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Editorial

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BNMS position statement on molecular radiotherapy

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Background

Molecular radiotherapy (MRT) refers to the treatment of benign and malignant disease with radiotherapeutics. Radioiodine (I-131 NaI), first used in 1941, has become a standard of care treatment for hyperthyroidism and, following thyroidectomy, for thyroid cancer [1]. Adult and paediatric neuroendocrine cancers, liver tumours and metastatic prostate cancer have been treated since the early 1990s in single-centre investigator-led studies, mainly with palliative intent. As a specialised area of cancer management affecting only a small number of patients with predominantly rare cancers, MRT has developed slowly and in a haphazard fashion over many decades, without national oversight or a national strategy [2].

Following the approval of Ra-223 in 2013 to treat prostate cancer metastatic to bone, and Lu-177 1,4,7,10-tetraazacyclodo-decane-1,4,7,10-tetraacetic acid coupled Tyr3-Octreotate in 2018 for the treatment of neuroendocrine disease [3,4], the field is now expanding at an unprecedented rate. Many new radioactive agents are now in phase II/III trials to treat common and rare cancers. In March 2021 in England, National Institute for Health and Care Excellence approved the use of Y-90 Selective Internal Radiation Therapy in all patients with unresectable hepatocellular cancer [5]. The demand for Lu-177 PSMA for the treatment of bone and soft tissue metastases from prostate cancer is expected to increase dramatically following favourable results from the recent 177Lu-PSMA-617 in Metastatic Castrate-Resistant Prostate Cancer trial [6]. However, the national service infrastructure for molecular radiotherapy services has not kept pace with that seen for external beam radiotherapy (EBRT) [3]).

MRT has conventionally been regarded as either an extension of diagnostic imaging, whereby each patient receives the same fixed level of activity, or as a form of 'radioactive chemotherapy' for which the administration may be modified according to patient weight or body surface area. This approach fails to realise the unrivalled potential of nuclear medicine to directly image the biodistribution of the radioactive drug. Quantitative imaging makes it possible to calculate the radiation doses delivered to both target volumes and to healthy organs that may be at risk. There is now an increasing impetus to consider MRT as 'systemic radiotherapy' with the acknowledgement that the outcome of treatment for any given patient is dependent on the radiation doses delivered to target volumes and to organs at risk. This is marked by the emerging field of 'theragnostics'.

The requirement to consider dosimetry in treatment planning is underlined by regulations and by national guidance. The Euratom 2013/59 directive [7] was incorporated into the UK IR(ME)R regulations in 2017 [8], which state that:

'In relation to all radiotherapeutic exposures the practitioner must ensure that exposures of target volumes are individually planned and their delivery appropriately verified taking into account that doses to nontarget volumes and tissues must be as low as reasonably practicable and consistent with the intended radiotherapeutic purpose of the exposure'.

The Administration of Radioactive Substances Advisory Committee (ARSAC) guidance published in February 2021 reflects these regulations [9]:

'Applications for therapy administrations both in routine clinical practice and research, are therefore expected to specify what dosimetry will be performed, per course, on an individual patient basis. Employers should ensure that appropriate resources are available'.

Compliance with these statements presents a number of challenges and opportunities for cancer management and for nuclear medicine in particular.

MRT is a highly specialised treatment, ideally requiring an understanding of diagnostic nuclear medicine, image

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processing, radiation dosimetry, radiation protection, radiation risk models, radiobiology, systemic therapy and radiation oncology. Those involved in the practice of MRT, including clinical and medical oncologists, nuclear medicine physicians, endocrinologists or interventional radiologists, require sufficient training in these techniques to ensure well tolerated delivery of treatment. Additionally, there is a legislative need for Medical Physics Experts to support the clinical team delivering MRT. All this needs a reorientation of training of those medical and scientific staff delivering MRT.

The use of radiotherapeutics has until recently been constrained to rare cancers, usually administered with palliative intent following surgery, EBRT or one or more courses of conventional chemotherapy. Administered activities are conservative and there is minimal risk of unmanageable toxicity. The treatment of benign or malignant thyroid disease is an exception, due to its specific targeting and wide therapeutic window. Consequently, MRT has seldom been perceived to merit the efforts necessary to optimise treatments on an individual patient basis.

BNMS position

The British Nuclear Medicine Society (BNMS) advocates that MRT should have the status held by EBRT, for which radiation dosimetry is an integral aspect of clinical practice. Pretherapy dosimetry for prospective treatment planning and post-therapy verification of the absorbed doses delivered is achievable with nuclear medicine imaging. This will facilitate treatment optimisation, informed risk estimates and the investigation of alternative methods of treatment if the uptake distribution indicates that further treatment is unlikely to be beneficial. Patient-based dosimetry should be actively encouraged as an essential design of prospective phase II and phase III clinical trials in MRT.

