



Molecular radiotherapy: guidance for clinicians

Second edition

**Report from the Intercollegiate Standing
Committee on Nuclear Medicine**

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Foreword

The third annual report from the Department of Health entitled *Improving outcomes: a strategy for cancer*,¹ published in 2013, emphasised the need to enhance outcomes across the board for those suffering from cancer, including measures to improve inequalities of access to treatment. Subsequently in 2015 NHS England published a five-year strategy entitled *Achieving world-class cancer outcomes*, and NHS England's National Cancer Programme released a progress report in October 2017 reporting that the NHS was on track to transform cancer services by 2020/21.² Despite these developments, access to specialised imaging and therapy using some medical radionuclides varies between different centres in the UK.

Furthermore, changes in disease prevalence, improved diagnostic options, developments in therapy, access to electronic patient data, the availability of multiprofessional guidelines and the advent of multidisciplinary working have implications for how medical professionals co-operate for the benefit of patients. Clinical disciplines that were once distinct are now required to combine their expertise to offer patients optimal treatment. For example, this is true of the disciplines of clinical oncology and nuclear medicine, where training in each of the disciplines will need to be more integrated.

The Intercollegiate Standing Committee on Nuclear Medicine (ICSCNM) is committed to the continuing development of molecular radiotherapy. Close liaison between clinicians from a number of different specialties is essential to ensure high-quality service delivery in radionuclide therapy across a range of clinical indications. This revised guidance (originally published in 2014 and updated to take account of recent changes and developments) provides a helpful framework for and sets out the roles and responsibilities of those who may be involved in molecular radiotherapy. It covers the licensing and organisational aspects of handling radioactive isotopes, as well as issues that relate to clinical practice, delegation and team working.

On behalf of the ICSCNM, I would like to thank, most sincerely, the working party who have greatly assisted me in revising this document: Jon Wadsley, Mark Gaze, Shaunak Navilkisoor, David Colville, Laura Moss and Louise Fraser.

This document has been published on the websites of the Royal College of Physicians (RCP) and The Royal College of Radiologists (RCR). Details of the publication will be made known to the relevant ICSCNM constituents: the Clinical Oncology Faculty of the RCR, the Royal College of Physicians of London, the Royal College of Physicians and Surgeons of Glasgow, the Royal College of Physicians of Edinburgh, the Royal College of Pathologists and the British Nuclear Medicine Society (BNMS), so that they can inform their members as appropriate.

Professor Andrew Scarsbrook

Chairman ICSCNM

1. Aims

This document aims to:

- Provide guidance for clinical teams delivering molecular radiotherapy, with a focus on medical staff
- Define the roles and key responsibilities of specialists involved in delivering molecular radiotherapy
- Emphasise the importance of training, skills and maintenance of competence for all staff involved in caring for patients receiving molecular radiotherapy
- Describe the requirement for close liaison within a skilled multiprofessional team and appropriate infrastructure to ensure high-quality molecular radiotherapy service provision
- Identify the specialists required in multidisciplinary teams delivering specific molecular radiotherapy treatments.

2. Introduction

A 2011 survey of molecular radiotherapy in the UK demonstrated significant geographic disparities in treatment availability and differences in practice between specialist centres.³ Taken with previous surveys, these data highlight the importance of practice guidelines to drive consistent standards of care in the UK. A recently published survey of UK centres conducted by the Internal Dosimetry Users Group (IDUG) has reported a significant increase in molecular radiotherapy use in oncology with almost three times as many treatments being carried out in 2015 compared with 2007.⁴

The complex infrastructure requirements of a high-quality service limit the delivery of molecular radiotherapy to hospitals that provide specialist expertise. Centres delivering molecular radiotherapy for malignant disease, for example, will also provide comprehensive diagnostic facilities, systemic therapy and radiotherapy services.

