The Use of Microspheres for Cancer Embolisation Therapy: Recent Advancements and Prospective

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KEYWORDS: biomaterials, chemoembolisation, embolic agent, radioembolisation

ABSTRACT: Embolisation therapy involving biomaterials has improved the therapeutic strategy for most liver cancer treatments. Developing biomaterials as embolic agents has significantly improved patients' survival rates. Various embolic agents are present in liquid agents, foam, particulate, and particles. One most applied is microparticles, such as microspheres (3D micron-sized spherical particles). Microspheres with added functionalities are currently being developed for effective therapeutic embolisation. Their excellent properties of high surface area and capacity for being loaded with radionuclides and alternate active or therapeutic agents provide additional advantage to overcome limitations from traditional cancer treatments. Microspheres (non-radioactive and radioactive) have been widely used and explored for localised cancer treatment. Non-radioactive microspheres exhibit improved clinical performance as drug delivery vehicles in chemotherapy due to their controlled and sustained drug release to the target site. They offer better flow properties and are beneficial for ease of delivery via injection procedures. In addition, radioactive microspheres have also been exploited for being used as an embolic platform in internal radiotherapy as an alternative to cancer treatment. This short review summarises the progressive development of non-radioactive and radioactive embolic microspheres, emphasising material characteristics. The use of embolic microspheres for various modalities of therapeutic arterial embolisation and their impact on therapeutic performance are also discussed.

INTRODUCTION

The prevalence of cancer is on the rise and continues to represent the second major worldwide problem related to mortality suffered by people of all ages that significantly affect different body parts impacting their life expectancy[1,2]. Cancer could arise from the primary tumour or metastatic cancer that causes morbidity and mortality. Metastatic cancer is advanced cancer that results from the rapid creation of abnormal cells known as metastatic cells that detach from the primary tumour and migrate and invade adjoining parts of the body, followed by spreading to other organs[2]. In order to combat cancer cells and reduce the burden of cancer, several treatments have been widely applied, such as surgery, chemotherapy (systemic cancer therapy using toxic drugs injected through the bloodstream)[3], targeted therapy (cancer therapy using inhibitor molecules or monoclonal antibodies targeted at proteins to control the proliferation of cancer cells)[4], radiation therapy (use of high doses of radiation to kill cancer cells and shrink tumour)[5], and also their combinations.

Cancer treatment options are usually decided by physicians considering the patient's condition. For example, patients with specialised diseases cannot be assigned cancer as one disease[6]. Indeed, the status of the patient and patient properties (age, gender, health status) are all important factors considered before planning the therapy. Despite the patient's condition, other factors can also influence the type of therapy, such as the prime location of cancer, metastatic cancer, tumour stage, or the cell type in the heterogeneous tumour tissue[6].

Embolisation therapy or embolotherapy is a nonsurgical and minimally invasive procedure for treating solid tumours and various conditions affecting different organs of the human body, such as varicoceles, organ ablation, haemorrhages, and vascular anomalies[7,8]. Tumour embolisation is a new pre-operative technique to shrink the tumour through occlusion of vascular structures and the blockage of vascular supply to tumours[8,9]. The blockage is usually performed via an endovascular approach in which the embolic agent is delivered through a catheter to block the blood flow within a target vessel[8,10]. Therapeutic embolisation was used in the early 1970s to treat arteriovenous malformations. Later, in 1972 selective arterial embolisation was used to intervene in acute bleeding. This procedure has been extensively applied for treating liver cancer, especially unresectable hepatocellular carcinoma (HCC), as a palliative treatment[8,11].

Arterial embolisation has been applied based on the microcirculation of the liver (< 100 μm in diameter of terminal blood vessels) where the hepatic parenchyma derives dual blood supply from the portal vein (70-80% of blood and rich in nutrients) and the hepatic artery (20-30% of blood and is rich in oxygen)[12]. Thus, trans-arterial embolisation (TAE) has been used to block blood flow to the liver preventing the cancer cells from receiving nutrients. TAE is also known as bland embolisation, in which the mechanism of action is disruption of tumour blood supply resulting in tumour ischemia/hypoxia using particles 100 – 300 μm in size without therapeutic agents[11]. Regarding that mechanism, arterial embolisation can be exploited to deliver therapeutic agents

such as chemotherapeutic drugs and radiation named trans-arterial chemoembolisation (TACE) and trans-arterial radioembolisation (TARE), respectively[11]. In TACE and TARE, therapeutic agents have been loaded into embolic particles, then block the hepatic artery, inhibit tumour blood supply, and eventually localized therapeutic agents lodged near or within the tumour[9,11]. The working mechanism of arterial embolisation with various modalities is shown in Figure 1.

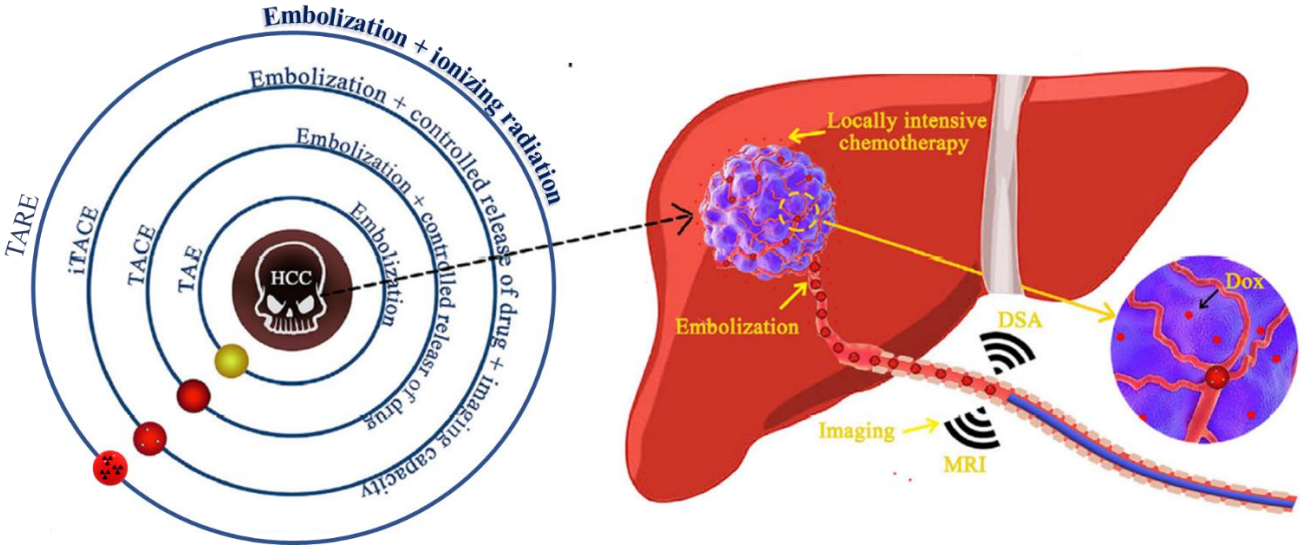


Figure 1. The working mechanism of arterial embolisation (Modified picture. Reproduced with permission from ref [9]. Copyright 2020, Elsevier).

It is essential to understand the characteristics of embolic agents used in arterial embolisation therapy (TAE, TACE, and TARE) to avoid damage to the hepatic microcirculation[13]. As arterial embolotherapy develops, so have biomaterials developed as embolic agents in many different forms, including particulate (micro and nano) or microparticles (non-spherical and spherical (microspheres)) with additional functionalities (drug carriers, active or therapeutic agents)[14,15,24,16–23]. The drawbacks associated with the use of micro- or nanoparticulate have included catheter clogging, incomplete occlusion of blood vessels, and unpredictable performance[25]. Due to their spherical morphology, microspheres have been developed to overcome the disadvantages of irregularly shaped particles as they result in smooth deliverability and are more predictable and potentially be explored for being loaded with radionuclides or therapeutic agents[9,13,25]. In TACE, microspheres are employed as embolic agents and chemotherapeutic drug delivery vehicles entrapped in small blood vessels (peritumoral vessels), interrupting the hepatic arterial flow to tumours where the drug can be released in a controlled manner directly to the target site[26]. The use of microspheres as drug delivery vehicles in TACE has improved the delivery of drugs over conventional chemotherapy regimens[27,28]. Furthermore, microspheres have also been widely used for internal radiation therapy, such as TARE, where the microspheres are doped with radionuclides and injected intravascularly or intra-arterially for radioembolisation. Here the microspheres block blood flow in hepatic capillaries' and deliver radioactive irradiation to the target site to shrink the size of the tumours[29]. The use of microspheres as an embolic agent for cancer embolisation therapy is illustrated in Figure 2 [30,31].

Solid microspheres have been exploited as an embolic agent in trans-arterial embolisation due to their superior delivery systems over irregular particles comprising high payload capacity, controlled and sustained drug release at the target site, and the ability to penetrate small capillary vessels[17]. These properties are beneficial in lodging localized therapeutic agents of TACE by reducing systemic side effects by decreasing the systemic absorption of drugs and maintaining a high local concentration of drugs at the target site[18]. Solid embolic microspheres, both non-radioactive and radioactive microspheres, have been produced commercially and widely applied for some cancer treatments. Further, porous microspheres could be explored as potential biomaterials for cancer treatment. Porous microspheres with interconnected porosity offer further advantages over solid microspheres, such as greater loading efficiency for optimizing treatments via biomolecules, drug delivery and release kinetics [32,33]. Several properties of porous microspheres, such as surface area, density, and degradation profiles, could also be tailored to the desired application by controlling pores' size, shape, and distribution within the microspheres[34]. Nevertheless, porous microspheres for cancer treatment will not be discussed here.

This review summarises the use of microspheres in cancer treatment development, especially in arterial embolotherapy. Application of microspheres (non-radioactive and radioactive) for various arterial embolotherapy (bland embolisation, chemoembolisation, and radioembolisation) will be discussed emphasising material characteristics and additional functionalities as embolic materials. The follow-on discussion provides an outlook on exploring radioactive microspheres for other cancer treatments.