Challenges and opportunities

There are a number of issues that must be urgently tackled to enable the UK to take advantage of the opportunities presented, for what is effectively emerging as a new form of cancer treatment. The BNMS, in collaboration with other stakeholders, will seek to address these.

Infrastructure

An ambitious programme of expansion in the national capacity to deliver MRT is needed to deliver a coherent and comprehensive service in the UK [3]. A service infrastructure must be developed to support multicentre studies that incorporate nuclear medicine imaging and patient-specific dosimetry. Networks of centres able to offer molecular radiotherapy will ensure equitable geographical access to treatment, access to expertise in each relevant discipline for each centre and sufficient facilities to offer a high-quality service. A hub-and-spoke model of service delivery, first proposed in a British Institute of Radiology report in 2011, will satisfy these criteria [2]. It is possible that MRT networks could work in conjunction with the newly established UK radiotherapy Operational Delivery Networks. A UK MRT service infrastructure will require an expansion in nuclear medicine provision. Centres must also have protected rooms for radioactive patients that may require isolation before discharge, and specialist nursing staff, technologists/radiographers and radiochemistry. It must be recognised that there is a legislative need for medical physics experts with expertise in patient-based dosimetry at centres which provide MRT. It is a requirement that treatments are performed under employer and practitioner licences under the Ionising Radiation (Medical Exposure) Regulations issued by ARSAC [10]. While some centres may have the capacity and expertise to perform dosimetry, there should be a facility for data transfer and archiving that would enable centralised data processing and analysis at 'dosimetry hubs'. Nationally, lead work is needed to evaluate the resources required to provide a nationwide comprehensive service.

Reimbursement

Reimbursement is required to perform quantitative imaging and patient-specific dosimetry for each administration. This may include planar or single photon emission computed tomography/CT (SPECT/CT) to verify radiation dosimetry, and SPECT/CT or PET/CT tracer studies to measure treatment-specific biomarkers prior to therapy and to stage response following therapy. This follows the model available for EBRT and brachytherapy procedures.

Cost efficiency

The costs incurred in the provision of an MRT service infrastructure may be offset by cost savings in overall patient care and informed treatments. This may include prevention of continued treatment in the event of insufficient uptake or radiation dose delivery, although dosimetry analysis may indicate that increased numbers of administrations and higher activities may be more effective and safely delivered. A feasibility exercise incorporating health economics and cost/benefit analysis is required to address this issue.

Research and development

Despite recent regulations, new radiotherapeutics are currently approved and introduced without imaging or dosimetry. Investigator-led phase III and phase IV clinical trials of established and radiotherapeutics are required to develop personalised treatments and to verify the anticipated benefits of new radiotherapeutics following approval. Alternative trial designs may be required to optimise the results of image-guided MRT. Funding is also needed to support basic research into radiochemistry, physics and radiobiology with a view to future implementation.

Training and education

The delivery of MRT, as with much of modern medicine, requires a multidisciplinary team. Training and

education, including introductions to fields for nonspecialists, is required to facilitate communication between disciplines.

Conclusion

The growth of MRT as a targeted treatment for a range of common and rare cancers heralds a new era of cancer treatment, as foreseen when radioiodine was first used 80 years ago. The BNMS recognises that the rapidly increasing use of radiotherapeutics offers new avenues for the treatment of cancer and introduces the potential for a level of personalisation of medicine not possible with other treatment modalities. The UK is world-leading in aspects of molecular radiotherapy and is well placed to take advantage of the opportunities afforded. The BNMS supports the development of nuclear medicine imaging and dosimetry for all patients undergoing MRT and will undertake to address the issues highlighted in this document.

Summary and action points

(1) The use of radioactive drugs to treat common and rare cancers is expanding rapidly.
(2) Nuclear medicine imaging enables informed treatment on an individual patient basis.
(3) Imaging and dosimetry for molecular radiotherapy should be reimbursed. Health economics and cost/benefit analyses are needed.
(4) Molecular radiotherapy should enjoy the status held by EBRT with respect to radiation dosimetry.
(5) The field of molecular radiotherapy necessitates a highly multidisciplinary framework which should be made available via a 'hub and spoke' model of service delivery.
(6) The disparate provision of service has led to a 'postcode lottery' in terms of accessibility to treatment with molecular radiotherapy.
(7) Training, education and research are necessary to promote multicentre clinical trials in molecular radiotherapy.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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