CTRad: identifying opportunities to promote progress in molecular radiotherapy research in the UK

NCRI
National Cancer Research Institute

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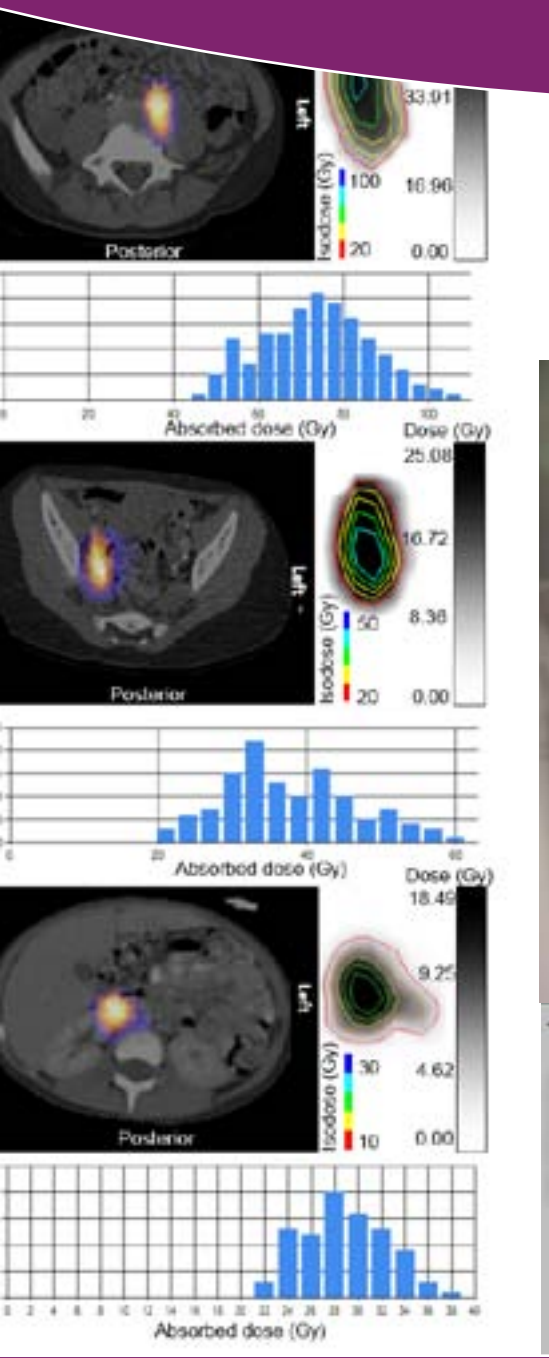

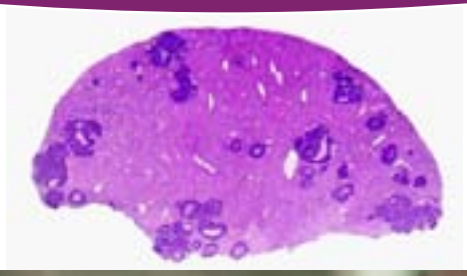

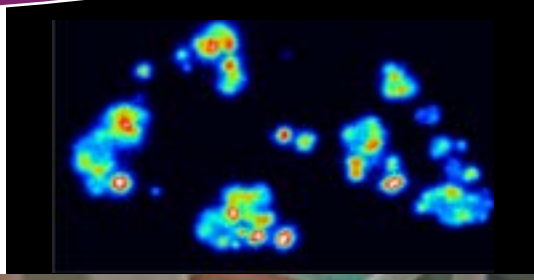

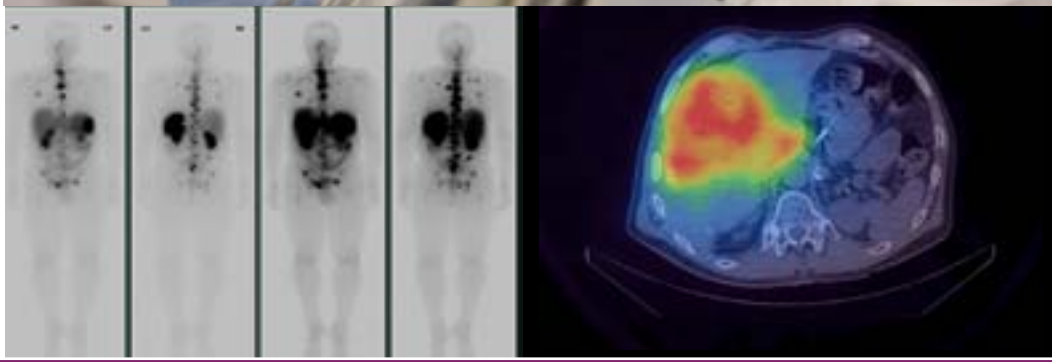

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Cover images (clockwise from left)

1. 3D tumour dosimetry in three children following an administration of I-131 mIBG for neuroblastoma. The top left image in each panel shows the absorbed dose map overlaid onto the corresponding CT slice, the top right image shows isodose contours, and the bottom image shows the dose volume histogram. Photograph used with kind permission of Dr Glenn Flux.

2. Highly selective localisation of radiolabeled anti-CEA antibody in colorectal liver metastases. Left: morphology (H&E) showing mouse liver (pink) containing metastases (purple); right: phosphorimage of same section showing radioantibody localisation in the same metastases. Reprinted from Dearling JLJ, Flynn AA, Qureshi U, et al. Localization of radiolabeled anti-CEA antibody in subcutaneous and intrahepatic colorectal xenografts: influence of tumor size and location within host organ on antibody uptake. *Nuclear Medicine and Biology*. 2009; 36(8):883-894. With permission from Elsevier.

3. Radiopharmacist preparing radiotherapeutic in aseptic hood. Photograph used with kind permission of Dave Bell at Some See Different.

4. Single-photon emission computed tomography (SPECT)/CT after selective internal radiation therapy with Yttrium 90 microspheres injected into segments IV, V and VIII. Photograph used with kind permission of Professor Ricky Sharma.

5. Post Lutetium-177 DOTATATE therapy whole body scan of a patient with metastatic paraganglioma. Photograph used with kind permission of Dr Mark Gaze.

Contents

Executive summary

Molecular radiotherapy (MRT) is a modality of treatment whereby unsealed radioactive sources are delivered systemically into a patient. These may be biologically targeted, when a radiopharmaceutical is physiologically concentrated from the circulation into target tissue, or physically targeted, for example including the use of small radioactive particles injected into the blood supply of a tumour or when a radioactive colloid is injected into a cyst cavity.

MRT has a role in the treatment of benign disease and a number of cancers where it is used to manage residual disease, as well as recurrence and disseminated metastases. Further developments in this area are likely to make an important contribution to patient care with recent innovations in MRT changing clinical practice in the NHS.

MRT has considerable potential to benefit patients, and could provide further scope for improved patient outcomes. However, research in MRT has lagged behind that of other cancer therapies. The National Cancer Research Institute's (NCRI) Clinical and Translational Radiotherapy Research Working Group (CTRad) envisages significant effort will be required to align research developments in MRT with progress made in external beam radiotherapy and drug treatment. To help assess the needs and opportunities in UK MRT research, CTRad consulted with the UK MRT community to ascertain the range of research activity and the barriers preventing progress. The feedback has identified opportunities for improvement as well as a number of barriers and challenges.

Realising the unfulfilled potential of MRT will require an integrated approach, increased investment and the active involvement of a range of individuals and organisations beyond the NHS. This report encompasses three strategic priorities, for each of which a number of recommendations are provided that will promote progress in MRT research.

Strategic priorities and recommendations

1. Enhancing research infrastructure and multidisciplinary working

The need

The MRT community considers the existing research infrastructure and workforce to be inadequate to foster and promote the development of new and effective treatments. There is a need for coordinated efforts to improve the supply and management of resources, to overcome geographical variation in MRT access, and to improve research funders' perceptions of MRT. Collaboration between nuclear medicine, oncology and referring clinicians within the multidisciplinary setting is vital to MRT research. Establishing MRT stakeholder groups and engaging with research funders are crucial for the generation of effective collaboration within the MRT research community.

Recommendations

1. A forum should be established through which the MRT community can engage collaboratively with research funders to better communicate the value of high quality MRT research, and to discuss the common obstacles encountered in MRT trials. This will encourage more suitable planning and allocation of research funding.

2. The number of staff within the nuclear medicine community appropriately trained in MRT (clinicians, physicists, technologists, nurses, clinical scientists and radiopharmacists) needs to be increased and research time needs to be protected.

3. Increased investment in specialised radiopharmacies is needed throughout the UK to facilitate and support wider access and to further develop new MRT strategies.

4. Greater accessibility should be explored using a 'hub-and-spoke' model whereby centres of excellence could provide treatments and clinical trials opportunities, supported by satellite centres.

2. Acquiring good evidence for best practice

The need

There is a clear need to strengthen the evidence base for MRT with phase I, II and III clinical trials. Multicentre prospective data collection studies are required to generate evidence-based guidelines, which can then be used to standardise practice.

Recommendations

5. Multicentre phase III clinical and early phase studies in MRT are needed to gather clinical evidence and to optimise treatment protocols. These will ideally be academically led.

6. A national database and consistent coding should be established to record MRT treatment, dosimetry and outcome data and so assess therapeutic efficacy of existing and new treatments.

7. A national quality assurance group to deliver full quality assurance (QA) in MRT trials should be established. The steps and resources necessary for incorporating QA in MRT trials should be evaluated.

3. Optimising MRT treatment

The need

In contrast to external beam radiotherapy, the majority of MRT treatments are not planned according to the radiation doses delivered and the absorbed doses delivered at therapy are seldom calculated. This prevents personalisation and optimisation of treatment, and is potentially in contravention to the forthcoming EU Directive on basic safety standards for protection against the dangers arising from exposure to ionising radiation. UK centres need to be equipped for the change, and this provides a research opportunity.

Recommendations

8. Dosimetry and MRT treatment planning should be individualised and be routine practice. This will require investment.

9. Protected time for research is necessary to develop dosimetry-based treatment planning.

10. Investment is necessary to support projects focused on optimisation and standardisation of dosimetry protocols.

1. Introduction

1.1 Background to molecular radiotherapy

Radiation therapy is a highly effective treatment for cancer. Ionising radiation deposits energy to cells and tissue as it passes through the patient's body. The main biological target of the deposited energy is deoxyribonucleic acid (DNA) in cancer cells. If this genetic material is damaged beyond repair, cell division will result in cell death. The eradication of cancer cells with the preservation of normal tissue function is in part due to better repair capacity in the normal cells, and in part due to higher radiation doses being received by tumour compared with normal tissues. A higher therapeutic ratio can be achieved by improved physical or biological targeting of the radiation to the tumour.

External beam radiotherapy (EBRT) is the most widely used form of radiation therapy and is delivered from outside of the body by using high energy X-rays (photons) or particle radiation. Brachytherapy delivers radiation internally using sealed radioactive sources in surface applicators placed within or adjacent to the cancer. This report concerns the delivery of radiation therapy administered systemically or loco-regionally with unsealed radioactive sources consisting of a radionuclide that may be attached to a pharmaceutical or particle. This treatment has been known by a variety of names including isotope treatment, unsealed source therapy, targeted radionuclide therapy, nuclear medicine therapy and also molecular radiotherapy; the term 'molecular radiotherapy' (MRT) will be used throughout this review. **Appendix 1** is a brief section on the principles of MRT use and **Appendix 2** shows radionuclides currently in clinical use.

MRT may be considered as a form of systemic radiotherapy that can target tumours and widely disseminated disease that cannot be treated with EBRT and brachytherapy. Although generally considered as a treatment option for cancer, radiopharmaceuticals are frequently used to manage benign disease. The most common example of this is the treatment of hyperthyroidism with Iodine-131 (^{131}I) - ^{131}I NaI treatment.[1] Delivery of this clinical service is closely linked to MRT treatments, but these treatments are outside the scope of this review.

