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Review

The Use of Biomaterials in Internal Radiation Therapy

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Academic Editor: Hossein Hosseinkhani

Special Issue: Applications and Development of Biomaterials in Medicine

Recent Progress in Materials
2020, volume 2, issue 2
doi:10.21926/rpm.2002012

Received: March 18, 2020
Accepted: May 06, 2020
Published: May 12, 2020

Abstract

Radiotherapy has become one of the most prominent and effective modalities for cancer treatment and care. Ionising radiation, delivered either from external or internal sources, can be targeted to cancerous cells causing damage to DNA that can induce apoptosis. External beam radiotherapy delivers either photon radiation (x-rays or gamma rays) or particle radiation (neutrons or protons) in a targeted manner to specific tumour locations. Internal radiotherapy involves placing radioactive sources within the body to deliver localised doses of therapeutic radiation to tumours using short range radionuclides. Biomaterials have been developed to allow more precise targeting of radiotherapy in order to reduce toxicity to surrounding healthy tissues and increase treatment efficacy. These unique biomaterials have been developed from polymers, glasses and ceramics. Polymeric materials have been used to both displace healthy tissue from tumours receiving radiation,

and to deliver radioactive sources into the body. These polymers can respond to various stimuli, such as radiation or reactive oxygen species, to deliver therapeutic payloads to target tissue during or post radiotherapy. Glass-based biomaterials doped with radionuclides have also been developed to provide *in situ* radiotherapy. Novel biomaterials that can enhance the synergistic effect of other treatment modalities, such as chemotherapy and immunotherapy, continue to be developed. Theranostic materials that are capable of providing diagnostic information whilst simultaneously delivering a therapeutic effect to enhance radiotherapy are also briefly reviewed.

Keywords
Radiation therapy; biomaterials; cancer; brachytherapy; radiotherapy; radionuclides; glass; oncology

1. Introduction

Radiotherapy has become one of the most common and vital modalities for effective cancer treatment and care, and is used either alone or in combination with surgery, chemotherapy and immunotherapy in approximately half of all cancer cases worldwide [1]. Ionising radiation is utilised for the treatment of cancer due to its ability to deposit energy that damages the genetic material of cells, resulting in their inability to survive and proliferate further. The unregulated manner in which cancer cells rapidly proliferate means that they are more susceptible to radiation-induced DNA damage than normal healthy cells [2]. Irradiation can damage the DNA double helix structure by inducing DNA single and double-strand breaks, which in turn induces cellular events such as apoptosis, necrosis and abnormal mitosis [3]. DNA can also be damaged indirectly by reactive oxygen species (ROS) and through free radicals generated in cells by radiation (see Figure 1) [4]. The genomic instability of cancer cells means that they are inefficient or lack the ability to effectively repair DNA damage induced by radiation in comparison to normal cells. This mechanism underpins radiotherapy's selectivity for inducing cancer cell death [5]. Unfortunately, radiation inadvertently causes damage to normal cells adjacent to cancerous cells, or those in the radiation path. As such, advancements in this field need to consider maximising the dose of radiotherapy to aberrant cancer cells whilst minimising exposure to normal healthy cells.

The dose of radiation can also directly influence the efficacy of treatment and in clinical settings the prescribed dose is usually a compromise between tumour control probability (TCP) and normal tissue complication probability (NTCP) [6]. The location of the tumour is the principal factor when considering NTCP and can vary throughout the body due to discrepancies in the radiosensitivity of different healthy and cancerous tissues. Since NTCP is the primary dose-limiting factor in radiotherapy multiple measures and techniques have been used to protect healthy tissue from radiation damage [7].

Depending on the type of cancer, radiotherapy can be used to cure localised cancer, either as palliative treatments to reduce symptoms, or to limit progression of the disease in incurable cases [8]. Radiotherapy is also often used in conjunction with other treatment modalities such as chemotherapy, immunotherapy and surgery. Radiotherapy can be delivered at different stages of

a patient's treatment regime. Neoadjuvant radiotherapy is performed pre-operatively with the aim of reducing the size of a tumour prior to surgical resection. Radiotherapy can also be used as an adjuvant therapy intra- operatively and post-operatively to help eliminate any residual tumour cells [9].

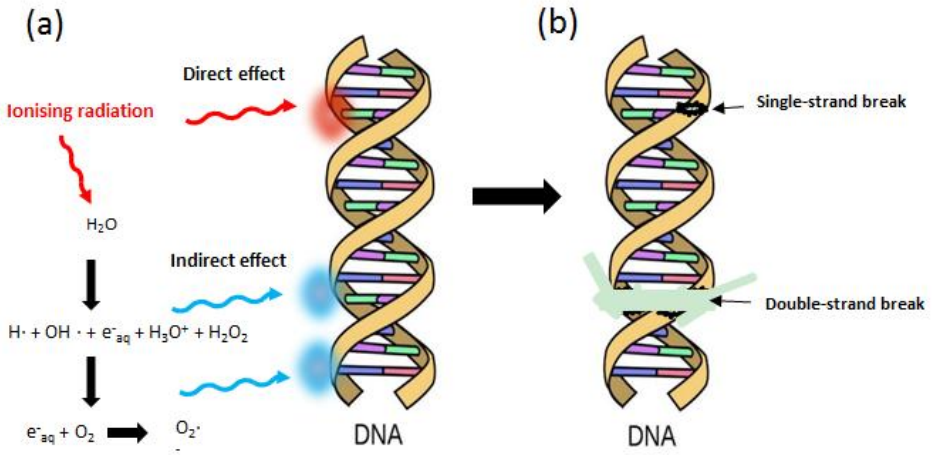

Figure 1 (a) Schematic of how ionising radiation utilised for radiotherapy can damage DNA. Radiation can directly damage DNA or indirectly damage it through the generation of reactive oxygen species (ROS). (b) DNA damage can occur as a result of single-strand breaks (SSB), double-strand breaks (DSB) or other interactions with DNA and proteins.

The radiation itself can be delivered to cancerous targets in two opposing ways, Externally or Internally. External beam radiotherapy is the most prevalent form of radiotherapy used in the clinical setting and involves aiming high-energy rays, in the form of photons (X-rays or gamma rays), protons or particle radiation, from outside of the body to the specific tumour site. Conversely, internal radiotherapy occurs as a result of placing radioactive sources within the body, usually adjacent to or directly into the tumour itself [10]. Technological advances are continuing to drive progression in both external and internal radiotherapy in order to improve its therapeutic efficacy and reduce adverse effects.

Technological advances in imaging techniques in conjunction with the ability to shape radiation beams have resulted in the development of highly conformal external beam radiotherapies (EBRT). These techniques can accurately target a tumour site and deliver a maximum ionising radiation dose to the target whilst minimising the dose to surrounding healthy tissue [11]. Photon radiation, either x-rays produced by accelerating electrons or gamma rays from the decay of radioactive substances, are considered low linear energy transfer (LET) electromagnetic rays. Despite their low LET, the progression of linear electron accelerators which produce energy-tuneable bremsstrahlung x-rays has led to them being the most widespread source for many current EBRT regimens [12]. Particle radiation where heavier particles than electrons, in the form of neutrons or protons, are targeted to the tumour can also be performed. These particles have higher LET than photons and subsequent increased ability to damage cancer cells. The associated costs of generating the particles used and delivering particle radiation at treatment facilities has so far limited their use [13]. The modality, total dose and fraction of the radiotherapy schedule are

considered on an individual basis and are dependent on both the condition of the patient and the location of the cancer [14].

There are several different types of photon beam radiotherapy used for cancer treatment. Three-dimensional conformal radiation therapy (3D-CRT) utilises computed tomography (CT) imaging to facilitate accurate determination of the tumour location and position of any potential adjacent critical structures. From this information, optimal beam placement from multiple directions can precisely match the shape of the tumour and therefore increase its irradiation whilst also identifying regions that necessitate shielding [15]. Intensity modulated radiation therapy (IMRT) is very similar to 3D-CRT with the advantage of being able to control the strength of the individual beamlets to certain regions. The intensity modulation ability of IMRT enables the delivery of irregular shaped radiation doses which can conform to the tumour whilst simultaneously avoiding critical structures [16]. Stereotactic body radiation therapy (SBRT) integrates these technological advances to precisely deliver very high individual doses of radiation over very few treatment fractions, to ablate well-defined small tumours. However, SBRT can subsequently damage adjacent tissue due to the elevated radiation dose [17].

Conformal external beam radiotherapies can allow for dose escalation to target regions whilst sparing normal tissue. This can lead to hypofractionated schedules, which involves the delivery of fewer, larger doses of radiotherapy in a highly precise manner which can provide radical curative effects at local tumour regions [18]. Despite this, clinical considerations such as location of the tumour and its subsequent proximity to surrounding critical organs and radiosensitive tissue can mean it may not always be possible to utilise EBRT. In such cases, internal radiotherapy becomes a viable option.

