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Combining External Beam Radiation and Radionuclide Therapies: Rationale, Radiobiology, Results and Roadblocks

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Abstract

The emergence of effective radionuclide therapeutics, such as radium-223 dichloride, [^{177}Lu]Lu-DOTA-TATE and [^{177}Lu]Lu-PSMA ligands, over the last 10 years is driving a rapid expansion in molecular radiotherapy (MRT) research. Clinical trials that are underway will help to define optimal dosing protocols and identify groups of patients who are likely to benefit from this form of treatment. Clinical investigations are also being conducted to combine new MRT agents with other anticancer drugs, with particular emphasis on DNA repair inhibitors and immunotherapeutics. In this review, the case is presented for combining MRT with external beam radiotherapy (EBRT). The technical and dosimetric challenges of combining two radiotherapeutic modalities have impeded progress in the past. However, the need for research into the specific radiobiological effects of radionuclide therapy, which has lagged behind that for EBRT, has been recognised. This, together with innovations in imaging technology, MRT dosimetry tools and EBRT hardware, will facilitate the future use of this important combination of treatments.

Key words: Combination; dosimetry; external beam radiotherapy; molecular radiotherapy

Introduction

External beam radiotherapy (EBRT) has been a mainstay of cancer medicine for over a century. Molecular radiotherapy (MRT), introduced in the 1940s with the use of 131-iodine for thyroid cancer, also has a long-established place among cancer therapies. Given the longevity of both treatments, it is surprising that there has been little research into their combined use and remarkably few examples of their pairing in clinical protocols [1]. The cardinal mechanism of cell killing by both treatments is ionising radiation-induced irreparable DNA strand breaks. However, the two modalities cause profoundly different biological effects, resulting from their dissimilar modes of administration, dose rates, dose distributions and molecular mechanisms of cytotoxicity. Recognition of the efficacy of radiopharmaceuticals, such as [^{177}Lu]Lu-DOTA-TATE for neuroendocrine tumours and radiolabelled PSMA ligands for prostate cancer, is driving a renewed research effort, including questions about how best to combine MRT with other treatments [2–5]. A significant obstacle to combining EBRT and MRT has been the lack of a dosimetric framework that relates the spatiotemporal pattern and amount of energy deposited by each treatment to the total biological effect of the two together [6,7]. This has been compounded by there being no recommendation, until recently, to tailor the amount of administered radioactivity in MRT treatments to individual patients. This has been partly remedied through the implementation of international directives recommending that MRT be individually planned, and its delivery verified, usually through single-photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging [8,9]. In this review, MRT is defined as the use of systemically or regionally administered radiopharmaceuticals that incorporate β-electron-, α-

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particle- or Auger electron-emitting radionuclides for cancer therapy. Many such radionuclides also emit γ-photons or positrons, enabling SPECT or PET imaging.

Rationale for Combining External Beam Radiotherapy and Molecular Radionuclide Therapy

Spatial Co-operation

The concept of spatial co-operation was first invoked to describe the advantages of combining EBRT with chemotherapy: EBRT can debulk a dominant tumour mass while co-administered systemic therapy contributes to the control of the primary cancer and simultaneously eradicates smaller widespread deposits [10,11]. As MRT is delivered systemically or, less frequently, regionally, this principle also applies to the combination of EBRT and MRT. This approach was shown to be technically feasible in the treatment of hepatocellular cancer (HCC), where multiple intrahepatic tumours were targeted using yttrium-90 selective internal radiation therapy ([^{90}Y]Y-SIRT), which involves the administration of radiolabelled microspheres into the hepatic artery, combined with EBRT to bulk lesions. Two studies demonstrated methods for combining the absorbed dose from [^{90}Y]Y-SIRT with that of EBRT [12,13]. Using the biological effective dose (BED) which is a quantitative measure of the biological effect of a radiotherapy treatment taking into account dose per fraction or dose rate and total dose, it was possible to compute the combined dose from both sources (Figure 1). These studies concluded that EBRT and SIRT can be given safely to patients with HCC. In another combination study, 11 patients with relapsed or refractory follicular lymphoma were treated first with EBRT to sites of bulk disease followed by [^{90}Y]Y-ibritumomab tiuxetan ([^{90}Y]Y-IT). The median progression-free survival was 17.5 months, which compared favourably with [^{90}Y]Y-IT alone; it was concluded that EBRT helped to prevent relapse at sites of bulk disease [14].

