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Smart Radiotherapy Biomaterials

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Abstract

Radiotherapy is a crucial component of cancer care, employed in the treatment of over 50% of cancer patients. Patients undergoing image-guided radiotherapy or brachytherapy routinely have inert radiotherapy (RT) biomaterials implanted into their tumors. The single function of these RT biomaterials is to ensure geometric accuracy during treatment. Recent studies have proposed that the inert biomaterials could be upgraded to 'smart' RT biomaterials, designed to do more than one function. Such smart biomaterials include next generation fiducial markers, brachytherapy spacers, and balloon applicators, designed to respond to stimulus and perform additional desirable functions like controlled delivery of therapy-enhancing payloads directly into the tumor sub-volume, while minimizing normal tissue toxicities. More broadly, smart RT biomaterials may include functionalized nanoparticles that can be activated to boost radiotherapy efficacy. This work reviews the rationale for smart radiotherapy biomaterials, the state-of-the-art in this emerging cross-disciplinary research area, challenges/opportunities for further research and development, and a purview of potential clinical applications. Applications covered include using smart RT biomaterials for boosting cancer therapy with minimal side effects, combining radiotherapy with immunotherapy or chemotherapy, reducing treatment time or healthcare costs, and other incipient applications.

1. INTRODUCTION

Radiotherapy (RT) is employed in the treatment of over 50% of cancer patients either alone or in combination with other treatments such as surgery or chemotherapy [1]. The ultimate goal of radiotherapy is to maximize damage to the cancer cells, while minimizing toxicities to healthy tissue. Major advances have been made over the past decades, as improvements in engineering and computing have enabled RT modalities such as intensity modulated radiotherapy (IMRT), stereotactic ablative radiotherapy (SABR), and image guided radiotherapy (IGRT) to be used in routine clinical practice.

Currently, many patients undergoing image-guided radiotherapy or brachytherapy routinely have inert radiotherapy (RT) biomaterials implanted into their tumors. These inert RT biomaterials can include fiducial markers, spacers, beacons, balloon applicators, engineered to be used in radiotherapy treatment of patients with lung, pancreatic, breast, prostate, liver cancer, and other tumors exhibiting motion or deformation during radiotherapy [2–6]. Currently, these inert radiotherapy biomaterials have only a single function, e.g. to ensure geometric accuracy during the treatment, to enhance therapeutic efficacy [7–11].

With these RT biomaterials already having such unfettered access to the tumor sub-volume, there is compelling rationale for upgrading those single function inert biomaterials to multifunctional or ‘smart’ ones that can deliver additional therapeutic or treatment enhancing benefits. In general, biomaterials are (other than foods or drugs) designed for specific medical uses, that interrelate with biological systems [12]. Smart biomaterials [13–16] are specifically designed to be sensitive to a specific stimulus, such as present in the tumor micro-environment, e.g. temperature, pH, the wavelength or intensity of incident light or an electrical or magnetic field; and to then respond in active ways including changing their structure for drug delivery, radioprotection, priming an immune response, or other functions that have the potential to cogently enhance therapy.

In 2010, Cormack et al. [11] proposed use of smart radiotherapy biomaterials (SRBs): brachytherapy spacers or fiducials loaded with radiosensitizing drugs that could be activated by tumor microenvironment, in the post implantation period, to sustainably deliver the specific drug directly into the tumor sub-volume. The authors concluded that drug loading of implantable devices routinely used in IGRT provides new opportunities for therapy modulation via biological in-situ dose painting. Later, xxx [8] reported on such brachytherapy spacers for delivery of localized chemoradiotherapy. Their results demonstrated that such spacers with customizable release profiles have potential in improving the combined therapeutic efficacy of chemoradiation treatment. High atomic number nanoparticles such as gold nanoparticles (GNPs) can also act as radiosensitizers [17]. Recently, such nanoparticles have been investigated as payloads loaded into smart polymers in spacers, fiducial markers or balloon applicators to boost radiotherapy efficacy [6,7,10,18]. Combining radiotherapy and immunotherapy using such smart radiotherapy biomaterials in treating metastatic disease, with minimal toxicities to healthy tissue is also being investigated [19].

Major advantages of using smart radiotherapy biomaterials (SRBs) (table 1) include the fact that sustained *in situ* delivery of drugs, nanoparticles or other payloads directly into the tumor sub-volume may overcome physiological barriers allowing direct delivery of sufficiently potent payload into the tumor. Standard intravenous delivery approaches typically result in less than 5% of payloads like drugs reaching the tumor [15], while SRBs will enable direct delivery into tumors. The SRB delivery approach would therefore also significantly minimize any systemic/overlapping toxicities. This takes into account the fact that nanoparticles such as GNP are relatively non-toxic [20], and that controlled in-situ release of payloads leads to minimal systemic toxicities [21,22]. Another advantage is that SRBs could simply replace currently used inert radiotherapy biomaterials and so can be employed at no additional inconvenience to cancer patients. Furthermore, the sustained or controlled release and intra-tumor bio-distribution of payloads from the SRBs can be customized or controlled by varying design parameters such as payload concentration, polymer type or weight, nanoparticle size, etc, allowing for optimization to radiotherapy schedules and for superior therapeutic efficacy.