2. Internal Radiotherapy

Radiopharmaceuticals are medicinal products that contain radioisotopes which can be used for diagnostic or therapeutic clinical applications [19]. Radioisotopes such as ^{153}Sa, ^{223}Ra, ^{131}I and ^{89}Sr can be combined with an excipient for the systemic treatment of certain types of cancer including bone, prostate and thyroid cancer (see Table 1) [20]. Radiopharmaceuticals can be administered orally or intravenously with the aim of delivering them to accumulate at the desired cancer site. Conjugation of a radioisotope to monoclonal antibodies or to peptides that target cancer-associated cell surface antigens has also been explored in order to deliver a high dose of radiation to the tumour in therapeutic approaches known as radioimmunotherapy and peptide receptor radionuclide therapy [21, 22].

Both ^{223}Ra and ^{89}Sr have been used for the treatment of secondary bone cancer, particularly when the cancer has metastasised to multiple bone sites, since they are both alkaline earth metals and follow very similar metabolic pathways *in vivo* to calcium [23]. As a result, these radiotherapeutic agents localise in bone mineral to act as bone-targeting therapies following intravenous injection. The uptake of these agents occurs preferentially at sites of active osteogenesis meaning that a greater concentration of these agents can occur at osteoblastic lesions and multiple metastatic sites simultaneously [24]. The ionising radiation emitted from these radiopharmaceuticals have varying tissue penetration depths and consequently are able to target bone metastases with minimal irradiation to adjacent soft tissues (see Table 1). The

systemic administration of radiopharmaceuticals is limited to only a small number of aforementioned anatomical tumour locations. The majority of cancers require the ablative radiation dose to be targeted and to occur directly at the cancerous tissue over a short time period, with a rapid fall-off in dose to ensure minimal irradiation of healthy tissues [25].

Table 1 Common radiopharmaceuticals used in the systemic delivery of radionuclides.

Radionuclide	Half-life (Days)	Type of emission	Tissue penetration depths (mm)	Type of cancer treated	Reference
^{89}Sr	50.5	β	2.4-8	Bone metastases	[20]
^{223}Ra	11.4	α	<0.1	Bone metastases	[23]
^{131}I	8.04	β,γ	0.6-2.4	Differentiated thyroid cancer, non-Hodgkin's lymphoma, neuroblastoma	[26]
^{177}Lu	6.7	β,γ	1-2.2	Neuroendocrine tumours	[27]
^{90}Y	2.7	β	2.5-11	Neuroendocrine tumours, Liver metastases, hepatocellular carcinoma, non-Hodgkin's lymphoma	[28]
^{153}Sm	1.9	β	0.6-3	Bone metastases	[27]

3. Brachytherapy

Brachytherapy is a type of internal radiotherapy that involves the placement of sealed radioactive sources adjacent to or within the interstitium of cancerous tissue. The location in which the radioactive source is placed is used to classify the type of therapy i.e. intracavitary brachytherapy, interstitial brachytherapy, intraluminal/intravascular brachytherapy or superficial brachytherapy [29]. Brachytherapy can be further classified according to the dose rate applied, using the International Commission on Radiation Units stating that 0.4 to 2 Gy.h^{-1} is a low dose rate (LDR); 2 to 12 Gy.h^{-1} is a medium dose rate (MDR) and a high dose rate (HDR) is regarded as being greater than 12 Gy.h^{-1} [30]. In pulse dose rates, pulses of 1 to 3 Gy.h^{-1} are used to deliver a large number of small fractions with short intervals. HDR brachytherapy typically involves the temporary placement of a radioactive source, whilst LDR usually involves permanent implantation.

The location of the tumour and various patient related factors determine the type of brachytherapy conducted. For example, low-energy photon emitting sources, such as ^{125}I and ^{103}Pd, have typically been used for LDR whereas high energy emitting ^{192}Ir and ^{60}Co sources have been used for HDR [31]. In many instances, brachytherapy facilitates the delivery of a highly localised radiation dose that is unable to be achieved using conventional external beam radiation therapy [32]. This is because the absorbed dose is inversely proportional to the square of the distance of the radioactive source [33]. This means that as you double the distance from the radiation source, you reduce the dose by a factor of four as the energy is spread over four times the area. Prostate, cervical, oesophageal and certain types of breast cancer are the predominant types that have been used for treatment with brachytherapy [34].

Advanced imaging modalities, such as magnetic resonance imaging (MRI), computed tomography (CT) and ultrasound, have also been used in conjunction with sophisticated treatment planning software to determine the precise location in which to place the radioactive sources [35]. Correct placement of these sources enables the optimal dose distribution at the target site to be achieved on a patient specific basis. This allows for the delivery of conformal radiotherapy tailored to the size and shape of the individual tumour (see Figure 2) [25].

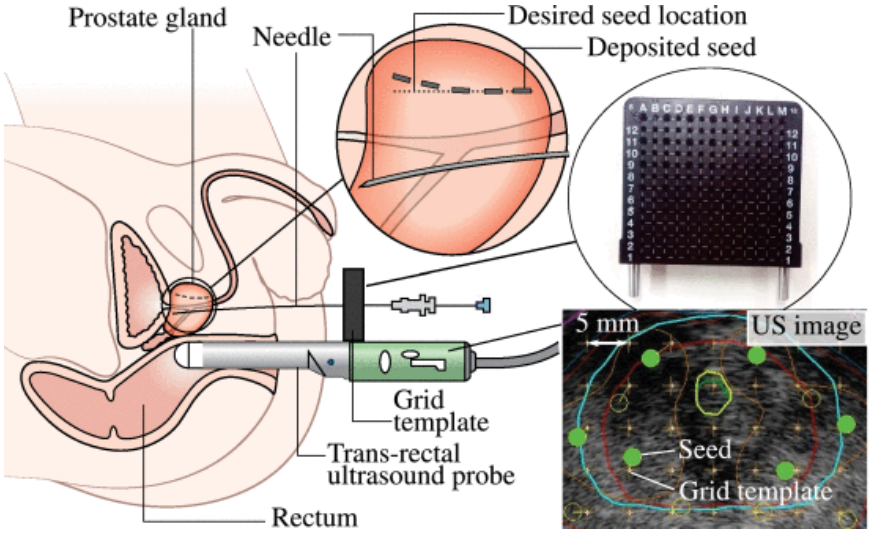

Figure 2 Schematic of prostate brachytherapy delivery. Radioactive seeds are implanted into the prostate using trans-rectal ultrasound (TRUS) guiding and a grid template. TRUS is performed to identify the location of seeds deposited within the prostate and dosimetric plan is generated. Reproduced with permission from [36] (Cancer Research UK/ Wikimedia Commons).

Brachytherapy is an invasive technique as it requires surgical insertion to deliver radioactive sources to specific cancer sites. In permanent brachytherapy, the radioactive source is sealed within a protective capsule to create a brachytherapy seed ready for implantation (see Figure 2). Titanium is the most common material used for conventional seeds as it provides structural integrity to the seed so that it remains *in situ* whilst also preventing the escape of the radioactive source [37]. The use of titanium also allows for MRI-guided insertion enabling improved accuracy of placement, which can be performed by remotely controlled afterloading devices, removing the need for manual handling and insertion of radioactive sources. Automation of this procedure can improve the accuracy of the therapy alongside significantly reducing radiation exposure to clinicians [38]. New seed and applicator devices continue to be developed along with alternative materials to address different clinical aspects associated with cancers at various body sites [39]. Improvements in applicator and seed design and geometry will allow for better visualisation from the various imaging modalities used, resulting in more accurate implantation and retention, which in turn will translate to more accurate and effective dosimetry at the target site. Custom applicators and seed devices are also desirable when conventional devices fail to conform or adapt to patient specific anatomy [40].

One novel brachytherapy implant device that has been developed is CivaSheet® (CivaTech, Durham, NC). Unlike traditional seed implants, CivaSheet is comprised of a flexible, planar

bioabsorbable membrane which contains multiple unidirectional radioactive sources, known as CivaDots, fixed within its proprietary polymer matrix at regular intervals (see Figure 3) [41]. The ^{103}Pd radiation source is placed on top of a thin gold shield which imparts directional radiation that can selectively target cancerous tissue whilst sparing healthy tissue on the shielded side. The gold disc serves to shield the radiation and as a radiopaque marker that can be visualised using CT imaging [42]. The device also enables clinicians to utilise custom sizes of the device and the malleable nature of its planar membrane means it can conform to various physiological structures depending on the location of tumour and the patients' anatomy. This device can be applied intraoperatively during tumour resection and can also be administered via less invasive methods during a treatment regimens [43]. As within any brachytherapy device, the dosimetric characteristics of the source must be established and requires numerous *in silico*, *in vitro* and *in vivo* studies to ascertain the feasibility of new devices [44].