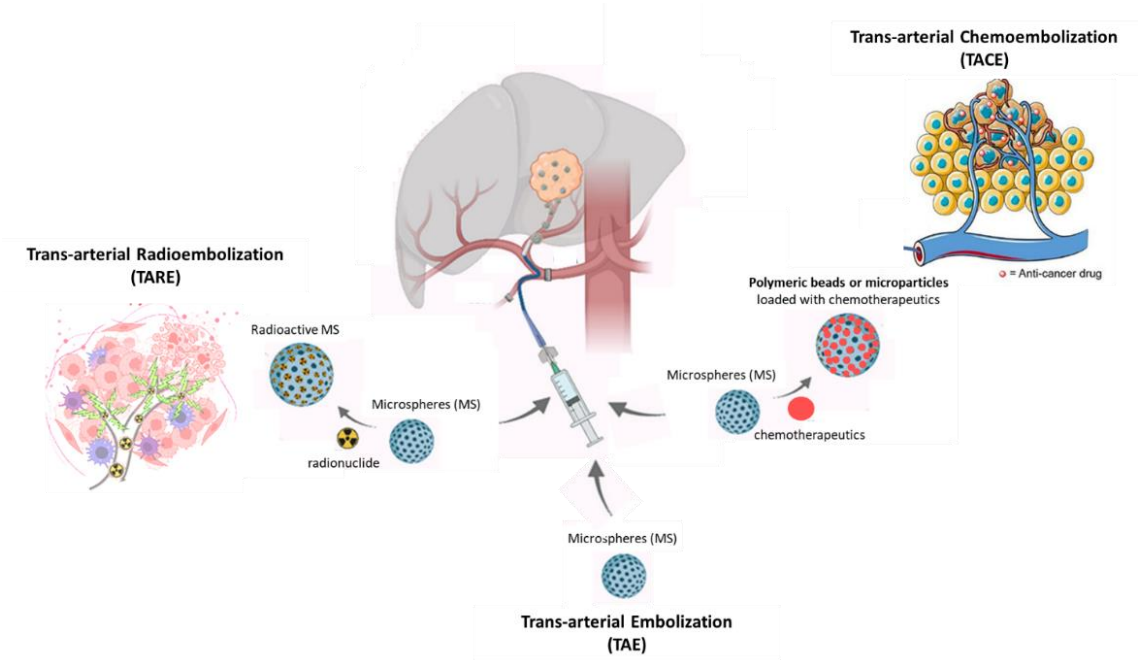


Figure 2. Schematic diagram of embolic microspheres for cancer embolization therapy (Modified picture. Reproduced with permission from ref [30,31]. Copyright 2023, ACS Publications and 2019, Frontiers Media SA published under a Creative Common Attribution Licence).

1. NON-RADIOACTIVE MICROSPHERES

For cancer treatment, non-radioactive microspheres were first used in 1997 for the treatment of hepatocellular carcinoma (HCC) in trans-arterial embolisation (TAE)[35]. TAE is also known as bland embolisation, referring to hepatic artery embolisation without a chemotherapeutic agent[8]. Later, non-radioactive microspheres were developed from 2006 as drug delivery systems combined with chemotherapeutic agents, clinically used in transcatheter arterial chemoembolisation (TACE)[8,27]. The development of embolic microspheres for the distinct functionality of embolisation depended on the material characteristics and properties including size, materials, and loading capacity[35].

As used for TAE and TACE, embolic microspheres were developed using a polymer as a basic material. The main advantage of using polymers is that their properties can meet the intended requirements, such as biocompatibility, lubricity, drug delivery, and the ability to biodegrade[36]. Polymeric microspheres also have the advantage of producing well-defined physical parameters with desired size range, resulting in predictable and more manageable injecting[7]. Further, polymer-based microspheres could be fabricated with various characteristics, including compressibility, elasticity, and rigidity[37]. In addition, their potential in controlled drug release or delivery systems is highly beneficial for cancer treatments[7]. In arterial embolotherapies, polymer-based microspheres acted as carrier matrices for drug delivery systems with controlled drug release either by polymer matrix degradation or drug leaching components[38].

Non-radioactive microspheres for TAE and TACE can be classified as non-biodegradable or biodegradable polymeric microspheres. These microspheres can be fabricated either from natural or synthetic polymers. Non-biodegradable microspheres were usually applied for permanent embolisation, while biodegradable microspheres were used for transient embolisation[35,39,40]. Non-biodegradable microspheres have also been produced commercially from synthetic polymers such as polyvinyl alcohol (PVA), poly (methyl acrylic acid), and polyethylene glycol (PEG). Natural polymers such as gelatin have also been used for reticulation with a copolymer of acrylamide-derived monomer forming the structure of tris acryl gelatin as non-biodegradable microspheres (see Table 1)[35,37].

On the other hand, biodegradable microspheres for TAE and TACE can be classified as natural polymers (starch, alginate, chitosan, cellulose) and synthetic polymers (PVA, PLLA, PLGA). Biodegradable microspheres offer biodegradability properties beneficial for the transient embolisation of tumour blood vessels with predictable degradation rates over several months[35]. Natural polymers have also been developed to fabricate embolic microspheres due to their excellent biocompatibility properties. However, natural polymers have poor mechanical properties and a tendency to undergo denaturation. As such, synthetic polymer microspheres are widely explored over natural ones to match the physiochemical properties with advantages such as ease of modification in fabrication, a large supply of raw materials, and the ability to control the degradation rates[41]. Table 1 summarises the various types of polymers used to produce microspheres for embolotherapy.

Polymeric materials gained interest not only for embolization but also for other cancer therapies and diagnosis. For example, study on dendritic polymer-based nanomedicine for cancer diagnosis, especially in early-stage tumours [42]. In addition, dendritic polymers have been widely applied mostly as drug or gene vehicles due to their advantageous properties, such as high biocompatibility, low viscosity,

excellent water-solubility, biodegradability, and stimuli-responsiveness. Their properties also benefit imaging applications comprising MR imaging, CT imaging, nuclear medical imaging, optical imaging, and multi-modality imaging [42]. Another study also reported that stimuli-responsive branched polymer prodrug could be applied for nanotheranostic systems in imaging-guided antitumour therapy [43]. One of the most studied branched polymer is poly[N-(2-hydroxypropyl)methacrylamide] (pHPMA), owing to high stability under physiological condition and excellent biocompatibility. Meanwhile, another type of branched polymer namely synthetic branched polymer-pyropheophorbide conjugate (BGSSP), has been studied for photodynamic therapy (PDT) and immunotherapy to enhance the therapeutic effect. Combining immunosuppressive and immunostimulatory effects enhanced the therapeutic effect due to their unique structure and a large molecular weight (MW) [44].

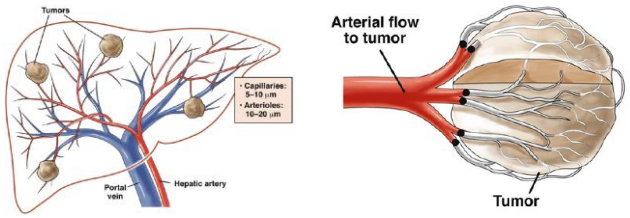
Besides the huge interest in using polymers as a carrier for cancer therapy and diagnosis, natural and synthetic polymers have some disadvantages. For example, natural polymers such as starch and collagen have low mechanical properties[41,45]. Despite that, collagen also tends to undergo denaturation and the possibility of disease transmission[46]. Meanwhile, other natural polymers, such as alginate has limitation in slow degradation properties. In addition, gelatine has a drawback in the possibility of immunogenic response, and chitosan has a variation of properties derived for each production batch[46,47]. As in the case of natural polymers, some disadvantages are also shown by synthetic polymers such as polyvinyl alcohol, which is not degradable, and poly(lactic-co-glycolic acid), which has a poor cell adhesion due to their hydrophobicity[48].

Table 1. Various types of polymers as the basic material of non-radioactive embolic microspheres

Material Classification	Material Type	Advantages	Disadvantages	Ref.
Natural	Starch	Biodegradable, ease of fabrication	Low mechanical properties	35,45
	Alginate	Biocompatible, Hydrophilic, Non-immunogenic, Ease of cell encapsulation, Affordable, ease of availability, and feasible synthesis method chosen for drug delivery	Slow degradation	41,49
	Gelatin	Controllable degradation rates, Ease of tailoring crosslink, Gentle gelling behavior, Ease of functionalization and modification	Possible immunogenic response	41
	Chitosan	Biocompatible, Antibacterial-like properties, Biodegradable	Variation of properties derived for each production batch	41,47
	Collagen	Desirable degradability, Non-immunogenic, Excellent biocompatibility	Poor mechanical properties, tendency to undergo denaturation, possibility of disease transmission	41
Synthetic	Polyvinyl alcohol	Good elasticity, compressibility, ability to load positive chemotherapeutic drugs, the ability for controlled release via ionic exchange	Non-degradable	48,50
	Poly (lactic-co-glycolic acid)	Possible to tune degradation and drug release kinetics	Poor cell adhesion due to hydrophobicity	41,51
	Polyethylene glycol	Biodegradable, ability to load a high number of drugs and sustained release	Hypersensitivity	52,53

1.1 Application in trans-arterial embolisation (TAE)

TAE has been applied clinically since the early 1980s as a therapeutic strategy to improve patients' survival rates[35]. This technique has been used to treat some types of liver cancer and neuroendocrine tumours resulting from debulking liver metastases[39]. Figure 3 demonstrates the mechanism of action of bland trans-arterial embolisation (TAE). Like the mechanism of HCC embolization therapy, Figure 4 shows the mechanism of uterine artery embolization (UFE). In this case, bilateral uterine artery characterization was applied due to the presence of bilateral uterine artery supply to a fibroid. In UFE, the uterine artery was catheterized with a microcatheter followed by injection of embolic material into the uterine artery to occlude the vessels of the fibroid [54].



(a) (b)

Figure 3. (a) illustrates the arterial blood supply to HCC and (b) the mechanism of action of bland embolisation in the disruption of tumour blood supply (Reproduced with permission from ref [11]. Copyright 2013, Elsevier).

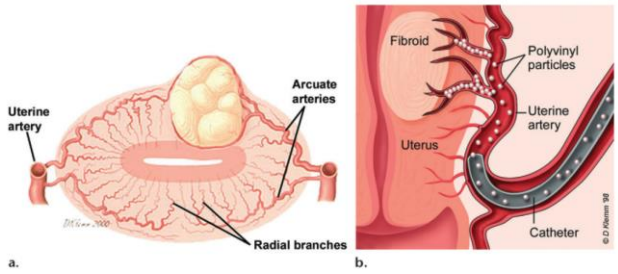


Figure 4. Illustration of (a) bilateral uterine artery supply to fibroid and (b) uterine fibroid embolization with polyvinyl particles instilled through a catheter (Reproduced with permission from ref [54]. Copyright 2012, RSNA).

Several commercial microspheres for bland embolisation are classified based on their function of embolisation type and material characteristics (size, homogeneity, and biodegradability). Mainly, non-biodegradable microspheres have been clinically applied for permanent embolisation, while biodegradable microspheres are used for transient embolisation. The first commercially available microspheres for TAE Embosphere® were authorised in 1997 and belonged to the non-biodegradable embolic microspheres class. The basic chemical structure of Embosphere® is tris acryl gelatine in the form of a hydrogel for consistent and durable occlusion[35,39,55]. Embosphere® has been clinically trialled on patients with neuroendocrine tumours, and the result showed that Embosphere® was a safe treatment that improved disabling endocrine symptoms[39]. In 2002, non-biodegradrable microspheres based on synthetic polymer (polyvinyl alcohol, PVA) were approved in Europe and the USA with the trade product Contour SE®. This product is a sponge-like microsphere with a highly microporous structure[35]. This product was developed as an embolisation agent to overcome issues with particulate PVA in irregular shapes resulting in aggregation that caused more variable and proximal occlusions and increased the risk of non-target embolisation by small particles as seen in Figure 5[36]. A clinical study for uterine fibroid embolisation using PVA microspheres (Contour SE®) showed comparable results to tris acryl gelatine (Embosphere®) as an embolic agent[56]. Nevertheless, PVA microspheres caused more distal embolisation because they could not recover their original size after catheter delivery[35].