From its development in the 1940s to treat thyroid cancer with ^{131}I NaI, MRT has established a relatively small but important role in the management of other cancers.[2] Advances in the understanding of the molecular biology of cancer have identified new molecular sites, receptors and biological processes as hallmarks of cancer and subsequent targets for MRT therapy. The development of new MRT agents has increased the number of clinical therapy options to treat several cancers in curative, adjuvant, and palliative settings.[3]

Ingested or administered by intravenous infusion or injection, MRT radiotherapeutics have relative specificity for the target cancer cells. In contrast to chemotherapy, whereby all proliferating cells are affected with treatment, circulating MRT molecules specifically interact with molecular sites or receptors on target cancer cells or the tumour microenvironment. An important consideration in the development of MRT radiopharmaceuticals is the stability of the treatment labelling to ensure that the attached radioisotope is not freely distributed throughout the body, which could cause unnecessary radiation exposure to organs. The emitted radiation will then interact with surrounding cells within the range of the isotope emission. This specificity results in relative sparing of normal cells, thereby reducing treatment side effects. Growing evidence supports MRT as a well-tolerated treatment that can improve both quality of life and survival in paediatric and adult cancer.[4-9]

1.2 Need for a review of molecular radiotherapy

The translation of scientific advances in MRT is impeded by several obstacles. Despite its history and undoubted place in the management of some cancers, MRT has been a relatively neglected area of medical practice, which has received little investment in research and support at clinical sites in the UK. Subsequently, a lack of scientific appraisal of the MRT portfolio has led to wide variation in clinical practice between NHS centres. A survey of UK MRT practices in 2007 by the British Institute of Radiology (BIR) Molecular Radiotherapy Working Party (results published in BIR Report 23) highlighted this discrepancy in treatment protocols as well as significant geographical disparities in treatment availability.[3]

Progress in MRT research is a concern to a number of stakeholder groups including the NCRI Clinical and Translational Radiotherapy Research Working Group (CTRad). CTRad was established in 2009 to provide leadership in the national effort to support radiotherapy research in the UK as well as helping to develop a portfolio of clinical trials.[10] Whilst there has been good progress in some areas, CTRad acknowledges that progress has been slower in other areas such as MRT, and envisages significant effort will be required to align research developments in MRT with progress made in EBRT and chemotherapy treatment practices.[11] The Independent Cancer Taskforce's 2015–2020 strategy report also highlighted that further investment, plus support from funders and the NHS is required in radiotherapy research, including MRT research and innovative radiotherapy techniques.[12]

1.3 Purpose of the review

The delivery of MRT can be complex, with unique practical and regulatory challenges, although there are significant opportunities available to the UK MRT community to help improve therapy practices and consequently outcomes for cancer patients. To assess the current state of MRT research in the UK, CTRad set up a review with the following remit:

- to identify the UK's strengths and weaknesses to participation in MRT clinical trials and research;
- to identify scientific opportunities for MRT in the UK;
- to identify barriers to progress;
- to make recommendations to overcome these barriers;
- to highlight the research evidence required to underpin the advancement of MRT treatments in the UK.

1.4 Scope of the review

This review covers discussion regarding MRT research. To assess the barriers to research in the UK, a questionnaire was sent to NHS nuclear medicine departments in May 2015. In addition, MRT professionals involved in UK MRT research activities and clinical trials were consulted.

A research-focused questionnaire

The CTRad MRT research questionnaire (see **Appendix 3**) was distributed to 58 NHS nuclear medicine departments using the online questionnaire platform SurveyMonkey, which was kept open for 10 weeks (between May and August 2015). The questions served to assess the current landscape of MRT research in the UK and to gather opinions regarding the experience of performing MRT clinical trials.

Interviews with MRT professionals

Discussions with members of the MRT community (including nuclear medicine physicians, clinical oncologists, pre-clinical scientists, physicists and radiopharmacists) focused on research topics considered as priorities in the MRT research agenda and the barriers preventing further research progress.

Ambitions for high quality MRT research in the UK

On the basis of this input from the community, this review highlights the ambitions of the MRT community and the actions necessary to help support the overarching goal of increasing high quality MRT research in the UK; it also seeks to provide an awareness of the multidisciplinary resources and expertise required to achieve this. The review builds on the recommendations highlighted in the BIR Report 23 which encourages key stakeholders to form collaborations to build a national MRT strategy to support an infrastructure for increased MRT research, development and clinical implementation, by seeking tangible actions for the research community and funders.[3] The emphasis of this report is on cancer, although the challenges and potential solutions have wider relevance to the treatment of benign disorders.

2. Current experience of MRT and research in the UK

Advances with novel biological agents have led to a parallel expansion in MRT treatment options in recent years allowing more disease indications to be treated. There is no central data collection of administered MRT treatments as has been developed for EBRT and brachytherapy within the National Radiotherapy Dataset (RTDS).[13] Consequently, there is currently no official record of the centres that offer MRT treatments or outcome data from the treated patients. The first insight into MRT practices and the number of patients treated in the UK was provided by the BIR report in 2011 which issued a survey on MRT administration and therapy protocol data for the treating year of 2007.[3]

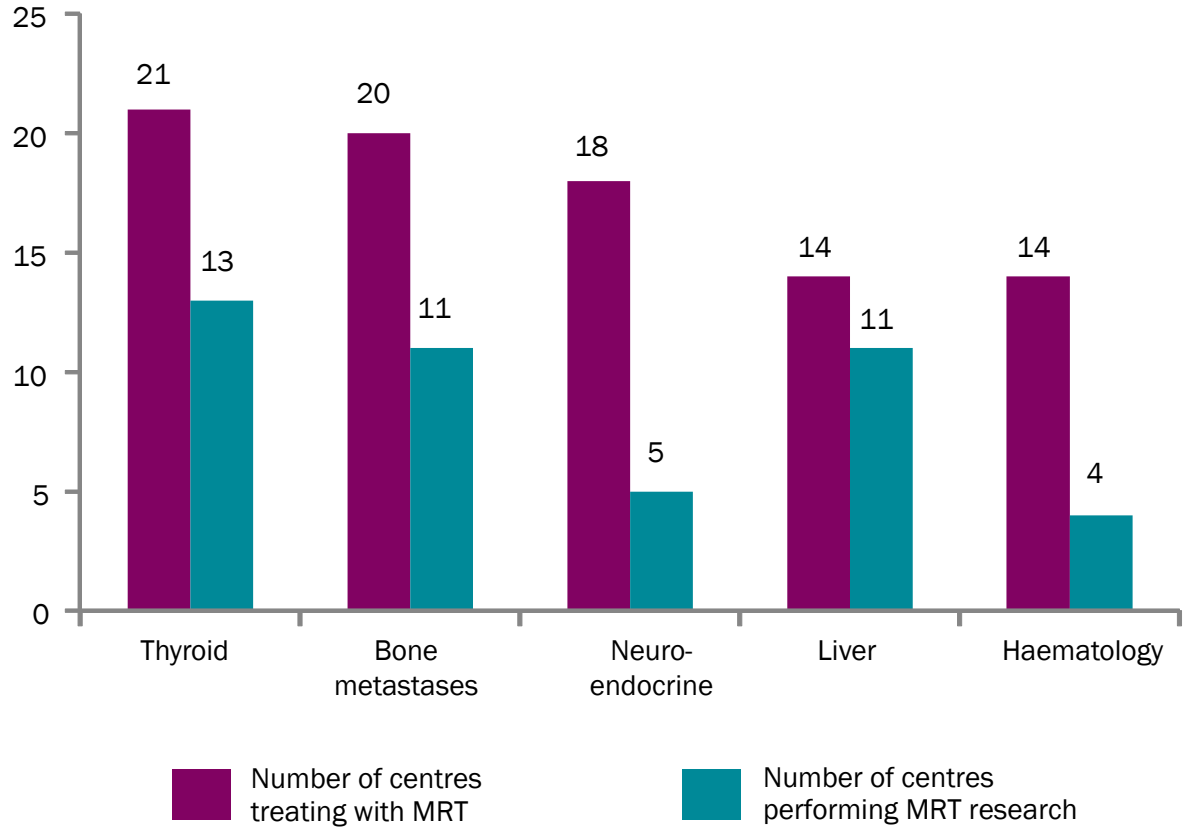
Following this, the Internal Dosimetry Users Group (IDUG) issued follow up surveys for 2011–2012 (see **Section 3** for further discussion). In the absence of a dataset, these surveys provide valuable insights into the use of MRT in cancer over a five-year period between 2007 and 2012, highlighting MRT as an area of strong growth in cancer care with the total number of MRT administrations rising by 38% during the period.[14]

2.1 CTRad MRT questionnaire results

To form a consensus on how further progress can be made in the area, CTRad developed a questionnaire concentrated on gathering opinion from the UK MRT community on their experience of developing and performing MRT research (discussed in **Section 3**). The questionnaire yielded responses from 23 out of the 58 NHS nuclear medicine departments surveyed across the UK that provided details on the disease areas treated and the volume of research underway (**Figure 1**), as well as a number of discussion points. Unsurprisingly, many sites have not adopted the entire range of MRT treatments in part due to the relatively small number of patients treated at individual sites, and the small pool of nuclear medicine experts available at sites to administer doses. Encouragingly, research engagement at the responding sites was 78% (18 sites). However, the volume of research at some sites was restricted to only one or two clinical trials in some cases. This is expected as the MRT clinical trial portfolio is relatively small and will require support to expand, as will be discussed later.

Nuclear Medicine departments also indicated the clinical trials their site had participated in during the last five years and studies that are currently recruiting (see **Appendices 4** and **5** for past and current trials at responding sites). All disease areas had trial activity; notably, the majority of these studies focused on treatment in the advanced disease setting. The following section covers MRT therapies and research that is prevalent in the UK and the possible treatment pathways for future investigation.

Figure 1. CTRad MRT research questionnaire: disease areas routinely treated with MRT and participation in research.



2.2 Differentiated thyroid cancer

The earliest and most established example of MRT is the use of ^{131}I for the treatment of differentiated thyroid cancer (DTC) following surgical removal of the thyroid. More than 3000 new cases were diagnosed in 2012 in the UK, and since its first use over 70 years ago, ^{131}I NaI remains the treatment of choice for the majority of patients owing to its efficacy and tolerability.[15] The long-term outcome of patients treated effectively for DTC with ^{131}I is favourable with an overall ten-year survival rate for middle-aged adults being 80-90%, while 9% of patients with thyroid cancer will die of their disease.[16]

Practice-changing thyroid trials

In the absence of evidence-based clinical trials, there is uncertainty over the optimal treatment to deliver, with administered activities of ^{131}I ranging from 1.1 GBq to 3.7 GBq for remnant ablation, and higher activities for therapy. This raises the concern that patients with low-risk DTC are being over-treated and it is important to minimise the risk of radiation-induced secondary cancers and other long-term negative effects. The first UK multi-centre randomised MRT phase III clinical trial (called HiLo) set out to determine whether treatment success rates are similar using the upper vs the lower range of activity in the low-intermediate risk patient group. Results from the study concluded in 2012 that the lower activity of 1.1 GBq was as effective as the higher activity of 3.7 GBq, with patients also having fewer side effects. This trial was practice changing and the British Thyroid Association guidelines were updated accordingly.[17-18]

There is, however, a lack of studies to tackle optimisation of treatment for medium- and high-risk thyroid cancer patients. A small proportion of these patients will develop radioactive ^{131}I-refractory advanced disease and subsequently have few treatment options. A new phase II trial, SEL-I-METRY, will investigate the potential clinical benefit of selumetinib in re-sensitising advanced iodine refractory DTC to radioiodine therapy in the UK for this patient group.[19] Importantly, the trial incorporates a dosimetry sub-study that will help to personalise MRT treatments on an individual basis which will be discussed further in **Section 3**.

2.3 Neuroendocrine cancer

An expanding role for MRT has involved the palliative treatment of patients with disseminated neuroendocrine tumours (NETs). Originating from cells within the endocrine and nervous system, NETs are a heterogeneous group of rare tumours with an estimated incidence of three per 100 000 in the UK.[20] This diverse group of tumours are generally slow growing. However, the majority of patients present late with large primary and disseminated disease, which cannot be managed surgically and are typically resistant to chemotherapy.[21]

The first radiopharmaceutical agent used to treat NETs was ^{131}I meta-iodobenzylguanidine (^{131}I-mIBG) in the 1980s. Clinical evidence for its use is largely based on small studies. Results from phase I/II trials report response rates ranging from 0% to 60% but with a wide variation in administered activities and methods of response assessment.[22-23] More recently a number of peptide analogues of somatostatin (DOTATOC, DOTATATE, DOTA-lanreotide), combined with radionuclides Yttrium-90 (^{90}Y) or Lutetium-177 (^{177}Lu), have been developed to target somatostatin receptors with high affinity to somatostatin receptor type 2 (SSRT-2).

Peptide receptor radionuclide therapy (PRRT) has grown rapidly in the UK with a 170% increase in the treatment of NETs with ^{90}Y-DOTATATE and ^{177}Lu-DOTATATE between 2007-2012.[14] Although no randomised, placebo-controlled trials using PRRT exist, PRRT therapies have been shown to cause tumour regression and symptomatic benefit in about 70% of NET patients.[24]

Another radiopharmaceutical for use in NET, Gallium-68 (^{68}Ga), is increasingly used throughout Europe. Although currently only available in a small number of UK centres, it is rapidly gaining a foothold in the UK, with at least

another six centres likely to introduce into routine clinical use in 2016. This could have a significant resource impact on radiopharmacy, as well as requiring substantial capital investment to establish the capability to deliver the service clinically.

Use of diagnostic imaging

An advantage of MRT for the treatment of NETs is that the rate of treatment success can be predicted by pre-therapy imaging. A new range of diagnostic nuclear medicine tracers are being pursued by groups looking to improve the sensitivity and specificity for uptake in cancer cells.