Given this rationale and advantages, SRBs represent a promising area of research and development. This should lead to a new generation of RT biomaterials, designed to perform their primary functions as inert radiotherapy biomaterials, but also controllably deliver therapy enhancing payloads in-situ, amongst other potential functions for optimal diagnostic and therapeutic efficacy.

More broadly, smart radiotherapy biomaterials may also include functionalized stimulus-responsive nanoparticles that can be targeted and activated to boost radiotherapy [7,23]. These and other smart nanomaterials [15,16] could themselves be incorporated into the traditional radiotherapy biomaterials [8]. Targeting the nanoparticles is desirable since once nanoparticles are released into the tumor microenvironment, their uptake and retention in cells is important, as well as functionalization to reach sub-cellular targets like the nucleus [24] or mitochondrion [25] in order to have maximal effect.

Research and development in smart radiotherapy biomaterials is still at an early stage, yet there are many lessons that can be adapted from previous work on smart biomaterials developed for other *in-vivo* applications as well. Research in this area demands for cross-disciplinary collaborations and may even leverage international collaborations given some of the applications being considered. This review examines the potential and state-of-the-art in this exciting and procedure changing area. It begins with coverage on the design of smart radiotherapy biomaterials and how this can be customized or programmed for different functions. Potential applications of SRBs in overcoming current radiotherapy limitations as well as emerging opportunities for research and development are discussed.

2. DESIGN AND STRUCTURE OF SMART RADIOTHERAPY BIOMATERIALS

Design

A smart radiotherapy biomaterial (SRB) is designed or structured to perform sensing and actuation during radiotherapy procedure. One design of an SRB is illustrated in figure 1.

This simple design integrates a commercially available radiotherapy biomaterial e.g. fiducials (figure 1A) into a smart polymer [16] coating which can sense and actuate or change structure to release a payload incorporated in its polymer matrix (figure 1B). The choice of smart polymer depends on the nature of the stimulus that will be used to initiate a response. A number of studies [7–9,26] have favored the use of biodegradable synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA), and/or natural biological polymers such as chitosan. PLGA is a polymer which is used in a host of Food and Drug Administration (FDA) approved therapeutic devices, owing to its biodegradability and biocompatibility, while chitosan is also widely used in a number of biological applications.

Once in place, the SRB can be activated by stimulus e.g. tumor micro-environment, heat, sound or electromagnetic wave, to controllably release the payload *in-situ*, directly into the tumor (figure 1C). In an example reported in recent studies [9,26] it was shown how gold fiducial markers can be coated with nanoporous polymer matrices incorporating nanoparticles. Different polymer types were investigated including the use of PLGA nanoparticles loaded with fluorescent Coumarin-6, serving as a model for a hydrophobic drug, in a biodegradable chitosan matrix. A free drug release system consisting of Doxorubicin, a hydrophilic drug, loaded into a non-degradable polymer poly(methyl methacrylate) (PMMA) coating was also demonstrated [9].

Other designs for smart RT biomaterials that have been developed include those where instead of coating commercially available SRBs, a completely new SRB is developed loaded with the payload. This later approach has advantage of higher loading capacity. In one example of such new design SRB, [8,27] the authors fabricated implantable chemoradiation therapy (INCeRT) spacers loaded with silica nanoparticles (SNPs) containing a drug, to act as a slow-release drug depot for simultaneous localized chemoradiation therapy. The spacers were made of PLGA as matrix and are physically identical in size to the commercially available brachytherapy spacers (5 mm × 0.8 mm). The silica nanoparticles, were conjugated with near infrared fluorophore Cy7.5 as a model drug. The INCeRT spacers were further doped with an anticancer drug, docetaxel. Studies considering the use of other chemotherapy drugs like cisplatin or carboplatin nanoparticles have also been reported [28–30].

Another design being investigated is that of hollow SRBs and a hybrid of the above design models to program or customize for different loading and release rates. These approaches could also be employed for any radiotherapy biomaterials including balloon applicators (figure 1D). Researchers are considering the coating of such balloon applicators with different nanoparticle types e.g. targeted GNP for boosting of dose to residual tumor cells during Accelerated Partial Breast Irradiation (APBI) [6] or using cerium oxide nanoparticles to selectively protect healthy breast tissue during the same, [18] or intraoperative radiotherapy.

Smart Nanoparticles for radiotherapy

The potent component of SRBs is the payload, which could be nanoparticles or so-called nanocarriers/-drones also carrying a payload. A number of excellent recent review papers have covered the field of nanoparticle-aided radiotherapy including high atomic number nanoparticles of: gold/gadolinium, hafnium oxide and so forth [7,31–37]. Growing

consensus remains that one major challenge is how to selectively deliver nanoparticles to cancer cells. Functionalizing nanoparticles is a widely-used technique that allows for conjugation of the nanoparticles with targeting ligands, which possess inherent ability to direct selective binding to cell types or states and, therefore, confer “smartness” to nanoparticles. Friedman et al.[38] recently published an article on ‘Smart Targeting of Nanoparticles’ describing the methods of ligand-nanoparticle functionalization, and a cross-section of various ligand classes used, including small molecules, peptides, antibodies, engineered proteins, or nucleic acid aptamers. PEGylation adds stealth, while multifunctionalization could include imaging moieties for different applications [39–45]. Biomaterials Scientists[46] have also developed targeted, biodegradable nano “drones” to deliver drugs which could be adapted for radiotherapy applications. Using prostate cancer as a model, Farokhzad and co-workers have reported significant work on such smart targeted nanoparticles including nanoparticles conferred with stealth [46–49]. In one study, docetaxel-encapsulated nanoparticles were formulated with biocompatible and biodegradable poly(D,L-lactic-co-glycolic acid)-block-poly(ethylene glycol) (PLGA-b-PEG) copolymer and surface functionalized with RNA aptamers that recognize the extracellular domain of the prostate-specific membrane antigen (PSMA). The approach highlights the potential of employing such nanocarriers to deliver payloads that could also enhance radiotherapy.

