Molecular radiotherapy (MRT) refers to the delivery of radiation to tissue (benign or malignant) via the interaction of a radiopharmaceutical with molecular sites or receptors, although the term is more generally applied to all treatments with radiotherapeutics. It is thus an inherently targeted treatment.

To date, the use of MRT to treat cancer has mainly been limited to a small number of niche indications, such as thyroid cancer and neuroendocrine tumours. However, in the last decade there has been a rapid increase in the number of publications relating to the use of MRT across a range of cancers, including colorectal, hepatocellular, breast and prostate [1]. Forecasts predict that radiotherapeutics are experiencing an 18% compound annual growth rate and there have been several large-scale mergers and acquisitions of radiopharmaceutical companies producing radiotherapeutics in recent years [2,3]. Although national data are not readily available, a report from the UK Internal Dosimetry Users Group reported an 80% increase in the number of treatments with radiopharmaceuticals over the previous 10 years [4], primarily due to the uptake of radium-223 (223Ra) for the treatment of castration-resistant prostate cancer. However, MRT is still only delivered by a relatively small number of centres. This rapid growth presents challenges for service delivery and healthcare economics at a national scale.

Although there is published evidence of the efficacy of these treatments, there is still much to be learnt about how treatments can be optimised and individualised. Most therapies in the UK are currently administered as standard, empirical activities (in Bq). There is considerable evidence that administering the same activity of an isotope can lead to widely varying absorbed doses (in Gy) to both the tumour target and to normal tissues [5—7]. As outcomes, both in terms of response and toxicity, are far more likely to be related to absorbed doses delivered to target and organs at risk, respectively, than to administered activity, it is very likely that many patients are currently under-dosed and some may be over-dosed [8]. There is also much that we do not fully understand regarding the radiobiology of these treatments, usually delivering a low dose rate over a very prolonged period of time, over a very short range.

Recognising the need for further research in this field, the National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group published a report in 2016 ‘Identifying opportunities to promote progress in molecular radiotherapy research in the UK’ [9]. The report identified three key themes. First, the need to enhance research infrastructure and multidisciplinary work, recognising that most who work in this field do not have protected research time and the need for specialised imaging equipment and software. Second, the need to acquire good evidence for best practice, expanding the clinical trials portfolio and developing consensus guidelines, recognising that at the time there was significant variation in practice across the country. Third, the need to optimise treatments through internal dosimetry, allowing personalisation and greater safety for these treatments. Although some progress has been made in the intervening years, there remains much to be done.

The gradual transition to managing MRT as a form of systemic radiotherapy, rather than as either a radioactive form of chemotherapy or an extension of nuclear medicine diagnostic imaging, is spurred by the potential to directly image the biodistribution of the active drug. This opportunity is probably unparalleled in medicine and enables dosimetry-based treatment planning on an individualised basis. Dosimetry in MRT has long been contentious [10,11]. However, in today’s era of personalised medicine and highly targeted external beam radiotherapy, surely it can no longer be acceptable to a clinical oncologist to deliver a radiation treatment without making some attempt to measure the absorbed doses delivered to both the target and to organs at risk.
risk? In line with external beam radiotherapy, a personalised approach to treatment is increasingly mandated following recent European regulations and international recommendations [12,13] that are now entering into national regulations, and guidance notes [14]. Indeed, the UK Administration of Radioactive Substances Advisory Committee published guidance in 2020 stating that ‘in cancer treatments with radioactive substances, the absorbed dose to the tumour and to non-target volumes and tissues, following each administration should be measured and recorded, to permit subsequent optimisation of total doses’ [15]. A revision of service delivery in the UK is under consideration as part of the National Health Service 10 year plan for the modernisation of radiotherapy services [16]. A recurring theme of the papers in this special issue is the imperative to acquire these data if we are to make best use of this treatment modality.

Probably the most well-known example of MRT is the use of iodine-131 (131I) in the treatment of benign and malignant thyroid disease, first administered 80 years ago, in 1941 [17]. Exploiting the sodium-iodide symporter, a membrane protein almost unique to thyroid cells, high doses of radiation can be delivered specifically to thyroid or thyroid cancer cells. 131I is an extremely effective treatment for thyroid cancer and can cure patients, even with metastatic disease.