A current study in paediatric patients with metastatic neuroblastoma is investigating a novel imaging practice using a positron emitter, Iodine-124 (^{124}I)-mIBG as a positron emission tomography (PET) tracer instead of the standard tracer Iodine-123 (^{123}I)-mIBG (^{124}I-mIBG study, see **Appendix 5**).[25] The group hypothesise that the superior spatial resolution of PET imaging will allow more precise localisation of small disease foci, offering reliable and reproducible quantitative assessment of the patient's disease extent. If successful, this new targeted imaging technique will offer improved evaluation of disease and could be used for treatment planning with ^{131}I mIBG.

Neuroendocrine research directions

Adult

To help improve the therapeutic benefit of MRT in NET patients, research groups are investigating integration of MRT multimodality treatment regimens with molecularly targeted therapies. A recent trial planned to utilise the kinase inhibitor vandetanib alongside ^{131}I-mIBG therapy in patients with unresectable phaeochromocytoma and paraganglioma.[26] The aim of the trial was to investigate synergistic interactions leading to improved clinical outcomes. The trial prematurely closed when vandetanib manufacture was taken over by another company, who decided not to sponsor it.

Paediatric

Attempts to increase the response rate in the paediatric population have led groups to look at PRRT in adults with good response and few adverse side effects. ^{177}Lu-DOTATATE is currently being investigated in the phase IIa trial, LuDo, in children with primary refractory or relapsed high risk disease to assess the response rate, progression free survival (PFS) and toxicity in patients that have already been heavily pre-treated.[27] Eligible patients for therapy undergo diagnostic imaging using the radionuclide labelled ^{68}Ga-DOTATATE PET combined with Computed Tomography (CT), allowing a higher sensitivity and improved spatial resolution of disease and individualised internal dosimetry is included.

2.4 Bone metastases

Bone metastases are a common and severe complication in advanced cancers associated with severe pain and skeletal-related events (SREs). Local field EBRT is highly effective for pain relief in patients with relatively limited bone metastases, but in cases of disseminated disease, systemic bone-seeking radionuclides can preferentially localise to disparate tumour deposits. In particular, the most established indication for radionuclide therapy for bone is in metastatic castration-resistant prostate cancer (mCRPC) patients who are no longer responsive to other systemic treatments.[28-29]

A number of bone-seeking radionuclides have been developed, including intravenous use of commercially available products, Strontium-89 (^{89}Sr) chloride and Samarium-153 (^{153}Sm) lexidronam pentasodium. Administration of these radiopharmaceuticals are standardised by the manufacturer guidelines and are not based on individual treatment planning. Although treatment can relieve pain rapidly, therapy can lead to

myelosuppression, limiting its use. A number of other radiopharmaceuticals have also been used, primarily Phosphorus-32 (^{32}P), Rhenium-186 hydroxyethylidene diphosphonate (^{186}Re HEDP) and Rhenium-188 (^{188}Re) HEDP, although they are not currently used in the UK.[3]

Alpha-particle emitting radionuclides

A new approach that has been the subject of considerable interest recently is the use of alpha particle emitters in mCRPC patients with bone metastases. These radiopharmaceuticals deposit their energy over a very short range compared to beta emitters, causing tumour cell death without significant impact on normal cells such as the bone marrow. The alpha emitter, Radium-223 (^{223}Ra) dichloride (brand name Xofigo®), is a calcium mimetic that is deposited in areas of high bone turnover, including sites adjacent to bone metastases.

A phase III study, ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer), with ^{223}Ra has led to the introduction of a new life-extending treatment option in the mCRPC patient group with bone metastases.[6] The study reported a statistically significant improvement in the overall survival of the group treated with ^{223}Ra, and a longer time to first occurrence of SREs compared with the placebo group during the 3 year follow-up period.[6] Following the positive results, ^{223}Ra was approved in September 2013 in the EU for treatment of CRPC patients with bone metastases.[30] In the UK, ^{223}Ra dichloride has recently been recommended by NICE as a possible treatment for relapsed prostate cancer patients who have bone metastases.[31]

Expanding radium use

The good safety profile and non-overlapping mechanism of action of ^{223}Ra make it potentially suitable for use in combination with other therapeutics in the management of mCRPC with bone metastases. However, individualised dosimetry practices are not routinely used in ^{223}Ra therapy. The use of radioisotopes in bone metastases is also not entirely focused on patients with prostate cancer and an increasing number of trials are investigating treatment of breast cancer patients with metastatic bone disease.[32] The notable presence of younger patients in this treatment group highlights concerns of the unknown long term side effects of these treatments and underscores the importance of individualised dosing in treatment plans.

2.5 Liver cancer

Primary liver cancer and secondary cancer in the liver are often non-resectable, and most patients rely on therapeutic approaches to achieve local control and to reduce symptoms. Locoregional therapies such as transarterial chemoembolisation, percutaneous ethanol injection, radiofrequency ablation and biological therapy with sorafenib can help achieve local control and improve symptoms.[33] Previously, radiotherapy only had a limited role in treatment due to a relative lack of precision and the possibility of significant toxicity to normal liver tissue. However, recent progress in radiotherapy techniques using radiopharmaceuticals is allowing delivery of focal, high dose radiation to liver lesions while sparing normal liver tissue.[34] This innovative therapy, selective internal radiation therapy (SIRT), uses resin or glass microspheres with ^{90}Y incorporated in the particles to target multiple sites of disease in the liver in a single procedure. This method offers local control with a limited toxicity profile by injection directly into branches of the hepatic artery. Local retention of the particulates leads to a high local absorbed radiation dose and tumour cell death.

SIRT in primary and secondary cancers

Following a review of research studies using SIRT to treat primary liver cancer, several studies report that SIRT appears superior to transarterial chemoembolisation in downstaging patients.[35-36] NICE subsequently reviewed SIRT therapy for patients with non-resectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma.[37-38]

For secondary liver cancers, SIRT is increasingly used to treat patients with hepatic metastases from colorectal cancer or NETs. Phase III trials in patients with advanced colorectal cancer that has spread to the liver are currently ongoing to establish the place of SIRT as a treatment option for these diseases.

Evidence for SIRT in non-resectable colorectal metastases in the liver

Evidence presented in abstract form in 2015 from the first randomised phase III trial, SIRFLOX (the 'FOLFOX' combination chemotherapy treatment verses FOLFOX + SIRT), confirmed SIRT can significantly improve local control in patients treated in the first-line setting for metastatic colorectal cancer (mCRC).[39] Those that received SIRT had a median improvement of 7.9 months local control compared to those treated without.

These data are consistent with NICE guidance in 2011 which stated that there was sufficient evidence that SIRT can delay time to progression of cancer in the liver; however, more evidence was required on overall survival and quality of life of patients.[40] The multicentre UKNIHR CRN phase III clinical trial FOXFIRE will address these survival and quality of life endpoints using rigorous quality of life data collection built into follow-up procedures. The aim of the trial is to compare chemotherapy alone (FOLFOX) with chemotherapy plus SIRT (SIR-spheres) in mCRC patients.[7] It has so far exceeded its target recruitment figure, and results including health economics are due to be published in 2017.

NICE also recommended comparative trials to determine whether SIRT prolongs survival compared to best standard of care in patient groups that have already received chemotherapy. Another multicentre phase III clinical trial, EPOCH, is studying patients with mCRC in the second-line setting, thus addressing the recommendation by NICE to study patients who have already received chemotherapy.[41] This comparative trial's primary endpoint is PFS and it will also determine the effect of SIRT on quality of life.

Commissioning through Evaluation

To evaluate SIRT in the 'real world' setting, and to augment data from clinical trials with specific reference to overall survival and quality of life, the treatment has been available for patients with mCRC and intrahepatic cholangiocarcinoma since December 2013 through NHS England's Commissioning through Evaluation (CtE) programme;[42] similar schemes followed in Scotland and Wales. These innovative CtE schemes accelerate adoption of complex, specialist treatments such as SIRT via rapid registry-based evaluation in a timescale significantly shorter than those of phase III clinical trials.[43]

2.6 Haematological cancer

Cancers derived from haematopoietic tissues encompass a broad range of disorders and are grouped under four categories: non-Hodgkin's lymphoma (NHL), Hodgkin's disease (HD), leukaemia (acute and chronic, myeloid and lymphoid), and myeloma. EBRT can be a curative treatment in early stage NHL disease or can palliate patients with tumour-related symptoms. However, haematological diseases are rarely confined to a single site and systemic chemotherapy or immunotherapy can offer the possibility of treating metastatic or diffuse tumours. The potential of radiolabelled antibodies delivering a therapeutic dose of radiation to cancer cells has shown greatest efficacy in follicular NHL and encouraging results in myeloma studies.[44-46]

Non-Hodgkin's lymphoma

The introduction of the monoclonal antibody (mAb) rituximab in 1997 directed against the highly expressed surface protein CD20 antigen found on malignant B-cells remains a valuable therapy for follicular NHL patient group when used in combination with a chemotherapy regimen.[47] However, despite the sensitivity to initial therapy, the majority of patients with advanced disease eventually relapse and become refractory. The conjugation of targeted mAb therapy with radioisotopes, known as radioimmunotherapy (RIT), is being

investigated as an important second-line of approach in this patient group.

The majority of international clinical trials have focused on anti-CD20 antibodies radiolabelled with ^{131}I (^{131}I tositumomab, trade name Bexxar® - withdrawn by its manufacturer in 2014) and ^{90}Y (^{90}Y ibritumomab tiuxetan, trade name Zevalin®). Since approval by the FDA in 2002, ^{90}Y ibritumomab tiuxetan therapy has been shown to double the response rate to rituximab and be well tolerated.[42] In addition, ^{90}Y ibritumomab tiuxetan consolidation treatment following induction chemotherapy prolonged PFS by a factor of three in patients with advanced follicular NHL.[45]

^{90}Y ibritumomab tiuxetan use in the UK

NICE has not yet assessed ^{90}Y ibritumomab tiuxetan treatment for NHS availability, which has likely influenced its relatively low use in the UK. The NHS Scottish Medicines Consortium (SMC) reviewed ^{90}Y ibritumomab tiuxetan and subsequently did not recommend the therapy as the manufacturer did not present a sufficiently robust economic analysis to gain acceptance. The limited adoption of RIT by the medical community, despite its efficacy, seems to have resulted from a combination of factors, including concerns about price. A review is much needed.

Multiple myeloma

Every year 4800 people in the UK are diagnosed with multiple myeloma (MM) and treatment options are focused on extending the lives of patients and improving their quality of life.[48] The disease initially responds to chemotherapy and annually 700 of these patients benefit from autologous stem-cell transplantation. The disease initially responds to therapy but eventually becomes refractory. Studies including intensification of the conditioning therapy, with the addition of RIT ^{90}Y-radiolabelled mAb targeting the CD66 antigen protein to standard conditioning therapy, have yielded some encouraging results.[49] Following a phase I dose escalation study of radiolabelled anti-CD66 therapy, a randomised phase II clinical trial was opened to test the efficacy when used with high dose chemotherapy in the conditioning prior to autologous stem cell transplantation.[50] These early phase clinical trials have demonstrated that targeted radiotherapy can be used safely in conjunction with standard conditioning prior to transplantation. The hope is that this additive approach can further increase the response rates after high-dose therapy leading to greater improvements in response duration.