Close liaison between all staff involved in managing patients undergoing molecular radiotherapy is a prerequisite for the delivery of a high-quality service. The training, competence and commitment of non-medical members of the molecular radiotherapy team are pivotal to high-quality service provision but lie beyond the scope of this document.

Compared with external beam radiotherapy, cytotoxic chemotherapy and biological therapies for cancer, molecular radiotherapy is applicable to a relatively small, but steadily increasing, number of patients. It is, nevertheless, an effective treatment for specific groups of patients and, as healthcare commissioning changes, it is essential that the funding allocation for molecular radiotherapy safeguards access for all patients who might benefit from this form of treatment. In support of this the National Institute for Health and Care Excellence (NICE) has recently approved molecular radiotherapy treatments including Radium-223 dichloride⁵ and Lutetium oxodotreotide.⁶

3. Safe patient care and treatment: clinical, legal and administration responsibilities

Team and individual responsibilities

Several clinicians may be involved with the care of an individual patient. Local protocols should be developed to facilitate close collaboration and clear communication pathways between members of the molecular radiotherapy team and referring specialists.

The principle of working in teams complies with the General Medical Council (GMC) document *Good medical practice*.⁷ Individuals working within a team remain accountable for their own professional conduct and for the care they provide. Care should only be delivered by doctors who have the appropriate training, knowledge and skills. The number of clinicians who have relevant expertise within the team must be sufficient to provide prospective cover, and robust arrangements should be in place to ensure continuity of high-quality care.

All staff involved in the care of patients receiving molecular radiotherapy must be appropriately trained and ensure that their knowledge and skills remain up to date through continuing medical education and professional development. It is essential that the volume of molecular radiotherapy work undertaken by staff is sufficient to maintain the necessary level of competence to deliver the highest standards of care.

Shared care between the referring specialist and clinician responsible for justifying, prescribing and delivering molecular radiotherapy should be underpinned by written protocols that clearly specify the responsibilities of individual specialists involved in delivering treatment and immediate post-treatment care and supervising follow-up. The doctor responsible for administering molecular radiotherapy must be satisfied that the patient is fit to proceed with therapy on the day of treatment administration and that robust arrangements for ongoing care are in place.

Molecular radiotherapy should be administered by appropriately trained staff who are competent in handling unsealed sources and are experienced in radiation protection.

In centres where it is difficult for clinicians to maintain competence in managing uncommon conditions, referral to another unit that has a higher specialist workload should be considered. Molecular radiotherapy for rare malignancies, for example neuroendocrine tumours (NETs) (mIBG or peptide receptor radiotherapy [PRRT]), should be limited to centres supported by a relevant tumour-specific, multidisciplinary team (MDT) that has expertise in delivering these treatments. In addition to site-specialised MDTs, where molecular radiotherapy may only be needed for a small proportion of their patients, it may be helpful to have a regular molecular radiotherapy MDT meeting (MDTM). This will bring together nuclear medicine physicians, physicists, technicians and radiographers with oncologists and referring clinicians. It is the responsibility of all clinicians prescribing molecular radiotherapy to work collaboratively on a national/European level to optimise therapy protocols and pool outcome data for rare diseases. Accreditation systems such as the European Neuroendocrine Tumour Society (ENETS) Centre of Excellence status provide a way of sites demonstrating they have the necessary expertise to provide molecular radiotherapy.

Management guidelines

Evidence-based management guidelines and protocols should be developed by the MDT, reflecting published guidance for high-quality care. MDTs should develop clearly documented referral pathways to ensure equity of access and that patients are referred appropriately for consideration for molecular radiotherapy. Where possible, patients should be offered the opportunity to participate in clinical trials.

Decision to treat

Treatment decisions for patients with benign conditions should be made jointly by the referring clinician and by an appropriately trained, experienced specialist who holds a practitioner licence issued under the latest Ionising Radiation (Medical Exposure) Regulations (IR(ME)R).⁸ Such decisions should also be made in accordance with local and national guidance.