Normal Tissue Protection

Another advantage of combining MRT and EBRT is that the organs at risk of toxic effects differ, making radiation-absorbed dose escalation to tumour possible while meeting normal organ dose constraints. In EBRT, beams often traverse healthy tissue to reach a tumour. To minimise off-target effects, conformal techniques, such as intensity-modulated radiotherapy or rotational arc therapy, spread the off-target dose over a large volume. In MRT, radionuclides irradiate tissue isotropically, such that the deposited dose falls off rapidly with distance from the source, obeying the inverse-square law. Although specific targeting can be imperfect, an advantage of MRT is that adjacent tissues are spared. The organs at risk in the case of EBRT are those closest to the tumour, whereas MRT toxicity depends on the pharmacokinetics of the radiopharmaceutical and its pattern of accumulation in normal organs. For example, dry mouth is a common side-effect of [^{177}Lu]Lu-PSMA ligands as they concentrate in the salivary glands [15]. In general, normal organs that are vulnerable following MRT are organs of excretion, particularly the kidneys, and the bone marrow, which may be irradiated as the radiopharmaceutical circulates freely post-injection [16,17].

Enhancement of Tumour Response

In addition to spatial co-operation and non-overlapping toxicity profiles, interactions between EBRT and MRT may lead to sensitisation of a tumour to one agent by the other, resulting in super-additivity. One example is their combined effect on the immune system. EBRT induces a plethora of immune-activating mechanisms and emerging evidence shows that MRT can also increase sensitivity to cytotoxic immune cells and promote lymphocyte recruitment and activation [18,19]. Early reports indicate that the timing of changes in the immune landscape may differ for the two treatments; it is plausible that these differences could be harnessed for therapeutic gain [19,20]. Another exploitable interaction is the increase in blood flow and vessel permeability after exposure to EBRT which, when immediately preceded or followed by MRT, can enhance intra-tumoural accumulation of radioactivity [21,22]. Using dynamic contrast-enhanced magnetic resonance imaging of SK-N-SH (human neuroblastoma) xenografts in mice, Corroyer-Dulmont *et al.* [23] showed a significant increase in intra-tumoural vessel permeability up to 72 h following EBRT. When [^{131}I]I-MIBG was administered 24 h after EBRT, there was a more than two-fold increase in the accumulation of radioactivity and radiation absorbed dose in tumour compared with single-agent MRT. A similar observation was made by Dietrich *et al.* [24] when [^{90}Y]Y-cetuximab was administered during a course of fractionated EBRT applied to FaDu (human head and neck squamous cell carcinoma) xenografts in mice. These investigators found that tumour uptake of cetuximab correlated with the pre-applied dose of external radiation (up to a threshold of 24 Gy), showing complete tumour control in animals receiving both [^{90}Y]Y-cetuximab (2.8 MBq) and EBRT (20–120 Gy, in 30 fractions).

It may also be possible to exploit molecular alterations induced in cancer cells by one modality to enhance the toxicity of the other. In one example, the cytotoxicity of an investigational radiolabelled antibody, [^{111}In]In-anti-γH2AX-Tat, was potentiated by prior EBRT. In this case, the molecular target, γH2AX, a marker of DNA double-strand breaks, was induced by external radiation, leading to enhanced accumulation of [^{111}In]In-anti-γH2AX-Tat, which then caused amplification of the pre-existing EBRT-induced DNA damage [25]. In another example, EBRT-induced somatostatin receptor type 2 expression in neuroendocrine and small cell lung cancers resulted in greater accumulation of [^{177}Lu]Lu-DOTA-Tyr3-octreotate [26,27]. The opposite sequencing of the two treatments to achieve radiosensitisation of one by the other is also possible: an experimental oligonucleotide-based radiopharmaceutical