As an improvement of previous commercial products, BeadBlock® and LC Bead® microspheres were fabricated and composed of acrylamide polyvinyl alcohol hydrogel[35,57]. Clinical studies for uterine artery embolisation showed that hydrogel PVA microspheres performed similarly to Embosphere® rather than non-hydrogel PVA (Contour SE®)[57]. A randomised trial of hepatic artery embolisation using BeadBlock® and LC Bead® showed no significant difference in the overall incidence of post-embolisation syndrome. This study reported similar results of the use of BeadBlock® and LC Bead® for the therapeutic effect of arterial embolisation with similar safety profiles, progression rates, and survival[58]. Other non-biodegradable microspheres commercially used were Embozene® and HydroPearl®. Embozene® is a poly (methyl acrylic acid) microsphere authorised in 2008 with a higher in vivo deformation resulting in a more distal occlusion within the vascular network[25,35]. Meanwhile, HydroPearl® was manufactured with a copolymer of polyethylene glycol (PEG) and diacrylamide[35,59].

These commercial microspheres (tris acryl-gelatin or PVA) lacked radiopacity resulting in invisibility for the interventional radiologist to monitor the number of materials and direction after being injected under standard clinical conditions (x-ray)[7]. Therefore, imageable microspheres were developed by mixing with a liquid contrast agent, resulting in radiopaque embolic microspheres[7,35]. EmboGold® was the first imageable microsphere impregnated with 2% elementary gold. This product showed improved visualization during handling and administration but did not offer real-time visualization within the body[35]. The development of radiopaque embolic microspheres was tailored further using an iodine-based liquid contrast agent, creating a network of blood vessels to be embolized or tantalum powder to impart radiopacity[60]. The two authorised radiopaque microspheres for TAE were X-SpheresTM, and LC Bead LUMITM. X-SpheresTM was a non-biodegradable microsphere composed of 3D macromolecular poly(methacrylate) network covalently bound to iodine-derivative. Meanwhile, LC Bead LUMITM was the counterpart of LC Bead® with radiopaque moieties (iodine) that was covalently bound to the PVA hydrogel[35].

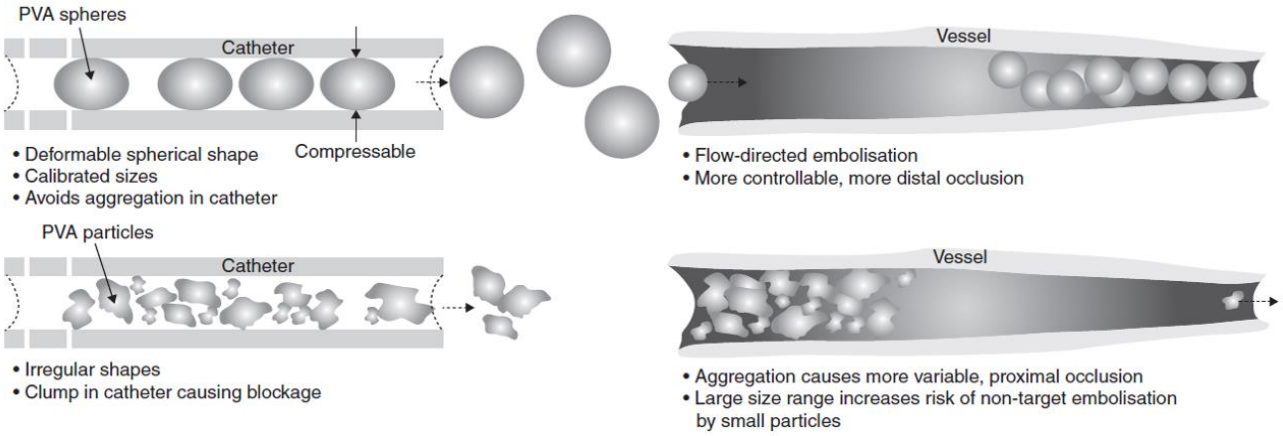


Figure 5. Illustration of PVA irregular particles and microspheres as an embolic agent concerning catheter delivery and level of vascular occlusion (Reproduced with permission from ref [36]. Copyright 2013, Elsevier).

Along with embolic microsphere development, biodegradable microspheres for transient bland embolisation were marketed with predictable degradation rates. Biodegradable microspheres were also developed for transient embolisation and to enhance their biocompatibility. In addition, the degradation rate of microspheres could be tailored following the TAE procedures that produced transient embolisation with the desired duration of tissue ischemia[35]. Several biodegradable microspheres were developed and commercially used, including starch microspheres, gelatine microspheres, and collagen-coated PLGA[61]. Spherex® and EmboCept® were commercial products composed of biodegradable starch microspheres representing short-term transient embolisation[35]. Pre-clinical studies using a swine model reported the success of EmboCept® for temporary arterial embolisation of liver parenchyma for 26 – 39 minutes[62]. In addition, biodegradable microspheres such as Occlusin-500® and Gel-Bead® were commercially tailored for long-term temporary embolisation[35]. OcclusinTM 500 is a biodegradable embolotherapeutic agent consisting of collagen-coated poly(lactic-co-glycolic acid) or collagen-coated PLGA microspheres for solid hypervascular tumours, including uterine fibroids[63]. Gel-Bead® was tailored from biodegradable gelatine-producing biodegradable microspheres with a specific degradation time of 4 – 12 weeks[35]. Several commercial products for bland embolisation are presented in Table 2.

Table 2. Commercial non-radioactive microspheres for bland embolisation or trans-arterial embolisation (TAE)

Product	Company	Materials	Size (μm)	Category	Type of Embolisation	Use	Ref.
Embosphere®	Merit Medical, South Jordan, UT, USA BioSphere, Rockland, Massachusetts, USA	Trisacryl with gelatin	40 – 120 50-100, 40–120, 100–300, 300–500, 500–700, 700–900, 900–1,200	Non-biodegradable	Permanent	Liver embolisation with neuroendocrine tumours, Uterine Artery Embolisation for Symptomatic Fibroids	35,39,55,64
Countour SE ®	Boston Scientific Corporation, BTG, London, UK	Polyvinyl alcohol (PVA)	70 – 150 100 – 300 300 – 500 500 – 700 700 – 900 900 - 1200	Non-biodegradable	Permanent	Uterine Artery Embolisation	35,56,64
Bead Block ®	Boston Scientific Corporation, BTG, London, UK	Biocompatible polyvinyl alcohol hydrogel	100–300, 300–500, 500–700, 700–900, 900–1,200	Non-biodegradable	Permanent	Embolisation of hypervascular tumours, including uterine fibroids and arteriovenous malformations (AVMs)	35,57
DC bead or LC bead	Boston Scientific Corporation, BTG, London, UK	Polyvinyl alcohol hydrogel modified with sulfonate groups	70–150 100–300 300–500	Non-biodegradable	Permanent	Embolisation of hypervascular tumours and arteriovenous malformations (AVMs)	35,57
Oncozene or Embozene	CeloNova BioSciences, Inc., San Antonio, TX, USA	Hydrogel core made of sodium poly (methacrylate) and outer biocompatible shell of poly (bis[trifluoroethoxy] phosphazene)	Oncozene (40 ± 10, 75 ± 15, 100 ± 25) Embozene (40, 75, 100, 250, 400, 500, 700, 900)	Non-biodegradable	Permanent	Kidney embolisation	25,35,64
HydroPearl	Terumo European Interventional	Hydrogel network of poly (ethylene	600 ± 75 800 1100	Non-biodegradable	Permanent	Prostate artery embolisation, embolisation of the shoulder,	59,64

Product	Company	Materials	Size (µm)	Category	Type of Embolisation	Use	Ref.
	Systems, Leuven, Belgium	glycol) and 3-sulfopropyl acrylate				uterine artery embolisation	
EmboGold Microspheres	Merit Medical, South Jordan, UT, USA	Trisacryl with gelatin	40–120, 100–300, 300–500, 500–700, 700–900, 900–1,200	Non-biodegradable	Permanent (With imageable properties)	Embolisation of hypervascular tumours and AVMs	[35]
X-Spheres	Interface Biomaterials	poly(methacrylate) network that covalently bound iodine-derivative	50	Non-biodegradable	Permanent (With imageable properties)	n.d.	[35]
LC Bead LUMI	Boston Scientific Corporation, BTG, London, UK	Biocompatible polyvinyl alcohol hydrogel beads containing a covalently bound radiopaque moiety	40–90 70–150	Non-biodegradable	Permanent (With imageable properties)	Embolisation of hypervascular tumours and arteriovenous malformations (AVMs)	[35]
Spherex®	Magle Life Sciences, Lund, Sweden	starch	100–300 300–500 500–700 700–1000	Biodegradable	Transient	n.d.	[35,65]
EmboCept®	PharmaCept, Berlin, Germany	starch	20 - 200	Biodegradable	Transient	arterial embolisation of liver parenchyma	[62,65]
Occlusion™ 500	IMBiotechnologies Ltd., Edmonton, AB	poly(lacticco-glycolic acid) (PLGA) coated with type I bovine fibrillar collagen	150 - 212	Biodegradable	Transient	Uterine artery embolisation	[63]
Gel-Bead	Teleflex	gelatine	100 – 300 300 – 500 500 – 700 700 - 1000	Biodegradable	Transient	Uterine fibroid embolisation	[64]

1.2 Application in trans-arterial chemoembolisation (TACE)

Trans-arterial chemoembolisation (TACE) is an intraarterial embolisation procedure involving the emulsification of a chemotherapeutic agent mixed with radiopaque ethiodized oil or embolic material that involves periodic injection[13,66]. TACE was developed to evolve TAE and alternative therapy to decrease systemic exposure to conventional chemotherapy[13,35]. There are two beneficial methods in TACE; (1) interruption of blood supply and postponement tumour growth by arterial embolisation and (2) administration of chemotherapy in delivering a high dose of cytotoxic drugs in the tumour area[8]. Representation of TACE is shown in Figure 6, where anti-cancer drugs, embolisation particles, drug-eluting beads, or drug-eluting microspheres can be delivered to the cancerous mass using catheters. The catheters were introduced through the skin into the femoral artery[36]. In addition, TACE has been recognised since the early 1970s as a one-step procedure for performing vessel occlusion and controlling local chemotherapeutic drug delivery[36].

In the TACE procedure, chemotherapeutic agents play the same role as chemotherapy with various action target mechanisms. Figure 7 shows the mechanism of action of the main chemotherapy agents, such as doxorubicin, cisplatin, carboplatin, 5-FU, gemcitabine, paclitaxel, docetaxel, trabectedin in cell cycle arrest and cell death[67]. Furthermore, chemotherapeutic agents target cells with a high basal level of proliferation and regeneration[68]. Figure 8 illustrates various mechanisms of action of another chemotherapeutic drug with different target, such as oxaliplatin targeting the nucleus and mitochondria, and vincristine targets microtubules and mitochondria[68].

