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COMMENTARY

Time to demand dosimetry for molecular radiotherapy?

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ABSTRACT

Molecular radiotherapy (MRT) has been used clinically for around 75 years. Despite this long history of clinical use, there is no established dosimetry practice for calculating the absorbed dose delivered to tumour targets or to organs at risk. As a result, treatment protocols have often evolved based on experience with relatively small numbers of patients, each receiving a similar administered activity but, potentially, widely varying doses. This is in stark contrast to modern external-beam radiotherapy practice. This commentary describes some of the barriers to MRT dosimetry and gives some opinions on the way forward.

Molecular radiotherapy (MRT) is an established technique in which unsealed radioactive sources are used in cancer and other medical treatments and has been in clinical use for many decades. The process consists of delivering a radioactive atom, via attachment to a carrier, directly to tumour cells. The first published use was in 1941 by Hertz using iodine-131 as a treatment for Graves' disease.¹ Since then, it has become extensively used for a wide variety of clinical indications¹ from cancer treatments to benign uses, such as for radiation synovectomy.²

In external-beam radiotherapy (XRT) treatment, it is possible to precisely specify the absorbed dose to target regions.³ By contrast, MRT treatments rarely specify absorbed dose—indeed, when the term “dose” is used, it is often used incorrectly to identify the amount of radioactivity that is administered to the patient. A fixed activity administered to a patient group is likely to result in a variation in dose delivered to each patient owing to differences in both the disease status and patient metabolism. MRT protocols are developed during clinical trials to establish the maximum tolerated activity (not dose) for a given patient population. This approach, known as “as high as safely administered”, ensures treatment is safe but is logically likely to undertreat the vast majority of patients (Figure 1). Unfortunately, there is no simple formula to relate administered activity to absorbed dose in patients undergoing MRT. It is largely owing to this complexity that the vast majority of MRT protocols rely on administering a fixed activity (sometimes adjusted for weight or renal function, for example) for which the absorbed dose can vary by several orders of magnitude. For example, with radioiodine (iodine-

131 sodium iodide) treatments for thyroid remnant ablation, it has been reported that, for a fixed activity administration, the dose to the thyroid remnant varied from 1.2–540 Gy.⁴ With yttrium-90 DOTATOC for neuroendocrine tumours, using a weight-based activity prescription, the reported absorbed kidney doses were 6–46 Gy in the kidneys.⁵

Within XRT, there has been an emphasis for many years on dosimetry with standardization-enabling routine clinical practice with precise and accurately delivered absorbed tumour doses. There is a lack of standardization in MRT, and it suffers from isolated efforts to optimize treatment, leading to a large range in absorbed doses delivered to tumours. The clinical impact of this wide variation of absorbed doses is unknown. However, our collective experience with XRT (where doses are routinely delivered to within 3–5%³) suggests that variation of such magnitude is likely to have a significant impact on each treatment's clinical effectiveness. As with XRT, there is increasing awareness of the potential impact in MRT of dosimetry at a cellular level and variation in the radiobiological sensitivity across a given patient population. However, it is the authors' belief that, initially, more widespread use of macroscopic dosimetry could optimize MRT treatment. Treatment would proceed if a sufficiently high absorbed dose can be shown to be delivered to the tumour, whilst limiting dose to normal tissue, as is currently performed for XRT.³ Personalized treatment strategies that cannot meet these goals would be unlikely to proceed. This would bring clinical MRT practice in line with current and imminent European Union Directive requirements (Directive

Figure 1. Bell curve showing that treating “as high as safely administered” means that the majority of the patients will be undertreated. Max, maximum.

2013/59 repeals 1997/43 but reinforces the requirement for optimization of all exposures for radiotherapeutic purposes).⁶

Unfortunately, some areas of MRT have suffered from a “vicious cycle” of clinical and scientific apathy: treatments are neither optimized nor developed through rigorous randomized controlled trials; perceived clinical outcome is sometimes poor or not statistically significant; lack of clinical and scientific interest/expertise leads to low levels of dosimetry use, hampering optimization; lack of progress or proven outcome leads to low investment, causing a lack of development in the field; and so on.¹

Whilst some may be tempted to conclude that this represents the slow decline of MRT, in fact a much more positive outcome is emerging. A multidisciplinary group of clinical and scientific professionals recently met [under the auspices of The British Institute of Radiology (BIR) and Internal Dosimetry Users Group (IDUG)] with the remit of identifying and discussing how to break out of the cycle identified above and how a sustainable future of optimized MRT delivery could be achieved. A wide range of issues was discussed, but treatment standardization and evidence base emerged as the clear leaders in the list of hurdles on the path to achieving optimized MRT. Three main clinical areas were discussed at this meeting: thyroid (radioiodine), neuroendocrine and hepatic carcinomas [using selective internal radiotherapy treatment (SIRT)].