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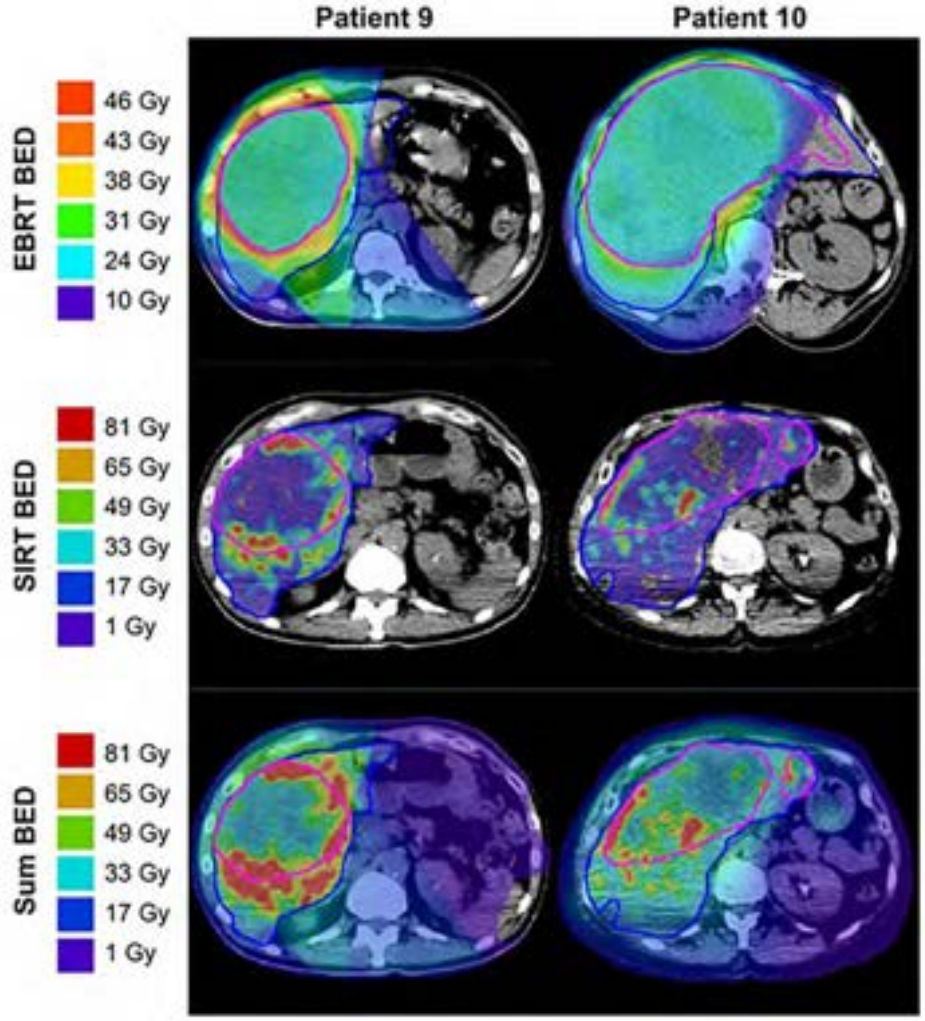

Fig 1. Biological effective dose (BED) maps for two representative patients who received external beam radiotherapy (EBRT) followed by yttrium-90 selective internal radiation therapy (^{90}Y-SIRT) for hepatocellular carcinoma. The rows illustrate the BED calculated from EBRT, ^{90}Y-SIRT and their voxel-wise sum determined through a contour and intensity-based deformation using MIM SurePlan LiverY90 (version 6.9.4; MIM Software Inc., OH, USA). To aid in visualising treated areas exceeding a 40 Gy physical dose constraint to normal liver, the SIRT and sum BED rows are displayed using differing scaling. In addition, tumour tissues had different BED scaling than the normal tissue due to the differing radiosensitivity parameters of each tissue. Liver is contoured in blue and tumour in magenta. Reproduced with permission from [12].

directed against telomerase RNA, hTR, has the fringe benefit of sensitisation to subsequent EBRT [28,29], as inhibition of telomerase enhances radiotoxicity [30,31].

Theranostic Benefits

Theranostic radiopharmaceuticals are designed to have both therapeutic and imaging capability. This is achieved by labelling the carrier molecule with a positron- or γ-emitting radionuclide for imaging and exchanging it for a therapeutic radionuclide (β-electron- or α-emitter) for treatment if sufficient tumour targeting is identified. Increasingly, companion diagnostics are used to assess biodistribution, including tumour uptake, to assist planning of MRT. It has been suggested that in combined MRT plus EBRT regimens, these preparatory images could, if tumour uptake is sufficient, be used, together with CT images, to delineate tumours for EBRT planning purposes [32,33], as well as informing MRT dose selection [34].