For radiotherapy, there is also growing consensus that delivery of nanoparticles within the tumor sub-volume may be necessary but not sufficient to enhance therapy, and that sub-cellular targeting may be crucial in maximizing therapeutic efficacy. This may be particularly important for high atomic number nanoparticles like GNP, which can boost radiotherapy by emission of short range photo-/Auger electrons with subcellular range. For example, Burger et al. [24] developed an approach to enhance the uptake of small GNP functionalized with DNA allowing for strong perinuclear focal accumulation (figure 2). These authors reported that only the GNP functionalized with DNA showed a significant radiosensitizing effect ($p=0.005$) on clonogenic survival using clinically relevant megavolt x-rays. Recently, other third generation (3G) [23] and fourth generation (4G) [7] nanoparticles have been optimized for targeted radiotherapy applications functionalized with other moieties like RGD.

In combination therapy approaches, smart or stimuli-responsive nanocarriers [15] loaded, for example, with chemotherapy drugs or immunoadjuvants have also been reported.[50] Gold nanoshells are currently being investigated as nanocarriers with both diagnostic and therapeutic applications, including photothermal ablation, hyperthermia, drug delivery, and diagnostic imaging, particularly in oncology [51,52]. These gold nanoshells are valuable for their localized surface plasmon resonance, biocompatibility, and easy functionalization hence can be readily adapted to radiotherapy applications leveraging the cross-section for the photoelectric effect. Recently, studies [51,52] have demonstrated that gold nanoshells are able to deliver antitumor drugs into cancer cells, which enhances the efficacy of treatment. It is now well established that GNPs have the advantage of being easily functionalized with active targeting ligands such as antibodies, aptamers, and peptides to increase the particles’ specific binding to the desired targets.

Nanoparticles loaded with immunoadjuvants [53,54] are particularly attractive as the use of nanoparticles may allow improved antigen stability and immunogenicity, but also targeted delivery and slow release. A number of nanoparticle vaccines varying in composition, size, shape, and surface properties have been approved for human use and the number of candidates is increasing [55]. However, challenges remain due to a lack of fundamental understanding on the *in vivo* behavior of nanoparticles, that could operate as either a delivery system to enhance antigen processing or as an immunostimulant adjuvant to activate or enhance immunity. *In-situ* delivery of such nanoparticles or immunoadjuvants to prime the abscopal effect [56] during radiotherapy is appealing. Besides nanoparticles, other nanocarriers such as, micelles, carbon nanotubes, water-soluble polymers, liposomes and dendrimers have been engineered as agents for targeted delivery to benefit tumor diagnosis and therapy [33,37,57] and could be adapted for enhancing radiotherapy.

Song and co-authors[58] have reported on smart GNPs designed for photoacoustic imaging, an image contrast agent responsive to the tumor microenvironment. Such nanoparticles could be employed to enhance radiotherapy treatment via the photoelectric effect while providing the imaging function. From this perspective, GNPs stand out as suitable multifunctional platforms for the development of efficient delivery, imaging and therapy enhancement systems. However, other nanoparticles are also being considered such as “Gadolinium Nanoparticles designed as Smart Molecular Magnetic Resonance Imaging Contrast Agents” [59].

Figure 3 shows the development of amphiphilic gold nanoparticles (amph-NPs) by XXX, composed of gold cores surrounded by an amphiphilic mixed organic ligand shell, which are capable of embedding within and traversing lipid membranes [60]. A strategy has been developed to transport such membrane-penetrating particles into tumor cells and promote their transfer to intracellular membranes for enhanced radiotherapy of cancer.[60] Microneedles have also been developed (figure 3B–C) designed as warheads that can be loaded with a therapeutic payload for sustained in-vivo release (figure 3D) [61,62]. Although these microneedles were originally designed for delivery of immunomodulators through the skin, similar structures might be adapted as SRBs e.g. for cervical cancer treatment. Previous studies have shown that delivery of a vaccine using micro-needles elicits major increase in proliferation of antigen-specific CD8⁺ T cells compared to injections [61]. The delivery of a payload sustainably over many days is expected to also be more effective as envisaged for SRBs.

Programming smart radiotherapy biomaterials (SRBS)

The design of SRBs with smart polymer components allows for programming these polymers to be activated at the appropriate time and site of action [63,64]. These polymers typically exhibit a nonlinear response to a small stimulus leading to a macroscopic alteration in their structure or properties. Fascinating features of such smart polymers arise from their versatility or tunable sensitivity. The versatility of polymer types and their combinatorial synthesis make it possible to program the action or delivery of payloads. In general the release kinetics and distribution of payloads from smart radiotherapy biomaterials can be customized or programmed by varying the polymer type or weighting or crosslinking, as

well as the payload concentration, size of nanoparticle and other factors, improving treatment efficacy [7,27,60,65–68].

