluting beads in transarterial chemoembolization for hepatocellular carcinoma, J. Clin. Pharm. Ther. 40 (1) (2015) 83–90.
[131] A. Cucchetti, F. Trevisani, A. Cappelli, C. Mosconi, M. Renzulli, A.D. Pinna, R. Golfieri, Cost-effectiveness of doxorubicin-eluting beads versus conventional trans-arterial chemo-embolization for hepatocellular carcinoma, Dig. Liver Dis. 48 (7) (2016) 798–805.

[132] W. Fateen, F. Khan, R.J. O'Neill, M.W. James, S.D. Ryder, G.P. Aithal, Healthcare costs of transarterial chemoembolization in the treatment of hepatocellular carcinoma, J. Hepatocell. Carcinoma 4 (2017) 123–130.
[133] W. Sieghart, F. Hucke, M. Peck-Radosavljevic, Transarterial chemoembolization: modalities, indication, and patient selection, J. Hepatol. 62 (5) (2015) 1187–1195.
[134] N. Rostambeigi, A.S. Dekarske, E.E. Austin, J. Golzarian, E.N. Cressman, Cost Effectiveness of Radioembolization Compared with Conventional Transarterial Chemoembolization for Treatment of Hepatocellular Carcinoma, J. Vasc. Interv. Radiol. 25 (7) (2014) 1075–1084.
[135] P. Antich-Isern, J. Caro-Barri, J. Aparicio-Blanco, The combination of medical devices and medicinal products revisited from the new European legal framework, Int. J. Pharm. 607 (2021) 17.
[136] E. Garin, L. Tselikas, B. Guiu, J. Chalaye, J. Edeline, T. de Baere, E. Assenat, V. Tacher, C. Robert, M. Terroir-Cassou-Mounat, D. Mariano-Goulart, G. Amaddeo, X. Palard, A. Hollebecque, M. Kafrouni, H. Regnault, K. Boudjema, S. Grimaldi, M. Fourcade, H. Kobeiter, E. Vibert, S.Le Sourd, L. Piron, D. Sommacale, S. Laffont, B. Campillo-Gimenez, Y. Rolland, D.-.S. Grp, Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial, Lancet Gastroenterol. Hepatol. 6 (1) (2021) 17–29.
[137] R. Salem, G.E. Johnson, E. Kim, A. Riaz, V. Bishay, E. Boucher, K. Fowers, R. Lewandowski, S.A. Padia, Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: the LEGACY Study, Hepatology 74 (5) (2021) 2342–2352.
[138] M.L.J. Smits, J.F.W. Nijsen, M. van den Bosch, M. Lam, M.A.D. Vente, W. Mali, A.D. van het Schip, B.A. Zonnenberg, Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study, Lancet Oncol. 13 (10) (2012) 1025–1034.
[139] J.F. Prince, M. van den Bosch, J.F.W. Nijsen, M.L.J. Smits, A.F. van den Hoven, S. Nikolakopoulos, F.J. Wessels, R.C.G. Bruijnen, M. Braat, B.A. Zonnenberg, M. Lam, Efficacy of Radioembolization with Ho-166-Microspheres in Salvage Patients with Liver Metastases: a Phase 2 Study, J. Nucl. Med. 59 (4) (2018) 582–588.
[140] N. Martelli, D. Eskenazy, C. Dean, J. Pineau, P. Prognon, G. Chatellier, M. Sapoval, O. Pellerin, New European Regulation for Medical Devices: what Is Changing? Cardiovasc. Interv. Radiol. 42 (9) (2019) 1272–1278.
[141] K. Fuchs, R. Duran, A. Denys, P.E. Bize, G. Borchard, O. Jordan, Drug-eluting embolic microspheres for local drug delivery - State of the art, J. Control. Release 262 (2017) 127–138.
[142] J. Chen, A.Y. Sheu, W.G. Li, Z.L. Zhang, D.H. Kim, R.J. Lewandowski, R.A. Omary, L.D. Shea, A.C. Larson, Poly(lactide-co-glycolide) microspheres for MRI-monitored transcatheter delivery of sorafenib to liver tumors, J. Control. Release 184 (2014) 10–17.
[143] J.N. Chen, S.B. White, K.R. Harris, W.G. Li, J.W.T. Yap, D.H. Kim, R.J. Lewandowski, L.D. Shea, A.C. Larson, Poly(lactide-co-glycolide) microspheres for MRI-monitored delivery of sorafenib in a rabbit VX2 model, Biomaterials 61 (2015) 299–306.