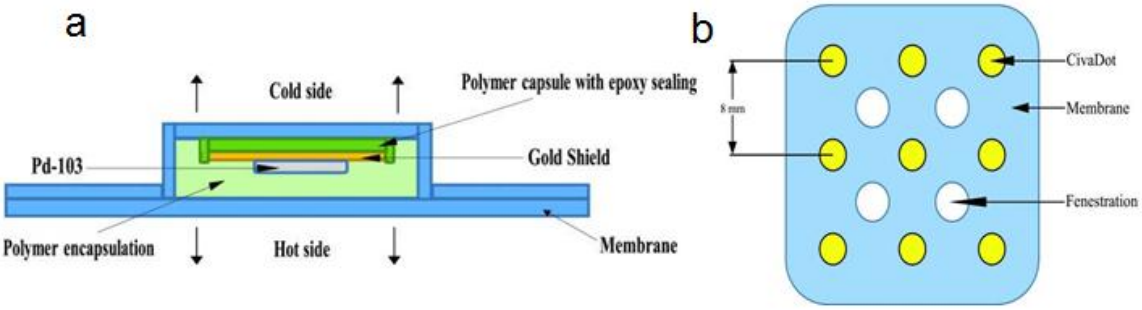

Figure 3 (a) Schematic of the cross-section of a CivaDot and its composition. (b) Illustration of a CivaSheet brachytherapy device. The CivaDots are orientated within the bioabsorbable membrane to provide unidirectional radiation. Adapted with permission from © Wiley [45].

One issue with permanent brachytherapy seeds, is that in certain instances they can require surgical removal. Sano *et al*. investigated the use of biocompatible, injectable thermos-responsive polymer labelled with ^{90}Y [46]. Poly (2-alkyl-2-oxazoline) (POZ) is an isomeric polypeptide material synthesised via the cationic ring-opening polymerisation of 2-oxazolines [47]. Modifications of the 2-substituent of the 2-oxazoline monomer allowed for modifications to the POZ polymer sidechains. POZ derivatives have a low critical solution temperature (LCST), and can self-aggregate above a specific transition temperature (Tt) that is determined by oxazoline composition and molecular weight of its polymers [48]. Sano *et al*. utilised the thermo-responsive characteristic of POZ derivatives to create polymers that were soluble at room temperature and upon intratumoral injection, rapidly self-aggregated into rigid structures retained within the tumour. The enhanced permeability and retention effect demonstrated to cause POZ accumulation within tumours and the ability to label a radioactive source to the polymer facilitated their potential use as injectable materials for brachytherapy (see Figure 4) [49].

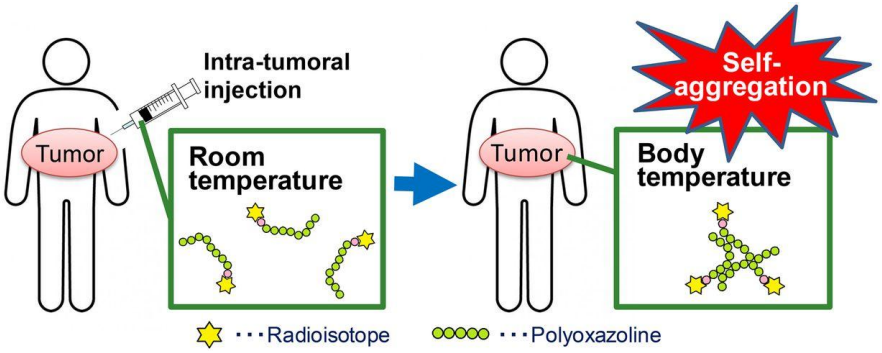

Figure 4 Concept of injectable, thermo-responsive, radioisotope labelled polymers that aggregate within tumours for brachytherapy applications. This research was originally published in JNM © SNMMI [46].

Rhenium loaded silicate-based glass seeds is another material that has been investigated for brachytherapy administration. Utilising the sol-gel processing method it was possible to incorporate stoichiometric amounts of rhenium within silicate-based glasses (with formulation 20% rhenium, 50% silicon and 30% calcium, neither weight nor mole % was provided) and fabricate seeds of a predetermined geometry [50]. ^{186}Re has a relatively short half-life of 16.9 hours and offers the possibility of releasing high energy β-emission over a short time period in comparison to other radionuclides with longer half-lives [51]. Knowing the geometry of the seed, the energy generated per seed and the dosimetric factors of the source, it was possible to calculate the number and location of seeds required to be placed in order to deliver effective brachytherapy to a tumour. Several rhenium based radiotherapy treatments are currently in early phases of clinical trials investigating the utility of ^{186}Re and ^{188}Re isotopes [52]. ^{186}Re has a lower β-emission than ^{188}Re with a maximum tissue penetration of 4.5 mm and a half-life of 3.6 days, making ^{186}Re an ideal candidate for treating small to mid-sized tumours. The larger tissue penetration depth of ^{188}Re, maximum of 11 mm, and its shorter half-life means that it could be employed for the treatment of larger tumours over a short time period [51]. Radiotherapy from ^{188}Re sources has been investigated for medullary carcinomas of the head and neck [53], hepatocellular carcinomas [54] and for brachytherapy of basal or squamous cell carcinomas [55].

An alternative device to typical brachytherapy seeds was the use of conical-shaped needles, similar to those used in microneedle arrays for transdermal drug delivery, to penetrate into solid tumours to deliver intratumoral doses of radiation. Kim *et al.* investigated using titanium (Ti) and molybdenum (Mo) needles coated using pulsed laser deposition or chemical vapour deposition with holmium (Ho) or rhenium (Re) that following neutron activation readily yield therapeutic radionuclides [56]. ^{166}Ho is produced following irradiation of ^{165}Ho in a neutron flux and decays to emit high energy, tumoricidal β-particles. ^{186}Re and ^{188}Re are also both β-emitters and like ^{166}Ho also emit photons (x-rays and γ-rays) which can be detected using Single Photon Emission Computer Tomography (SPECT) facilitating their use as theranostic agents [57]. Pulsed laser depositions was used to ablate Ho foil within a vacuum using an intense pulsed laser causing the formation of a Ho plasma plume that condensed on to Ti needles. Ti was chosen as the needle material due to its high biocompatibility and strength as well as the ease at which needles of specific sizes and geometries can be fabricated. Importantly, Ti produces a very low amount of radioactive isotopes, following neutron activation, that are deemed negligible and unable to cause

significant cellular damage, further validating the choice of material [58]. Despite the ability to control the amount of Ho coated onto Ti needles and therefore tailor the amount of radioactivity, Ho deposition was found to dissociate from the needle when in acidic conditions that mimicked the intracellular environment of solid tumours. In the same study, Re of varying thickness (25, 75 and 125 μM) was uniformly deposited on Mo needles by chemical vapor deposition. This process involved passing a rhenium pentachloride containing precursor vapour over a heated Mo needle. Stability studies demonstrated only minimal leaching of radioactive Re was observed in neutral and acidic (pH 3.5) environments. Unlike Ti, following neutron irradiation Mo produces undesirable radionuclides and daughter isotopes that would have to be considered when calculating radiation dosimetry for patients. In order to prevent the generation of such radionuclides, a gadolinium (Gd) shield was created that housed the base of the device to absorb neutrons. The very high neutron cross-section of Gd prevents the Mo base from neutron activation, whilst allowing the protruding Re-coated Mo needle to become radioactive [59]. These neutron-activated biomaterials offer the possible to provide personalised internal radiotherapy treatment by optimisation of the needle material, geometry and quantity, the thickness of radionuclide coating as well as the radionuclides used based upon the size and location of the tumour to be treated. The advantageous nuclear properties of Ho and Re, such as their high neutron capture cross-sections, half-lives and resultant radionuclides upon decay make them attractive elements to form theranostic devices.

4. Polymeric Biomaterials, Applicators and Spacers

The benefits of radiotherapy when combined with the surgical resection of breast tumours for example, has been validated in multiple clinical studies and is considered a preferential breast conservation therapy in early stage breast cancer [60]. Accelerated partial breast irradiation (APBI) involves radiotherapy targeted directly to the lumpectomy bed and a 1-2 cm margin as opposed to radiotherapy delivered to the entire breast [61]. This process spares adjacent healthy tissue and enables a higher dose of radiation to be delivered to the target in a shorter treatment period. Combination therapy has been shown to decrease local recurrence of cancer as well as improve overall survival rates in patients with early-stage breast cancer [62]. Several different approaches have been employed to deliver the radiotherapy including intra operative radiation therapy and conformal EBRT although multicatheter interstitial brachytherapy and balloon catheter brachytherapy are most commonly used [63]. For these procedures and other types of temporary brachytherapy, catheters are used to place radioactive sources within an applicator into a predetermined location for a set period of time.

The development of flexible polymer-based catheters and applicators that are able to accurately place, using image-guided techniques and afterloading equipment, to retain radioactive sources in the correct location and orientation have been central to the progression of therapies such as APBI [64]. Numerous polymers such as silicone, nylon, polyurethane, polyethylene terephthalate (PET) and thermoplastic elastomers are utilised for the generation of commercially available and custom catheters. The combination of polymeric components provides desirable characteristics and can be manufactured and tailored for specific applications [65]. Polymer based devices that have multiple regions where a radioactive source can be accurately placed that derive from a single entry device are now common practise within the clinic [66]. Devices such as the

Strut Adjusted Volume Implant [67] device (Cianna Medical, California) comprises of a central strut encircled by either 6, 8 or 10 peripheral struts and ClearPath (North American Scientific, California), where inner and outer catheters can be independently expanded to give varying expansion radii, are becoming more prevalent due to their enhanced ability to conform to the lumpectomy cavity during APBI [68, 69]. The combination of radio-opaque markers located within the peripheral struts and the ability to differentially load the struts with high-dose radiation sources facilitate accurate treatment processes [70]. The catheters are inserted at predetermined distances between them to ensure sufficient coverage of the lumpectomy region plus an acceptable margin [64].