Table 2 shows examples of smart polymers considered for SRBs and which stimuli they are responsive to. For some applications, sensitivity to more than one stimulus may be advantageous.

While there are many smart polymers, the most commonly reported polymer being used to develop smart biomaterials is PLGA or chitosan given their biocompatibility and biodegradability [23,27,31,69]. Some studies have reported the potential to use multiple polymer types as highlighted by Yang et al. [67] They designed a release system made of cross-linked chitosan containing both free drug molecules and drug-loaded PLGA nanoparticles. Before exposure to acid or pH stimulus, the chitosan can keep their structural integrity without leakage of the encapsulated substances. Upon acid-triggering, there is first a burst release due to the acid-induced decomposition of the chitosan. The encapsulated free drug molecules and drug-loaded PLGA nanoparticles are rapidly released. Next, the drugs loaded in the PLGA nanoparticles are slowly released over many days to achieve sustained release based on the synergistic effect of drug diffusion and PLGA degradation. Such systems with programmed sequential release proffer more versatility for controlled release in biomedical applications and could be adapted for radiotherapy biomaterials. Adaptations of PLGA (PLGA–PEG–PLGA triblock copolymers) and chitosan are also thermosensitive polymers [70]. In response to a small temperature change, such thermosensitive polymers undergo abrupt change in their solubility to release payloads.

Another exciting class of smart polymers that can be employed for SRBs are based on materials that respond when irradiated at particular wavelengths [68,71]. The features shared by photon-activated polymeric biomaterials involve photons interacting with the material, which triggers photochemical reactions that alter the structure of the cross-linked polymer network. Many such structural alterations result in an evolution of the polymer network, and subsequent macroscopic deformation enabling release of the therapy enhancing payload. Some authors have considered smart biomaterials that can be activated by combination of PH and light [72]. For radiotherapy, a range of wavelengths could be used to stimulate release, including UV light present in the form of Cerenkov radiation during external beam radiotherapy.

A new light-sensitive polymer containing multiple light-sensitive triggering groups along the backbone and incorporating a quinone-methide self-immolative moiety was recently developed and formulated into nanoparticles encapsulating a model dye Nile Red [73]. Triggered burst-release of the payload upon irradiation and subsequent degradation of the nanoparticles was observed. This system is designed to be versatile where the triggering group can be sensitive to a number of wavelengths [73]. At the nanoscale, studies show that smart gold nanoshells can also be spatially and temporally triggered to release controlled quantities of drugs inside target cells when illuminated with photons [51,52]. In general, photon-responsive polymers are very attractive for triggering payload release because of the ability to control the spatial and temporal triggering of the release. The encapsulated payload can be released following irradiation with a photon source from outside the body. Visible

and infrared[64] photon-sensitive polymers are traditionally preferred over UV-sensitive polymers because of the deeper penetration of photons at higher wavelengths, safety and ease of use. However, one area worth exploring in radiotherapy applications is if the UV-range Cerenkov radiation present in the tumor during radiotherapy could be exploited for activating SRBs. Such Cerenkov radiation is currently being considered for quality assurance, [74–76] and therapy applications.[77,78]. Other researchers have also been investigating the use of targeted upconversion nanoparticles that emit high-energy photons upon excitation by near-infrared light to boost tumor cell kill [79]. The results suggest that such a targeted nanoplatform has potential to serve not only as a imaging reagent but also as a therapeutic agent for the treatment of large or deeply seated tumors.

Besides varying the polymer type, another approach to program or customize the release kinetics of nanoparticles or drug payloads from SRBs is by varying the smart polymer weight or cross-linking [9,80]. The structure of some smart polymers can be readily tuned by controlling the density of cross-links. For polymers activated by the tumor microenvironment, their affinity or interaction with the environment could also be customized by varying the cross-links. The porosity of the polymer matrix enables subsequent drug release at a rate dependent on the diffusion coefficient of the nanoparticle or macromolecule through the polymer matrix. Indeed, the benefits of polymers for drug delivery may be largely pharmacokinetic. This is specifically useful with a depot formulation created in the matrix from which the payload can slowly elute, maintaining a high local concentration of the payload over an extended period [70].

The sustained release of payload from the SRBs is important in determining success. The release of the payload can be tuned based on the composition of SRBs and the encapsulated payload. Studies already show that the release kinetics of nanoparticles or drugs from SRBs can be programmed or customized to radiotherapy schedules [7]. Figure 4A shows an electron microscopy image of prototype new design SRB. In-vitro release of payload can be customized for rapid release (figure 4B) or relatively more sustained release over many days (figure 4C).

In-vivo release of a payload with fluorescent label to track distribution has also been investigated, with representative results illustrated in figure 5. Live animal *in-vivo* optical fluorescence imaging with the mice implanted with prototype SRB is shown in figure 5A.