In this issue of Clinical Oncology, the range of applications of MRT are summarised in several articles. The current controversies regarding the need for treatment with radiiodine in low- and intermediate-risk patients are elegantly presently by Eilsberger and Verburg [18], while the potential for treatment optimisation of high-risk thyroid cancer is reviewed by Beasley and Garcez [19]. The treatment of bone metastases from prostate cancer, first given with phosphorus-32 in the 1930s, has since been subject to investigation with a large number of targeted radiotherapeutics, including 223Ra, the first alpha-emitting radiotherapeutic to be licenced. The eagerly awaited results of the VISION trial (NCT03511664), testing lutetium-177 (177Lu) PSMA-617 in metastatic castrate-resistant prostate cancer may well result in a further surge in demand for this modality of treatment. The various treatment options are covered in the article by Murray and Du [20].

The treatment of liver tumours with intra-arterial administrations is an example of targeting without reliance on molecular interactions. 131I lipiodol was used in 1995, but the field is now developing rapidly with yttrium-90 (90Y)- and holmium-166-radio labelled microspheres. The unique aspects of this treatment modality and future prospects are comprehensively covered by Alsultan et al. [21].

The treatment of neuroendocrine tumours, initially with 131I meta-iodobenzylguanidine (mIBG), is a further example of the resurgence of MRT. Radiolabelled peptides have subsequently become a treatment of choice for neuroendocrine tumours. Both indium-111 octreotide and 90Y-DOTATATE have been used and 177Lu-DOTATATE has now become a standard treatment since being licenced. Currently given as four administrations with fixed activities of 7400 MBq (200 mCi), there is now the opportunity to explore personalised treatment regimens incorporating dosimetry and radiobiology [22].

Investigator-led clinical trials are essential to the development of MRT, particularly for children and young people. 131I mIBG treatment of neuroblastoma has in many respects led the way for the development of personalised treatment with radiotherapeutics. Aldridge et al. [23] present an overview of the challenges of treating younger patients and review several clinical trials, including the VERITAS [131I mIBG] trial that is now running in centres throughout Europe.

The feasibility and challenges of investigator-led multi-centre trials incorporating dosimetry are discussed in a review of current publications by Lassmann et al. [24] and by Taprogge et al. [25] who address the steps needed for multicentre and multinational clinical trials. This is surely the future of MRT, given the relatively low numbers of patients treated at any one centre.

Scientific developments of the last decade and future directions for dose calculations for MRT are covered by Bardies and Gear [26] who show not only that the dosimetry may be calculated with an accuracy that can facilitate personalised treatment prescriptions but that the uncertainties involved in these calculations can be isolated, quantified and minimised.

Finally, a BIR report in 2011 raised the necessity for national oversight of MRT in the UK [27]. There are major issues to address, including standardisation and data collection. The nuclear medicine aspects of treatment and the need to establish a national infrastructure to allow geographical equality of access, probably within the radiotherapy networks now developed, are considered by Buscombe [28] who looks to the future of MRT.

MRT, despite being an early starter, has proved to be a slow developer. However, in an era of treatment personalisation and evidence-based medicine, MRT is moving from the blind treatments of ‘radioactive chemotherapy’ to a branch within conventional radiotherapy.

It is our hope that the papers collected in this special issue will stimulate greater interest in this fascinating treatment modality and inspire further research to optimise and personalise treatments to allow the greatest benefit to our patients.

Conflicts of Interest

J. Wadsley reports research funding from AstraZeneca and Sanofi Genzyme and honoraria for advisory work from AstraZeneca, Sanofi Genzyme and Advanced Accelerator Applications.

Acknowledgements

National Health Service funding was provided to the National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden and the Institute of Cancer Research. The MEDIRAD project has received
funding from the Euratom research and training programme 2014–2018 under grant agreement no. 755523. The Radiotherapy Trials Quality Assurance group is funded by the NIHR. We acknowledge infrastructure support from the NIHR Royal Marsden Clinical Research Facility Funding. This report is independent research funded by the NIHR. The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service, the NIHR or the Department of Health and Social Care.

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