The treatment plan for patients with malignant disease should be discussed and agreed by the appropriate tumour-specific MDT, and also, if relevant at that hospital, the molecular radiotherapy MDT, in accordance with national guidance, and to ensure that the full range of treatment options available to patients is considered. The outcome of the MDTM may be to recommend a specific radionuclide therapy, but the final decision and legal responsibility for treatment delivery rest with the licensed practitioner.

Informed consent

Patients or their parents or legal guardians must give written informed consent for the treatment being delivered. The doctor taking consent must have the relevant training and experience of using the radiopharmaceutical prescribed and be able to discuss the aims and potential benefits, risks and side-effects of treatment. In practice, consent will usually be taken by the licensed practitioner, but this duty may be carried out by an appropriately trained and entitled operator under IR(ME)R.

Patient fitness for treatment

The patient's fitness to proceed with treatment safely, particularly where therapy requires a period of isolation for radiation protection reasons, must be assessed by the licensed practitioner or by an appropriately trained doctor or other entitled operator under IR(ME)R. It may be necessary to delay molecular radiotherapy to allow time for significant co-morbidities to be treated or for radiation protection arrangements to be put in place. The reasons for any treatment delay, which may include a formal risk assessment, should be documented in the patient's notes.

Responsibility for molecular radiotherapy administration

The clinician responsible for the justification of molecular radiotherapy must possess a practitioner licence for the radiopharmaceutical being administered.⁹ The employer must also hold a licence for each procedure at each site where radioactive substances are administered. The employer is responsible for provision of appropriate facilities and equipment, for training of supporting staff involved in the administration of molecular radiotherapy and for establishing procedures and protocols required by IR(ME)R. Guidance on licensing requirements is available from ARSAC.⁹

Treatment delivery

All treatment will be delivered according to locally agreed protocols for molecular radiotherapy, in an appropriate facility, within designated areas for therapy handling and administration of radionuclides.

Unsealed radioactive sources should be handled in a safe, designated area that meets statutory requirements.

Outpatient therapies should be administered in a specified location. Delivery of inpatient molecular radiotherapy and subsequent care of radioactive inpatients should be undertaken in an appropriately designated room.⁸ Staff involved in caring for patients should be trained in radiation protection and the condition being treated.

Dosimetry

Molecular radiotherapy is usually prescribed as a fixed activity or fixed activity adjusted for body mass or surface area taking into account other relevant factors such as renal function. In the absence of randomised clinical trial evidence, activities are prescribed according to published experience supported by clinical judgement and specialist expertise within the MDT. Other methods of dose prescription, for example to a desired whole-body radiation absorbed dose, are available. Where possible, patients should be recruited into clinical trials to establish whether prospective dosimetry-based individual treatment planning improves outcomes.⁹ Personalised treatment planning and verification of treatment delivery is mandated in Regulation 12(2) of IR(ME)R.⁸

Radiation protection

Under IR(ME)R, the employer is responsible for establishing a framework for radiation protection including written procedures and protocols. In practice, associated tasks are often delegated to appropriately trained duty holders under the regulations. A medical physics expert (MPE) with expertise in molecular radiotherapy must be consulted when setting up a service. An MPE must be present for all administrations other than those for where a standard protocol is followed. For standard treatments, an MPE must be available on site or at least contactable. Systems must be in place for reporting, recording, analysing and responding to errors in delivery of molecular radiotherapy.

Patients must be informed of radiation protection precautions that they should observe post-therapy in accordance with the local protocol. Radiation protection advice provided by the doctor taking consent should be reiterated by another suitably trained member of the molecular radiotherapy team (for example, medical physicist, clinical scientist, technologist or radiographer) and documented in the patient's notes.