Further investigation with RIT anti-CD66 therapy is being explored in MM patients with amyloid light-chain (AL)-amyloidosis, characterised by the deposition of protein fibrils in organs causing severe impairment in their function. AL amyloidosis MM patients are more difficult to treat as they have significant toxicities associated with standard high dose therapy. A phase I RIT trial is currently underway to find the optimal radiation dose that can be delivered safely to patients and to determine if this is associated with a reduction in the production of amyloidogenic protein.[51]

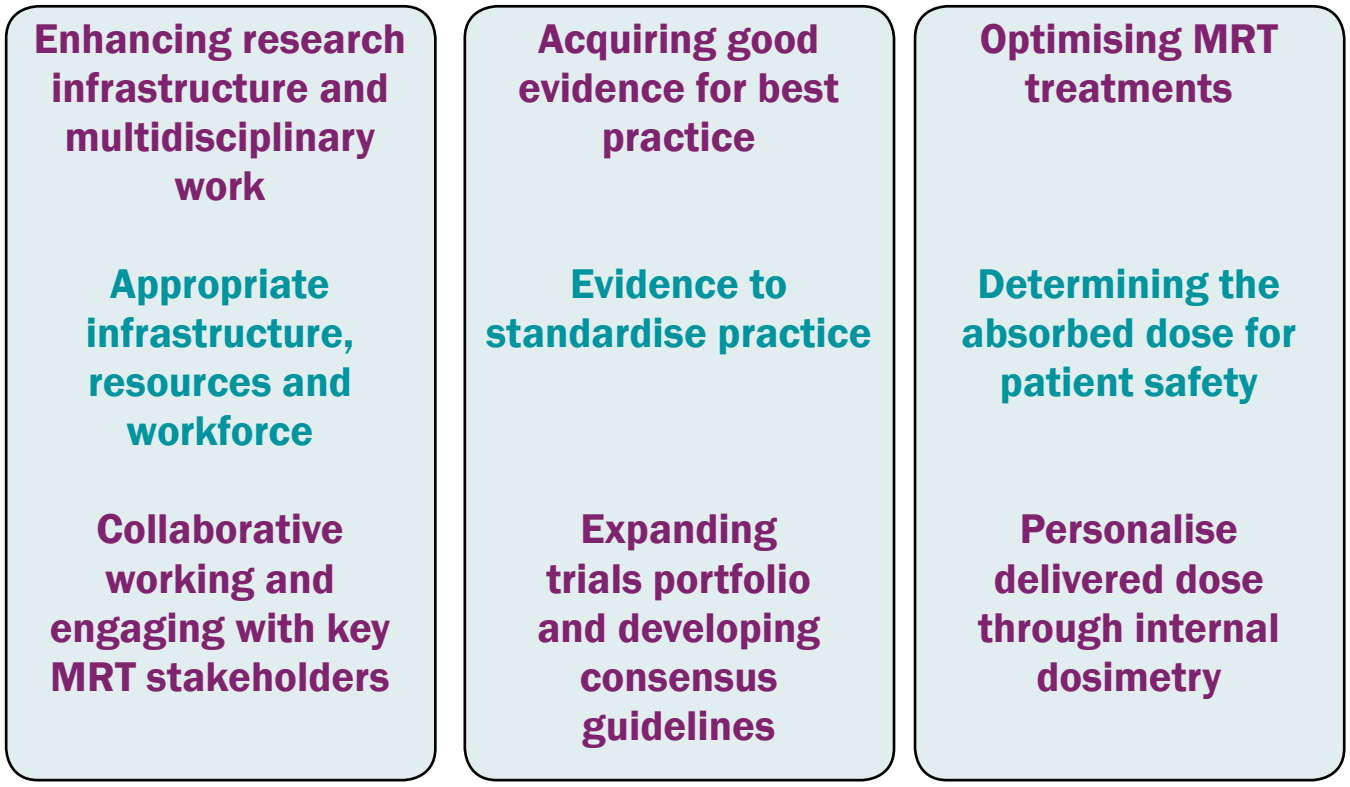
A phase I study using MRT as part of the conditioning prior to allogenic stem cell transplantation in adults continues to recruit, as well as a new study using the same approach in paediatric transplantation, as a collaborative study between the Royal Free Hospital, University College London Hospital and Great Ormond Street Hospital in 2016.

3. Ambitions for molecular radiotherapy research in the UK

Advances in several areas of biomedical research including antibody engineering and conjugate chemistry are expanding the range of available MRT agents in the treatment of various cancers, as described above. Although low, the volume of MRT clinical research underway at NHS sites is steadily gaining momentum and is establishing MRT as a valuable therapy in the patient treatment pathway. As we move towards personalised medicine in cancer care where patient treatment strategies are tailored based on the molecular characteristics of their disease, there are a number of unresolved issues which are restricting the UK's ability to perform high quality MRT research. Much work is required to align MRT research activity with the progress made in advanced EBRT techniques, and the challenge facing the MRT community is to develop strategies that will elicit optimal treatment response for patients.

A high degree of commonality in CTRad's survey responses was identified amongst the experts that were consulted. The results of this consultation support a three-point plan focusing efforts on how important unresolved issues can be tackled through a multidisciplinary approach to increase the volume of MRT research in the UK. The key elements of the approach are highlighted in **Figure 2**.

Figure 2 Ambitions for the UK MRT research agenda



3.1 How do we deal with the multidisciplinary aspects of MRT?

Development of MRT research infrastructure

Research and innovation underpin the radiotherapy service. The UK has pioneered many MRT developments with the emergence of a number of groups focused on different aspects of research. Given sufficient coordination and resourcing, the UK is well placed to be an international leader in MRT research. However, the existing research infrastructure and available resources are considered inadequate and uncoordinated by the MRT community, and are unlikely to foster and promote the efficient development of new and effective treatments. In addition, the research community believe there is a lack of understanding by research funders as to the challenges and timelines required to set up MRT research. Removing these road blocks are key to building a MRT research portfolio and bringing new effective treatments to the clinic in a timely manner.

UK MRT stakeholders

The interest in MRT is shared by a diverse group of medical professionals including, but not limited to, physicians, physicists and other scientists, as well as members of industry and patients. In recent years, a number of groups have emerged in the UK to focus on various aspects of MRT research. Their cooperation on the research planning and a focus to address issues in MRT practice will help change the culture and profile of MRT research in the UK.

British Nuclear Medicine Society (BNMS)

The BNMS established a MRT group in December 2012 with the remit to promote optimisation of practice in the UK, to investigate resource issues to support clinical practice and to support research and clinical development and education. The BNMS MRT group has fostered ongoing communication and collaboration between the other groups about ongoing projects.

Cancer Research UK (CRUK), ECMC and UK Radiopharmacy Group Taskforce (CERT)

CERT was established in 2012 to help provide researchers, funding bodies and regulators with a common understanding of the regulatory requirements for clinical trials that involve MRT. The main goal of CERT is to actively influence clinical trial regulations and guidelines to take into account the specialised nature of MRT development, in order to ensure coherent implementation of clinical research using MRT across the UK. To help researchers negotiate the regulatory hurdles during trial development, CERT has created a resource area with guidance and advice related to the set up of clinical trials using radiopharmaceutical Investigational Medicinal Products (IMP). This has proven to be an important resource for groups already active in the field of MRT or an aid to those planning to enter.

NCRI Clinical and Translational Radiotherapy Research Working Group (CTRad)

Established in 2009, one of the core objectives of NCRI's CTRad is to support the development of radiation-related research concepts to enable them to progress through successful applications to become active clinical trials. MRT is an area for which CTRad envisages significant effort is required over the next 3-5 years to promote progress in the field. This review forms part of this work package.

Internal Dosimetry Users Group (IDUG)

IDUG is an independent group founded in 2011 by NHS medical/clinical physicists, with the aim of promoting the use of practical dosimetry in MRT through education and collaboration. Building on the work of the BIR report 23 national MRT survey, IDUG has since issued surveys for 2011 and 2012, designed as continuations of the BIR-MRT work, with the aim of updating information on practices and statistics, as well as providing some

understanding of the use of dosimetry in the UK. They also recognise the importance of access to training in MRT and dosimetry and have started running training sessions at BNMS conferences.

Institute of Physics and Engineering in Medicine (IPEM)

IPEM is a professional organisation for physicists, clinical and biomedical engineers and technologists in delivering healthcare, research, industry and innovation in medicine including cancer care. Focusing on MRT progress, an IPEM working group is concentrating their efforts on quantifying the workload of a good quality MRT service including dosimetry and quality assurance (QA) parameters.

National Physical Laboratory (NPL)

NPL is the UK's national measurement institute which develops and applies measurement standards that ensures accuracy and consistency critical to research and development, including MRT. They are leading on the Metrology for MRT (MetroMRT) within the European Metrology Research Programme, which brings together expertise in metrology and nuclear medicine research in order to determine the radiation dose to patients receiving MRT. This project will be mentioned further in **Section 3**.

Royal College of Radiologists (RCR)

The RCR is the professional body for the specialties of clinical oncology and clinical radiology in the UK, and works to influence national and international developments in these fields. The RCR is committed to the continuing development of MRT, and their Intercollegiate Standing Committee on Nuclear Medicine produced a guidance document in 2014 setting out the roles and responsibilities of those who may be involved in MRT, and covers the licensing and organisational aspects of handling radioactive isotopes, as well as issues that relate to clinical practice, delegation and team working.[88]

Other stakeholders

The multidisciplinary nature of MRT also necessitates close collaboration and networking between other various stakeholder groups, including advisory and professional bodies (such as the Administration of Radioactive Substances Advisory Committee, European Association of Nuclear Medicine, International Commission on Radiological Protection, British Society of Interventional Radiology), government departments and research councils (NHS, NICE, Science and Technology Facilities Council), research and support groups (NCRI Clinical Studies Groups, national Radiotherapy Trials Quality Assurance Group), charities (CRUK, Bloodwise, Prostate Cancer UK, Children with Cancer, UK and Ireland Neuroendocrine Tumour Society) and industry.

Aims for UK MRT stakeholders

The coordinated efforts of these stakeholders have produced guidelines for best practice and various reports and surveys on clinical practice, availability of radiotherapeutics and capacity for imaging, dosimetry and nursing. To date, these have helped highlight and evaluate current issues with the existing MRT infrastructure to be addressed.

Improving perceptions of MRT

There is a growing interest in MRT but perceptions of MRT remain relatively low with few funding grants being awarded to MRT research projects. Two key stumbling blocks to setting up new clinical trials using MRT are the added complex requirement that the IMP is required to be manufactured for each individual treatment, and that the treatment involves a much larger support team to deliver. This generally leads to protracted set-up periods and more expense. A large part of the set-up time is also committed to the extra regulatory burden as well as development of the manufacturing processes in the radiopharmacy, which are low cost compared to the trial itself.

From the consulted MRT community's experience, previously grants have been activated as soon as they are awarded with no understanding of the protracted set-up time. The outcome of this can be withdrawal of funding before the clinical trial has been opened, or in more serious cases during study recruitment. Subsequently, a key action for the MRT community will be to engage with the research funders to better communicate the value of MRT and these common obstacles seen in MRT trials to safeguard funding allocation.

To help researchers wishing to set up MRT trials, CERT established a web-based resource to help promote a common understanding and provide a road map to direct groups through the preparation and set-up of MRT trials within the complex regulatory framework. They also host a virtual network of experts that can provide support and guidance at all stages of MRT projects, from basic experimental work through pre-clinical and clinical development including advice on good manufacturing practice manufacture of MRT IMPs. Due to the wide variation in the form and manufacture of IMPs, CERT has prepared guidance notes for researchers who need to prepare the Investigational Medicinal Product Dossier (IMPD) including examples of approved IMPDs.

Enhancing research infrastructure and multidisciplinary working

Recommendation 1

A forum should be established through which the MRT community can engage collaboratively with research funders to better communicate the value of high quality MRT research, and to discuss the common obstacles encountered in MRT trials. This will encourage more suitable planning and allocation of research funding.

Increasing and managing resources

Staffing: supporting the research workforce

The workforce and resources required to deliver MRT safely and effectively are highly specialised. To develop services for patient benefit, senior staff should promote innovation in the workplace, and staff at all levels should engage in MRT innovation and receive specific training. However, as previously highlighted with personalised dosimetry planning, research and new practices require staffing above and beyond the time given for routine clinical service. New models of working will be critical to the delivery of new MRT treatments and practices and to support care across radiotherapy; funding should also be identified to train staff on new services. The IPEM MRT working group is currently concentrating efforts to quantify the workload of a good quality MRT service including

dosimetry and QA parameters. Ensuring a strong academic workforce is supported is a collaborative endeavour, and CTRad has played a major part by engaging professional bodies proactively by promoting involvement of new as well as established researchers.

Enhancing research infrastructure and multidisciplinary working

Recommendation 2

The number of staff within the nuclear medicine community appropriately trained in MRT (clinicians, physicists, technologists, nurses, clinical scientists and radiopharmacists) needs to be increased and research time needs to be protected.

Supply and management of resources

The UK relies heavily on overseas sources for the importation of radiopharmaceuticals for MRT treatments, and some centres rely on importing raw materials in order to manufacture the appropriate treatments locally. Consequently, the supply of commercial radiotherapeutics is particularly prone to shortages causing disruption to patients receiving MRT treatments.[52] A few UK hospitals have their own cyclotrons, which are generally used to make radiopharmaceuticals with very short half-lives; there are only a small number of radiopharmacies that hold the Manufacturer's Authorisation for Investigational Medicinal Product - MIA(IMP) in the UK, and are able to manufacture radiopharmaceutical IMPs. The efficient use of resources for MRT within the UK should therefore be reviewed taking into account that few centres have substantial numbers of patients and that many resources could be shared between centres. Service levels should also be defined to determine the resources and expertise required to deliver various MRT treatments. This system will require a heightened degree of co-operation in the community, which will likely increase the output of research projects through collaborative work and increase the number of patients participating in research projects.

Another issue relates to the small number of Qualified Persons (QPs) in the NHS. QPs are required to certify batches of products under either a full Manufacturer's Authorisation or an MIA(IMP), to cover materials manufactured for use in clinical trials. Whilst the new revision to the EU Clinical Trials Regulations will remove the necessity to hold an MIA(IMP) to manufacture diagnostic radiopharmaceuticals used as IMPs, the provision will remain for therapeutic radiopharmaceuticals. The UK currently has a number of QP(IMPs) who were 'grandfathered' into the role on the basis of prior experience. The provision for these transitional QPs will be removed in the new legislation, and whilst the Medicines and Healthcare Products Regulatory Agency (MHRA) has indicated that they are aware of the problem and are seeking a solution, it is not clear what that might be and what impact that could have on MRT clinical trials, which will, by definition, involve the manufacture of therapeutic radiopharmaceuticals defined as IMPs, which will continue to require QP certification prior to release and use.