Balloon catheter brachytherapy is routinely used in APBI and are similar in respect to multicatheter devices in that they are single entry devices that are expanded to provide conformance of the lumpectomy cavity to the balloon. The MammoSite® (Hologic, Massachusetts) and the Contura balloon device (SenoRX, California) are FDA approved brachytherapy devices and consists of a silicone balloon connected to a dual-lumen catheter which controls the inflation and delivery of the radioactive source [71, 72]. A saline solution containing control material is used to inflate the balloon to the desired diameter and ^{192}Ir can be remotely after-loaded into the device at the prescribed radiation dose. The diameter of the inflated balloon, the distance of the balloon to the skin and the dose distribution are all interrelated factors that must be considered in order for effective treatment using this method [73]. Axxent electron brachytherapy system (Xoft, California) is another balloon-based applicator that differs slightly in that an electronic 50 kilo-voltage x-ray source is used to deliver radiation as opposed to ^{192}Ir. Since an x-ray tube is used within the balloon catheter this process eliminates the need for a high dose rate afterloader and the use of a shielded vault meaning that this procedure may be more accessible for some patients [74].

Researchers continue to develop novel balloon applicator designs that are able to increase the therapeutic effect they have whilst *in situ* [75]. Balloon applicators designed using alternative biomaterials at their interface have been investigated for localised delivery of therapeutic payloads. The added treatment intervention can be seamlessly integrated into conventional treatment practise as they do not compromise the primary function of the balloon applicators or require additional interventional procedures. Ouyang *et al.* investigated coating balloon applicators with a degradable polymer film that could release cerium oxide nanoparticles (CONPs) to act as radical scavengers during APBI (Figure 5) [76]. An inherent feature of radiotherapy is its inability to discriminate between healthy and cancerous tissue which leads to unwanted adverse effects. The radiation-induced generation of reactive oxygen species (ROS), such as hydroxyl radicals (OH·) and hydrogen peroxide (H_2O_2), can cause unrepairable DNA damage to healthy and cancerous cells [77]. CONPs have been have shown to be capable of the catalytic removal of ROS and thereby could help to protect normal cells from ROS-induced apoptosis [78]. The selective protection is driven by the pH dependence of the CONP induced catalysis and normal cells have a neutral intracellular environment whereas cancerous cells tend to be acidic [79]. Ouyang *et al*. proposed that CONPs could diffuse from polymer films as they degrade within the body and accumulate in the surrounding tissue of the lumpectomy cavity. The rate of diffusion into the tissue could be tailored by the concentration of CONPs and the degradation rate of the polymer film so that the radioprotective effect could be matched to the radiation schedule to increase the effectiveness of treatment [76].

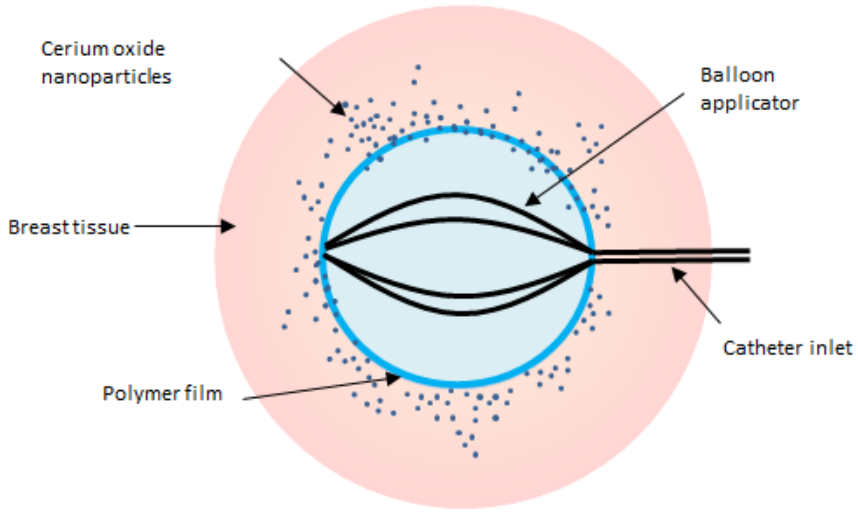

Figure 5 Schematic of a potential balloon applicator that is coated with a polymer film loaded with cerium oxide nanoparticles for radioprotection of healthy tissue during accelerated partial breast irradiation.

One method used in brachytherapy, as well as in EBRT, to achieve maximal tumour radiation dose whilst limiting the exposure of surrounding healthy tissue is the incorporation of radioprotective spacers. Spacers are surgically positioned into predetermined locations and manually displace healthy tissues and adjacent organs from the tumour. When the radiation source is active at the tumour site, healthy tissues are pushed further away and therefore receives a lower absorbed dose [80]. This helps to alleviate damage to healthy tissue and reduce radiation-induced adverse events. Spacers are predominantly, although not exclusively, used in cancers of the abdominal and pelvic regions and are widespread in the treatment of cervical and prostate cancer due to the relative ease of implantation [81]. The size, shape and material used for radiotherapy spacers is dependent on the anatomical site of the tumour. Natural materials such as human collagen [82] and hyaluronic acid [83] have been investigated as spacers due to their biocompatibility and biodegradability. Although the preliminary clinical indications on the use of hyaluronic acid and human collagen were encouraging, hyaluronic acid was found to be unstable when exposed to radiation and highly viscous making accurate injection a technical challenge, whereas the availability of human collagen has limited its utilisation [84]. Polyethylene-glycol (PEG) hydrogel is a non-toxic, non-immunogenic and bioresorbable material and is commonly employed as a radioprotective spacer for use in prostate cancer treatment [85]. SpaceOAR™ (Augmenix Inc., Waltham, MA) is currently the only FDA approved hydrogel for use in prostate cancer radiation therapy [86]. The hydrogel is placed between the rectum and the prostate, thereby controlling the spatial distribution and accuracy of radiation from brachytherapy seeds within the prostate, whilst decreasing rectal damage during radiotherapy (see Figure 6). Spacers can be used in brachytherapy as well as being utilised in EBRT, in particular in conjunction with stereotactic body radiotherapy (SBRT), where the large fraction sizes used suggest that there is a greater need to protect adjacent healthy tissue from damage [87]. In similar studies, PEG hydrogel micro particles containing covalently bound iodine have been investigated as radiopaque fiducial markers and spacers for gynecologic and pancreatic cancer treatment [80, 88]. The presence of iodine enables it to be visible using CT, cone beam computer topography and mammography whilst the high

water content of the hydrogel makes it visible via MRI and ultrasound. It has therefore been proposed that hydrogels such as this could be accurately placed in regions between the head of the pancreas and the radiosensitive duodenum to allow dose escalations of radiotherapy in cases of unresectable pancreatic cancer [80].

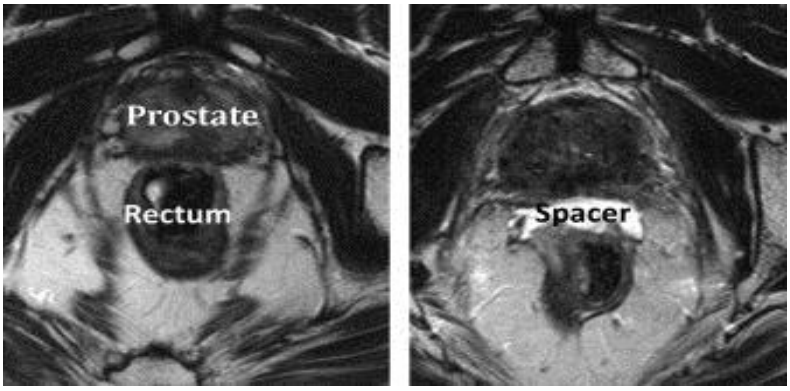

Figure 6 Axial T2 MRI images of a patient (a) prior to hydrogel spacer injection, (b) post implantation. Reproduced with permission from [89].