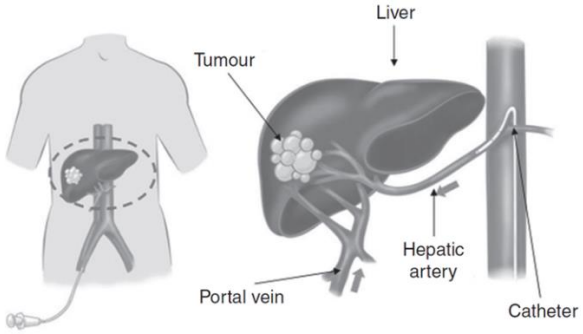


Figure 6. Illustration of TACE principles (Reproduced with permission from ref [36]. Copyright 2013, Elsevier).

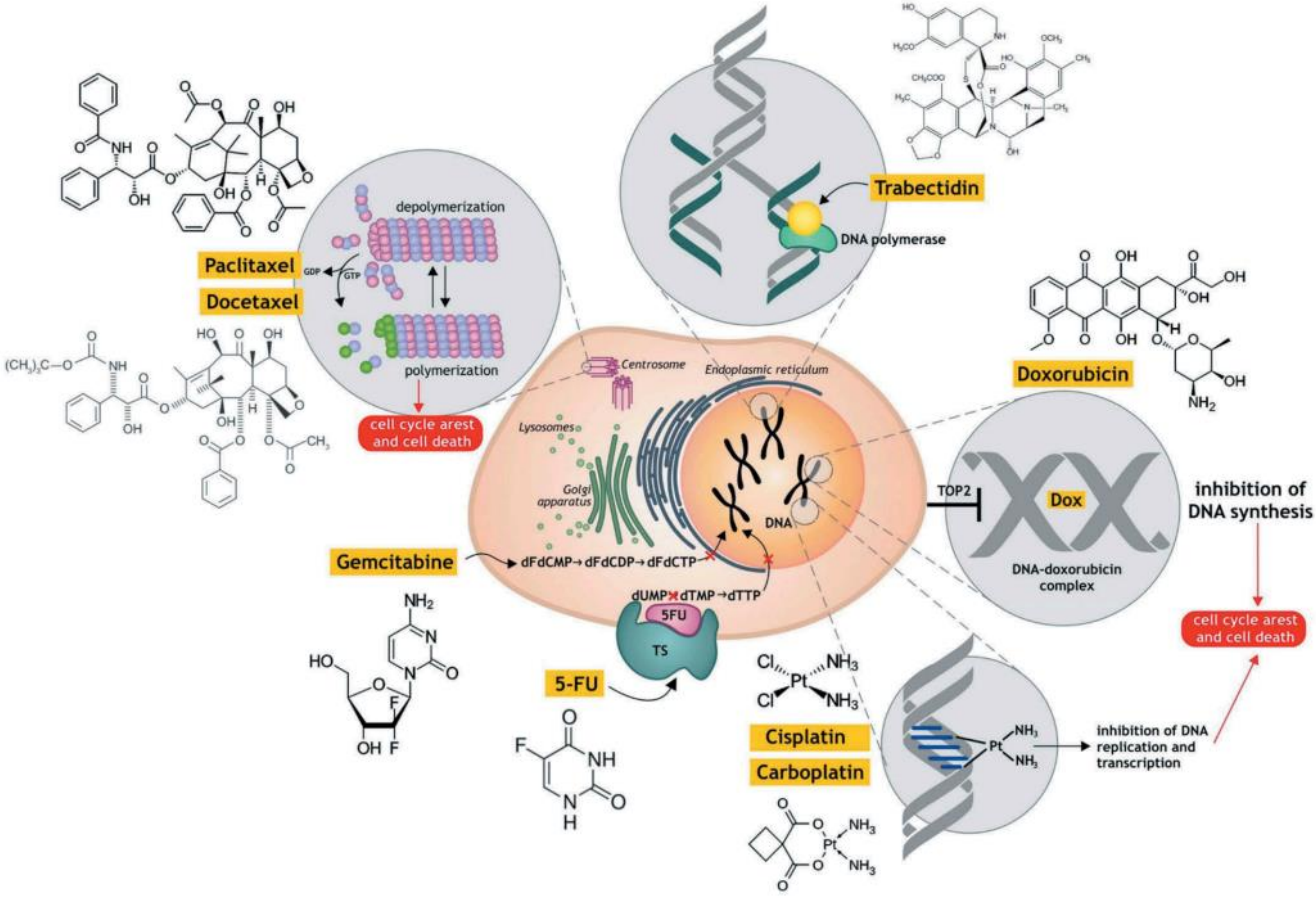


Figure 7. The mechanism of action of the main chemotherapy agents (Reproduced with permission from ref [67]. Copyright 2019, Taylor&Francis Group, LLC).

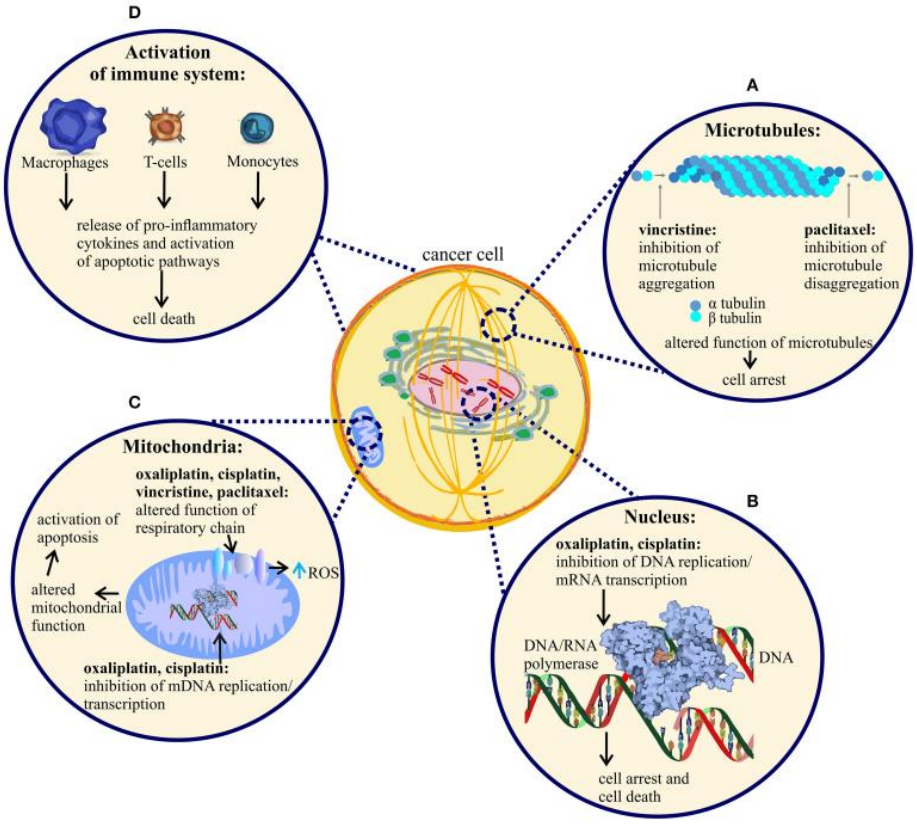


Figure 8. Mechanism of action of several chemotherapeutic agents in (a) preventing microtubules aggregation or disaggregation, (b) binding to nuclear DNA disrupting DNA replication and RNA transcription, (c) disrupting respiratory chain function of mitochondria, and (d) activating immune cells in tumour cell degradation (Reproduced with permission from ref [68]. Copyright 2017, Frontiers Media SA published under a Creative Common Attribution Licence).

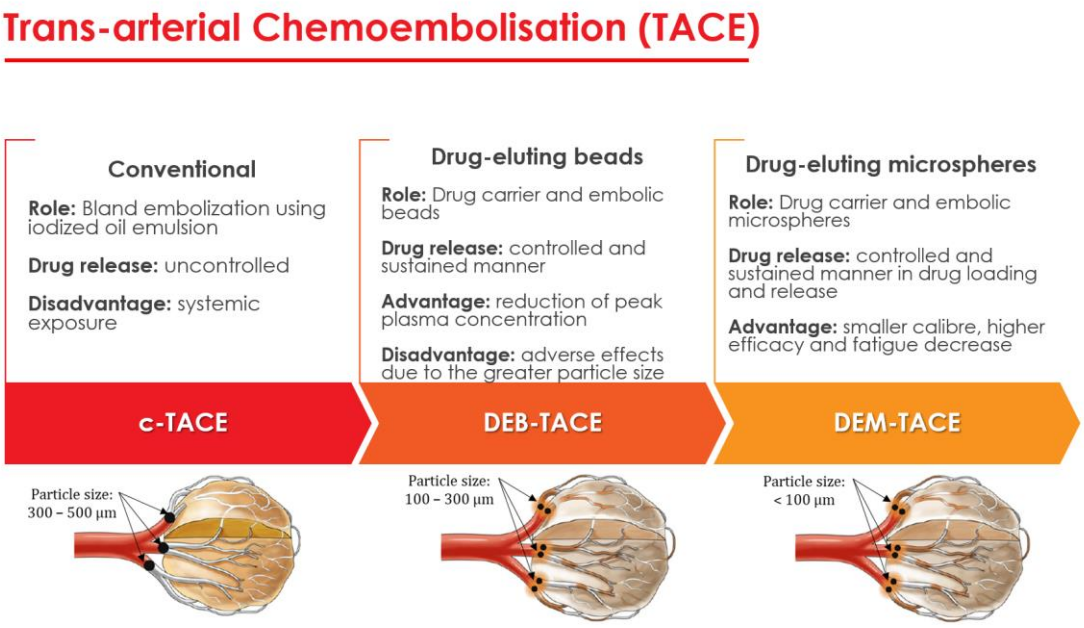


Figure 9. Modalities of the TACE procedure (picture illustration is reproduced with permission from ref [11]. Copyright 2013, Elsevier).

TACE is the standard curative treatment and is a well-established procedure for patients with unresectable HCC, according to the Barcelona Clinic Liver Cancer (BCLC) algorithm[24,69,70]. In addition, TACE has also been used for metastatic neuroendocrine liver metastases as a palliative treatment[71]. This procedure offers a high dose of chemotherapeutic agents to the tumour tissue while preserving the surrounding normal hepatic parenchyma[71]. Currently,

there are three modalities of the TACE procedure: conventional TACE (cTACE), drug-eluting bead TACE (DEB-TACE), and drug-eluting microspheres TACE (DEM-TACE), as illustrated in Figure 9.