Enhancing research infrastructure and multidisciplinary working

Recommendation 3

Increased investment in specialised radiopharmacies is needed throughout the UK to facilitate and support wider access and to further develop new MRT strategies.

Geographical variation in MRT access

According to the Department of Health's *Improving Outcomes: Strategy for Cancer* report, access to innovative radiotherapy techniques is critical to improving patient outcomes.[53] As well as geographical variations in the availability of MRT therapies and the unreliable supply chain, patients also face access issues depending on policies of local funding authorities and local interests for new innovative MRT therapies.

From the BIR report, sites in the South East and North West of England are the best served localities for MRT therapies and clinical trials,[3] which is consistent with the CTRad survey. Due to the inherently complex nature of MRT therapy that requires appropriate specialist knowledge, experience and facilities, patients joining MRT trials require referral to larger MRT centres for initial treatment planning. To manage the workflow and referral pattern, the BIR report proposed a 'hub-and-spoke' design, linking large teaching hospital centres with small, local departments.[3, 54] The large centres with an associated academic partner could act as 'treatment facilitators' to optimise work flows, support delivery of treatment where there is patient demand and develop best practice and research projects. These larger centres will have the greatest research expertise on site and so be more research active with various MRT clinical trials open. However, smaller sites and notably 22% (five sites) of the responding sites to the CTRad survey indicated their site did not participate in any research, and were limited to treating only one or two disease groups. To ensure access to open clinical trials for all patients, clinicians should, where possible, provide the opportunity for patients to be included in clinical trials at other sites.[88] A clinical network of MRT trials should be set up so sites know what trials are open and where.

Enhancing research infrastructure and multidisciplinary working

Recommendation 4

Greater accessibility should be explored using a 'hub-and-spoke' model whereby centres of excellence could provide treatments and clinical trials opportunities, supported by satellite centres.

Collaborative MRT strategy

To ensure that MRT practice is at the forefront of innovation, it is important that there is a dedicated focus on MRT research becoming an integral part of radiotherapy services. The projected increase in the use of MRT and the need for increased capacity will require a dramatic increase in resources in nuclear medicine departments. Due to the multidisciplinary nature of MRT, close collaboration and networking between all stakeholder groups is essential. In the absence of a national body, an umbrella group is proposed to champion clinical service delivery, education and training, and pre-clinical and clinical research in MRT. The group should focus on critical evaluation of clinical needs, patient groups and the development of treatment protocols. Further aims should require the coordinated efforts of all stakeholders and a comprehensive strategy.

3.2 How can we acquire the evidence for best practice?

Building a MRT clinical trial portfolio

The fundamental challenge for MRT therapy is to deliver toxic doses of radioactivity selectively to cancer cells while sparing normal tissues as much as possible. To achieve this, careful evaluation of these agents is necessary to explore their suitability for clinical use and for their sustainable place in the treatment portfolio. Despite the progress made, the BIR report and the recently consulted MRT community are in agreement that the rationale underlying methods of MRT administration in the UK is lacking a strong evidence base. This is confirmed by the BIR report findings that wide variations in treatment protocols for the same conditions exist at clinical sites across the UK.[3] Subsequently, patients from different sites may receive different treatments and so have potentially different outcomes. The consulted MRT community also postulated that the potential efficacy of MRT treatments has not been fully appreciated and better patient outcomes could be realised.

Contributing to the variations, fundamental issues remain unresolved in MRT treatment protocols including the level of administered activity or the frequency of administration for MRT treatments (**Figure 3**).[3] Some clinical trials lack strong clinical research questions at the early stages of research and development. This subsequently leads to limited room for their evaluation in the clinic once the treatment has prescribed methodology. It is therefore crucial that prospective clinical trials are well designed to provide evidence-based medicine.

Figure 3 Common unresolved issues in MRT treatment protocols

- The inclusion criteria to determine the optimal radiopharmaceutical and regimen to use and the optimal stage in the disease course for their use.
- The level of administered activity.
- The frequency of administration.
- The delivered and absorbed tumour dose necessary to achieve clinical benefit (progress in dosimetry practices).
- Evaluation of response.

Clinical opportunities with existing MRT agents

As well as investigation of the optimal activity and frequency of administration, there is a wealth of clinical opportunities to explore in an attempt to optimise current MRT treatment protocols (**Figure 4**). The inclusion of personalised patient dosimetry studies will be integral to all protocol evaluations.

Figure 4 Clinical opportunities with existing MRT agents

Radiopharmaceutical cocktails and concomitant treatments

Synergistic combinations of therapeutic radiopharmaceuticals with chemotherapeutic agents or EBRT have the potential to enhance efficacy and minimise toxicity in patients. Chemotherapeutic agents often radiosensitise tumours to targeted radionuclide treatment and cytotoxic effects are additive.[55-57]

Introduce MRT at earlier stage of disease

MRT is traditionally considered as a last line therapy for patients with advanced disease. However, there is growing interest in extending the role of some MRT therapies beyond palliation and towards treatment delivery with tumouricidal intent. For example, adjuvant treatment with bone-seeking MRT in patients with asymptomatic metastases after EBRT has been shown to delay the progress of painful metastatic sites.[58] Patients treated with smaller disease burden will in turn have better performance status and so may seek more long term benefit from treatment. However patient referrals are often made in the last few months or left until the patient's health has already deteriorated, which in turn impacts treatment efficacy and perceptions of the therapeutic value of MRT.

Extending use of therapies to other primaries

The scope of the diseases treated with MRT could be broadened. For example, successful bone-seeking MRT therapy ^{223}Ra used in CRPC patients is under investigation in primary breast cancer.[59]

Prospective MRT clinical trials: building an evidence-base

With the exception of a small number of MRT clinical trials, there is a relative paucity of data available to highlight the evidence for treatments given or the outcome. With the current trend towards the development of new radiopharmaceuticals and with the increased interest in the value of MRT, there is a renewed effort to ensure that prospective treatment protocols include strong research questions to facilitate evidence-based guidelines. In response, prospective MRT trials should be performed as multicentre studies due to the relatively low number of patients being treated with MRT at any one centre, and as simultaneous phase I/II/III trials with standardisation of eligibility criteria with individualised patient dosimetry. The addition of translational studies including tissue and biomarker studies and quality of life questionnaires is important as many MRT treatments are palliative in nature. These results can be used to standardise practice and will act as a stimulus for further development.

In commercially-funded clinical trials, treatment protocols for radiopharmaceuticals are standardised by the pharmaceutical company with little room for optimisation. To a large extent, industry has had little interest in investing in this arena, as the perceived markets, even for an ultimately successful treatment, are small in comparison with the cost to perform the research. A small number of academically driven trials have been conducted, although these are difficult to fund and perform due to restrictions imposed by the Clinical Trials Directive. Difficulties have also been compounded by a lack of research funding for MRT trials and the much larger support team (compared to small molecules or most biological therapies) to deliver the trial. More support for academically-led multicentre clinical trials would ensure UK competitiveness, and would determine the evidence base for protocol optimisation. **Figure 5** shows a recently funded academic-industry MRT clinical trial.

Figure 5 Development of academic-industry MRT clinical trial

MRT therapeutics developed in the academic research sector allows more independence on the translation of the therapy to the clinic. The SEL-I-METRY trial is an industry-academic collaboration between CRUK and AstraZeneca investigating the potential clinical benefit of Selumetinib in re-sensitising advanced iodine refractory differentiated thyroid cancer to radioiodine therapy. The nature of this collaboration allows freedom for the investigator to explore important objectives including the role of lesional dosimetry. In the study, ^{123}I SPECT-CT is used to predict the patient's response to radioiodine therapy.

SEL-I-METRY [Funded by CRUK and AstraZeneca]

Investigating the potential clinical benefit of Selumetinib in re-sensitising advanced iodine refractory differentiated thyroid cancer to radioiodine therapy

Phase: II

Exploratory objective: To investigate the role of lesional dosimetry using ^{123}I SPECT-CT to predict response to radioiodine therapy.

Acquiring good evidence for best practice

Recommendation 5

Multicentre phase III clinical and early phase studies in MRT are needed to gather clinical evidence and to optimise treatment protocols. These will ideally be academically led.

Data collection for MRT

The collection of high quality data plays a vital role in the research and development of therapies. Clinical sites in England are required to provide NHS England with monthly reports on EBRT and brachytherapy treatments for the RTDS; this resource is acknowledged to have the potential to plan services at a local and national level and evaluate future innovations. For MRT, there is currently no record in the UK of the number of treatments delivered, the number of centres offering MRT treatment, or the details or outcome of the treatments themselves. The only insights into practices and patient numbers have been gained from the BIR report and surveys issued by the IDUG group. However, to best assess practice and help improve therapeutic efficacy of MRT, prospective MRT data collection should also be a core activity for clinical sites. Data collected will consist of details of treatment, dosimetry, biomarkers and treatment outcome and should be retained in a national database. Great efforts will be required to ensure that data are properly collected and standardised.

Acquiring good evidence for best practice

Recommendation 6

A national database and consistent coding should be established to record MRT treatment, dosimetry and outcome data and so assess therapeutic efficacy of existing and new treatments.

Quality assurance in MRT clinical trials

To develop valid and reliable evidence in radiotherapy clinical trials, it is important that there is consistency across research treatments. In EBRT multicentre research, accuracy is supported by external independent QA programmes that provide data on consistency of dose and treatment, and assess adherence to the protocol. This is an integral part of EBRT clinical trials as it has been recognised that delivery of EBRT did not always adhere to the clinical trial protocols, and that this influenced the outcome of the individual patient and the interpretation of the trial itself. Radiotherapy QA procedures can overcome this; ensuring outcomes reflect the scheduled treatment rather than departures from the trial protocols. This has yet to be introduced for MRT research, but many of the aspects of QA that would be introduced to MRT research are similar to those employed in EBRT. This may be particularly key as internal dosimetry is introduced into clinical trials and clinical practice. Currently, the national Radiotherapy Trials Quality Assurance (RTTQA) group design and implement quality assurance programmes for all EBRT trials on the NIHR CRN Clinical Research Portfolio, and are proposed to be best placed to support this evaluation of QA in MRT research.

Acquiring good evidence for best practice

Recommendation 7

A national quality assurance group to deliver full QA in MRT trials should be established. The steps and resources necessary for incorporating QA in MRT trials should be evaluated.

Funding streams for MRT therapy

The NHS is facing perhaps the toughest financial climate in its history requiring sustainable solutions that improve patient care and reduce costs. Following the complex journey through trial activities, new drugs are not widely prescribed by the NHS until they are licensed and, in most cases, recommended by a tumour advisory body.

There is a broad spectrum of cost for MRT. Long established treatments such as ^{131}I NaI for thyroid disease are inexpensive and are either supplied directly from companies or manufactured in-house; ^{131}I NaI also has a reasonable shelf life because of its relatively long half-life. However, the costs of more recently developed radiopharmaceuticals manufactured by commercial companies continue to escalate. Across most of the UK, local health bodies use guidance produced by NICE to decide which drugs should be available on the NHS. Some unlicensed drugs currently not available on the NHS are accessible through the Cancer Drugs Fund (CDF).[60] Several MRT therapies had previously been on the CDF's approved list, including ^{177}Lu Octreotate or ^{90}Y Octreotide for advanced neuroendocrine disease and ^{223}Ra dichloride for the treatment of mCRPC (**Table 1**).

Table 1 Number of treatments delivered to patients with previously listed MRT agents on the Cancer Drugs Fund list

MRT agent	Indication	Number of patients treated between April 2013 – March 2014	Number of patients treated between April 2014 – March 2015
^{177}Lu Octreotate or ^{90}Y Octreotide	Treatment of advanced neuroendocrine tumours	4	229
^{223}Ra dichloride	Treatment of CRPC patients with bone metastases	16	601

These MRT therapies' subsequent delisting in November 2015 has important implications for hundreds of patients, where these treatments represent some of their few remaining treatment options and will encourage further regional disparities.[61-62] In response to the delisting decision, the CDF panel highlighted, amongst other issues, that stronger evidence of efficacy in phase III studies was necessary to award funding. This decision underscores the importance of robust trial design to ensure trial outcomes are as successful as possible. The associated care costs, such as inpatient stay for MRT treatments, and various tests and diagnosis scans also need to be taken into account in the cost of MRT care.

New MRT therapies should ideally be tested for cost effectiveness during the research process, and practices should be optimised with the inclusion of dosimetry to ensure that only necessary treatments are administered. The lack of reimbursement mechanisms for MRT therapy discourages companies to invest and investigate dosimetry practices. An important mechanism for radiotherapy innovation is the CtE programme.[42] This commissioning methodology has the potential to widen access to innovative treatments for patients, where research evidence is less likely to be available in more specialised treatments, and patient numbers may be too small to support research data requirements. There are further challenges in the devolved nations in terms of the commissioning of new MRT technologies which remain to be resolved.