Domb *et al.* developed biodegradable balloons as alternative devices capable of acting as spacers that can displace the irradiated prostate away from the surrounding tissues, such as the rectal wall, in patients undergoing radiotherapy for prostate carcinoma. Biodegradable PLCL polymers are used to fabricate the biodegradable balloons (bio-balloons) which can be inserted via a minimally invasive procedure through the perineum in a deflated, rolled up conformation before being inflated *in situ* to form a structure with a defined size and volume [90]. The bio-balloons were designed to remain inflated and to retain their structural integrity over a period that exceeds the radiotherapy treatment, typically around 6 weeks, but fully degrade in the body within a year with no residual parts of the device remaining *in situ*. Both the polymer of choice and the methodology used to fabricate the balloon were vital in creating the device with the desired physical and mechanical properties. The balloons needed to be formed from a highly homogenous, flexible and elastic material that maintains its mechanical properties whilst folded prior to inflation and also whilst inflated *in vivo.* Poly-l-lactide-co- ε-caprolactone (PLCL) was the polymer used since this had the necessary mechanical properties and had an optimum degradation profile that was shorter than other polyhydroxyacid based biomaterials, such as polycaprolactone (PCL) [91]. The bio-balloons were fabricated using a dip coating technique in order for the balloons to be formed from a continuous single unit that minimised the number of connecting parts and regions where parts were joined/glued. Regions such as these are susceptible to deformation and leakages that could cause premature deflation of the bio-balloons *in situ*. An agarose mould of the desired size and shape of the bio-balloon and its nozzle was first formed and subsequently dipped into a polymer solution containing 14% w/v of PLCL in the organic solvent dichloromethane. This was performed under a dry nitrogen atmosphere to prevent condensation forming on the PLCL layer whilst the solvent evaporated. The agarose mould underwent three successive cycles of dipping and drying to fabricate balloons with an optimal and homogenous wall thickness of ~100 μm. Following completion of the dip coating, the agar mould is removed by dissolving in distilled water at 90°C and squeezed out of the balloon nozzle [92]. The balloon is then sterilised using ethylene oxide, in order to retain its chemical and mechanical stability, and can be implanted into the

desired region *in vivo,* inflated using physiological saline and sealed using a PLCL plug to displace the irradiated prostate from surrounding healthy tissue. Clinical trials have demonstrated the safety of the bio-balloons and their ability to increase the rectal-prostate interspace from 0.22 ± 0.2 cm to 2.47 ± 0.47cm throughout the duration of radiotherapy [93]. The separation decreased the radiation exposure to the rectum, thereby reducing the adverse events and facilitating dose escalation of the radiotherapy to improve treatment efficacy.

Endorectal balloons made from silicon or latex have also been routinely employed to physically move the dose-limiting structure of the rectum during prostate cancer radiotherapy and to reduce prostate motion during treatment [94]. Endorectal balloons have the potential to change the dose exposure of surrounding healthy tissue but can increase exposure to the anterior rectal wall meaning accurate and controlled placement is vital [95]. Parsai *et al.* developed a novel, detractable device to temporarily displace the rectum to prevent damage during treatment of tumours in the pelvic cavity [96]. A Nitinol shape memory wire was placed inside a clinical approved endorectal balloon that could be activated by joule heating and controlled through an electrical conductor that produces thermal energy as current passes through it. The Nitinol wire functions as an actuator that allows the shape of the device to be tailored *in situ* to accurately move the organs adjacent to the body cavity in specific directions. Nitinol is a nickel-titanium alloy that is biocompatible and commonly used for medicinal and orthopaedic applications and displays biomimetic actuation due to a reversible crystalline phase transformation. Nitinols unique reversible shape memory property is due to its two crystalline structures: martensite and austenite [97]. Prior to insertions of the endorectal balloon device, Nitinol is soft and flexible due to its martensite phase. Once inserted, barium is injected to allow proper localisation of the balloon where it can then be inflated and orientated into the correct position. Nitinol is than actuated via joule heating causing the transformation of the Nitinol to its austenitic phases, thereby causing the Nitinol wire to change its shape. This results in the controlled movement of the balloon device that displaces the posterior rectum wall and a subsequent movement of the anterior rectum wall away from the proposed radiation field. Following the completion of HDR brachytherapy or EBRT, a reduction in temperature causes the Nitinol to return to its original martensitic phase and shape so that the device can be deflated and removed from the patient with minimal discomfort. Devices such as this have the potential to alleviate morbidities to the rectum and facilitate the delivery of escalated, ablative dose of radiation to tumours.

Currently, the majority of image-guided brachytherapy procedures routinely use inert radiotherapy biomaterials for devices such as spacers, seeds and their applicators. The sole purpose of these inert biomaterials is to ensure geometric accuracy for the duration of therapy in order for a predictable and calculated dose of radiation to be achieved at the cancerous site. Recent studies have investigated developing a new generation of radiotherapy biomaterials that are multifunctional and capable of enhancing current treatment and delivering additional therapeutic effects [98]. These ‘smart’ biomaterials are being designed to be responsive to specific stimuli, such as temperature or pH, and responding directly to cancer induced changes due to the conditions of the tumour micro-environment. Innovative smart biomaterials can have an active response or change in structure thereby facilitating additional functions that could enhance treatment, such as targeted drug delivery or initiation of an immune response [99].

Although spacers have become critical components for accurate radiation delivery, they provide no direct therapeutic benefit. The close proximity of the spacer to the tumour site has

driven the rationale that this may also be harnessed for *in situ* delivery of therapeutic payloads to the cancer cells. Kumar *et al.* [100] developed Implantable Nanoplatforms for Chemo-Radiation Therapy (INCeRT) spacers formed using PLGA polymer matrix containing silica nanoparticles (with a size of 254 ± 5 nm) embedded within. These spacers were biocompatible with the same dimensions as clinically used spacers. The nanoparticles acted as drug/fluorophore depots that were released from the PLGA matrix due to its dissolution within the body. The nanoparticles then released encapsulated cargo upon interaction with biological fluid enabling the local delivery of therapeutics in a controlled and sustained manner. Nanoparticles have the added ability to passively target cancerous tissue and accumulate within tumours for an extensive time period due to the enhanced permeability and retention (EPR) effect [101]. Nanoparticles, such as those used on the INCeRT spacers, that can encapsulate both therapeutic and diagnostic payloads can allow for the qualitative assessment and extent of drug distribution within the tumour. Such methods could allow for a targeted, high dose of drug to be delivered with greater spatial distribution within the tumour. A delivery system like this could offer benefits over many typical chemotherapy regimens where systemic toxicities prevent their use throughout the duration of radiotherapy. The synergistic effect of radiation and chemotherapy could also be enhanced if effective radiosensitisation of the target tissue could be achieved whilst simultaneously sparing the neighbouring healthy tissue [102].

Polymers are attractive materials for sustained use or controlled release of therapeutic payloads due to multiple parameters that can be altered to create an optimal release profile. The molecular weight and the specific polymer used as well as type, concentration and size of payload can be tailored to customise the loading and release rates [103]. Synchronising the radiosensitisation or radioprotective effects of the payload with the radiation dosage could produce superior therapeutic efficacy [100]. Materials that facilitate this and increase the biodistribution of the payload to the target allow for optimisation of individual radiotherapy schedules and are therefore hugely desirable [104]. Many radiosensitising and radioprotective agents suffer from poor bioavailablity and rapid metabolism, along with having high systemic toxicity and therefore must be delivered in a controlled and targeted manner.

Utilising biomaterials for radiotherapy to deliver nanoparticles that either achieve radiosensitisation of surrounding tissue producing a radiation boost or those that can act as radioprotectants continues to be an area of intense research [105]. Nanoparticles can be fabricated to contain various different payloads and numerous techniques have been explored to incorporate them into and within existing biomaterials. Despite this, issues still remain regarding the use and delivery of sufficient concentrations of nanoparticles to the tumour site or surrounding tissue if this is the intended target. Nanoparticles that do not reach their target site could end up in systemic circulation, resulting in off-target effects that could be detrimental to the patients' health [106].

5. Glass Biomaterials and Selective Internal Radiation Therapy

Bioactive glasses differ from non-bioactive glasses as they are able to form a continuous interface with host tissue upon implantation in the body without triggering fibrosis. This phenomenon has led to extensive investigations into their use for a range of potential therapeutic applications. The ability to tailor the glass properties by altering the composition of the glass with

network modifiers and modifying oxides has been fundamental to these studies [107]. Alterations in the glass formulation affect the glasses physico-chemical and mechanical properties, bioactivity and dissolution rate. Novel glass formulations have been developed to improve the properties and to enhance the clinical translatability of bioactive glasses in order for them to address specific medical needs and elicit therapeutic responses [108].

The versatility of bioactive glasses have led to them being investigated for use in radiotherapy since various radionuclides that emit alpha, beta or gamma radiation can be chemically incorporated into their structure. Beta-emitting radionuclides have been most extensively studied due to their ability to deliver tumoricidal doses of radiation with sufficient levels of tissue penetration [109]. The properties of the radionuclide can be used to identify the best candidate to deliver the desired dose of radiation, over the appropriate distance, to achieve effective treatment of a specific organ or tissue [110]. During the manufacturing and processing procedure, the non-radioactive radionuclide is incorporated into the chemical and physical structure of the glass. Various processing techniques can be used to fabricate bioactive glasses into an array of different practical morphologies [107]. The ability to tailor the size and shape of bioactive glass microspheres facilitates their transport and delivery to specific locations to provide *in situ* radiotherapy. These glass microspheres are irradiated (i.e. made radioactive) by neutron activation of the radionuclides. Since neutron activation is the last step of the manufacturing process this provides an inherent safety benefit during glass fabrication. The time from activation to when they are actually delivered to clinic for administration can also be used to ensure the radiation dose required is provided to the patient.