1.2.1 Conventional TACE (c-TACE). cTACE is not recommended in the early stages of HCC but is recommended for HCC patients with no vascular invasion or extrahepatic spread as first-line therapy[71]. In conventional TACE (cTACE), an emulsion composed of iodized oil (Lipidol®) and the chemotherapeutic agent (doxorubicin or cisplatin) is delivered by infusion into arteries feeding the tumour, followed by bland embolisation (absorbable gelatin, unloaded beads)[28,72]. Lipiodol plays an important role in cTACE as a drug-carrying, tumour-seeking, and embolizing agent. Meanwhile, the dose of the chemotherapeutic agent (doxorubicin) emulsified in lipiodol is 30 – 75 mg/m2 and, at maximum, 150 mg in 5 – 20 mL of lipiodol[72].

Generally, after the injection of Lipiodol® into the hepatic artery, an embolic agent (100 – 500 μm bland occlusive particles) is applied immediately for some purposes such as (1) obtaining an embolic effect by assisting lipiodol to be sustained, (2) preventing washout of chemotherapeutic drug, and (3) causing ischemic necrosis[11,71,72]. Several embolic agents used in cTACE are gelfoam, polyvinyl alcohol (PVA) particles, and trys-acryl gelatin microspheres[72]. Gelfoam® is a gelatin sponge that facilitates the slow release of doxorubicin from Lipiodol®, increasing the drug concentration inside the tumour[71]. Other embolic agents such as polyvinyl alcohol (PVA) particles and trys-acryl gelatin microspheres are similar products used in TAE, explained in the previous section. Several commercial embolic agents used in cTACE are Contour SE®, Bead Block®, and DC/LC Bead®[71].

This procedure results in better drug delivery to tumour cells, and the embolic agent induces hypoxia and cell death in hypervascular tumours[66]. Unfortunately, this procedure also has several limitations, including the relatively high incidence of systemic toxicity, one of which is caused by the potential for embolic damage to the liver. Also, a single lesion requires high recurrence after cTACE and multiple TACE sessions[66,69]. Those limitations arise from several drawbacks, including (1) motility of Lipiodol® in reducing the concentrations of chemotherapeutic agents, (2) uncontrolled drug release, and (3) inhomogeneity in the technique and treatment schedules[72].

1.2.2 Drug-eluting beads TACE (DEB-TACE). Drug-eluting beads (DEB-TACE) have been an advanced breakthrough technology in TACE with controlled release and sustained concentration of chemotherapeutic delivery[28,66,69]. DEB-TACE has been considered a more standardised procedure than cTACE. In this procedure, various drugs are loaded into beads through a mechanism of ion exchange. Drug-loaded beads are injected via segmental or subsegmental catheterization of the hepatic artery branch(es), feeding the tumour and delivering the chemo embolic agent[24,27,72]. Beads in TACE are mainly used for local drug delivery by intra-arterial injection resulting in tumour necrosis and shrinkage[28]. The beads remain trapped in the tumour vasculature and deliver chemotherapy locally and at a sustained rate, with a decreased risk of hepatic and systemic doses[66].

DC/LC Bead® was the first commercial product for DEB-TACE in the early 2000s. DC/LC Bead is a non-biodegradable embolic agent manufactured from PVA hydrogel modified with sulfonate groups loaded with calibrated chemotherapeutic drugs[71,72]. Several positively charged drugs, such as doxorubicin, epirubicin, or irinotecan, could interact with PVA hydrogel by Coulomb charge interactions due to the presence of the anionic sulphonate group[71]. Thus, strong interactions are raised between the hydrogel sulfonate or carboxyl counter ions and anionic drug moieties during the ionic exchange process[11,71]. The drug loading mechanism via ion exchange is upon submersion of the microspheres in a drug solution. The bead size ranges from 100 – 900 μm, with drug loading varying from 5 to 45 mg/mL hydrated beads[71].

Pre-clinical studies of drug-eluting beads (DC/LC Bead) in animal models (pig and rabbit) showed the sustained release of doxorubicin as a pharmacologically active agent targeting cancerous tissues over several weeks via controlled distribution of beads in cancerous and surrounding tissue vasculature[13,73]. Additionally, the size of the embolic beads influenced product performance, such as tumour necrosis. The in vivo study reported that doxorubicin-eluting beads of 100 – 300 μm in size induced more necrosis than 700 – 900 μm beads[73]. Moreover, a clinical study in HCC patients under chemoembolisation with doxorubicin-eluting beads (LC Bead®) showed sustained delivery of a drug released within the first few hours which was maintained for at least one month[74].

Other non-biodegradable beads loaded with chemotherapeutic drugs via an ion exchange mechanism are HepaSphere®[28], which are hydrophilic and expandable microspheres with conformable and swelling properties upon exposure to aqueous media[71]. The network structure of HepaSphere® is sodium acrylate and vinyl alcohol copolymer with a negatively charged carboxyl group that is calibrated in the dry state[35,71]. In contrast with DC Bead, the drug loading mechanism in HepaSphere is swelling, so the dry microspheres will quickly absorb fluid-containing drugs and swells up within several minutes[35,71]. The bead size of the HepaSphere ranges from 30 – 200 μm, with the maximum loadable drug referred to as the dry amount of microspheres[35]. A pre-clinical study using 30 – 60 μm HepaSphereTM microspheres resulted in more distal occlusion and denser embolized territory than 50 – 100 μm[27]. In addition, a clinical study on intermediate-stage HCC patients using HepaSphere was successful, with no deaths or a shallow complication rates at 30 days[27,75].

In contrast with TAE, the absence of biodegradation of embolic microbeads or microspheres was intended for carrying and modulating the delivery of chemotherapeutic agents in biostable systems[36]. Interestingly, the network structure of the beads influences the drug uptake through interaction with the ionic group. For example, HepaSphere® interacts poorly with irinotecan compared to DC Bead, resulting in rapid and incomplete drug release. Likewise, the drug's loading also influences the embolic beads' attributes, mechanical properties, and clinical outcomes[35,36]. For example, doxorubicin loading into HepaSphere® beads could decrease the average diameter due to

the displacement of water content with drugs from hydrogel systems[36].

On the other hand, Embozene Tandem® stems from Embozene® are another commercial non-biodegradable bead for permanent embolisation. The material structure of Embozene Tandem® is polymethacrylate hydrogel microspheres coated with Polyzene-F with smaller particle size than a bland embolic agent (Embozene®). Similar to DC Bead and HepaSphere, Embozene Tandem® was authorised for DEB-TACE in 2010 for loading doxorubicin and irinotecan[35]. Embozene Tandem® also has a similar mechanism in drug loading with LC Bead through ionic interaction between the negatively charged polymer backbone and positively charged drugs[28,35,76]. Compared to DC bead, Embozene Tandem® showed a more prolonged release of irinotecan and a sustained release of doxorubicin[76].

For imaging purposes, radiopaque beads for chemotherapeutic drug delivery were also produced. DC Bead LUMITM is an imageable non-biodegradable embolic bead developed from DC Bead chemistry with a covalently bonded iodine offered long-term radiopacity. Doxorubicin-loaded radiopaque beads (DC Bead LUMITM) could be visualised using fluoroscopy, computed tomography (CT) or magnetic resonance imaging (MRI)[28]. Doxorubicin-loaded DC Bead LUMITM was visualized in vivo in VX2-tumour-bearing rabbits under fluoroscopy. The result showed the ability to track the beads, enabling the physician to target the area of treatment precisely[77].

Unfortunately, other studies reported that DEB-TACE has no significant difference compared to cTACE in treatments related to severe adverse effects that might be caused by the greater particle size[24]. In addition, current embolic beads have a main drawback related to time-consuming drug loading onto microbeads before being used in a clinical setting. Typically, drug loading onto microbeads was performed through an ion exchange reaction by immersing the beads in the drug solution for more than 30 minutes. Another difficulty encountered was controlling the drug release from microbeads as it depended on the exchange of drugs with endogenous ions in the blood vessels[78]. Table 3 shows several commercial products for DEB-TACE.

Table 3. Commercial non-radioactive microspheres for drug-eluting beads trans-arterial embolisation (DEB-TACE)

Product	Company	Materials	Drugs loaded	Category	Size (μm)	Use	Ref.
DC bead or LC bead	Boston Scientific Corporation, BTG, London, UK	Polyvinyl alcohol hydrogel modified with sulfonate groups	Doxorubicin, irinotecan	Non-biodegradable	70–150 100–300 300–500 700 - 900	Embolisation of malignant hypervascular tumours	13,35,71,72
HepaSphere	Merit Medical, South Jordan, UT, USA	Poly (vinyl alcohol-co-sodium acrylate) hydrogel	Doxorubicin, irinotecan, epirubicin	Non-biodegradable	Dry state (50 – 200) Hydrated state (120 – 800)	Embolisation of hypervascular tumours, including hepatoma and peripheral AVMs	28,35,36,71
Embozene TANDEM	CeloNova BioSciences, Inc., San Antonio, TX, USA	Hydrogel core made of sodium poly (methacrylate) and outer biocompatible shell of poly (bis[trifluoroethoxy] phosphazene)	Doxorubicin, iritonecan, idarubicin, epirubicin	Non-biodegradable	Embozene (40, 75, 100, 250, 400, 500, 700, 900)	Embolisation of hypervascular tumours	28,35,76,79
DC Bead LUMI	Boston Scientific Corporation, BTG, London, UK	Biocompatible polyvinyl alcohol hydrogel beads containing a covalently bound radiopaque moiety	doxorubicin	Non-biodegradable	40–90 70–150	Embolisation of hypervascular tumours and arteriovenous malformations (AVMs)	28,35,77
DC Bead M1	Boston Scientific Corporation, BTG, London, UK	Biocompatible, sulphonatemodified, N-Fil hydrogel	doxorubicin	Non-biodegradable	70–150	Embolisation of hypervascular tumours	79

1.2.3 Drug-eluting microspheres TACE (DEM-TACE).

Along with the development of TACE, a drug-eluting platform utilizing microspheres has been developed called drug-eluting microspheres TACE (DEM-TACE). The use of highly spherical microspheres provides abilities to control drug loading and drug release rates[80]. In addition, the smaller calibre microspheres (< 100 μm) provided better outcomes without influencing patient safety[27]. These drug-eluting microspheres offered advantages in highly spherical and smaller sizes compared to microbeads, resulting in higher treatment efficacy and decreased fatigue[24]. Thus, drug-eluting microspheres could increase the distal penetration and embolisation of target tissue, decreasing post-embolisation syndromes[24]. Indeed, the microsphere size has been considered a critical factor in drug release rate and significantly affected product performance and safety. When microspheres were injected intravenously, larger particles could initially produce capillary obstruction and influence the syringability of the product[81].