Figure 5B shows 2-dimensonal view of increased intensity (in more image pixels) over time as the fluorescent payload is gradually released in mouse tumor. Figure 5C highlights quantification of the fluorescence intensity. The results demonstrate the potential for customizing the release. In one case with the use of nanoparticles, there is a constant increase in intensity for 14 days as opposed to the second case where there is rapid release and then decrease over the same time frame. A number of publications have reported on efforts to model the distribution of released payload from SRBs [10,11]. Conclusions include the fact that ultrasmall nanoparticles may be more appropriate for radiotherapy application. More experimental work is needed to validate some of these models and develop optimized algorithms based on experimental data that can benefit further research and the development of treatment planning tools in preparation for potential clinical

translation. Such data could be in the form of look-up tables mapping design parameters to function.

3. POTENTIAL APPLICATIONS FOR SMART RADIOTHERAPY BIOMATERIALS

Despite remarkable advances in the development of radiotherapy modalities such as IMRT, SABR or IGRT, major limitations remain in extending the benefits of radiotherapy to many more patients to increase their survival and quality of life. SRBs offer opportunities to address some of these limitations in potential clinical applications:

Dose-painting or radiation boosting

In radiotherapy practice, a persisting limitation is obviously that of normal tissue toxicity [7,37,81]. Clinical studies indicate that radiation boosting or dose-painting leads to significant increase in survival for cancer patients.[82,83] For example, it has been estimated that an increase in every 1 Gy boost of biologically effective dose could lead to 4% relative improvement in survival [83]. However, current modalities for radiation boosting are critically limited by normal tissue toxicity, compounded by respiratory or intra-/inter-fraction tumor motion [82]. An American medical task group report notes that new treatment strategies that can overcome these limitations, allowing an enhanced dose to the tumor while sparing normal tissue, will significantly improve the balance between complications and cure [82].

Nanoparticle-aided radiotherapy e.g. using gold nanoparticles (GNPs) is emerging as a promising new treatment strategy for overcoming these limitations, to enable substantial radiation boosting with minimal toxicity to neighboring healthy tissue [7]. Such targeted nanoparticle-aided radiotherapy with GNP involves first targeting the tumor cells with nanoparticles, and then targeting the nanoparticles during radiotherapy to enhance radiotherapy (RT) efficacy. In a study by Hainfeld et al, [17] the use of GNP with 250 kVp x-rays/photons produced 86% long-term survival as compared to 20% when radiation was used alone, indicating major therapeutic enhancement due to the GNP. Other experimental work has also demonstrated the amplification of damage to tumor cells by GNP. [7,24,60,84,85]. However, the delivery of sufficiently potent concentrations of nanoparticles to the tumor to boost RT at clinical beam configurations (e.g. 6 MV), is limited, by physiological barriers, especially when administered intravenously [7]. These physiological barriers in the tumor vasculature are a problem that is particularly pronounced in cancers like pancreatic cancer [65]. The use of SRBs could overcome these limitations and therefore is an active area of research for applications in radiation boosting with minimal toxicities to normal tissue.

Furthermore, some nanoparticles like gold nanoparticles or gadolinium nanoparticles can serve as multifunctional platforms or theranostic agents i.e. providing imaging contrast while also enhancing therapy. The potential of nanoparticles to provide imaging contrast may benefit treatment planning during nanoparticle-aided radiotherapy or in image-guided drug-delivery, since nanoparticles could also selectively deliver therapeutic agents [86]. The development of quantitative *in vivo* imaging methods for image-guided drug-delivery is an area of research that could advance the ability to guide, monitor, and evaluate drug delivery

across different physical and physiological scales in order to interrogate biodistribution, and therapeutic response. There may also be utility in the combination of smart radiotherapy biomaterials with radioisotopes for imaging and therapeutic delivery as shown with some nanoparticles [87]. Research in this direction could allow for non-invasive imaging during local delivery of the therapeutic payload loaded on nanoparticles to tumors, while providing microanatomical and functional imaging feedback during treatment.

Leveraging the abscopal effect

Another intrinsic limitation to radiotherapy is that it is generally prescribed for treatment of localized disease. However, in 1953, Mole described the abscopal effect, [88] whereby localized radiotherapy at one site may lead to regression of metastatic cancer at distant sites, which were not irradiated. This potent effect could extend the use of radiotherapy from treating localized disease to treat metastatic or systemic disease. In 2004, XXX and co-authors originally connected the abscopal effect with mechanisms involving the immune system [56]. More recent studies corroborate these findings that the abscopal effect is mediated by the immune system [89]. However, the effect is rare because immune-tolerance mechanisms may hamper the development of therapeutically effective responses [88]. A combination of radiotherapy and immunoadjuvants (figure 6), could overcome immune-suppression and lead to vigorous anti-tumor T cell responses [89,90]. However, while such combinations of radiotherapy and immunoadjuvants are promising, their systemic/overlapping toxicities are a major obstacle reported in many studies [89]. The use of SRBs proffers an innovative approach that would minimize such toxicities, and enable slow/sustained in-situ delivery of nanoparticles with immunoadjuvants, which is expected to enable greater therapeutic efficacy [21]. Early research and previous work from vaccine studies (figure 3 above) suggests such an approach could indeed be more effective [68]. Investigations in this area are therefore also ongoing for leveraging the abscopal effect more effectively.

The modus operandi for such an approach is illustrated in figure 7 with potential for the SRB to be activated either by the tumor microenvironment, sound, heat or electromagnetic waves or other stimuli for controlled in-situ release of the payload, directly into the tumor. The SRB's release kinetics can be customized or programmed for sustained release (blue curve) compared to repeated injections (black curve with multiple peaks) [9]. The use of SRBs could thus be optimized to significantly enhance local and metastatic tumor cell kill, during radiotherapy with minimal toxicity or side effects for patients. Such an innovative approach could transform radiotherapy practice extending the use of radiotherapy to treatment of metastatic disease, hence many more patients.

