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The Royal College of Radiologists

Royal College of Physicians

IPEM
Institute of Physics and Engineering in Medicine

Review of molecular radiotherapy services in the UK

November 2021

Contents

Foreword

As this document amply demonstrates, innovation remains at the heart of diagnosis and cancer treatment. Molecular radiotherapy services have for many years been an important, but much neglected, pillar of cancer care. Research investment has paid dividends and a number of new drugs are poised to revolutionise the management of certain cancers over the coming years. However, if the UK population is to fully benefit from molecular radiotherapy advances in terms of hard won improvements in both symptoms and survival, patients need to be able to access the agents easily, regardless of where they live. In turn, this requires the healthcare systems within the four nations to effectively commission the new agents, as well as rapidly invest in the workforce and physical environments to ensure their safe delivery.

I am very proud that all the stakeholders involved in molecular radiotherapy services have come together to produce this truly multi-professional overview. This highlights the importance of bespoke local solutions being developed and implemented to support local service delivery – one size will most definitely not fit all. The document fully illustrates that skills and competencies are more important than traditional role descriptions. Moving forward, the remote working, information sharing and peer support which became routine during the pandemic, will need to be continued and expanded to ensure the implementation of best practice in safe molecular radiotherapy service delivery.

This document provides the four nations with a comprehensive, pragmatic blueprint to allow the development of molecular radiotherapy services in preparation for the new agents which are soon to arrive. In turn, this enables patients to have equitable access to these innovative treatments, minimising health inequalities and ensuring the promised improvements in survival can be delivered to all those who could gain from them.

Dr Jeanette Dickson, President RCR

Background

This document presents a review of the present state for the provision of molecular radiotherapy services across the United Kingdom (UK), concentrating on unequal provision across the four nations and proposals as to how these issues can be addressed to ensure equity of access to molecular radiotherapy services.

This review was undertaken by a task and finish group set up by four main stakeholders:

- British Nuclear Medicine Society
- Institute for Physics and Engineering in Medicine
- Royal College of Physicians
- The Royal College of Radiologists.

The members of the task and finish group are as follows:

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Executive summary

Major findings:

1. The provision of molecular radiotherapy services across the UK is not uniform.
2. There is no clear 'ownership' of molecular radiotherapy services in the UK. Services are delivered by different medical specialties, often depending on locally available skills, with no coordinated national leadership to ensure an equitable, high-quality provision of services.
3. The provision of a particular form of molecular radiotherapy that a patient may benefit from may depend on where they live within the UK (so called postcode lottery).
4. Stated reasons regarding why this variation exists include lack of trained staff, lack of physical facilities and variations in NHS reimbursement for these treatments in different parts of the UK
5. The requirement to deliver molecular radiotherapy is likely to increase dramatically over the next decade. Most UK regions and nations are not prepared for this oncoming change.
6. This dramatic increase in demand for molecular radiotherapy services may begin by 2022 especially if Lu-177 PSMA is licenced and approved by the National Institute for Health and Care Excellence (NICE) for treatment of metastatic prostate cancer.

Recommendations

1. A UK-wide strategy for the equitable delivery of molecular radiotherapy services needs to be delivered rapidly.
2. Patients must be at the heart of the delivery of these services and the relevant patient advocacy groups should be involved in determining the shape of molecular radiotherapy services in the UK.
3. An agreed UK set of standards for the safe, equitable and efficient delivery of molecular radiotherapy should be determined and applied across the UK
4. The delivery of molecular radiotherapy services should be the responsibility of the devolved national health ministries/offices in the devolved nations and the 11 operational delivery networks (ODNs) in England. These bodies would apply national standards to ensure delivery of the full range of molecular radiotherapy within each nation or network within the UK
5. Each devolved nation or radiotherapy ODN should appoint a 'molecular radiotherapy champion' who would have sufficient time set aside in their job plan and sufficient managerial support to drive local delivery of molecular radiotherapy.
6. The first role of each 'molecular radiotherapy champion' would be to perform a rapid but comprehensive gap analysis of the devolved national/ODN's current provision of molecular radiotherapy services and outline which gaps exist.
7. A devolved national/ODN network plan should be created to ensure a full range of molecular radiotherapy services can be delivered. This would involve training of additional staff and identifying new staff and facilities that may be required and a time-limited plan to deliver these changes.
8. It should be understood that what a practitioner is called matters less than skills and competencies. A flexible approach should be implemented to involve all local staff to their full potential to deliver equitable molecular radiotherapy services

9. Flexibility in job plans within and between hospitals/trusts is required to deliver molecular radiotherapy services, especially for nuclear medicine/radiology and clinical oncology.
10. New technology and strategies learnt during the COVID-19 pandemic should be used to ensure efficient use of staff with skills to deliver molecular radiotherapy. This could include virtual multidisciplinary teams (MDTs), virtual mentoring and shared dosimetry skills
11. It is necessary to ensure the training schemes for nuclear medicine physicians, clinical oncologists and nuclear medicine clinical scientists deliver the required skills for the high-quality equitable and safe delivery of a full range of present and expected molecular radiotherapy services across the UK.
12. Closer cooperation between the nuclear medicine community and the Clinical Oncology Faculty of The Royal College of Radiologists is needed.