Microspheres for DEM-TACE can also be prepared from non-biodegradable or biodegradable polymeric materials. LifePearl (Terumo European Interventional Systems, Leuven, Belgium) is a commercial non-biodegradable microsphere with negatively charged that can upload various chemotherapeutic drugs via an ion exchange mechanism[27,28]. Along a similar loading mechanism with previous drug-eluting beads (DC Bead®, HepaSphere®, and Embozone Tandem®), LifePearl® could be loaded with doxorubicin and irinotecan[35,82]. Nevertheless, LifePearl® is the only non-biodegradable embolic microsphere that could be loaded with another chemotherapeutic drugs such as idarubicin and epirubicin[35]. LifePearl® is a stem from HydroPearl® composed of a hydrogel network of PEG and 3-sulfopropyl acrylate[35,82]. LifePearlTM offers longer suspension than DC Bead and HepaSphere when loaded with doxorubicin. The longer time in suspension was also seen when LifePearlTM was loaded with irinotecan compared to DC Bead and Tandem[82]. Longer time in suspension brings an advantage in smoother embolisation procedure without any interruption to resuspend the microspheres. A clinical study of LifePearl for DEM-TACE patients with HCC showed safety and efficacy for the HCC patients, shown by the overall survival with good tolerance, acceptable toxicity, and high tumour response into satisfactory disease control[83].

Furthermore, studies on degradable embolic microspheres (i.e. degradable starch microspheres) have been conducted to increase product efficacy for DEM-TACE and enable therapeutic benefits with repeated cycles and better tolerance[84]. Degradable embolic microspheres overcome the limitation of non-degradable microspheres, leading to permanent vascular occlusion, thus limiting repeated treatments. Degradable starch microspheres were then developed to impart several benefits such as near-term reproducibility, higher accumulation rates of co-applied drugs, reduced toxicity, less postembolisation syndrome, and possibilities of combination drugs and other treatment techniques[85]. Degradable starch microspheres (DSM) are commercial embolic microspheres with an active ingredient called Amilomer derived from partly hydrolysed starch, then cross-linked and substituted with glycerol ether groups[84]. The DSM sphere was approximately 50 μm with the short-term temporary vessel occlusion after embolisation (35-50 minutes)[70]. The study reported that DSM spheres reduced post-embolisation syndrome with less pain and ischemic damage to the tumour-bearing organ[84].

The development of biodegradable embolic microspheres is ongoing with various polymeric materials such as alginate, chitosan, albumin, gelatin, PEG methacrylate, polylactic acid (PLA), polylactic-co-glycolic acid (PLGA) with various drugs having been explored[28,81]. A study reported on the effect of membrane emulsification techniques on preparing uniform-sized polymeric microspheres (PLGA containing Adriamycin and daunomycin anthracycline anti-cancer drugs). The results showed smooth uniform spherical spheres were produced. Other research evaluated the efficacy and toxicity of intratumoral mitoxantrone-loaded albumin microspheres (2 – 10 μm) in a murine breast cancer model[86]. Albumin microspheres demonstrated localized and sustained release of chemotherapeutic drugs, thus increasing the intratumoral dose and antitumour efficacy.

Moreover, the results showed significantly improved survival and decreased systemic toxicity[86]. Albumin microspheres were also studied to encapsulate another anti-cancer drug named Gemzar (Gemcitabine HCl) for renal cancer therapeutics. An in vitro study using renal cancer cells (RCC, 786-O cells) showed that Gemzar encapsulated in Bovine Serum Albumin (BSA) microspheres was active and able to kill RCC cells at 10 ng/ml Gemzar. The anti-cancer activity was observed by the drug's rapid release at the target site due to availability of protease in the target environment[14].

Figure 10 shows the SEM images of commercial microspheres (Callispheres, CSM) loaded with oxaliplatin with various particle sizes[87]. Meanwhile, Table 4 shows several non-radioactive microspheres commercially used for DEM-TACE.

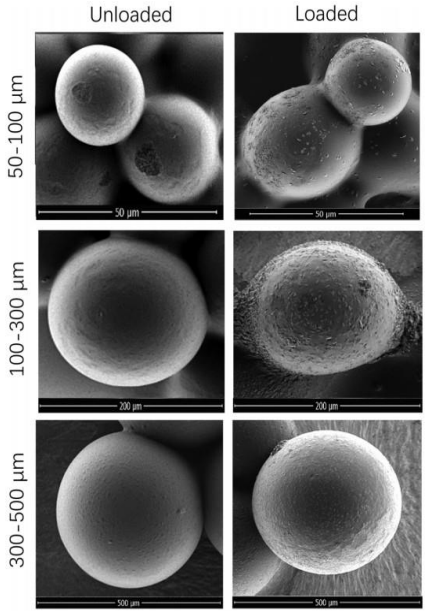


Figure 10. SEM morphology of CalliSpheres microspheres (CSM) with 3 sizes (50-150 mm, 100-300 mm, and 300-500 mm) before and after 20 mg oxaliplatin loading (Reproduced with permission from ref [87]. Copyright 2019, SAGE Publications published under a Creative Common CC-BY-NC Licence).

Table 4. Various types of non-radioactive microspheres for drug-eluting microspheres trans-arterial embolisation (DEM-TACE)

Product	Company	Materials	Drugs loaded	Category	Size (μm)	Use	Ref.
LifePearl	Terumo European Interventional Systems, Leuven, Belgium	Hydrogel network of poly (ethylene glycol) and 3-sulfopropyl acrylate	Doxorubicin, iritonecan, idarubicin, epirubicin	Non-biodegradable	100 ± 25 200 ± 50 400 ± 50	Embolisation of hypervascular tumours	27,28,35,82,83
CalliSpheres® microspheres (CSM)	China	polyvinyl alcohol hydrogel microspheres	doxorubicin, pirarubicin, oxaliplatin, and arsenic trioxide	Non-biodegradable	100 – 300 300 – 500	Embolisation of hepatocellular carcinoma	69,87,88
BioPearl	Terumo European Interventional Systems, Leuven, Belgium	n.d	Doxorubicin, idarubicin, epirubicin	Biodegradable	n.d	Embolisation of hypervascular tumours	35,89
DSM-TACE EMBOCEPTc	PharmaCept GmbH, Berlin, Germany	Active ingredient – Amilomer DSM 35/50. Partly hydrolyzed starch, crosslinked and substituted with glycerol ether groups	doxorubicin	Biodegradable	50	Embolisation of hypervascular tumours	70,84,85,90
PEGMA	Resmic, Occlugel, Jouy-en-Josas, France	PEG methacrylate	DOX, IRI	Biodegradable	n.d	Uterine fibroids	28
Bovine Serum Albumin (BSA) microspheres		Bovine serum albumin	Irinotecan (IRI)	Biodegradable	2 - 10	n.d	86
Gelatin microspheres		Gelatin	Cisplastin	Biodegradable	n.d	n.d	28
PLA		Poly(D,L-lactic acid)	Sorafenib, Cisplatin, Sorafenib+Cisplatin	Biodegradable	n.d	n.d	28
PLGA		Poly(lactic-co-glycolic acid)	Sorafenib, DOX	Biodegradable	n.d	n.d	28

2. RADIOACTIVE MICROSPHERES

Radioactive microspheres have been extensively exploited for radiotherapy by doping with varying radionuclides or isotopes instead of drugs[91]. Radiotherapy involving ionising radiation offers advantages, such as non-invasive and local treatment, direct induction of cancer cell apoptosis, and a wide range of applicable tumours[5,16]. In radiotherapy, radionuclide microspheres have been widely used in brachytherapy and internal radioactive therapy. Radioactive microspheres have also been widely applied for trans-arterial radioembolisation (TARE) therapy of tumours and cancers. In this therapy, radioactive microspheres were injected into hepatic arteries following administration, which then get trapped in the web of small blood vessels and deliver a high concentration of radioactivity to the target area without causing much damage to the surrounding tissues[91]. Like the TACE procedure in chemotherapy, this technique has been an alternative treatment for hepatic cancer patients. This procedure is also deemed palliative, especially for patients who have failed other therapies or need tumour downstaging treatment[92]. Both radionuclides (acting as radioactive embolism agents) and microspheres (acting as an embolic platform) have suitable physicochemical characteristics for therapeutic purposes.

2.1 Materials used to produce Radioactive Microspheres

Trans-arterial radioembolisation (TARE) has a different embolisation mechanism from TAE and TACE. In TARE, microspheres are the key factor of arterial embolisation where the therapeutic effects are dependent upon the radiation carried by the microspheres and not by any ischemic effect[93]. The different features of the microspheres' materials will have different regulatory handling, physical properties, and radioactivity levels[94]. Indeed, physical differences in radioembolic microspheres will impact clinical performance[35]. Several basic materials of microspheres are loaded with radioisotopes authorised for treating HCC comprising glass and polymer[93–95]. In addition, radioactive microspheres are divided into non-biodegradable and biodegradable microspheres, either for permanent or transient embolisation, like TACE.

Non-biodegradable microspheres loaded with radioisotope are used for permanent TARE. There are two commercial radioembolic microspheres authorised and approved for permanent TARE (see Table 5). The first authorized radioembolic microsphere since 1999 was TheraSphere®, and the second is SIR-Spheres® since 2002. In 2005, TheraSphere® was licensed as a Class III medical device for the treatment of hepatic neoplasia[95]. TheraSphere® and SIR-Sphere® are two commercial radioactive microspheres loaded with 90Y that are FDA-approved[35]. TheraSphere® is a glass-based microsphere filled with 90Y (produced by Boston Scientific). The glass structure of TheraSphere® is a non-biodegradable oxide-aluminosilicate glass matrix. Each glass sphere has a range diameter of 20 – 30 μm containing approximately 2.500 Bq[95,96]. Due to the higher activity for each sphere, TheraSphere® has minimal embolic power to prevent vascular statis and reflux during administration[93]. TheraSphere® has also been approved as a neoadjuvant to surgery to treat unresectable hepatocellular carcinoma[94].

On the other hand, SIR-Spheres® have significant embolic power with a higher number of microspheres injected. This high number tends to achieve adequate and homogeneous lesion coverage[93]. SIR-Spheres® are the other commercial product for HCC cancer treatment with Aminex A-5 resin-based ^{90}Y microspheres with diameter of 20 -60 μm containing approximately 50 Bq[95]. SIR-Spheres® have also been used in treating hepatic metastatic colorectal cancer with adjuvant intra-arterial floxuridine[94].

Due to the difference both in physical properties and activity per sphere between glass and resin, their mode of administration varies as does their clinical performance[35,93]. Hence, glass radioembolic microspheres are administered with saline, whilst resin microspheres use dextrose of 5% plus sterile water[96]. In addition, SIR-Spheres® with high embolic power can achieve more homogeneous tumour coverage compared to TheraSphere®[35].

A more recent development has been polymeric microspheres loaded with 166Ho produced in 2015 with the trade name Quirem-Spheres® (Quirem Medical B.V, The Netherland) as a biodegradable and imageable radioembolic agent. Quirem-Spheres® are radioactive 166Ho-loaded polylactic acid (PLLA) microspheres (maximum specific activity of 450 Bq[35]) with a diameter size of 20 – 60 μm and applied especially for hepatocellular carcinoma (HCC)[97,98]. Quirem-Spheres® is the only product that enables visualisation and quantification of the microspheres during and after administration of the microspheres based on high-resolution magnetic resonance imaging (MRI) and computer tomography (CT)[98].