Finance in MRT

Within the NHS, MRT is funded via local commissioning groups. Unfortunately, local commissioners would not get many requests for funding, as the treatment is expensive and there is a lack of robust evidence for therapy. Local commissioners would therefore find decision making about MRT difficult. Referring clinicians may often be called to an appeal about funding for individual patients, the timeliness of which may adversely impact the patients' disease management. National work is ongoing via the NHS England Clinical Reference Group for Radiotherapy to redress this.

The coding and costing of MRT is also far from ideal. Although there are many codes for therapy, some are 'unusual' and work is ongoing to rationalise the coding with the Health and Social Care Information Centre. Following this work, a realistic costing exercise for MRT is also needed but this will take some time.

3.3 How can we optimise MRT treatments?

Clinical need for internal dosimetry: patient safety

Accurate determination of the radiation energy that is absorbed by tissue is critical to the success of radiotherapy. This physical quantity, described as 'absorbed dose' (in Gy), is integral to the calculations used to plan treatments and enable the delivery of therapies to be tailored to maximise the tumour absorbed dose, whilst minimising normal tissue toxicities. In EBRT and brachytherapy, this process of patient-specific dosimetry has been embedded into routine practice for many years, providing individualised radiotherapy treatments to patients with accurately delivered absorbed tumour doses.[63]

By contrast, patients receiving MRT treatments rarely have their absorbed doses calculated. Therapy is traditionally delivered based upon standard levels of administered radioactivity, often unadjusted from the prescription first established during phase I clinical trial toxicity response of a small cohort of patients. However, there is increasing evidence of absorbed dose response relationships in MRT. Studies have shown that in individuals who received the same activity of radiopharmaceutical, the quantity taken up and retained in the tissues varied widely, owing to differences in both the disease status and patient biokinetics.[64-67]

The clinical impact of this is unknown, although it is recognised that failure to account for patient variability is leading to patients being sub-optimally under- or over-dosed, which has serious radiation protection implications.[54] If the routine application of patient-specific dosimetry was aligned with EBRT practices, patients who were determined to tolerate higher activities of MRT could receive higher absorbed tumour doses, whilst patients potentially at risk would have their administered activities mediated accordingly. The application of internal dosimetry practice would subsequently bring clinical practice in line with current and imminent EU Directive requirements (Directive 2013/59/Euratom of 5 December 2013),[68] which mandates by 6 February 2018 that individualised absorbed dose prescriptions for radiotherapeutics are satisfied.[68]

As well as patient benefit, the move from population-based administration to routine application of patient-specific dosimetry is expected to have a positive impact on several areas (**Figure 6**).

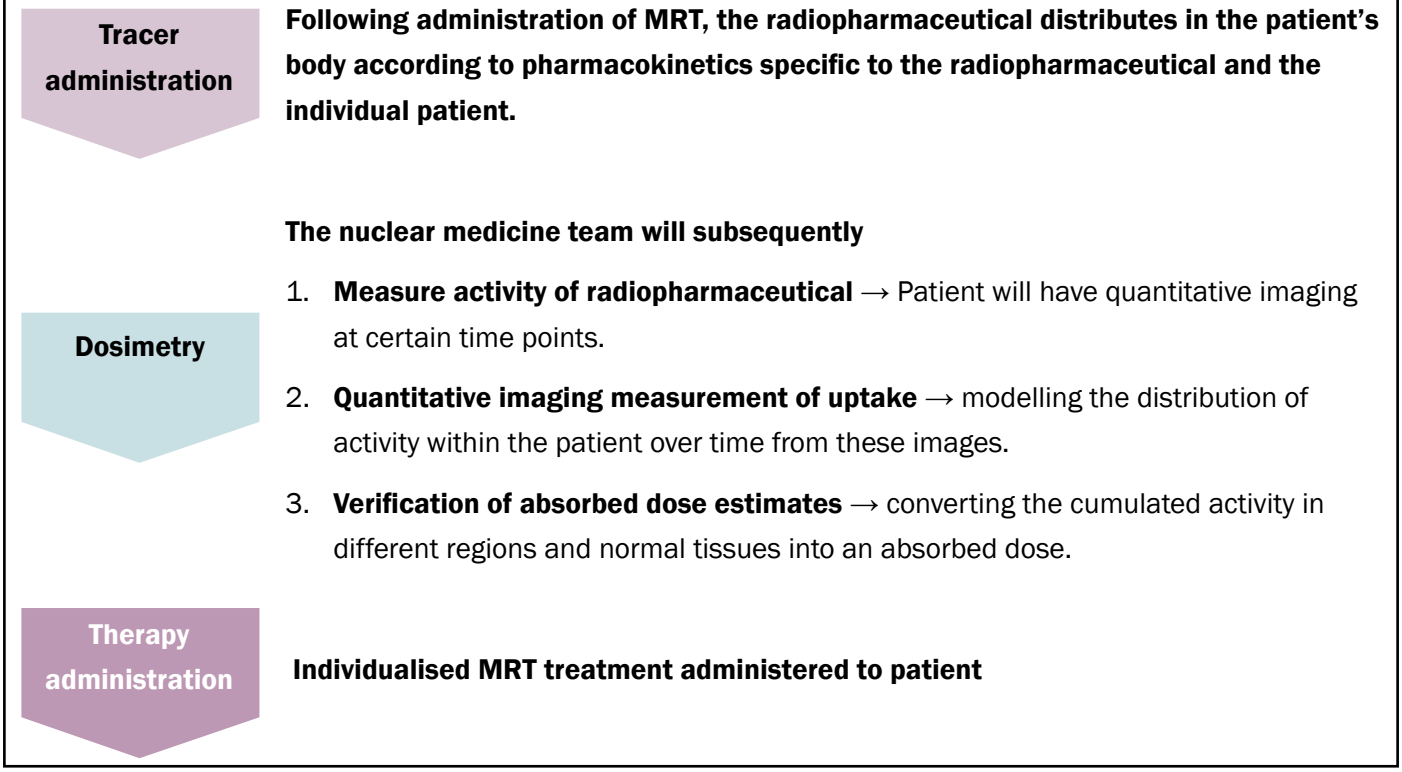
Figure 6 Potential impact of internal dosimetry

- Patients: improving management of cancer treatment, leading to improved outcomes.
- The NHS: saving scarce funding resources by making MRT a more effective and efficient treatment modality.
- Research: giving access to absorbed dose data will improve statistics in clinical trials, allowing for more effective and informed decisions on approving new treatments.
- Radiopharmaceutical industry: by allowing more effective evaluation of new products.

Internal dosimetry: how to measure the absorbed dose for MRT

A number of steps are involved in planning patient absorbed doses, each of which has its own associated challenges. Accurate quantitative imaging of a tracer is performed with single-photon emission computed tomography (SPECT) or PET, the patient's biokinetics are modelled, and then the resulting absorbed dose is calculated. A simplified summary of the process is shown in **Figure 7**.

Figure 7 Absorbed dose planning MRT using quantitative imaging techniques



Internal dosimetry techniques

The most widely used framework for calculation of absorbed dose to patients was devised by the Medical Internal Radiation Dose (MIRD) committee of the Society of Nuclear Medicine in the 1960s,[69] which involves calculation of the average tumour-absorbed dose based on modelling systems.[70] Although the MIRD schema represents the current best practice, the model has its limitations. MIRD assumes a uniform distribution of radionuclide in the tumour and organs, whereas spatial heterogeneity of internalised MRT exists. A further assumption is that the organ sizes and shapes in the patient are the same as those in the standard human phantoms used in the scheme, subsequently causing inaccurate calculated doses.

A more accurate method is to perform a pre-therapeutic scan (SPECT or PET). One option is to use a small tracer amount of the therapy radiopharmaceutical to determine the tumour and organ absorbed doses, and the activity administered can then be accurately determined for therapy. A second option would be to use a different radiopharmaceutical for the tracer, which is more suitable for imaging to better define the absorbed dose to calculate the administered activity (for example, ϒ-emitting radionuclide imaging radionuclide Indium-111 (^{111}In)-DOTATATE pairs with ^{90}Y-DOTATATE therapy). Another alternative arises when patients' MRT treatment course has multiple sessions within a few weeks or months, in which case it would be possible to plan a treatment according to the biokinetics obtained from a previous therapy (for example, measurements made during therapy two are used to calculate administered activity for therapy three and so on).[67]

Unresolved issues in internal dosimetry

Despite the growing evidence for individualised patient-treatment planning, the uptake of routine dosimetry methodologies into clinical MRT practice is low in the UK, as highlighted by the recent IDUG survey of UK nuclear medicine departments in 2011 and 2012, shown in **Table 2**.[14]

Table 2 IDUG 2011/2012 survey: Centres performing dosimetry in selected treatments

	Centres in the UK performing dosimetry for MRT treatments in 2011/2012					
	^{131}I NaI		mIBG		PRRT	
	2011 (n=23)	**2012** (n=23)	**2011** (n=14)	**2012** (n=13)	**2011** (n=9)	**2012** (n=12)
Internal dosimetry	1	1	1	1	5	5
Whole-body dosimetry	2	6	2	6	3	5

The IDUG 2011/2012 survey requested responding UK nuclear medicine centres to outline their dosimetry practices at their site including whole body and internal dosimetry. Low adoption of routine dosimetry was seen across centres, with the lowest number of sites participating in dosimetry with ^{131}I NaI treatment and the most dosimetry performed alongside PRRT therapy.

Despite a lack of routine dosimetry, the majority of sites responding to the CTRad survey identified that greater support for MRT research dosimetry studies is a national priority. This theme is strongly illustrated in the growing MRT literature, reiterating the importance of calculating accurate dosimetry and the need to invest in advanced dosimetry research projects to help determine correlations between absorbed doses, response and toxicity.

Currently the number of clinical trials including a dosimetry sub-study is low. The LuDo trial and FOXFIRE trial complete pre- and post-therapy quantitative imaging to provide patient-specific absorbed doses.[71-72] It is assumed that accurate calculation of the whole-body tumour and organ-sensitive doses will subsequently improve the therapeutic index. However, limitations exist in the FOXFIRE dosimetry model, as the calculation relies on the assumption that activity is distributed uniformly throughout the liver and does not separate tumour tissue from non-tumour tissue.

In previous MRT trials without dosimetry sub-studies, the relative success of the trial results may be underestimated due to sub-optimal therapy delivery. For instance, the ALSYMPCA trial demonstrated improved survival and symptom control following six fixed activity injections.[6] Further improvements in clinical efficacy could be postulated if dosimetry had been applied to patients, facilitating personalised treatment.

Optimising MRT treatment

Recommendation 8

Dosimetry and MRT treatment planning should be individualised and be routine practice. This will require investment.

Service constraints on research: workforce and nuclear medicine resources for dosimetry

Acknowledging that dosimetry methodology is currently relatively complicated and time consuming, sites also indicated a number of unresolved issues hampering their participation in planning treatment methods related to the workforce and department resources.

Unlike EBRT, as internal dosimetry is not currently routinely performed at clinical sites, medical physicists and physicians involved in MRT treatments receive little training in dosimetry methods, and there are few opportunities to support research studies; improved training in internal dosimetry should be provided. The

lack of training and opportunities, in conjunction with staff shortages and increasingly busy nuclear medicine departments, leads to staff being unable to accommodate the scans required to perform dosimetry, preventing studies necessary to evaluate its potential to improve treatment efficacy and the cost-effectiveness of MRT. Feedback from the survey also mentioned that insufficient research time was built into medical physics and technologist work plans, which in turn restricts dosimetry work and related research studies to be undertaken. Staffing issue is beyond the scope of this review although is an important consideration as staffing will impact on research in internal dosimetry.

Optimising MRT treatment

Recommendation 9

Protected time for research is necessary to develop dosimetry-based treatment planning.

Internal dosimetry: research progress in MRT

Despite the low adoption of dosimetry carried out at sites in the recent survey, a small number of clinical research centres are developing new methods of assessing the absorbed dose delivered to tissues from radiopharmaceuticals, based on quantitative imaging technology and radiobiological studies exploring the biological effects of MRT radiation. These emerging areas use more complex dosimetry methodology which offers the ability to predict the absorbed dose pattern and to assess response after administration.[73-74] However, given the inherent challenges and large amount of work still required to validate these new methodologies, significant investment will be necessary to enable this fundamental change in dosimetry practice.

Standardisation of dosimetry protocols with molecular imaging

Comparison of the results of individual research centres developing dosimetry methods can be challenging. Standardisation of dosimetry procedures would bring consistency of procedures between nuclear medicine departments and would readily allow obtained results to be compared.