Reducing treatment time or healthcare costs

With increasing advances in radiotherapy from conformal to IGRT and proton therapy, radiotherapy is perceived by many as an expensive treatment modality, especially in resource poor settings with weak healthcare systems. Today, two-thirds of cancer deaths occur in low- and middle-income countries (LMICs). A drastic shortage of radiotherapy infrastructure in LMIC means that up to 70% of cancer patients in LMIC who may benefit from radiation medicine do not receive this essential curative or pain relieving treatment. The International

Atomic Energy Agency (IAEA) has been working to bring together radiotherapy equipment suppliers and radiotherapy users in developing countries to help make radiotherapy infrastructure more affordable or accessible to LMIC populations.

Given the vast disparities in disease burden between developed countries and LMICs, researchers are also working to accelerate the production of new technologies that may help to bridge this gap. The National Cancer Institute Center for Global Health and others are now also increasing funding mechanisms to promote the development of lower cost technologies that can make treatments including radiotherapy more affordable in LMICs. Affordability is inextricably linked to value, quality, efficiency, equity and accessibility. To this end the use of SRBs, which could boost radiotherapy is being considered as an approach to enable hypofractionation, which could in turn potentially reduce treatment times or healthcare costs. The use of SRBs to leverage the abscopal effect in treating metastatic disease is also an attractive approach that could benefit many more patients and increase survival allowing for greater return on investment, especially for state-sponsored radiotherapy centers, common in LMIC [91]. This would yield major benefits in developing countries where patients often present with cancer already at the late stages. Partnerships or collaborations will be very important in this effort to develop lower cost technologies or adaptations of these that are more affordable. Pioneering efforts developing the use of SRBs in this direction are currently in progress [19]. Here, instead of treating patients with many fractions, these SRBs could replace currently used radiotherapy biomaterials (e.g. fiducials and spacers) for highly localized radiation boosting with minimal toxicity to healthy tissues [7]. The potential to hypofractionate or reduce treatment times could avail patients in LMIC countries because the wait times can be unacceptably long for many patients even after trekking hundreds of miles to a radiotherapy center. Prolonged waiting times for receiving treatment can even affect the timing between the administration of radiotherapy doses, hence compromising clinical outcomes and treatment effectiveness. In carrying out research for SRB technology applications in lower-cost radiotherapy, collaborations with developing country partners could be highly beneficial.

4. CHALLENGES AND OPPORTUNITIES FOR FUTURE RESEARCH AND DEVELOPMENT

Despite the potential of SRBs, many challenges remain with opportunities for research and development. Overall, the challenges and opportunities for further research and development described in other reviews for nanoparticle-aided radiotherapy [7] also apply in the development of smart radiotherapy biomaterials. A major advantage is that physiological barriers prior to nanoparticles reaching the tumor or penetrating into the tumor sub-volume could be obviated using SRBs.

One area requiring more work includes optimizing current SRB prototypes. Work still needs to be done optimizing the release and space-time biodistribution profiles, interactions (cellular uptake and retention) of payloads e.g. of nanoparticles including at the subcellular level as a function of design parameters such as payload concentration, nanoparticle size and functionalization, polymer type or weight etc. Various experimental approaches such as

nanoscopy, [92] electron microscopy, CyTOF, MRI and CT imaging will avail such efforts. The establishment of space-time biodistribution profiles/look-up tables, optimized nanoparticle interaction, uptake, localization, retention with cells would be a significant milestone. It is anticipated that the intratumoral distribution of the released payloads will not be uniform. However, it may be more important to have a sufficiently potent distribution of the released payload in the tumor sub-volume for dose-painting or for priming a robust T-cell response. Detailed studies using different polymer types/weight or nanoparticle size, functionalization would allow to optimize distribution. The results of such work should provide more robust data or information on the optimal material parameters and distribution/interaction of nanoparticles. This could also allow more effective modeling of the biodistribution benefiting further research and treatment planning efforts towards clinical translation

Another active area of research is to further elucidate the mechanisms of interactions of SRBs and associated payload with the tumor micro-environment and cells for optimizing therapeutic response. This could involve the use of different nanoparticle types including those with chemotherapy or immunoadjuvant payloads. More research to optimize synergistic interactions of nanoparticle with radiotherapy photons and dosing; and refining computer models to predict or maximize outcomes is needed. Recent work [24] showing that sub-cellular targeting increases the radiosensitization effect of nanoparticles, suggests the need to further optimize radiosensitization efficiency and enhanced understanding of mechanisms for maximizing therapeutic efficacy.

Another attractive area is in the development of imaging and treatment planning software tools when using SRBs. Based on experimental findings and elucidation of mechanisms availing the clinical application of SRBs, such tools could include treatment algorithms that can be subsequently evaluated or optimized in a clinical setting. The tools could also be used for further research and education purposes.