Responsibility for patient care following molecular radiotherapy

Local protocols should clearly document arrangements for patient care following administration of molecular radiotherapy. The doctor prescribing treatment carries responsibility for the delivery of molecular radiotherapy and for any complications arising from that treatment; follow-up may be undertaken by this clinician (such as the licensed practitioner) or by another appropriate doctor (for example, the referring clinician, an endocrinologist or general practitioner). The licensed practitioner must be satisfied that suitable arrangements for continuing care are in place before radiopharmaceutical administration, otherwise the administration cannot be justified.

Access to clinical trials

Clinicians should, where possible, provide the opportunity for patients requiring molecular radiotherapy to be included in well-designed clinical trials to strengthen the evidence for molecular radiotherapy and improve outcomes.¹¹

Paediatric molecular radiotherapy

A small minority of children with cancer may benefit from molecular radiotherapy. Children have special requirements and should be managed only in recognised specialist paediatric molecular radiotherapy centres. The requirements for these are detailed in *Good practice guide for paediatric radiotherapy*.¹² In essence (see **Table 1**), these centres have dedicated inpatient molecular radiotherapy suites within paediatric oncology facilities staffed round the clock with paediatric nursing and medical staff, co-located with nuclear medicine facilities. It will be possible for parents to stay safely with their children, if their exposure as a comforter and carer is justified and dose constraints established by the employer are adhered to.¹³ As the evidence base for molecular radiotherapy in children is limited, it is highly desirable for children to be entered into National Cancer Research Institute (NCRI) portfolio clinical trials when appropriate. Particularly given the desire to avoid unnecessary exposure to ionising radiation in children wherever possible, whole-body and tumour dosimetry is strongly encouraged. General anaesthesia may be necessary for younger children to have scans but input from play specialists should keep this requirement to a minimum.

Table 1: Requirements for centres giving molecular radiotherapy to children¹⁵

Experienced paediatric clinical oncologists

Therapeutic radiographers with special expertise

Play specialists

Physicists including a therapeutic nuclear medicine MPE for radiation protection and dosimetry

Facilities in an age-appropriate environment with paediatric cover

Nuclear medicine facilities for scanning with general anaesthetic available

The indications for molecular radiotherapy in children are not dissimilar from adults. Differentiated thyroid cancer is a relatively common indication. As children have a greater likelihood of lymphatic and haematogenous metastases than adults, there may be a greater need for therapeutic radioactive iodine administration after radioiodine remnant ablation.

The most common NET is neuroblastoma, for which mIBG therapy has an established role,¹⁴ and PRRT has been explored in trials.¹⁵ 'Adult' type NETs are less commonly encountered in children, but mIBG and PRRT may be of value in patients with metastatic disease. Other indications are the subject of clinical trials, for example radioimmunotherapy as a potential alternative to whole-body irradiation for bone marrow transplant conditioning.

4. Recommended approaches for specific radionuclide therapies

Benign disease

Radioiodine (¹³¹I) for benign thyroid disease

The extent to which nuclear medicine specialists, endocrinologists or clinical oncologists participate in the decision-making process and supervise treatment delivery should be agreed locally and clearly documented. Arrangements will vary between hospitals depending on the training and expertise of the medical staff. The employer is responsible for ensuring that written protocols are in place and normally consults with the licensed practitioners to ensure that they are consistent with national guidance and best practice.¹⁶

Intra-articular therapy (radiation synovectomy) using ⁹⁰Yttrium, ¹⁶⁹Erbium and ¹⁸⁶Rhenium

Decision-making with respect to the administration of intra-articular therapy may involve rheumatology, orthopaedic, haematology, musculoskeletal radiology, nuclear medicine or clinical oncology specialists. Aseptic cannulation of the joint space, drainage and administration of intra-articular radiopharmaceuticals may be performed by the licensed practitioner or by an appropriately trained and entitled operator. Protocols should clarify responsibility for patient preparation, for example when treating patients with haemophilia, and for supervising aftercare with respect to immobilisation of the treated joint.