[144] J.W. Choi, J.H. Park, H.R. Cho, J.W. Chung, D.D. Kim, H.C. Kim, H.J. Cho, Sorafenib and 2,3,5-triiodobenzoic acid-loaded imageable microspheres for transarterial embolization of a liver tumor, Sci. Rep. 7 (2017) 13.
[145] A.S. Mikhail, M. Mauda-Havakuk, A.H. Negussie, N. Hong, N.M. Hawken, C.J. Carlson, J.W. Owen, O. Franco-Mahecha, P.G. Wakim, A.L. Lewis, W.F. Pritchard, J.W. Karanian, B.J. Wood, Evaluation of immune-modulating drugs for use in drug-eluting microsphere transarterial embolization, Int. J. Pharm. 616 (2022) 8.
[146] X. Wu, L. Ge, G. Shen, Y. He, Z. Xu, D. Li, C. Mu, L. Zhao, W. Zhang, 131I-Labeled Silk Fibroin Microspheres for Radioembolic Therapy of Rat Hepatocellular Carcinoma, ACS Appl. Mater. Interfaces 14 (19) (2022) 21848–21859.
[147] Y.Y. Qian, Q.F. Liu, P.L. Li, Y.B. Han, J.P. Zhang, J.J. Xu, J.W. Sun, A.H. Wu, S.L. Song, W. Lu, Highly Tumor-Specific and Long-Acting Iodine-131 Microbeads for Enhanced Treatment of Hepatocellular Carcinoma with Low–Dose Radio-Chemoembolization, ACS Nano 15 (2) (2021) 2933–2946.
[148] F.W. Pang, Y.H. Li, W.J. Zhang, C.C. Xia, Q. He, Z.L. Li, L. Xiao, S.M. Song, P. Dong, H.J. Zhou, T. Shao, H.W. Cai, L. Li, Biodegradable (131)Iodine-Labeled Microspheres: potential Transarterial Radioembolization Biomaterial for Primary Hepatocellular Carcinoma Treatment, Adv. Healthc. Mater. 9 (13) (2020) 10.
[149] M.J. Chen, G.F. Shu, X.L. Lv, X.L. Xu, C.Y. Lu, E.Q. Qiao, S.J. Fang, L. Shen, N.N. Zhang, J. Wang, C.M. Chen, J.J. Song, Z. Liu, Y.Z. Du, J.S. Ji, HIF-2a-targeted interventional chemoembolization multifunctional microspheres for effective elimination of hepatocellular carcinoma, Biomaterials 284 (2022) 15.
[150] J.W. Choi, S.Y. Lee, E.J. Cho, D. Jeong, D.D. Kim, H.C. Kim, H.J. Cho, Gas generating microspheres for immediate release of Hsp90 inhibitor aiming at postembolization hypoxia in transarterial chemoembolization therapy of hepatocellular carcinoma, Int. J. Pharm. 607 (2021) 10.
[151] Y.J. Wang, D.G.M. Molin, C. Sevrin, C. Grandfils, N.M.S. van den Akker, M. Gagliardi, M.L. Knetsch, T. Delhaas, L.H. Koole, In vitro and in vivo evaluation of drug-eluting microspheres designed for transarterial chemoembolization therapy, Int. J. Pharm. 503 (1–2) (2016) 150–162.
[152] D. Huang, H.T. Dai, K.Y. Tang, B. Chen, H.Z. Zhu, D.B. Chen, N. Li, Y.Z. Wang, C.W. Liu, Y.H. Huang, J.Y. Yang, C. Zhang, R. Lin, W.L. He, A versatile UCST-type composite microsphere for image-guided chemoembolization and photothermal therapy against liver cancer, Nanoscale 12 (38) (2020) 20002–20015.
[153] Y.J. Liang, H. Yu, G.D. Feng, L.L. Zhuang, W. Xi, M. Ma, J. Chen, N. Gu, Y. Zhang, High-Performance Poly(lactic-co-glycolic acid)-Magnetic Microspheres Prepared by Rotating Membrane Emulsification for Transcatheter Arterial Embolization and Magnetic Ablation in VX2 Liver Tumors, ACS Appl. Mater. Interfaces 9 (50) (2017) 43478–43489.