Another challenge highlighted from previous work [15,72], is that the clinical translation of smart biomaterials is not straightforward. This could be explained by the usual sophisticated designs of such biomaterials, which makes the development more complex, especially in terms of the manufacturing process, reproducibility and quality control. Furthermore nontrivial optimizations or improvements are often required to translate stimulus-responsive biomaterials from preclinical experimental models to the bedside. In particular, endogenous stimuli may be hard to control because they may vary from one patient to another (such as the pH of a tumor). Hence systems responsive to external stimuli appear more feasible, if issues due to tissue-penetration depth of the stimulus and its focusing to avoid damage to healthy tissues are addressed. Radiotherapy biomaterials responsive to radiotherapy photons or UV light generated by Cerenkov radiation may also be worth investigating. Interestingly, smart polymeric biomaterials made of PLGA and chitosan are well known and characterized and therefore are a promising reason why most SRBs under development employ these polymers. As a general rule, the simpler and easier the development of a smart biomaterial is, the better its chances of reaching the clinic.

Going forward, the prospect of increased collaborations to extend radiotherapy to systemic therapy via the abscopal effect is exciting and attractive and SRBs provide an opportunity for further research and development in combining radiotherapy and immunotherapy via such an approach. SRBs slowly eluting immunotherapy agents may provide a means of achieving greater effectiveness, and overcoming systematic toxicity due to intravenous administration, and also increasing accumulation of these agents at the tumor site or draining lymph nodes since the agents are delivered locally within tumor [93]. So there is likely going to be a growth in number of studies using different immunoadjuvants delivered with SRBs during radiotherapy. In general one advantage of using smart radiotherapy biomaterials for in-situ delivery of payloads is that this could minimize toxicity compared to intravenous or systemic delivery of such payloads. However, more studies are needed to cogently establish this.

Irradiation of a volume of tissue leads to a change in the surface antigens of the blood vessels (several of the ICAMs are upregulated). Targeting of nano-particles may be improved when a tumor containing volume of tissue is pre-irradiated, nano-particles coupled to antibodies versus the upregulated surface antigens are injected intravenously, these nano-particles get (more or less) selectively attached to the pre-irradiated vessel walls close to the tumor. By this, the local concentration is higher and in addition to the enhanced permeability and retention effect, the interstitial/intracellular concentration of the nano-particles is selectively increased.

Another potential direction of research in SRBs is in *in-situ* labeling of cancer cells. SRBs could be used to label cancer cells in-situ, right at the source tumor. A factor motivating research in this direction is cancer metastasis, which accounts for over 90% of cancer associated suffering and death [94], involving circulating tumor cells (CTCs) shed by the primary tumor into the blood vessels or lymph nodes, especially after the start of fractionated radiotherapy [95]. The detection of such CTCs is valued in cancer management to monitor disease progression, tumor aggressiveness or treatment response. However, current methods to detect CTCs are limited by the scarcity of the CTCs in blood [96]. Only 1 to 10 CTCs are present in 1 mL of blood which contains millions of white blood cells and almost a billion red blood cells [97]. As such, the direct detection of metastatic or rare CTCs remains a formidable technological problem when using currently available methods. For example, although the detection of the CTCs in lymph nodes is an attractive approach in diagnosing how aggressive a tumor is, the methods to do so are mostly suboptimal, accompanied by significant morbidities. The approach to label tumor cells *in-situ* using SRBs has potential to significantly enhance labeling effectiveness, detection and isolation efficiency of CTCs, and non-invasive nodal status assessment for cancer patients.

Some like Baumann et al. [98] suggest that with recent technological advances in radiotherapy, new research and developments should focus less on improving the dose distribution and more on reducing treatment times [99]. If the use of SRBs for radiation boosting or priming the abscopal effect can lead to hypofractionation, the anticipated benefit of reducing treatment times would resonate with this suggestion. Reducing the treatment times could also help with reducing costs. This is supported by recent studies [100] showing that use of hypofractionation results in a significant reduction in the financial costs

associated with treating breast cancer patients. In general, lower cost technologies have the potential to change the lives of millions of individuals living in LMIC and other resource-poor-settings. With the emerging global radiation oncology movement, physicists, biologists, mathematicians, chemists, engineers, physicians and other scientists will likely also now focus on developing lower cost technologies or adaptations of current technologies that can make radiotherapy more affordable and accessible in such settings.

There are indubitably other potential applications that will emerge from the development of SRBs. Those highlighted in these review may not be comprehensive but provide a useful reference, especially for cross-disciplinary collaborations towards the development and translation of such technologies. Creating opportunities and training programs for cross-disciplinary research for individuals engaged in these areas should also be encouraged to significantly accelerate work on SRBs, facilitate clinical translation and create new applications.

CONCLUSION

Biomaterials have already had an enormous impact on health care, as seen in myriad prosthetic and drug delivery device applications. Research on smart radiotherapy biomaterials is proffers compelling rationale for upgrading the currently used inert radiotherapy biomaterials to smarter ones or developing stimuli-responsive nanoparticles that can deliver additional therapy enhancement benefits during radiotherapy. The anticipated range of applications for such smart devices could lead to increased survival and quality of life for cancer patients, and extend the benefits of radiotherapy to many more patients including in LMIC. Cross-disciplinary and international collaborations could highly avail development of smart radiotherapy biomaterials for future applications.

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Figure 1.