Radionuclide-doped microspheres used for intra-arterial therapy should ideally comprise (1) high mechanical stability to breakdown and pass easily through the capillary network, (2) high chemical stability to resist elution of radioactive label, macrophage removal, or radiolysis, (3) uniform size, (4) density or specific gravity to prevent settling or streaming, and (5) the relative ease of radioisotope doping[99]. Research on safety, tumour response, and survival using TheraSphere® showed that 90Y microspheres provided a safe and effective method for liver cancer patients. TheraSphere's clinical trials of 43 prospectively enrolled patients with unresectable HCC provided clear evidence of reduced tumour viability and demonstrated encouraging survival results[100]. Another study which trialled two types of ^{90}Y microspheres (TheraSphere® and SIR-Spheres®) to treat unresectable HCC[95], reported improved functional well-being and health-related quality of life at three months for 14 patients treated with TheraSphere® compared with the group treated with a hepatic artery infusion of cisplatin.

Nevertheless, complications occurred due to microsphere shunting (inadvertent flow) from the liver into the lung, gastrointestinal tract, or pancreas. Shunting of the microspheres can cause several adverse effects, such as gastrointestinal ulceration, pancreatitis, cholecystitis, radiation pneumonitis, and radiation hepatitis[95]. Therefore, the development of radioactive microspheres with alternate materials and radionuclides has been extensively studied to improve the limitations found in some commercial products. For example, there is a study developing radioactive holmium phosphate microspheres (HoPO4-MS) using

holmium acetylacetonate microspheres (HoAcAc-MS) via an emulsification and solvent evaporation method[101] (see Figure 11). The study reported a stable radioactive microsphere with the following properties: 34.2 ± 1.0 μm in diameter, holmium content of 46.2 ± 0.8 wt%, and a density of 1.7 g/cm3. Exploration of radioactive microspheres with various basic materials are shown in Table 6.

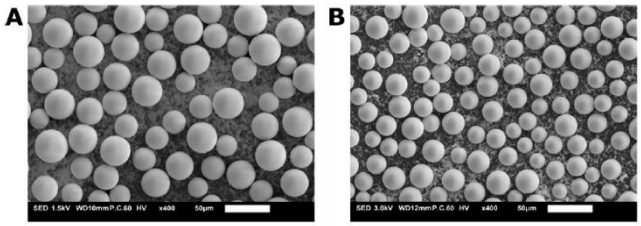


Figure 11. Scanning electron micrograph of (a) holmium acetylacetonate microspheres (HoAcAc-MS) and (b) holmium phosphate microspheres (HoPO4-MS)(Reproduced with permission from ref [101]. Copyright 2018, Elsevier).

Table 5. Commercial radioactive microspheres for trans-arterial radioembolisation (TARE)

Product	Company	Materials	Radionuclide	Type of embolisation	Category	Size (μm)	Imaging technique	Ref.
TheraSphere	MDS Nordion, Ottawa, Canada	Glass (Aluminosilicate)	Yttrium (^{90}Y)	Permanent	Non-biodegradable	20 – 30	SPECT/CT	93–96
SIR-Sphere	Sirtex Medical, Sydney Australia	Resin (Aminex A5)	Yttrium (^{90}Y)	Permanent	Non-biodegradable	20 – 60	SPECT/CT	93–95
Quirem-Sphere	Quirem Medical B.V, The Netherland	Polymer (PLLA)	Holmiun (^{166}Ho)	Transient	Biodegradable (with imageable properties)	15 – 60	SPECT/CT, MRI	35,101

Table 6. Exploration on basic materials of radioactive microspheres

Material Classification	Material Type	Diameter of microsphere (μm)	Radioisotope	Purpose	Ref.
Polymer	Albumin (Human bovine serum albumin)	17 – 40	^{188}Re	Endoradiotherapy of tumors (Lung tumours, radiosynovectomy)	102
	Resin (Aminex A-27)	45 – 75	^{90}Y	Kidney tumours in pigs	103
	Resin (BioRex-70)	30 – 100	^{166}Ho	Liver cancer	104
	Polylactic acid	20 – 50	^{166}Ho	Liver tumours in rats, Head and neck cancer in rabbit	105,106
Glass	Aluminosilicate	25 – 35	^{90}Y	Liver cancer	99,107,108
		2 – 5	^{166}Ho	Tumour of mice	109
	Aluminosilicate	20-30	^{32}P ^{186}Re/^{188}Re ^{90}Y ^{166}Ho	Primary and metastatic cancer	110
	Lithium silicate				
	Magnesium alumino silicate				
	Potassium silicate				

2.2 Radionuclides and Doping Techniques

2.2.1 Radionuclide. The selection of suitable radionuclides and doping techniques is crucial in cancer therapy. The choice of suitable radionuclide influences the success of radionuclide therapy in delivering a high local radiation dose to the tumour cells with a low radiation dose to the healthy tissues. Also, the doping method influences the binding affinity of the targeting agent and cellular radionuclide retention and biodistribution[111].

Radionuclide(s) used in radiation therapy are either deposited on or in the target and emit energy during their decay locally. Irradiation of healthy tissues should be minimised as much as possible. For example, the use of radionuclide-doped microspheres in HCC radiotherapy is illustrated in Figure 12. Several physical properties influence successful radionuclide therapy comprising of (1) particulate radiation emitted from radionuclide, (2) the physical half-life of the radionuclide, (3) radioactivity, (4) labeling yield, and (5) the radiocatabolites[111].

First, particulate radiation emitted from radionuclides influences radiation dose distribution. The nature of emitted radiation from radionuclides can be classified as α-particle emitters, β-particle emitters, conversion electron (CE) emitters, or Auger electron emitters (AE)[112]. Moreover, a large group of radionuclides emits γ-rays during decay (after the emission of either α- or β− particles)[112,113]. However, since the γ-rays energy is not too high, γ-emitters are used primarily for diagnostic purposes because they also match the γ-camera[113].

On the other hand, alpha particles are positively charged ions consisting of two protons and two neutrons. They are emitted during the radioactive decay of many nuclei with high atomic numbers[113]. Amongst the other particulate emissions, α-particles have the highest linear energy transfer (LET), leading to radiation damage to biological systems. LET is the measure of the energy transferred to the medium as ionizing radiation passes through it and is also used to quantify the effect of ionizing radiation on the medium, such as a biological specimen[112]. Due to high LET, α-particle irradiation can contribute to extraordinary cytotoxicity, about 5 to 100 times more toxic than β- and γ-radiation even at low doses (1 – 2 Gy)[113].

Moreover, α-particles are very difficult to distribute in radioactive microspheres homogeneously[113]. Likewise, radionuclides emitting α-particles are effective for some cancers, such as ^{213}Bi treating leukemia cancer cells in the vascular system and ^{223}Ra to treat skeletal cancer metastases. In addition, α-particle emitters are more compatible for oncologic applications, especially for treating blood-borne cancers and tumours with small diameters where their localization within the tumour is homogenous[112]. In contrast, the most extensively used radionuclides for a broad series of radiotherapeutic applications are radionuclides emitting β− particles due to their availability and suitability to treat large tumour volumes[112,113]. In contrast with α-particle emitters, β− particle emitters produce a nearly homogeneous radiation dose distribution[112]. Figure 13 illustrates the interaction of different types of particulate radiation with DNA and the LET values influenced by the amount of particulate radiation that passes to the material [112,114]. Yttrium (Y^{90}) is the most widely used radioactive moiety in several targeted radioimmunotherapies to treat a variety of solid organs and hematological malignancies. This β-emitter forms the premise for radioembolisation as it enables the radiation exposure zone to the vicinity of the local tumour tissue with tolerable levels of nontumorous exposure[94].

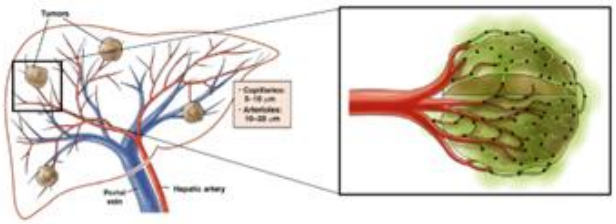


Figure 12. Intra-arterial radiotherapy of liver cancer by radioactive microspheres (20 – 60 μm) providing local, high-dose tumour radiation that affects tissues 2.5 – 11 mm from the delivered microsphere (green)(Reproduced with permission from ref [11]. Copyright 2013, Elsevier).

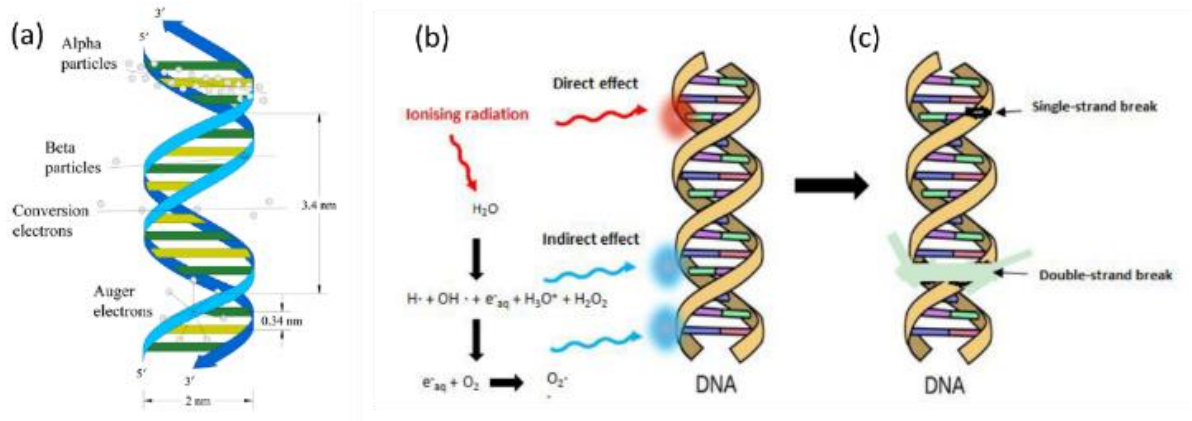


Figure 13. (a) The interaction of various particulate radiations with DNA (Reproduced with permission from ref [112]. Copyright 2015, ACS Publications), (b) Schematic of how ionizing radiation utilized for radiotherapy can damage DNA. Radiation can directly damage DNA or indirectly damage it through the generation of reactive oxygen species (ROS), (c) DNA damage can occur as a result of single-strand breaks (SSB), double-strand breaks (DSB), or other interactions with DNA and proteins (Reproduced with permission from ref [114] . Copyright 2020, LIDSEN Publishing Inc. published under a Creative Common CC-BY-NC Licence).