Malignant disease

Radioiodine (¹³¹I) for differentiated thyroid cancer

All new patients with differentiated thyroid cancer should be managed via an appropriate (head and neck cancer or thyroid cancer) MDTM and, if appropriate, a molecular radiotherapy MDT. Patients on defined care pathways may not require formal meeting discussion and MDT members with appropriate expertise could make decisions about patients. Local pathways for the management of thyroid cancer should be agreed in accordance with national guidance.¹⁷

Patients should have ready access to all specialists who may contribute to their care (clinical oncologists, endocrinologists, nuclear medicine specialists and surgeons). Decisions regarding the administration of radioiodine may involve several members of the clinical team, with specialists in clinical oncology and nuclear medicine taking a lead role. While patients understand that different specialists are involved in their care, it is helpful if a lead clinician and key worker (for example, clinical nurse specialist or specialist therapeutic radiographer) is identified for each patient to ensure clarity and consistency of communication.

The management of patients with recurrent or metastatic disease should be done by the MDT to ensure that all treatment options are considered.

¹³¹I-meta-iodo-benzyl-guanidine (¹³¹I mIBG) for NETs

A treatment plan for NET patients should be discussed and agreed in an appropriate, specialist MDTM. Patients should have ready access to all specialists who may contribute to their care (clinical oncologists, endocrinologists, medical oncologists, nuclear medicine specialists and surgeons).

Due to the rarity of these tumours and the relative complexity of ¹³¹I mIBG treatment, it is recommended that this therapy is provided by a small number of hospitals that offer specialist expertise and have the infrastructure to support treatment delivery. This necessitates the development of clear referral pathways to ensure that all appropriate patients have access to ¹³¹I mIBG treatment.

¹³¹I mIBG therapy for children requires close co-operation between paediatric oncology and adult molecular radiotherapy teams – both of which should contribute to decisions about treatment in the context of a paediatric cancer MDTM. It is recommended that this treatment is provided only by a small number of hospitals that offer both molecular radiotherapy and paediatric oncology expertise in line with the National Institute for Health and Care Excellence (NICE) *Improving outcomes guidance for the management of children and young people with cancer*.¹⁸

Peptide receptor radiotherapy (PRRT) for somatostatin receptor-positive NETs

Treatment plans for all NET patients should be managed by an appropriate NET MDTM. Local pathways for NET management should be agreed in accordance with published guidance.¹⁹ The first licensed PRRT agent is ¹⁷⁷Lu-oxodotreotide (Lutathera). A recent phase 3 randomised controlled trial (NETTER-1) showed significantly superior progression-free survival (PFS) of ¹⁷⁷Lu-oxodotreotide over high-activity octreotide long-acting release (LAR) in mid-gut NET patients.²⁰ A technology appraisal by NICE endorsed the use of ¹⁷⁷Lu-oxodotreotide in line with its marketing authorisation, that is in patients with gastro-entero-pancreatic NETs (GEP-NETs).⁶

Patients should have ready access to all specialists who may contribute to their care (cardiologists, clinical geneticists, clinical oncologists, endocrinologists, gastroenterologists, medical oncologists, nuclear medicine specialists, palliative care and surgeons). Patient selection for PRRT should be managed via a NET MDT where available therapeutic options are discussed. Decisions regarding the administration of PRRT and radiopharmaceutical selection may involve several members of the clinical team, with specialists in clinical oncology and nuclear medicine taking a lead role.

Given the rarity of NETs and relative complexity of radiopeptide treatment delivery, particularly in patients with functioning NETs, it is recommended that this therapy is restricted to a small number of hospitals that offer specialist expertise and have the infrastructure to support high-quality, safe treatment delivery. This necessitates the development of clear referral pathways to ensure that all appropriate patients have access to radiopeptide treatment.