Metrology for molecular radiotherapy (MetroMRT)

The UK's NPL is leading on MetroMRT, a joint collaborative project between national metrology centres and universities across Europe, to develop and provide a standardised dosimetry method with quantitative imaging to establish a routine individual MRT patient dosimetry, which will benefit cancer patients.[75] The project takes the well-established dosimetry formalism used for EBRT as a model, and is formulating MRT dosimetry in an analogous way. The outcomes from this project will enable patient-specific treatment planning, which will have a direct and potentially significant benefit on personalised therapy. Its open availability to the clinic will hopefully in turn encourage non-research sites to take up dosimetry practices. The structure of this consortium, and its strong links with clinical and research departments, will help ensure that progress is made coherently throughout Europe.

Theragnostics: better targeted diagnosis and treatment

MRT innovation requires well-designed clinical trials which include routine personalised patient dosimetry. Crucial to the progress made in the development of internal dosimetry are the improvements made in quantitative molecular imaging tools (SPECT and PET).[76] Non-invasive imaging of both normal and cancer biochemical pathways in patients is possible with the use of specific molecular targets such as hypoxia, angiogenesis, receptor expression and metabolism. MRT agents in development utilise radionuclides that emit positron or gamma emitters that can be imaged as well as therapy targeted specifically by the vector at molecular level. Implementation of these steps potentially creates treatments that are better targeted, which

in due course will save health systems money by identifying therapies not likely to be effective for patients, and to obtain a better understanding of comparative effectiveness.[68] This emerging field, known as 'theragnostics', allows staging and treatment planning prior to therapeutic procedures and response monitoring following therapy. The ability to directly image the agent responsible for treatment is unique to MRT, which offers better targeted therapy and significant savings of time and other resources through developing a 'drug' that can serve two purposes. Examples of theragnostics using two radionuclides are seen in the treatment of neuroendocrine patients with a ^{68}Ga-labelled tracer followed by therapy using ^{177}Lu-labelled radiopharmaceutical, and ^{111}In for imaging/dosimetry followed by ^{90}Y for therapy in the anti-CD66 trials.[77]

Radiobiological models

As well as the impact of dosimetry on planning MRT treatments, radiobiological studies are also required to tailor MRT in the clinic to estimate the absorbed dose necessary for tumour control. Most of the knowledge about radiation effects concerns EBRT which cannot easily be extrapolated to MRT. MRT radiobiology will become an area of focused research in the future.[65]

Optimising MRT treatment

Recommendation 10

Investment is necessary to support projects focused on optimisation and standardisation of dosimetry protocols.

4. Opportunities for action

4.1 Proposed actions for the MRT community and other stakeholders

There are areas of strong MRT research activity in the UK that need to be supported to succeed. To increase the amount of high quality MRT research conducted in the UK, a series of interlinked activities as well as investment of both time and money across the board is required. Drawing from challenges and the ambitions for UK MRT research in **Section 3**, this review concludes by putting forward 10 recommendations outlined in **Table 3.**

Table 3 Proposed actions for the research community and stakeholders to support MRT research

	Recommendation	Action by stakeholder
Enhancing research infrastructure and multi-disciplinary working	1. A forum should be established through which the MRT community can engage collaboratively with research funders to better communicate the value of high quality MRT research, and to discuss the common obstacles encountered in MRT trials. This will encourage more suitable planning and allocation of research funding.	• **MRT researchers** • **Professional organisations** • **Clinical research networks and associated groups** • **Research funders**
	2. The number of staff within the nuclear medicine community appropriately trained in MRT (clinicians, physicists, technologists, nurses, clinical scientists and radiopharmacists) needs to be increased and research time needs to be protected.	• **Professional organisations**
	3. Increased investment in specialised radiopharmacies is needed throughout the UK to facilitate and support wider access and to further develop new MRT strategies.	• **Research funders**
	4. Greater accessibility should be explored using a 'hub-and-spoke' model whereby centres of excellence could provide treatments and clinical trials opportunities, supported by satellite centres.	• **Professional organisations** • **Research funders**
Acquiring good evidence for best practice	5. Multicentre phase III clinical and early phase studies in MRT are needed to gather clinical evidence and to optimise treatment protocols. These will ideally be academically led.	• **MRT researchers** • **Research funders** • **Methodology hubs**
	6. A national database and consistent coding should be established to record MRT treatment, dosimetry and outcome data and so assess therapeutic efficacy of existing and new treatments.	• **MRT researchers** • **Professional organisations** • **Research funders**
	7. A national quality assurance group to deliver full QA in MRT trials should be established. The steps and resources necessary for incorporating QA in MRT trials should be evaluated.	• **MRT researchers** • **Professional organisations** • **Research funders**
Optimising MRT treatment	8. Dosimetry and MRT treatment planning should be individualised and be routine practice. This will require investment.	• **MRT researchers** • **Professional organisations** • **Research funders** • **Regulatory bodies**
	9. Protected time for research is necessary to develop dosimetry-based treatment planning.	• **MRT researchers** • **Professional organisations**
	10. Investment is necessary to support projects focused on optimisation and standardisation of dosimetry protocols.	• **Research funders**

This review has been prepared with a focus on MRT in cancer. It calls upon the UK MRT research community, professional organisations and research funders to consider their roles in supporting MRT research development to help overcome barriers in research, and also to work together to expand and sustain a vibrant community of research in MRT.

Appendix 1. Principles of molecular radiotherapy use

Unsealed radioactive sources are used for both diagnostic investigations and for therapy in the treatment of cancer and non-cancer indications. Patients are most likely to encounter radioisotopes during diagnostic functional imaging with positron emission tomography (PET) or gamma camera scanning in nuclear medicine departments; in therapy, the main applications of molecular radiotherapy (MRT) are the use of Iodine-131 (^{131}I) NaI to treat differentiated thyroid cancer (DTC) and the palliation of bone disease with selected radioisotopes. However, recent advances in molecular biology have led to a better understanding of the cancer hallmarks underlying disease and subsequent targets, leading to an increase in the applications of MRT in cancer therapy.[78-79]

A1.1 Choice of radionuclide and vector for MRT therapy

Various radioisotopes and carrier molecules called vectors are used to deliver MRT to cancer tissue. The efficacy of the MRT therapeutic is crucially dependent on a number of factors including the viability of the cancer cells being treated (including radiosensitivity and proliferation rate) and the characteristics of the MRT radioisotope-vector relationship. The requirements of an effective biologically targeted MRT radioisotope-vector may be divided into two main categories, namely physical and biochemical characteristics.[80]

Physical characteristics

The physical characteristics of the tagged radioisotope, such as the type of radiation emitted (α-, β-particles and Auger electrons) and the physical half-life, must be appropriate for the disease being treated. The ideal radionuclide will have a physical half-life long enough to allow accumulation in the target cells.[81] **Table 4** shows examples of common radionuclides used in MRT and **Appendix 2** shows radionuclides currently in clinical use. Due to their natural decay, radioisotopes cannot be stockpiled and so their shelf life is considerably shorter in comparison with chemotherapeutics. This is exemplified by treatments for metastatic bone cancer. The chemotherapy agent docetaxel has a shelf life of 36 months, in contrast to the radiotherapeutic Radium-223 (^{223}Ra) dichloride which has a half-life of just 11 days.[82]

Table 4 Commonly used radionuclides for therapy

Radionuclide	Therapeutic radiation	Average Energy	Half-life
^{131}I	Beta/Gamma	180keV	8.0 days
^{177}Lu	Beta	130keV	6.7days
^{90}Y	Beta	940keV	2.67 days
^{223}Ra	Alpha	5.78MeV	11.4days
^{111}In	Auger electron	5-25 eV	3 days

Biochemical characteristics

The fundamental challenge for therapy is to deliver tumouricidal absorbed doses to cancer cells while sparing normal tissues. A variety of platforms have been used to design radiotherapy agents, from radiolabelling small molecules that mimic the *in vivo* behaviour of the natural substances, to the use of much more complex molecules such as antibodies. Example vectors used in MRT treatments are shown in **Table 5**.

The pharmaceutical or biological vector carrying the tagged radioisotope should preferentially accumulate in cancer cells to allow targeted delivery of radiation.

Table 5 Example vectors commonly used in MRT

Vector type	Example vector name	Target
Monoclonal antibody	IgG2a	Cell antigen
Antibody fragment	Fab	Cell antigen
Peptide	DOTATATE	Somatostatin receptor
Small molecule	mIBG	Adrenergic tissue
Microsphere	Glass or resin	Liver tumour capillaries

A1.2 Treatment setting for MRT

Delivery of MRT treatment

The hospital nuclear medicine department covers all applications of unsealed radioactive materials for diagnostic imaging and for treatment, while the radiopharmaceuticals are often manufactured in the hospital's radiopharmacy department. Therapeutic radiopharmaceuticals may also be delivered directly from the manufacturer requiring little pharmacy input. The delivery of the service is provided by a multidisciplinary team that can include nuclear medicine physicians, endocrinologists, haematologists, clinical oncologists, nuclear medicine technologists, medical physicists, radiographers, nurses and radiopharmacists. Significant input is required from a number of disciplines to ensure safe delivery of the therapies and to provide the patient's aftercare, more so than compared to preparation and delivery of chemotherapeutic drugs.

The responsible clinician must be approved by the Administration of Radioactive Substances Advisory Committee (ARSAC) to administer specific MRT agents.[83] Further regulations control health and safety legislation, which in the UK was developed from European Directives produced by the European Community, and also under a framework provided by the Ionising Radiation (Medical Exposure) Regulations 2000 (IR(ME)R).[84] Procedural guidance for the medical physics team is also provided by nuclear medicine organisations such as the European Association of Nuclear Medicine (EANM).[85-87]

MRT patient pathway

Different types of MRT treatment require different levels of service infrastructure. Some procedures can be administered as an out-patient appointment whereas other procedures will require hospitalisation for a number of days in dedicated inpatient facilities with radiation protection. The MRT therapy patient pathway is shown in **Figure 8**.

Figure 8 MRT therapy patient pathway

Decision to treat

The patient's suitability for MRT treatment will usually be discussed in a tumour-specific multidisciplinary team (MDT) meeting, and could be confirmed in an MRT MDT within departments.[88] The treatment plan will then be discussed with the patient and/or guardian to explain possible treatment options.

Treatment work up

The patient may or may not have pre-therapy imaging. The treatment administration may then be planned to within limits of the critical organs, a process known as internal dosimetry. If no internal dosimetry is performed, the clinicians will typically administer treatment at a fixed level of radioactivity.

Radiopharmaceutical preparation and administration

The radiopharmaceutical will be prepared according to the planned administration. The radiopharmacy team are responsible for accuracy of the measurement of the radionuclide used and for the purity of the therapeutic product.[89] MRT therapies are Prescription Only Medicines and cannot be prepared ahead of scheduled administration due to their short shelf life. Compared to small molecule or biological therapies, radiopharmaceuticals require a large support team to manufacture and dispense the tailored treatment. Most radiopharmaceuticals are administered by intravenous injection, so preparation needs to be performed under aseptic conditions.

MRT administration

The MRT agent will then be administered in a designated facility with appropriate shielding and radiation monitoring equipment. This may or may not require in patient hospital care. If the MRT therapy can be delivered on an outpatient basis, the physics team will ensure the radiation from the patient is at an acceptable level before discharge, and will advise the patient to follow radiation protection precautions at home.

Post treatment

Following MRT treatment, some patients may have further quantitative imaging, typically up to five days at various intervals depending on the treatment. The images will be used to map radionuclide distribution in the patient's target tissue and organs and allow planning for subsequent treatments to be best calculated if necessary.

Appendix 2. MRT treatments as of August 2015

Nuclide	Chemical	Indication
^{198}Au	colloid	Malignant disease
^{131}I	Iodide	Thyroid
^{32}P	PO4---	Polycythemia vera and related disorders
^{89}Sr	chloride	Bone metastases
^{131}I	mIBG	Neuroendocrine disease
^{32}P	colloidal chromic phosphate	Cystic intracranial lesions
^{32}P	PO4---	Leukaemia
^{131}I	lipiodol	Hepatic malignancy
^{90}Y	microspheres	Hepatic malignancy
^{153}Sm	EDTMP	Bone metastases
^{186}Re	HEDP	Bone metastases
^{90}Y	DOTATOC	Malignant diseases
^{90}Y	ibritumomab tiuxetan (Zevalin) ®	Non-Hodgkin's lymphoma
^{223}Ra	dichloride	Bone metastases in castration-resistant prostate cancer
^{177}Lu	DOTATATE	Neuroendocrine tumours
^{90}Y	DOTATATE	Neuroendocrine tumours
^{90}Y	DOTANOC	Somatostatin expressing tumours
^{111}In	DTPA-hEGF	Breast Cancer
^{177}Lu	DOTATOC	Neuroendocrine tumours
^{177}Lu	DOTANOC	Somatostatin expressing tumours
^{177}Lu	DOTA-HH1	Non-Hodgkin's B-cell lymphoma

Appendix 3. CTRad MRT Questionnaire

National Cancer Research Institute
Clinical and Translational Radiotherapy Research Working Group (CTRad)

Molecular radiotherapy research survey in the UK

About this survey

The National Cancer Research Institute (NCRI) radiotherapy research initiative, the Clinical and Translational Radiotherapy Research Working Group (CTRad), is circulating this survey to assess molecular radiotherapy (MRT, or radionuclide therapy) research and development in the UK. A previous survey conducted by the British Institute of Radiology (BIR) in 2010 of MRT clinical services identified a wide variation in clinical practice across the UK which motivated a report with recommendations to improve MRT use and its effectiveness. This 2015 survey will focus on barriers to participation in research and clinical trials. The survey responses will allow CTRad to draw key conclusions of what is needed to move MRT research forward, both in basic science and clinical trials.