Radiobiological Considerations

Radiobiological modelling of MRT is often based on extrapolation of data from EBRT; however, EBRT and MRT are not radiobiologically equivalent [6]. The need for better understanding of the radiobiological effects of MRT has been highlighted recently by expert commentators [35–37]. One fundamental difference is that EBRT is delivered at a high dose rate, inflicting each fraction of the tumoricidal dose in a few minutes (≈1 Gy/min). In contrast, MRT is a low dose rate treatment (≈0.01 Gy/min), delivering dose over a protracted period, dictated by the physical half-life of the radionuclide and the extent of accumulation

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and rate of efflux from the tumour or normal organs. Several studies have reported the *in vitro* cancer cell killing effects of low dose rate radiation in comparison with high dose rate exposures [38,39], showing that low dose rate radiation allows repair of sublethal DNA damage during irradiation, such that a higher total absorbed dose is required from MRT to achieve the same proportion of cell kill as EBRT. For example, Gholami *et al.* [38] compared responses to ^{90}Y and EBRT in colorectal cancer cell lines using a cell viability assay. It was concluded that ^{90}Y is less potent than EBRT, as a dose of ≈56 Gy from ^{90}Y delivered over 8 days was radiobiologically equivalent to a single fraction of ≈8 Gy EBRT. In a similar study by Lee *et al.* [39], colorectal cancer cells were exposed to but not in direct contact with ^{90}Y in a set-up intended to simulate conditions during SIRT, where ^{90}Y-loaded microspheres are trapped in the capillary bed of the tumour but not internalised into cancer cells. The absorbed dose of 60 Gy from [^{90}Y]Y-SIRT equated to doses of 17.6 and 19.3 Gy from EBRT in 10 Gy fractions (EQD10) for two colorectal cancer cell lines. To enable combined EBRT plus MRT treatment planning, it is necessary to include radiobiological parameters for improved calculation of normal tissue complication (NTCP) and tumour control (TCP) probabilities, but few studies have incorporated NTCP and TCP in MRT planning [40]. Van and co-workers [41] used TCP- and NTCP-derived parameterised prescription charts to guide clinical decision-making in patients with HCC or metastatic liver disease treated with ^{90}Y glass microspheres. An NTCP of 75 Gy applied to the normal liver was shown to increase the TCP on average from 3% with current standard doses to 22%.

Hypoxia is common in tumours because of their disordered blood supply and high oxygen consumption. As low linear energy transfer (LET) radiation, such as conventional photon EBRT (LET = 0.3 keV/μm), is less effective in low oxygen environments, hypoxia is a major determinant of radioresistance. Alpha-particles, however, are densely ionising (LET = 150–200 keV/μm) and their cytotoxicity has been shown to be independent of oxygen partial pressure [42]. This suggests a potentially useful interaction where treatment with targeted α-particle therapy could be applied to reduce the hypoxic fraction, followed by EBRT to more effectively treat the normoxic tumour fraction.

Over the last few years, genome-, proteome-, and metabolome-wide studies of the effects of ionising radiation have uncovered previously unrecognised determinants of patient- and tumour-specific radiosensitivity [43–45]. Although these have the potential to guide radiotherapy in the future, the application of systems biology approaches is more challenging for radionuclide therapy because of the relatively small size of the treated population, which limits the number of tissue samples available for analysis. However, the adoption of anticancer radiopharmaceuticals for the treatment of common malignancies, such as prostate cancer, should allow meaningful analyses in the future. The potential importance of future 'omics' research to MRT has been highlighted by thought leaders in the field and may inform how best to combine MRT and EBRT in due course [46].

Advances in Molecular Radiotherapy Dosimetry Facilitate Combination with External Beam Radiotherapy

The successful combination of MRT with EBRT requires a sound grasp of the radiation absorbed dose-effect relationship of both modalities in malignant and normal tissues. The dose-effect relationship of EBRT is based on an extensive body of evidence that underpins clinical protocols designed to maximise dose to tumour while avoiding radiotoxicity in normal tissue. Equivalent evidence is largely lacking for MRT, with the result that treatments are not always dose-optimised. The European Association of Nuclear Medicine recently acknowledged the need for improved prediction of efficacy and adverse effects in a position paper on the role of radiobiology and dosimetry in nuclear medicine [46].