Table 7. Current interest in therapeutic radionuclides[112,113]

Radionuclide	Half-life	Particle energy (keV)	Max. range in tissue	Specific radioactivity
α-particle emitters				
^{225}Ac	10.0 d	5935	48 Φm	
^{211}At	7.2 h	5982	65 Φm	
^{213}Bi	45.6 min	5982	43 Φm	
^{223}Ra	11.4 d		43 Φm	
β-particle emitters				
^{32}P	14.3 d	1710.2	8.7 mm	
^{90}Y	64.1 h	2280.0	12.0 mm	High
^{131}I	8.0 d	806.9	2.4 mm	Relatively high
^{153}Sm	46.5 h	808.2	3.0 mm	Moderate
^{165}Dy	2.3 h	1286.7	6.4 mm	
^{166}Ho	26.8 h	1853.9	10.2 mm	
^{177}Lu	6.7 d	497.8	1.7 mm	Moderate
^{186}Re	89.2 h	1069.5	5.0 mm	Moderate
^{188}Re	17.0 h	2120.4	11.0 mm	Moderate
^{198}Au	2.7 d	960.7	4.4 mm	
γ- emitters				
^{51}Cr	27.7 d			
^{67}Ga	78.2 h			
^{99m}Tc	6.0 h			
^{111}In	2.8 d			
^{123}I	13.2 h			
^{125}I	60 d			
Auger electron emitters				
^{125}I	59.40 d	12.24		High
^{111}In	2.80 d	6.75		High
^{67}Ga	3.26 d	6.26		

Furthermore, the radionuclide's physical half-life should match the targeting protein's biological half-life[111]. Short-lived radionuclides can be used to optimise the radiobiological aspects of therapy[113]. The physical half-life of 1 to 14 days would be optimal, depending on in vivo pharmacokinetics of the targeting agent[111]. Table 7 shows current interest in therapeutic radionuclides of various particulate emitters. The following two factors influencing radionuclide therapy are radioactivity and labelling yield. The specific radioactivity of the conjugate should be as high as possible, and the labelling yield should be maximised in terms of high radiochemical purity and stability[111].

2.2.2 Labelling. Polymeric microspheres (gelatine, PLA, PLGA, albumin) can be labelled with radioactive particles either during or after their preparation. This technique prepares the microspheres in a sterile non-radioactive kit that can be stored for extended periods. Then, radiolabelling is achieved by radio pharmacists shortly before use in the nuclear medicine department. The preparation of sterile non-radioactive microsphere kits depends on the particles making it possible to enclose the activity, label throughout the entire volume, or label only certain structures, such as the surface, the outer or inner wall, the lipophilic or hydrophilic liposome compartment (see Figure 2 in Ref. [113]). Radiolabelling during the microsphere's preparation can be obtained using radioactive colloids. In this method, the size range of colloids depends mainly on the preparation conditions, such as temperature and pH, and the form of the precipitating agent. This procedure also facilitates the production of homogeneous albumin microspheres that incorporate many kinds of radioactive colloids by including the radiolabelled compound method. Moreover, other methods are used for preparing radioactive microspheres during the formation of microspheres, such as isotope exchange, lipophilic inclusion, and in situ production[113].

On the other hand, another radiolabelling technique by neutron activating pre-made microspheres. This technique effectively prevents leakage of the radioactive isotope(s) from the microsphere because the radioisotope is sealed inside the microsphere matrix. The pre-made microspheres are prepared by manufacturing microspheres with the addition of a non-radioactive precursor of the radioisotope. They are then activated in a nuclear reactor by bombardment with thermal neutrons shortly before use, in which glass material (aluminosilicate glass) is the most stable matrix for microsphere activation. This method was introduced by Day and Ehrhardt for therapeutic radioactive microspheres by manufacturing aluminosilicate glass containing 17 mol% Y_2O_3[113].

3. PROSPECTIVE OF RADIOACTIVE MICROSPHERES FOR BONE CANCER TREATMENT

As reported previously, metastatic disease contributes to significant deterioration in the quality of life for many cancer patients, and bone metastases are the most frequent incident in advanced cancer, especially from breast and prostate cancer[115,116]. Metastatic bone cancer occurs due to the migration of cancer cells from the primary tumour that

enters the bloodstream, followed by extravasation to the immune system leading to colonisation in the bone (which is the third most frequent site of metastasis)[117–119]. Bone metastatic cancer can cause catastrophic consequences for the patient, including bone pain, impaired mobility, and hemopoietic complications (i.e. spinal cord compression, pathologic bone fracture, bone marrow aplasia)[115–118,120]. Bone pain in patients is usually associated with mechanical pain resulting from the pressure of tumour tissue within the bone and loss of bone strength[121]. Therefore, research on developing new strategies to tackle bone cancers should be conducted to reduce the incidence of bone metastases, palliate skeletal disease, and tackle primary bone tumours. Biomaterials-based strategies focused on microspheres have been highlighted above and could also potentially be explored for curative and palliative treatment of bone metastases and primary bone cancers using radiotherapy approaches. Radiotherapy could be used not only as primary palliative therapy but also as an adjuvant reducing the later expression of metastases and reducing the frequency of retreatment due to the taken up at the preferential site for osteoblastic metastases[121].

Research on radioactive micro particulates for cancer or bone disease treatment, such as rheumatoid arthritis (RA) has been explored[122–124]. Here the materials used were based on hydroxyapatite ceramics with a particle size range of 20–60 μm due to their excellent biocompatibility and ease of labeling with lanthanides. ^{177}Lu was used in this study as the viable radionuclide due to some advantages, especially its usefulness for imaging during or after the application of radioactive microspheres[125]. Their gamma lines were suitable for imaging the in-vivo localisation with a gamma camera. In addition, several considerations for the use of ^{177}Lu have been proposed, such as (1) having a half-life of 6 days comparable with the half-life of ^{90}Y (64 h ≈ 3 days), and (2) its gamma emission which enables imaging of delivery and location[125].

A preliminary clinical study in patients with chronic knee joint painful synovitis of rheumatoid origin was assessed by Radiosynovectomy (RSV) using ^{177}Lu-labeled hydroxyapatite (^{177}Lu-HA)[123]. The study demonstrated the efficacy of ^{177}Lu-HA particles in RSV after intra-articular administration delivered a 333 ± 46 MBq dose of the agent. The study indicated the agent's potential as a viable and cost-effective radiopharmaceutical for the treatment of chronic RA in knee joints. Imaging and biochemical tests confirmed RSV efficacy via significant pain relief and improved mobility was observed in all patients. Moreover, there was minimal radiation risk involved in the procedure, which showed that it could be performed on an outpatient basis. In short, ^{177}Lu-HA is showed potential as a promising candidate for RSV[123]. A similar result was obtained in another preliminary clinical study showing the effectiveness of ^{177}Lu-HA for RSV in pain control, functional improvement and prevention of disease progression[124]. In this study, ^{177}Lu-HA was formulated as ready-to-use single vial kits. The availability of these kits for HA particles for facile preparation of ^{177}Lu-HA is expected to expand the scope of its broader utilisation in RSV.

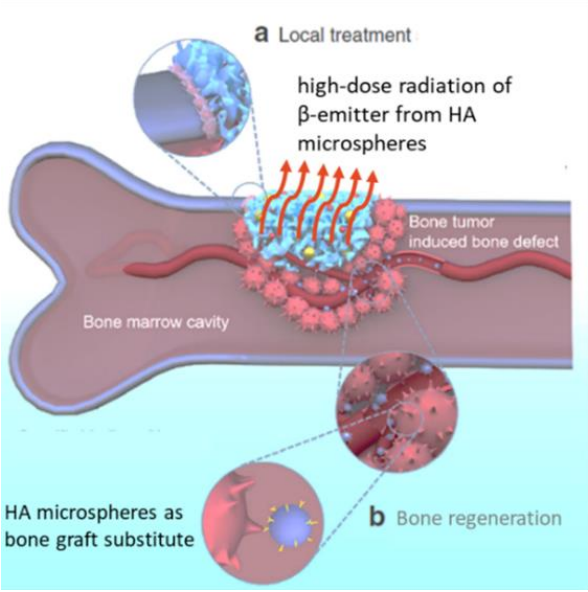


Figure 14. Illustration of radionuclide doped-hydroxyapatite as bifunctional biomaterials for internal radiation therapy comprising (a) local treatment with high dose radiation of β-emitter and (b) bone regeneration with hydroxyapatite microspheres as bone graft substitute (Modified picture. Reproduced with permission from ref [126]. Copyright 2021, Springer Nature published under a Creative Common CC BY Licence).

The above studies highlight that hydroxyapatite ceramics could potentially be further explored for bone cancer treatment. Furthermore, developing hydroxyapatite in microsphere form (to enhance its properties and doping with other radionuclides) could lead to developing a potentially new bone cancer therapy treatment. The use of radionuclide-doped hydroxyapatite could have beneficial impact on bone oncology therapy by damaging cancer cells using high-dose radiation, which once dissipated could be exploited to enhance bone repair and regeneration with hydroxyapatite serving as a bone graft substitute.

Radionuclide-doped hydroxyapatite microspheres could be developed as bifunctional biomaterials for internal radiation therapy of bone cancer. High dose radiation of β-emitter delivered from the microspheres provides a local treatment to kill the cancer cell. Meanwhile, hydroxyapatite microspheres play a role as bone graft scaffold targets on bone tissue growth and regeneration [126]. An illustration of radioactive microspheres (radionuclide-doped hydroxyapatite) as bifunctional biomaterials for internal radiation therapy is presented in Figure 14 [126].

CONCLUSION

The review shows the microspheres (non-radioactive and radioactive) clinical application in cancer treatment as drug carriers, active, or therapeutic agents, particularly arterial embolization. They have shown viable performance as trans-arterial embolisation (TAE), transarterial chemoembolisation (TACE) or transarterial radioembolisation (TARE) for liver cancer treatment.

The non-radioactive microspheres exhibit excellent properties as superior drug delivery systems due to their high drug-loading capacity and controlled drug delivery at the target site. With this, the cancer treatment efficacy can be improved. For further development, the non-radioactive microspheres application for cancer treatment can also be extended into combined therapies. As example, combination of chemotherapy and immunotherapy may be simultaneously conducted by loading the anti-cancer drugs and immunomodulatory therapeutics into the non-radioactive microspheres. Another development involves controlling the size and distribution of microspheres' pores. Having a controlled size and porosity, it is expected that the loading capacity of the microspheres can also be improved. The homogeneity of pores in the microspheres offers additional benefits in promoting tissue regeneration by providing a template for cell infiltration and attachment.

The radioactive microspheres are effective as an embolic platform in TARE therapy of several tumours and cancers, such as liver cancer. TARE therapy using radioactive microspheres has successfully improved functional well-being and health-related quality of life. Furthermore, by applying it directly to the target site, radioactive microspheres could be explored as a new strategy for oncology applications, especially bone cancer. Analogue to the development of non-radioactive microspheres, controlling the size and distribution of pores can also improve the efficacy of radioactive microspheres. This respect to the possibility of combining radioactive materials and bioactive materials for tissue engineering. Example given is the use of radionuclide doped-hydroxyapatite microsphere as a bone graft scaffold containing radionuclide to kill cancer cells and promote bone tissue regeneration.

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