A) currently used commercially-available inert radiotherapy biomaterials e.g. fiducials (CIVCO Medical); B) one design (not to scale) of the Smart radiotherapy biomaterial (SRB); SRB could simply replace the inert biomaterials used for image-guided radiotherapy e.g. for lung cancer (figure 1C). D) Accelerated Partial Breast Irradiation with balloon applicator (loaded here with cerium oxide nanoparticles (CONPs) for selective protecting of healthy breast tissue); Once in place the SRB can be activated to sustainably release the payload in-situ directly into the planning target volume. The release and distribution of payload could be customized or optimized to radiotherapy schedules.[6,10,18]

Figure 2. (left) Localization microscopy-assisted quantification of GNP in HeLa cells after treatment shows that, functionalizing the GNP via the addition of transfection (GNP-T and GNP-DT) resulted in a significantly increased number of GNP/cell. The GNP linked to DNA and transferred into HeLa cells by transient transfection GNP-DT showed the most efficiency. (Right) Clonogenic survival of HeLa cells after 6 MV x-ray irradiation showing significant decrease in SF for GNP-DT compared to non-functionalized GNP (figure from Burger et al. Nanomedicine 2014, 10:1365–73).

Figure 3.

A) amphiphilic gold nanoparticle; B) optical image of microneedles to load gold nanoparticles or other payloads C) Electron microscopy image of silk microneedle tip (left scale bar 500 μm) D) quantitative analysis of model protein (OVA) payload release from micro-needle overtime *in vivo* for silk tips or methanol-treated silk tips that release entrapped protein more slowly; E–G) sustained/slow vaccine release profile elicits increased proliferation of antigen-specific CD8 $^{+}$ T cells (reference xxx)

Figure 4. (A) Electron Microscopy Image ($1\mu\text{m}^2$) of prototype SRB. The polymer matrix is marked with an x and the arrow in the figure points to payload. (B–C) Customizable in-vitro release of payload from the prototype SRB showing the ability for rapid release (figure 4B) or sustained release (figure 4C [reference xxx])

Figure 5.

A) Live animal *in-vivo* optical fluorescence imaging with the mice implanted with prototype SRB. B) Optical fluorescence (same intensity scale) of live mouse tumor over time. Day 1 represents image 1 day after implantation, and so on. C) quantification of the fluorescence intensity highlighting the ability to customize the release kinetics of the payload (reference xxx).

Figure 6. Abscopal effect in cancer patient using immunoadjuvants: (Left) CT cut of an apical lesion (see arrow) not included in the radiation field; (Right) The same lesion two months after treatment of a different, caudal metastasis with radiation and the immunoadjuvant GM-CSF (reference xxx)

Figure 7. Illustration of A) new radiotherapy approach using SRB (PRImEr) loaded with gold nanoparticles (GNP) and immunoadjuvant. The SRB will simply replace current routinely used inert radiotherapy biomaterials; B) GNP amplify local damage to tumor cells during radiotherapy. C) Sustained slow release of immunoadjuvant to prime metastatic cell kill expected to be more effective than repeated injections. APC = antigen presenting cells

Table 1**Advantages of Smart RT biomaterials (SRBs)**

1. Direct delivery of therapy enhancing payloads into the tumor sub-volume from SRBs overcomes physiological barriers allowing direct delivery of sufficiently potent payload into the tumor compared to intravenous approaches where less than 5% of payloads arrives the tumor even with the Enhanced permeability and retention effect
2. Local delivery of payload from SRBs allows for sub-volume radiotherapy boosting with minimal toxicity to healthy tissue. Hence this could minimize systemic/overlapping toxicities especially when combining radiotherapy with other treatment modalities like chemotherapy
3. SRBs can be designed/programmed for sustained release of the payload compared to repeated injections. Sustained in-situ delivery has also been shown to be more effective for certain applications and should be advantageous when combining radiotherapy and immunotherapy.
4. SRBs could simply replace currently used inert radiotherapy biomaterials and so can be employed at no additional inconvenience to cancer patients
5. SRBs could be multifunctional, including payloads with image contrast for theranostic applications or other therapy enhancing agents in combining radiotherapy with other approaches like chemotherapy or immunotherapy

Table 2

Examples of stimuli-responsive polymers of interest in development of smart RT biomaterials

Polymer type	Stimulus type	Response	Reference example(s)
Poly Lactic-co-Glycolic Acid (PLGA)	Hydrolysis, tumor microenvironment	PLGA biodegrades into lactic and glycolic acid	[69], [70]
Chitosan	Temperature, Mg 2+, PH	Gelation through interactions, which involve electrostatic attraction with an inorganic ion.	[9], [26] [67], [72], [73]
Azobenzene, Polyacrylamide-tri-phenylmethane leuco derivatives, Poly (N-vinyl carbazole) composite	UV, IR radiation	Photosensitiveness induces structural changes to deliver payload	[15] [71]
Dodecyl isocyanate-modified PEG-grafted poly (HEMA), Perfluorocarbon nanoemulsions	Ultrasound	Thermal or mechanical effects generated by cavitation or force	[15], [71]
PNIPAAm hydrogels containing ferromagnetic material, PNIPAAm-co-acrylamide	Magnetic field	Magnetic force or a temperature increase when an alternating magnetic field is applied	[15], [71]
Dendrimers, Poly (ethacrylic acid)	pH	Acid sensitive bonds or polymers that undergo conformational or solubility changes in response to pH variation	[15], [71]