A major factor driving progress towards personalised MRT dosimetry is advanced image quantification in nuclear medicine [47]. [^{90}Y]Y-SIRT pre-treatment dose planning involves SPECT imaging with a surrogate tracer, [^{99m}Tc]Tc-macroaggregated albumin, for biodistribution information. The use of a non-identical compound for pretreatment assessment has led to discrepancies between pre- and post-SIRT dose estimates [48,49]. However, moving from SPECT to superior resolution ^{90}Y PET has led to more accurate ^{90}Y dose estimations [50,51]. Regardless of pre-treatment imaging, the tumour and normal liver absorbed dose estimation relies on post-delivery imaging. Holmium is paramagnetic and so quantitative magnetic resonance imaging is possible with this element, giving more detailed maps of microsphere distribution compared to SPECT/CT. Real-time MR-guided [^{166}Ho]Ho-SIRT could pave the way to combination therapy with EBRT delivered using an MR-LINAC [52]. A novel approach using dual isotope SPECT imaging, combining holmium-166 microspheres as a scout and [^{99m}Tc]Tc-colloid to identify the healthy liver, enables automatic identification and delineation of the tumour and healthy tissue within a single SPECT/CT scan [53]. With these improved imaging techniques, more accurate and personalised calculation of radiation absorbed dose is now possible in SIRT. This, together with the incorporation of radiobiological modelling that accounts for differences in the biological effects of ^{90}Y and EBRT [54], increases the feasibility and safety of offering SIRT as a first option, followed by EBRT, to patients with unresectable hepatic metastases.

Accurate MRT dosimetry is based on imaging at intervals following administration, to track the amount of residual radioactivity in the tumour and normal organs over time and so calculate the total integrated dose. This approach is resource intensive and onerous for patients as they must attend for several scans. However, recently it has been shown that, with prior knowledge of the biokinetics of the MRT agent, it is possible to estimate the integrated activity and, therefore, dose from imaging data acquired at a single time point [55]. In a 2021 study by Hou *et al.* [55], the optimal SPECT imaging time point was determined to be 72 and 48 h

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after administration of [^{177}Lu]Lu-DOTATATE and [^{177}Lu]Lu-PSMA, respectively. In a 2018 study reported by Hänscheid *et al.* [56], a single time point quantitative activity measurement on SPECT/CT at 96 h post-administration of [^{177}Lu]Lu-DOTA-TATE or [^{177}Lu]Lu-DOTA-TOC could be used to estimate absorbed doses. These measures to simplify dosimetry make the integration of MRT into complex multimodality regimens more practicable.

Technological Advances that Facilitate External Beam Radiotherapy plus Molecular Radiotherapy Combinations

EBRT typically relies on CT imaging for the anatomical information needed to design treatment plans that account for variations in tissue density, which affect the absorption of radiation dose. Standard imaging techniques for MRT (PET/SPECT) are necessary for quantifying the distribution of dose from direct emissions of the radionuclide source. These imaging techniques are used together in hybrid scanners (e.g. SPECT/CT and PET/CT) to correct for attenuation effects in MRT dosimetry. Density maps reconstructed from CT are paired with the SPECT or PET images in attenuation-correction algorithms, which correct for missed counts due to scattering of ionising radiation through dense tissues. As such, specialist hardware may aid in precise patient-specific delivery of both EBRT and MRT. A recent innovation, still in the development stage, is PET/CT-LINAC technology, which combines PET imaging capability with a therapy LINAC [57]. Following administration of a tumour-seeking PET tracer, this device enables real-time motion tracking of tumours (the radioactivity within the tumour acts as a fiducial marker) and near immediate delivery of EBRT. Although the main future advantage of this machine is predicted to be in the management of patients with metastatic disease, as accurate EBRT of multiple sites is facilitated, it is intriguing to speculate that a single PET tracer could be used to plan MRT dosing and guide EBRT, thus raising the possibility of a more harmonised approach to dual-modality treatments.

Whole-body PET technology has moved apace in the last few years, with the first clinical scanners now installed [58]. As they allow low-dose imaging, rapid image acquisition and increased sensitivity, such that tracers can be detected for longer periods, their adoption into practice will help streamline MRT planning [59]. The instantaneous acquisition of whole body administered activity allows total body dosimetry analysis, which is not possible with standard smaller field-of-view PET systems [60].