Selective internal radiation therapy (SIRT) (also known as radioembolisation) is one method that has been employed to treat unresectable hepatocellular carcinoma to great effect. The proximity of the liver to adjacent critical organs can prevent the use of conventional EBRT [111]. SIRT is a form of internal radiotherapy that involves the delivery of radioactive microspheres to selectively irradiate tumours within the liver. The radioactive microspheres are administered via the hepatic arteries due to the fact that normal liver cells are predominantly vascularised by portal venous flow whereas cancer cells almost exclusively receive arterial blood. The liver vascularisation therefore results in the preferential deposition of these microspheres within hepatic tumours due to their increased vascularity (see Figure 7) [112]. Following administration, the microspheres migrate to and become trapped in hepatic vasculature supplying the tumour. The proximity of the microspheres to the tumour results in localised delivery of lethal doses of radiation to the tumour whilst sparing healthy parenchyma [113]. The microspheres can simultaneously cause a degree of embolisation by occluding the blood vessels to prevent blood and nutrient flow to the tumour [114]. There are currently two commercially available, FDA approved ^{90}Y containing products used for SIRT [115]. TheraSphere (BTG International, London, United Kingdom) are alumina silicate glass microspheres, whereas SIR-Spheres (Sirtex Medical, Sydney, Australia) are resin-based microspheres. ^{90}Y is used as it is a pure β-emitter with a tissue penetration depth ranging from 2.5-11 mm, capable of delivering therapeutic doses of ionising radiation. Despite the differences in physico-mechanical properties between the two different materials, both types of microspheres have exhibited comparable efficacy in clinical trials [116].

The ^{90}Y containing resin-based SIR-spheres were developed in the late 1980s and approved by U.S. Food and Drug Administration in 2002 for the treatment of hepatic metastases secondary to colorectal adenocarcinoma [117]. SIR-spheres are comprised of a proprietary biocompatible microsphere that is coated with a cross-linked cation exchange polystyrene resin. ^{89}Y is integrated into and immobilised within the resin matrix via ion exchange of sodium for yttrium followed by its precipitation as a phosphate salt. This prevents ^{90}Y leaching out of the microspheres, following neutron activation, to a level that would be deemed to be physiological important *in vivo* [118].

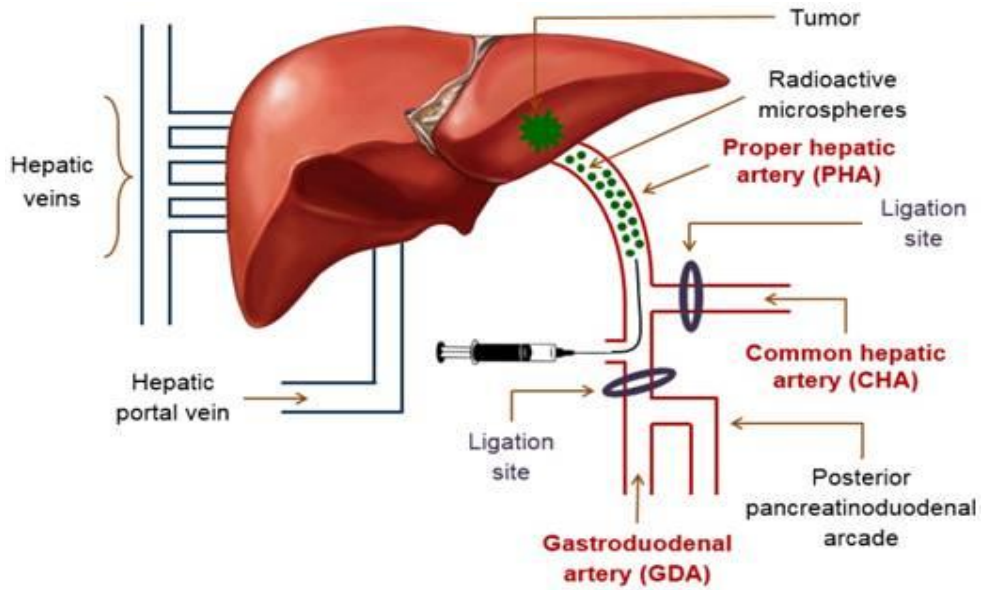

Figure 7 Schematic of SIRT and the use of radioactive microspheres for the treatment of liver cancer. Microspheres are administered via a catheter into the hepatic vasculature. Microspheres emit beta radiation to the tumour cells whilst having an embolic effect to further induce tumour apoptosis. Reproduced with permission from [119].

Traditional melt-quenching technique involving ^{89}Y, aluminium oxide and silicon dioxide is used, followed by flame-spheroidisation for Therasphere glass microsphere manufacture [115]. The yttrium alumina silicate glass microspheres are composed of 17.1 mol% Y_2O_3, 18.9 mol% Al_2O_3 and 64.0 mol% SiO_2 and range from 20-30 µm in diameter (see Table 2). The microspheres are non-toxic, non-biodegradable and chemically resistant to body fluids [120]. These glass microspheres undergo neutron bombardment which causes ^{89}Y to be transduced into the β-emitter ^{90}Y whilst the other elements within the glass remain non-radioactive. The ^{90}Y-doped aluminosilicate glass microspheres demonstrate high chemical durability, which is essential for neutron activation and prevention of ^{90}Y leakage [121]. Since the yttrium is incorporated in the glass structure and not a surface coating, it can only leach out of the glass and the target organ if the microspheres degrade *in vivo* during the time its radioactive [122]. The half-life of ^{90}Y isotope is 2.7 days meaning that the radioactivity of the microspheres declines to a negligible level within 21 days from initial neutron bombardment [123].

Table 2 Characteristics of commercially available ^{90}Y containing microspheres used in Selective Internal Radiation Therapy. Adapted from [124].

Feature	SIR-Spheres	TheraSpheres
Isotope	^{90}Y	^{90}Y
Half-life (hr)	64.2	64.2
Material	Resin	Glass
Diameter (μm)	20-60	20-30
Activity per particle (Bq)	50	2500
Spheres per 3 GBq	$40\text{-}80\times10^6$	1.2×10^6
Specific gravity (g/mL)	1.6	3.2
Embolic effect	Mild	Negligible
Contrast injection	During infusion	No
FDA approved indication	CRC liver metastases with intrahepatic floxuridine	HCC

*FDA=Food and Drug Administration; CRC: Colorectal cancer; HCC: Hepatocellular carcinoma.

Phosphate-based glass microspheres have also been investigated for radiotherapy applications. The use of phosphate based glasses is advantageous due to their relatively low melting point to allow ease of manufacture and post processing techniques into different practical morphologies. Alteration to the composition of phosphate glasses have been shown to control their degradation rate over several orders of magnitude, ranging from minutes, days, months to years [125]. This makes them attractive resorbable materials to be implanted into the body that can be tailored to degrade *in vivo* at a rate that is optimum for a specific clinical application. Non-degradability is the main disadvantage of currently available silicate glass microspheres for SIRT as the glass microspheres would remain in the body as an impurity in the target area after radioactive decay of ^{90}Y [126].

^{31}P can also be neutron activated into the β-emitter ^{32}P, which has a half-life 14.3 days [126]. ^{32}P could potentially provide localised radiotherapy and enable the possibility of being incorporated into the glass structure of the microspheres simultaneously with another radionuclide such as ^{90}Y. Masakazu *et al.* studied the effect of phosphorous ion implantation into a number of yttrium containing silica glasses to examine the possibility of enhancing their radiotherapeutic effect due to the longer half-life of ^{32}P. Whilst high chemical durability was obtained, phosphorous can be a problem for some silicate glasses as it plays an integral role in nucleation of crystalline phases [127]. Sene *et al.* investigated the effect of phosphate glass microspheres (P_2O_5-Al_2O_3-SiO_2-MgO) for radiotherapy application and found that the glass composition $42P_2O_5$-$12Al_2O_3$-$4SiO_2$-44MgO (in weight%) showed the best chemical durability and resistance to crystallisation, displaying the feasibility of using phosphate-based glass microspheres for radiotherapy applications [128]. The high durability of ceramic yttrium phosphate microspheres, composed of Y_2O_3 and YPO_4, have also been explored as potential materials capable of delivering radiotherapy [126]. Glass microspheres made from alumina borate glass doped with rhenium have also been considered for *in vivo* radioembolisation therapy since rhenium is composed of two isotopes (^{185}Re and ^{187}Re) that can be converted to beta-emitting ^{186}Re and ^{188}Re radioisotope respectively, after neutron bombardment (see Table 3) [129].

Prior to microsphere administration during SIRT, a diagnostic angiography is conducted to assess the vasculature of the liver and tumour. Technetium-99m macroaggregated albumin (^{99m}Tc-MAA) particles, that are comparable in size to the ^{90}Y microspheres, are injected as a scout dose and their distribution within the liver studied. Due to ^{99m}Tc emitting readily detectable gamma rays, single-photon emission CT (SPECT) can be used to estimate the dose to the tumour and surrounding parenchyma and to evaluate the potential of pulmonary and extrahepatic shunting [130]. Although ^{99m}Tc-MAA SPECT dosimetry is accurate for SIRT, alternate methods are being developed that can combine the therapeutic radiotherapy with the ability to simultaneously achieve diagnostic information at the tumour site. This theranostics based approach could provide real time information on the biodistribution of radiotherapeutic agents within a tumour, help determine the optimal dose and monitor the response to treatment [131].