Selective internal radioembolisation therapy (SIRT)

SIRT has been extensively evaluated in the treatment of non-resectable liver metastases (predominantly colorectal). Combined analysis of three multicentre randomised phase 3 trials of first-line SIRT combined with chemotherapy in liver-dominant metastatic colorectal carcinoma did not improve overall survival compared with chemotherapy alone.²¹

Consequently, SIRT is not funded for this indication in England. NHS England has recently published a clinical commissioning policy and now funds the use of SIRT for patients with chemotherapy refractory/intolerant metastatic colorectal carcinoma.^{21,22} There is more limited evidence on the use of the treatment in patients with hepatocellular carcinoma and intrahepatic cholangiocarcinoma and it is not funded by NHS England for these indications.^{23,24} Patients should be selected for SIRT by a hepatobiliary cancer MDT. It is recommended that eligible patients are offered the opportunity to be entered into clinical trials where possible.

Treatment decisions will involve several members of the clinical team taking a leading role, including specialists in interventional radiology, oncology and nuclear medicine. It is recommended that this treatment is provided by hospitals that offer specialist expertise in all these areas and is a prerequisite for funding via NHS England as part of its new commissioning policy.²²

Treatment for bone metastases

Radium-223 dichloride (²²³RaCl₂)

²²³RaCl₂ is licensed for the treatment of skeletal metastases due to castrate-resistant prostate cancer, following, or for those unable to have, docetaxel chemotherapy.⁵ Local treatment pathways should be developed by the MDT, in accordance with published evidence, to ensure that all treatment options are considered for and are available to all appropriate patients with metastatic disease.

Treatment decisions are likely to involve specialists in oncology, nuclear medicine and palliative care. Written protocols should clarify responsibility for clinical supervision and monitoring between treatment cycles.

Samarium-153 lexidronam

Samarium-153 lexidronam treatment for bone pain palliation in patients with skeletal metastases should be managed by the relevant, disease-specific MDT. Treatment decisions should involve oncology, nuclear medicine and palliative care specialists.

Miscellaneous

⁹⁰Y-ibritumomab tiuxetan

⁹⁰Y-ibritumomab is licensed for use in adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL), and as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma. Patients should be managed via an appropriate haematology MDTM.

Treatment decisions are likely to involve clinical oncologists and/or nuclear medicine specialists and a lymphoma haemato-oncologist or medical oncologist. It is essential that appropriate follow-up and support are in place to manage post-treatment cytopenias.

Prostate-specific membrane antigen (PSMA) targeted molecular radiotherapy

¹⁷⁷Lutetium PSMA is an emerging treatment in patients with metastatic prostate cancer that has shown some promise in initial trials with evidence of biochemical response.^{25,26} However its efficacy in overall and disease-free survival is still to be fully assessed and is currently the focus of ongoing multicentre trials. It is recommended that centres involved

in these trials have experience in molecular radiotherapy administration and relevant infrastructure and governance arrangements in place. Decisions regarding treatment should involve appropriate members of a specialist MDT (oncology, nuclear medicine and palliative care).

Novel treatments and research

Due to the complexity of administration, expertise required and radiation protection issues surrounding molecular radiotherapy, it is recommended that novel treatments and research trials should be undertaken only by specialist centres that have experience in providing molecular radiotherapy and have the relevant infrastructure in place.

5. Summary

The provision of molecular radiotherapy requires effective, cross-specialty collaboration and multidisciplinary teamwork.

- Employer and practitioner licences are required to administer radioactive materials for therapeutic purposes.
- Molecular radiotherapy should be delivered in accordance with agreed written protocols that define the duties and responsibilities of all specialists involved in an individual patient's management.
- Children should be treated in recognised paediatric molecular radiotherapy facilities.
- Individual team members remain accountable for their own professional conduct and the standard of care they provide.
- Molecular radiotherapy for patients with rare malignancies should be managed by a small number of designated individuals working in specialist hospitals, capable of providing the expertise, patient throughput and infrastructure to support treatment.

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The Royal College of Radiologists
63 Lincoln's Inn Fields
London WC2A 3JW

+44 (0)20 7405 1282
enquiries@rcr.ac.uk
www.rcr.ac.uk
@RCRadiologists

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