Clinical Experience of External Beam Radiotherapy plus Molecular Radiotherapy Combination Protocols

Most published examples of combined MRT and EBRT consist of retrospective series, describing patients who received both treatments, although not always as a pre-planned dual-modality protocol. The number of reported prospective trials that include an intention to treat with both MRT and EBRT from the outset is small, although a few are currently underway. A prospective clinical trial reported in 2013 compared the analgesic effectiveness of samarium-153 alone (37 MBq/kg) or combined with EBRT (8–30 Gy) in 177 prostate cancer patients with multiple painful bone metastases [61]. Use of the Visual Analogue Pain Score revealed complete resolution of pain in 42.5% and 62.5% of patients in the MRT and combination arms, respectively. Kreissl *et al.* [62] conducted a feasibility study of [^{177}Lu]Lu-DOTA0-Tyr3-octreotate (7.0–7.9 GBq) followed by EBRT (mean dose, 53 Gy) in 10 patients with unresectable meningioma. The treatment was well tolerated: the CTCAE scores were <2 for all patients. In a long-term follow-up study of the same patient cohort, the authors reported disease stabilisation in seven of the 10 patients, with a median progression-free survival of 107.7 months (range 47.2–111.4 months) versus 26.2 months (range 13.8–75.9 months) for patients with meningioma progression [63]. Anderson *et al.* [64] reported the first use of radium-223 for osteoblastic bone metastases from osteosarcoma in a series of 15 patients. As well as radium-223 (55.13 kBq/kg per cycle, up to six cycles), 12 patients received stereotactic body radiotherapy (SBRT; mean dose, 40 Gy in five fractions) or other EBRT (45 Gy in 15 fractions) either concurrently, concurrently and sequentially or sequentially. After radium-223, patients who had or did not have additional EBRT had a median overall survival of 13 and 4 months, respectively, supporting the use of combined radium-223 in addition to EBRT. An example of a phase II trial currently underway is the RAVENS trial (NCT04037358), in which patients with prostate cancer and three or fewer metastases with at least one bone metastasis are randomised to SBRT alone or SBRT + radium-223, with progression-free survival as the primary end point [65]. A further phase II study combining EBRT (pelvic volumetric modulated arc therapy) with [^{177}Lu]Lu-PSMA for PSMA-avid recurrent pelvic nodal metastatic prostate cancer is planned (TARGET trial, ACTRN12618001667202p) [66].

The finding of a sustained response to [^{177}Lu]Lu-PSMA has been demonstrated in relatively small volume nodal disease in metastatic prostate cancer, both in the hormone-sensitive and castrate-resistant settings [67]. In these patients, post-therapy imaging with [^{68}Ga]Ga-PSMA PET/CT may show a partial rather than a complete response to treatment at some sites, such that an oligometastatic remnant remains. In other cases, a complete metabolic response may be seen at most sites, but stable disease or progression at a few sites. In these circumstances, the addition of SBRT or volumetric modulated arc therapy for persistent or radioligand-resistant disease may be considered attractive and potentially desirable to prolong treatment response by eradicating these radioligand poorly- or non-responsive clones. However, the long-term efficacy and outcomes from this approach have yet to be tested in a formal trial design.

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Obstacles to Introducing Combined Protocols

The combination of EBRT with MRT is conceptually appealing, yet is not currently endorsed in consensus guidelines. As noted above, the reasons for this include empirical approaches to MRT dosimetry and the added complexity of combining absorbed dose contributed by two modalities. There are also organisational aspects that explain why the two treatments have not frequently been given together. In most healthcare systems they are delivered in different departments (nuclear medicine and radiation oncology) by different clinical teams and this has perhaps, in the past, impeded a unified approach to dosimetry. Combining MRT and EBRT increases the time it takes to plan and deliver treatment. There are also practical considerations, particularly if synchronous treatment is envisioned: patients who have received therapeutic amounts of radionuclides and who are to be treated immediately with EBRT may present radiation safety problems in the radiotherapy department. Currently, most combined treatment is not protocolised but is decided on a case-by-case basis. Regulatory systems are ready to adapt but this hinges on clinics intentionally adopting common treatment combination practices and working with academic and commercial partners to solve logistical and dosimetric challenges. A recognition that the role of therapeutic radiopharmaceuticals in cancer medicine is expanding will probably drive efficiencies in clinical workflows, which, in turn, will facilitate more complex multimodality treatments [68]. Managing side-effects from a combination of EBRT and MRT is also an area with little knowledge and expertise. Monitoring for potential cumulative toxicities becomes paramount and managing potential cumulative side-effects is a further practical consideration as combined EBRT and MRT regimens are developed.

Conclusions

At present, intentional combination protocols for MRT and EBRT do not exist as standard-of-care. Clinically exploitable synergies between the two modalities represent the strongest case for consolidating the costs into a single comprehensive protocol. A call-to-action now exists for combination EBRT and MRT to be further explored and instituted to enhance patient outcomes.

Conflict of interests

N. Lenzo is a shareholder in GenesisCare and a consultant for Telix Pharmaceuticals and GE.

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