There are a number of different steps involved in performing MRT dosimetry, each of which has its own challenges. A grossly simplified summary would be:

- quantitative imaging of the patient at certain time points
- modelling the distribution of activity within the patient over time from these images
- converting this cumulated activity in different regions into an absorbed dose.

To perform quantitative imaging, there are a variety of factors that must be addressed to acquire quantitative data from patient scans, these depend on which modality is used [single-photon emission CT or positron emission tomography (PET)] and the isotope selected. These factors include dead time, reconstruction parameters, reconstruction algorithm, scatter and partial volume corrections,

collimator choice and energy window selection. There is not scope within this commentary to discuss all of these issues, but a comprehensive review of them is given in a report by the Society of Nuclear Medicine and Molecular Imaging (SNMMI)⁷ and more recently by the Medical Internal Radiation Dose (MIRD) Committee.⁸ A collaborative project between national metrology centres and universities across Europe, called MetroMRT, is currently investigating some of these issues and is due to report its findings in May 2015 (Vere Smyth, personal communication). Modelling the distribution is dependent on the radioisotope used and tumour site. Converting this activity into an absorbed dose can be performed following guidance from the SNMMI MIRD Committee using what they have termed S factors.⁹ The MIRD Committee is planning to substantially revise and update their primer on absorbed dose calculations during 2015.¹⁰

The use of iodine-131 for thyroid MRT treatments was first introduced in the 1940s.¹ Despite this long history, the latest set of guidance from the British Thyroid Association¹¹ states that “most of the evidence ... derives from studies where empirical activities of I-131 were used” and “the role of dosimetry and its impact on clinical outcomes, compared to empirical use of I-131 therapy is unclear”. This illustrates the acknowledgement that further evidence on dosimetry is needed before recommendations on its use can be made.

For neuroendocrine tumours, there are two main radioisotopes used for MRT treatments—yttrium-90 and lutetium-177. The former is a pure beta emitter and so presents a challenge in terms of imaging tracer distribution. This can be performed using Bremsstrahlung radiation or by administering a γ -emitting radioisotope alongside the yttrium-90, which is imaged.¹² For these peptide therapies, there is potential for a significant dose to be absorbed by the kidneys. Therefore, during administration, techniques are used to limit kidney uptake—and so dose—to prevent radiation nephropathy.¹² For this class of treatment, MRT dosimetry provides an option whereby the maximum possible absorbed dose to tumour can be calculated and delivered whilst keeping the kidney dose within appropriate limits.¹³

For SIRT treatments, the radionuclide (yttrium-90) is administered via the hepatic artery and becomes trapped within the liver. Thus the movement of the tracer can be considered negligible, which simplifies that part of the dosimetry process and reduces the imaging requirement to a single time point. Recent work has suggested that it is possible to image the yttrium-90 from these treatments on a PET/CT scanner, and so there is great potential for performing dosimetry for these treatments. A future international trial is planned to investigate correlations between absorbed dose from these treatments with clinical outcomes, which will be a very welcome addition to the dosimetry evidence base.

Throughout the clinical indications discussed, there were two key themes that need addressing by the nuclear medicine therapy community: standardization and evidence. Standardization is needed both in terms of MRT administration and for any dosimetry that is carried out. Expert groups, such as IDUG, can help standardize dosimetry, providing practical and pragmatic protocols. This will complement the excellent, but broader, published MRT guidance (for example, that from SNMMI⁹ and the European

Figure 2. Oxford Centre for Evidence-Based Medicine levels of evidence scale.¹⁴

Association of Nuclear Medicine) and enable sites to make consistent choices within existing guidance. Such standardization must reflect the operational limitations faced by most sites, in terms of trained staff, equipment availability and bed availability.

Currently, on the Oxford Centre for Evidence-Based Medicine levels of evidence scale (Figure 2), the evidence for MRT is—at best—at the level of cohort study. There is thus obviously room for much

improvement, and it is hoped that future trials will allow higher level evidence to be collected and the usefulness of personalized dosimetry for MRT, as has been carried out for XRT, to be proven. A prime candidate for a future MRT dosimetry trial would be lutetium-177 DOTATATE, which is becoming increasingly popular as a NET treatment option following the recent introduction of a commercial licensed product. As lutetium-177 is a γ emitter, it is relatively easy to image and, as mentioned previously, there is a clinical rationale to quantify the dose to the renal system.¹²

At a time of MRT growth and expansion,¹⁵ it is the authors' belief that there is an urgent need for MRT dosimetry to become routine for treatments in a similar way as dosimetry is for XRT treatments. Funding bodies should be actively encouraged to support MRT trials based on patient-specific dosimetry to optimize the activity given based on absorbed dose, rather than the current, often empirical, methods. Owing to its targeted nature, MRT has the potential to offer significant benefits in terms of clinical efficacy but further investment is required to increase the level of evidence available and it is critical that this be collected in a standardized way.

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