Barros Filho *et al.* explored the use of holmium doped phosphate-based glass microspheres as alternative materials for SIRT that could also provide theranostic potential [132]. Traditional melt-quenching method was used to prepare these glasses followed by flame spheroidisation or gravitational falling within a furnace was performed to obtain microspheres of the desired geometry (see Table 3). Neutron activated ^{166}Ho is comparable to ^{90}Y in that it is a β-emitter, with a mean tissue penetration of around 2.5 mm, although it has a significantly reduced half-life of 26.8 hours [133]. The advantage of using ^{166}Ho is that it is also a gamma emitter, meaning that it can be detected using SPECT, as well as its paramagnetic properties allowing for Magnetic Resonance Imaging [35, 134]. These clinical imaging techniques could facilitate the real time visualisation of the holmium-doped microspheres during and post-treatment and can be used to quantitatively measure ^{166}Ho distribution *in vivo* [133, 135].

Radioactive ^{166}Ho loaded poly(L-lactic acid) (PLLA) microspheres (^{166}Ho-PLLA) (QuiremSpheres®, Quirem Medical B.V., The Netherlands) have been developed as an alternative to glass microspheres for SIRT [136, 137]. The use of ^{166}Ho-PLLA has the potential to eliminate the need of a scout dose, such ^{99m}Tc-MAA, followed by a therapeutic dose since the ^{166}Ho-PLLA microspheres are capable of performing both roles concurrently. The diagnostic feature of ^{166}Ho-PLLA could enable monitoring of intrahepatic behaviour of the microspheres during and post treatment [138]. Knowledge of the amount of microspheres that reach the cancerous and normal liver tissue of each patient allows clinicians to adjust the treatment plan accordingly and identify tumours that may be receiving an inadequate dose [139]. Poly(lactic acid) microspheres that contain 30 weight% rhenium for liver cancer treatment have also been investigated. Polymers susceptibility to degradation due to the use of high neutron fluxes during neutron activation and the difficulty in achieving a high enough activity to produce a therapeutic effect must be circumvented when developing microspheres for SIRT [140].

Currently, research has predominantly focused on glasses containing only a single radioactive element that can be used to deliver *in situ* radiation to cancerous tissue. It is feasible that glasses could be prepared containing multiple elements that can become radionuclides following neutron activation of the glass. The radionuclides could simultaneously irradiate the target tissue and the differences in half-lives and emission energies could be utilised to optimise the radiation delivered to the tumour, dependent on it its size and location [141].

Table 3 Materials used to fabricate microspheres and investigated for *in situ* delivery of radiation therapy.

Material	Particle size (μm)	Manufacturing Method	Application	Advantage	Disadvantage	Reference
Yttrium alumina silicate MS	20-50	Flame spheroidisation	Radiotherapy application	Safe, highly durable	Non-degradable	[121] [120] [142]
Yttrium silicate MS	20-50	Silicon oil method	Radiotherapy	Low leaching ability	-	[143]
Yttrium phosphate ceramic MS	20-30	W/O emulsion	Deep-seated cancer	High phosphorous content	Low chemical durability	[144]
Yttrium oxide MS	20-30	Enzymatic reaction	Deep seated cancer	Low density, high chemical durability	Microspheres may accumulate in the blood vessels of patients	[145]
Phosphate glass MS	20-30	Flame spheroidisation	Radiotherapy	Easy to prepare, controllable chemical durability	Loss of phosphorous content during processing	[128]
Holmium doped phosphate based glass MS	45-63	Flame spheroidisation and spheroidisation by gravitational falling in a tubular furnace	Radiotherapy	Low density, high amount of Holmium, gamma emitter allowing for SPECT detection	Partial crystallisation may be occurred during spheroidisation	[132]
Alumina borate glass doped with rhenium MS	25-32	Flame spheroidisation using propane/air flame	In vivo radioembolisation therapy	Neutron activated within 10 hours, Imaging of biodistribution possible, safe radiation release	Non degradable	[129]
Alumina silicate glass MS doped with yttrium and lutetium	20-40	Sol-gel method	Treatment of hepatic tumors with SPECT imaging capabilities	Bio-distribution is possible via SPECT imaging	Inhomogeneous microspheres	[146]

*MS= Microspheres.

6. Bone Cements and Radiotherapy for the Treatment of Spinal Metastases

Vertebral metastases are a common manifestation of many cancers and the proximity of vertebral metastases to the spinal cord can result in debilitating pain as well as severe neurological complications in the event of vertebral collapse. In cases of metastatic spinal cord compressions, the treatment regimens must address the tumour itself as well as restoring the structural integrity of the vertebrae [147]. Vertebroplasty or kyphoplasty is performed in such instances and are surgical procedures involving the injection of a bone cement into the vertebral body to restore strength. This is conventionally followed by multiple session of external beam radiation therapy to control and arrest tumour growth as well as providing pain relief. Despite advances in conformal EBRT, concerns about the safety of this technique arise due to potential irradiation of adjacent radiosensitive spinal cord tissue [148]. An alternative approach that has been considered is the incorporation of radionuclides into the bone cement.

Polymethylmethacrylate (PMMA) is the most commonly used material to form bone cement due to its good mechanical properties and its ability to be administered via a minimally invasive percutaneous procedure [149]. Donanzam *et al.* investigated combining PMMA with calcium phosphate ceramics that contained β-emitting radionuclides integrated within their structure as novel biomaterial to treat spinal metastases [150]. Calcium phosphate based biomaterials have been extensively studied for bone repair and regeneration due to their bioactivity, osteoconductive properties and similarity of their chemical composition to that of bone [151]. They offer flexibility in their composition and synthesis by techniques such as sol-gel and melt quenching. In their work, Donanzam *et al.* formed composite PMMA with multiphasic calcium phosphates that incorporated either holmium or samarium. Upon neutron activation the radioisotopes ^{166}Ho and ^{153}Sm were produced with activates calculated to be 32.5 and 14.5 MBq/mg, which was considered to be clinically suitable for site specific radiotherapy. PMMA injection itself was believed to have antitumour effects which were driven by the exothermic reaction of its polymerisation *in vivo*. The hyperthermia induced death of the tumour cells and its neovascular network can arrest tumour growth in addition to the bone cement inhibiting the region in which the tumour can grow into. The synergistic effect of PMMA cement and radiotherapy is anticipated to lead to a more efficacious treatment [152]. Other radionuclides such as ^{32}P, ^{188}Re and ^{153}Sa have also been investigated as radionuclides that could augment the symptomatic relief provided by vertebroplasty to patients with vertebral metastases [153, 154]. Although preliminary studies, biomaterials such as these provide a novel approach to integrate radiotherapy with vertebroplasty to form a convenient, single treatment procedure with enhanced clinical benefits over a sustained period [155].

The incorporation of radionuclides onto or within the structure of various biomaterials can facilitate the targeted and sustained delivery of radiotherapy to cancerous tissue. Each radionuclide has their own characteristic energy spectrum and particle emission [153]. The different particle energies and half-lives can be utilised to increase the spatial-temporal localisation of radiation and be used to customise the length and intensity of the absorbed radiation dose received (see Table 4). Sophisticated software and modelling programs can be used to predict the dose distribution from the radionuclide source, or combination of different sources, and can evaluate the suitability of potential new treatment methods.

Table 4 Characteristics of β-emitting radionuclides that have been investigated for the *in situ* delivery of radiation therapy. Mev, mega-electronvolts; keV, kilo-electronvolts.

Radionuclide	Half-life (days)	Maximum β particle energy (MeV)	Maximum γ particle energy (keV)	Maximum tissue penetration range (mm)	Reference
^{32}P	14.3	1.71	/	8.7	[156]
^{47}Sc	3.4	0.600	159.4	3	[157]
^{67}Cu	2.6	0.575	184.6	2.2	[158]
^{89}Sr	50.5	1.492	/	8	[20]
^{90}Y	2.7	2.284	/	11	[112]
^{131}I	8	0.81	0.364	2.4	[26]
^{153}Sm	1.95	0.808	103	3	[154]
^{161}Tb	6.9	0.593	74.6	3	[159]
^{166}Ho	1.1	1.84	81	8.7	[132]
^{177}Lu	6.7	0.497	208	2.2	[27]
^{186}Re	3.8	1.07	137	4.5	[140]
^{188}Re	0.7	2.118	155	11	[51]

7. Utilising Biomaterials for Targeted Drug Delivery during Radiotherapy

The synergistic effect of chemotherapy and radiotherapy has the potential to enhance cancer treatment efficacy and a consequential reduction in the treatment time for patients. Chemotherapy is commonly employed as an adjuvant therapy prior and following radiotherapy to enhance its tumorcidal ability. Chemotherapy is predominantly administered systemically and is often non-selective, which can cause radiosensitivity of healthy tissue and therefore limits drug dosage and potential efficacy [160]. Strategies involving the use of biomaterials have been adopted capable of delivering chemotherapeutics in a site-specific manner to increase the efficacy of radiotherapy.