Why is CTRad asking for your views?

MRT is a rapidly developing field with a constant emergence of new agents and applications. There is a significant opportunity for the UK community to make a major contribution in shaping clinical practice. However, there are areas that restrict the UK's ability to perform high quality MRT research. This survey is being distributed to UK nuclear medicine sites to help build a picture of molecular radiotherapy development in the UK. Please complete the survey online by following the link: https://www.surveymonkey.com/s/molecularradiotherapysurvey2015 As a guide of the content, please find the survey format below. If you wish to complete survey using this word document, please send you responses to fiona.mckirdy@ncri.org.uk.

What will happen next?

CTRad will collate the information gathered here as a basis for further discussion with the CTRad MRT working group. Conclusions will be published thereafter in a rapid review which will be posted to sites that respond to the survey. The responses will be kept anonymous although we do request some contact information. Thank you in advance for your participation.

Site name and contact:	
Section 1: Delivered treatments	
a) Does your site use molecular radiotherapy to treat benign or malignant disease?	☐ Yes ☐ No (If No, please go to **Section 2. Research and Development activity)**
b) Which of the following cancers does your site treat with MRT? (please tick which clinical application)	**Cancer types:** ☐ Thyroid ☐ Hepatic ☐ Neuroendocrine ☐ Haematological ☐ Bone metastases ☐ Other, please specify _____
c) Does your site perform prospective internal dosimetry on patients?	☐ Always ☐ Sometimes ☐ Never
d) Does your site perform post-therapy internal dosimetry on patients?	☐ Always ☐ Sometimes ☐ Never
Section 2: Research and Development activity	
MRT research	
a) Does your site take part in any research activities related to therapy?	☐ Yes ☐ No

Research and Development activity - MRT research continued	
b) If yes, please indicate your research interests. Please provide as much detail as possible of these research projects.	**Radiopharmacy** - Radiotracer development ☐ - Radiopharmaceutical optimisation ☐ - *in vitro*, *in vivo* evaluation ☐ - early phase clinical evaluation ☐ **Nuclear Medicine** - Image quantification and dosimetry calculations ☐ -Molecular imaging - characterising cancer cell growth/response to treatment ☐ **Please provide brief details of research projects at your site:**
c) Has your site received any funding grants for MRT research in the past 5 years? If yes, please detail which funding body and which project was awarded?	Yes ☐ **Funding body and awarded project:** 1 _____ 2 _____ 3 _____ 4 _____ No ☐
Research priorities	
d) Please identify two research topics you consider to be priorities in MRT research.	Topic 1: Topic 2:
MRT clinical trials	
e) Does your site participate in MRT clinical trials or has it done in the past? Please list past and current trials that your site has participated in.	Yes ☐ No ☐ **Title of clinical trial**
Barriers to MRT research	
f) A number of key challenges have been identified as barriers to delivering scientific and clinical MRT developments. Please rank these barriers on a scale of 1 (most important) to 10 (least important) according to their importance in alleviating MRT research challenges at your site.	**Research time** **Protected research time** Most important 1 2 3 4 5 6 7 8 9 10 Least important **Support for MRT QA activities** Most important 1 2 3 4 5 6 7 8 9 10 Least important **R&D and Trials unit support for MRT trials** Most important 1 2 3 4 5 6 7 8 9 10 Least important **Resources** **Access to specialised facilities** eg. Radiopharmacy preparation facility, In-patient treatment suites Most important 1 2 3 4 5 6 7 8 9 10 Least important **Access to specialised equipment** eg. Scintillation camera, computing software Most important 1 2 3 4 5 6 7 8 9 10 Least important **Staffing levels in nuclear medicine dept.** Most important 1 2 3 4 5 6 7 8 9 10 Least important
Barrier to MRT research continued: Please detail any further comments regarding barriers to scientific and clinical MRT developments at your site:	Notes:

3.	**Workforce in nuclear medicine department**	
a)	How many Qualified Practitioners (QP) do you have in your department?	
b)	How many dedicated research/development posts do you have in your nuclear medicine department?	
c)	Do staff have a time allocation for research/development?	☐ Yes ☐ No
d)	How could the workforce be developed to allow more research and development in MRT?	

Survey completed

Thank you for taking the time to complete this survey about MRT. CTRad will be collating the responses received to help inform future activities.

If you have any further comments or questions, please contact fiona.mckirdy@ncri.org.uk

Appendix 4. Closed MRT clinical trials indicated in the CTRad MRT survey as of August 2015

Closed MRT clinical trials

Tumour type	Title	Acronym	MRT agent	Phase	Stage of disease	Patients recruited	Trial category	Trial funder
Thyroid	A multicenter randomized trial of high-versus low-dose radioiodine, with or without recombinant thyroid stimulating hormone, for remnant ablation after surgery for differentiated thyroid cancer	HiLo	^{131}I	III	Early	468	Academic	CRUK
Neuroendocrine	A study comparing treatment with 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours	NETTER	^{177}Lu-DOTA0-Tyr3-Octreotate	III	Advanced	280	Commercial	Advanced Accelerator Applications
	A phase I trial of Vandetanib combined with 131I-mIBG radiotherapy in patients with advanced phaeochromocytoma and paraganglioma	VIBRANT	^{131}I mIBG	I	Advanced	0	Academic	CRUK, Astrazeneca
Bone metastases	A randomised phase II/III study of Docetaxel plus Prednisolone vs. Docetaxel plus Prednisolone plus Zoledronic acid vs. Docetaxel plus Prednisolone plus Strontium-89 vs. Docetaxel plus Prednisolone plus Zoledronic acid plus Strontium-89 in Hormone Refractory Prostate cancer metastatic to bone.	TRAPEZE	^{89}Sr (multistage study)*	II	Advanced	Unknown*	Academic	NIHR Health Technology Assessment
	A phase III study of radium-223 dichloride in patients with symptomatic hormone refractory prostate cancer with skeletal metastases	ALSYMPCA	^{223}Ra	III	Advanced	921	Commercial	Bayer
Liver metastases	An open-label randomised phase III trial 5-Fluorouracil, Oxaliplatin and Folininc acid +/- interventional radioembolisation as first line treatment for patients with unresectable liver-only or liver-predominant metastatic colorecetal cancer	FOXFIRE	^{90}Y-particulates	III	Advanced	360	Commerical	The Bobby Moore fund, CRUK, Sirtex
Haematological	A prospective phase II open label, non-randomised trial looking at short chemo-radioimmunotherapy in follicular lymphoma using Zevalin	SCHRIFT	^{90}Y-ibritumomab tiuxetan	II	Relapsed	60	Academic	CRUK
	Phase II Study of Fractionated 90Y Ibritumomab Tiuxetan (Zevalin) Radioimmunotherapy as an Initial Therapy of Follicular Lymphoma (FIZZ)	FIZZ	^{90}Y-ibritumomab tiuxetan	II	First line treatment in high risk	76	Commercial	Bayer
	A randomised phase II clinical trial using targeted radiotherapy delivered by an yttrium-90 radio-labelled anti-CD66 monoclonal antibody with high dose melphalan alone, prior to autologous stem cell transplantation for multiple myeloma.	Anti-CD66	^{90}Y	II	First line treatment in high risk	90	Academic	Leukaemia and Lymphoma Research

Appendix 5. MRT clinical trials indicated in the CTRad MRT survey as of August 2015

Open clinical trials

Tumour type	Title	Acronym	MRT agent	Phase	Stage of disease	Planned cohort of patients	Trial category	Trial funder
Thyroid	Is ablative radioiodine necessary for low risk differentiated thyroid cancer patients	IoN	^{131}I	III	Early	570	Academic	CRUK
	Investigating the potential clinical benefit of Selumetinib in resensitising advanced iodine refractory differentiated thyroid cancer to radioiodine therapy	SEL-I-METRY (In-set up)	^{131}I	II	Refractory	60	Academic	CRUK, Astrazeneca
Neuroendocrine	A Phase IIa trial of ^{177}Lu DOTATATE in children with primary refractory or relapsed high risk neuroblastoma	LuDo	^{177}Lu-DOTATATE	II	Refractory/ Advanced	24	Academic	CRUK
	A phase I/II proof-of-study to compare the novel technique ^{124}I-mIBG PET/CT to ^{123}I-mIBG scintigraphy in paediatric patients with met neuroblastoma.	^{124}I mIBG	^{124}I mIBG	I/II	Diagnostic	33	Academic	CRUK, Rising Tide Foundation
Bone metastases	Systemic Therapy in Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy - Androgen Suppression-Based Therapy Alone or Combined With Zoledronic Acid, Docetaxel, Prednisolone, Celecoxib, Abiraterone, Enzalutamide and/or Radiotherapy in Treating Patients With Locally Advanced or Metastatic Prostate Cancer	STAMPEDE	^{89}Sr (multistage study)*	II/III	Advanced/ relapsed		Academic	CRUK
		Further ^{223}Ra studies in prostate and breast patients (in-set up)		II/III	Advanced		Commercial	Bayer
Liver metastases	A phase III clinical trial evaluating TheraSphere® in patients with metastatic colorectal carcinoma of the liver who have failed first line chemotherapy	EPOCH	^{90}Y-particulates	III	Refractory	360	Commercial	BTG International
	Evaluation of Sorafenib in Combination With Local Micro-therapy Guided by Gd-EOB-DTPA Enhanced MRI in Patients With Inoperable Hepatocellular Carcinoma	SORAMIC	^{90}Y-particulates	II	Advanced	665	Commercial	Sirtex Technology
Haematological	Radiolabelled anti-CD66 monoclonal antibody in the conditioning regimen prior to haematopoietic stem cell transplantation: phase I study in patients with poor-risk disease. Disease	Anti-CD66 in conditioning	^{90}Y	I/II	High risk patients	55	Academic	NHS R&D Local Leukaemia Charity
	A Phase I/II Study of 177Lu-HH1 (Betalutin)Radioimmunotherapy for Treatment of Relapsed CD37+ Non-Hodgkin Lymphoma	LYMRIT-37-01	^{177}Lu-DOTA	I/II	Relapsed	42	Commercial	Nordic Nanovector

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Glossary

ARSAC	Administration of Radioactive Substances Advisory Committee
ASCT	Autologous Stem-Cell Transplantation
BIR	British Institute of Radiology
BNMS	British Nuclear Medicine Society
CDF	Cancer Drugs Fund
CERT	CRUK, ECMC UK Radiopharmacy Group Taskforce
CtE	Commissioning Through Evaluation
CRUK	Cancer Research UK
CRPC	Castrate-Resistant Prostate Cancer
CTRad	NCRI Clinical and Translational Radiotherapy Research Working Group
DTC	Differentiated Thyroid Cancer
DNA	Deoxyribonucleic Acid
EANM	European Association of Nuclear Medicine
EBRT	External Beam Radiotherapy
ECMC	Experimental Cancer Medicine Centres
HD	Hodgkin's Disease
IDUG	Internal Dosimetry Users Group
IMP	Investigational Medicinal Product
IPEM	Institute of Physics and Engineering in Medicine
IRMER	Ionising Radiation (Medical Exposure) Regulations
mAb	Monoclonal Antibodies
MDT	Multidisciplinary Team
MetroMRT	Metrology for Molecular Radiotherapy
mIBG	meta-Iodobenzylguanidine
MIRD	Medical Internal Radiation Dose
MM	Multiple Myeloma
MRT	Molecular Radiotherapy
NCRI	National Cancer Research Institute
NET	Neuroendocrine tumour
NHL	Non-Hodgkin's Lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPL	National Physical Laboratory
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PRRT	Peptide Receptor Radiation Therapy
QA	Quality Assurance
QP	Qualified Person
RCR	Royal College of Radiologists
RIT	Radioimmunotherapy
RTDS	Radiotherapy Dataset
RTTQA	Radiotherapy Trials Quality Assurance
SIRT	Selective Internal Radiation Therapy
SMC	Scottish Medicines Consortium
SPECT	Single-Photon Emission Computed Tomography
SRE	Skeletal-related event
SSRT2	Somatostatin receptor type-2

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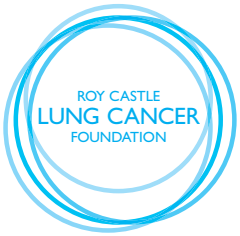

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