Gliomas are the most prevalent form of brain tumour and require intratumoral delivery of chemotherapeutics during radiotherapy in order to reduce toxicity to surrounding critical tissue and to circumvent the blood brain barrier [161]. Liang *et al.* investigated the use of oxidised hyaluronic acid/adipic acid dihydrazide (oxi-HA/ADH) hydrogel as a biocompatible, thermogelling material to be used for the targeted, sustained delivery of the antineoplastic agent carboplatin [162]. The oxi-HA/ADH hydrogel was injected intratumorally in a cool liquid form, where it then configured into a gel-like matrix at body temperature within 1 to 8 minutes depending on operational temperatures. The hydrophilic carboplatin was administered with the hydrogel and retained in the matrix structure following crosslinking. The naturally occurring hyaluronidase enzymes can gradually degrade the hydrogel facilitating the sustained release of carboplatin. Carboplatin forms inter-strand and intra-strand cross links with purine bases of DNA causing

inhibition of DNA repair and therefore augmented radiation-induced DNA damage and subsequent apoptosis [163].

Biomaterials that are responsive to radiation are being developed for novel approaches such as drug delivery vehicles at sites being irradiated. Fan *et al.* synthesised a gamma radiation-responsive amphiphilic polymer with tellurium-containing side-chains (PEG-b-PAA-g-Te) for targeted drug delivery [164]. Tellurium-containing compounds have been explored as anticancer agents since they are capable of increasing intracellular oxidative stress, generating ROS and converting less-reactive-ROS into higher reactive species [165]. The PEG-b-PAA-g-Te polymer coordinated with anticancer agent cisplatin and was self-assembled in an aqueous solution. This resulted in cisplatin being retained in the hydrophobic core of the polymer nanoparticles. The coordination of the two anticancer agents provisionally reduced their cytotoxic effects and thereby reduced to an extent some of the adverse off-target effects associated when administered. A low dosage of gamma radiation caused the tellurium side-chain of the polymer to become oxidised. This oxidation increased the hydrophilicity of the polymer and caused the nanoparticles to disassemble. The oxidation and subsequent disassembly caused weakening of the coordination between cisplatin and the tellurium, resulting in both compounds being exposed and able to elicit their cytotoxic tumour effects [164]. Cisplatin inhibits DNA replication and repair during the S phase of cell cycle and can therefore enhance radiation-induced apoptosis of irradiated cancer cells [166]. The material is responsive to the radiation and can enhance the delivery of anticancer agents in a site-specific manner whilst sparing the tissue that is not-being irradiated to reduce off target effects.

It has been well established that elevated levels of ROS are produced within cells following targeted radiation of cancerous tissue which is succeeded by intracellular reoxygenation post irradiation [35]. Utilising the high oxidative reactivity of ROS has been explored as an internal stimulus to selectively enhance drug delivery within irradiated tumours. Liu *et al.* developed ROS-responsive poly(tehiodiethylene adipate) (PSDEA) and PEG-PSDEA-PEG polymers as a drug delivery system to synergistically enhance the efficacy of radiotherapy by local ROS-activated chemotherapy [167]. The PSDEA and PEG-PSDEA-PEG polymers were synthesised into drug loaded nanoparticles via a nanoprecipitation method and self-assembly. This resulted in the encapsulation of hydrophobic anticancer camptothecin analogue, SN38, within the polymer nanoparticles, by hydrophobic association, thereby enhancing the stability of the drug under physiological conditions. The hydrophobic sulphide residues of the polymer chains were found to undergo ROS-mediated oxidation into hydrophilic sulfoxide groups. As a result, polymer nanoparticles experienced structural changes such as swelling and partial dissociation which caused significant unloading of SN38 from the nanoparticles (see Figure 8). *In vivo* studies showed that tumour growth was significantly inhibited in mice that received dual treatment modality of local X-ray irradiation in conjunction with intratumoral injection of SN38-loaded polymer nanoparticles when compared to either single treatment modality. This nanoparticle biomaterial system improves selective drug delivery by utilising nanoparticles preferential accumulation within tumours and alleviated issues associated with hydrophobic drug delivery [168]. Materials that respond to the local changes that radiotherapy, delivered internally or external, can induce to liberate drugs from their structure in a controllable manner can increase the spatio-temporal delivery of chemotherapeutics that have the ability to significantly improve the efficacy of radiotherapy.

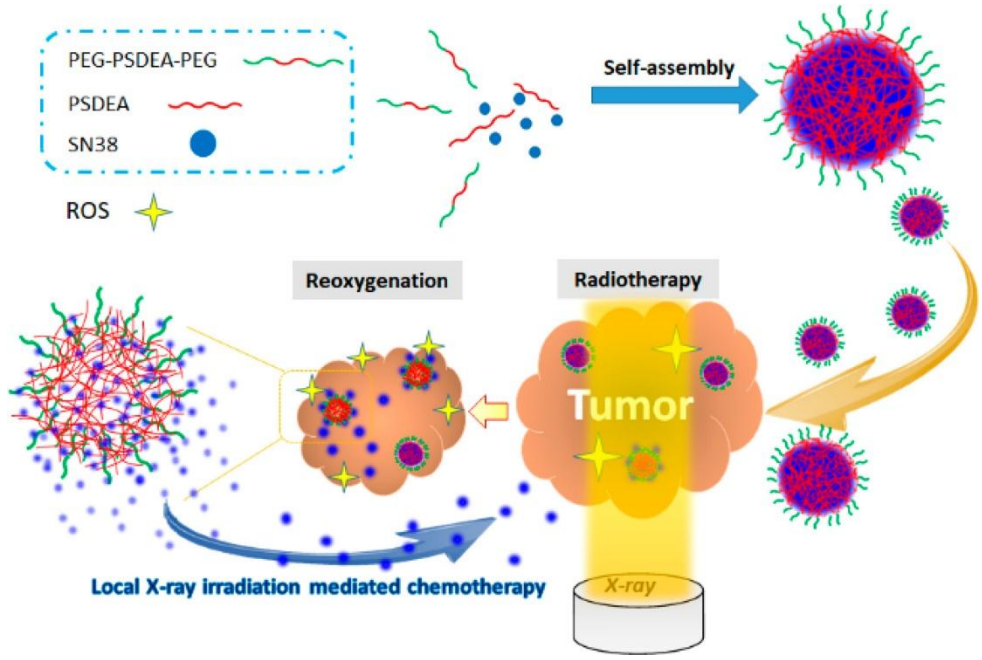

Figure 8 Schematic of the fabrication and mechanism by which ROS-responsive polymer nanoparticles can selectively release SN38 to synergistically enhance the efficacy of radiotherapy by local ROS-activated chemotherapy. Reproduced with permission from Copyright (2018) American Chemical Society [167].

Biomaterials can be used to augment current methods of radiation delivery and in many instances their use can be integrated in current treatment procedures. These biomaterial devices can be placed in close proximity to cancerous regions allowing the *in situ* delivery of radiation in a targeted manner. Novel biomaterials continue to be developed that can enhance the synergistic effect of other treatment modalities, such as chemotherapy and immunotherapy, and that can respond to various stimuli to deliver therapeutic payloads to target tissue to improve treatment efficacy.

8. Conclusions

The majority of improvements in EBRT have been as a result of technological advances in imaging modalities used to plan procedures and equipment to accurately deliver the radiation dose. Despite the ability to control their intensity and to modulate the shape of several beams from multiple angles, externally administered radiation has to pass through tissue to reach its target which can limit application and utility for treatment of certain cancers. Internal radiation is advantageous in that much larger localised doses of therapeutic radiation can be delivered using shorter range radionuclides. Polymer based materials, such as PEG hydrogels, have been explored to displace adjacent healthy tissue to prevent radiation-induced toxicities and as drug delivery vehicles to locally administer chemotherapeutics to enhance radiotherapy. Glass-based biomaterials doped with radionuclides, such as ^{90}Y and ^{166}Ho, have been developed and processed into microspheres capable of selectively irradiating tumours following their implantation into the body. These alpha, beta or gamma producing radionuclides have been chemically incorporated into glass compositions and the ability to process glass into desired sizes and practical

morphologies facilitates their transport and delivery to specific target locations to provide *in situ* radiotherapy. Theranostic materials capable of providing diagnostic information whilst simultaneously delivering a therapeutic effect to enhance radiotherapy continue to be developed. Enhancing conventionally employed biomaterials, such as PMMA bone cements, to also deliver radiation has the potential to improve cancer treatment efficacy. New biomaterials continue to be developed to enhance the synergistic effect of other treatment modalities, such as chemotherapy and immunotherapy, by responding to radiation-induced stimuli and providing localised delivery of therapeutic payloads.

Acknowledgments

This work was supported by the Engineering and Physical Sciences Research Council (EPSRC) Thematic Studentship Centre for Doctoral Training in Bioinstructive Materials for Healthcare Applications [EP/R512321/1] through a doctoral training grant.

Author Contributions

BM: Writing-original draft preparation, Reviewing and Editing; AA: Writing-original draft preparation, IA, AT and RL: Conceptualisation, writing-reviewing and editing.

Funding

This work was supported by the Engineering and Physical Sciences Research Council (EPSRC) Thematic Studentship Centre for Doctoral Training in Bioinstructive Materials for Healthcare Applications [EP/R512321/1] through a doctoral training grant.

Competing Interests

The authors have declared that no competing interests exist.

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