Abbreviations

Ac-225	Actinium-225 (an alpha-emitting therapeutic radionuclide)
ARSAC	Administration of Radioactive Substances Advisory Committee
BNMS	British Nuclear Medicine Society
Ca	Carcinoma (of)
CDF	Cancer Drug Fund
CT	Computed tomography
CTE	Commissioning Through Evaluation
DOTATATE	A linker molecule that attaches to a specific tumour target
EA	Environment Agency
Ga-68	Gallium-68 a radionuclide that emits positrons
HCC	Hepatocellular cancer
Ho-166	A beta-emitting radionuclide
I-131	Iodine 131 (A beta-emitting radionuclide used for therapy)
ICSCNM	Intercollegiate Standing Committee for Nuclear Medicine
IDUG	Internal dosimetry users group
IPEM	Institute of Physics and Engineering in Medicine
IR(ME)R	Ionising Radiation (Medical Exposures) Regulations
Lu-177	A beta-emitting therapeutic radionuclide
mIBG	Meta Iodo-benzyl guinidine
MDT	Multidisciplinary team
MPE	Medical physics expert
NET	Neuroendocrine tumour
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
ODN	Operational Delivery Network (often shortened to network)
P-32	Phosphorus-32 (A beta-emitting therapeutic radionuclide)
PET	Positron emission tomography
PSMA	Prostate specific membrane antigen
Ra-223	Radium-223 (An alpha-emitting therapeutic radionuclide)
RCP	Royal College of Physicians
RCR	The Royal College of Radiologists
SIRT	Selective internal radio(nuclide) therapy

SPECT	Single photon emission computed tomography
Tc-99m	Technetium-99m (A gamma-emitting SPECT radionuclide)
Th-227	Thorium-227 (An alpha-emitting therapeutic radionuclide)
UK	United Kingdom (of Great Britain and Northern Ireland)
Y-90	Yttrium-90 (A beta-emitting therapeutic radionuclide)
Yorks	Yorkshire

1. Introduction

1.1 Definition

Molecular radiotherapy in this report means those radioactive substances which are 'unsealed' and administered as a solution or emulsion of nanoparticles. This means their mode of action is primarily pharmaceutical but can also be loco-regional. The administration of these unsealed sources is governed by the Administration of Radioactive Substances Advisory Committee (ARSAC). It does not include the use of 'solid' radiotherapy sources such as seeds or wires. Molecular radiotherapy is sometimes called radionuclide therapy, radioligand therapy or nuclear medicine therapy. In this report we will use the term 'molecular radiotherapy' throughout.

1.2 Stakeholders

The stakeholders involved in the production of this report are the Royal College of Physicians (RCP), The Royal College of Radiologists (RCR), the Intercollegiate Standing Committee on Nuclear Medicine (ICSCNM), the Institute of Physics and Engineering in Medicine (IPEM) and the British Nuclear Medicine Society (BNMS).

1.3 Introduction to molecular radiotherapy

Over the past five years there has been an increase in the use of new molecular radiotherapy techniques.[1] The provision of these services has been uneven, with centres who have trained staff and enthusiastic clinicians offering these services to their local population and a lack of provision in other centres who lack these staff. In some instances patients have had to travel long distances to be able to receive treatment.

There has been a perception of a 'post code' lottery where some areas of the country may have reduced access to molecular radiotherapy services. This may be due to several compounding factors. First, there is no clear national ownership of the treatment modality which can be reflected at local level. Service provision may follow patterns depending on how and where these treatments are delivered. Treatments may be lead by nuclear medicine physicians or clinical oncologists. Since the cancer strategy documents of 2000 onwards, the distinction between who leads and provides molecular radiotherapy has become less significant as patients are now managed through appropriate multidisciplinary teams (MDTs).[2]

Second, historically there has been a strong service provision in molecular radiotherapy in London and the North West with less comprehensive provision elsewhere. This has – to some extent, but not exclusively – followed training and employment of therapy-based nuclear medicine physicians who have been concentrated in these areas of the UK.[3]

Third, services for the three most recent forms of molecular radiotherapy in England have previously relied on approval for funding via the Cancer Drug Fund (CDF). Approval is now via national or local commissioners after assessment by the National Institute for Health and Care Excellence (NICE). Even though commissioning is local it may only be possible if that centre is recognised by NHS England. This led to some significant anomalies. For example, in north London the site chosen for treatment with radium-223 was at the extreme eastern edge of the city. This made patient journeys both long and difficult, effectively reducing patient access. In the past 12 months some of these issues have been resolved. However, it is still true that there are centres in or near big population centres that are not delivering a molecular radiotherapy service despite having the appropriately trained staff and facilities. This results in additional travel time for patients to access treatment.

A further issue which has compounded these situations is that the decision-making process can be volatile. Lu-177 DOTATATE funding has been intermittent. This makes it very difficult for individual trusts/hospitals to forward plan molecular radiotherapy service provision, especially as this requires the employment of a specialist workforce.

To understand the current situation this report focuses on the provision of three treatments which have been introduced in the past decade and have a degree of NHS funding. These three treatments are:

1. Y-90 SIRT
2. Radium-223
3. Lu-177 DOTATATE.

These treatments are also covered by most private insurance providers.

1.4 The types of treatments being considered in this review:

1.4.1 Y-90 SIRT

Y-90 SIRT is a non-systemic treatment which comes in two forms. Both involve the use of Yttrium-90, a beta emitting radionuclide. In one form, the radionuclide is attached to the outside of small resin spheres, in the other form it is an integral part of small glass beads. The size of both these particulates is measured in micrometres and the product comes as an emulsion or temporary suspension. When injected into the hepatic artery via a radiologically placed catheter, these particles lodge in the tiny blood vessels surrounding primary and secondary tumours in the liver (Figure 1). Normally it is a single treatment but if both liver lobes need treatment then the two lobes can be treated six weeks apart. Until February 2021 the only scenario in which NICE approved funding was in metastatic colorectal cancer with between one and four unresectable liver metastases and no systemic metastases. This has resulted in a very small number of patients being treated.

In February 2021 the use of SIRT was approved as third-line treatment in unresectable primary hepatocellular carcinoma (HCC).[4,5] There is significant concern that after many years without funding for this technically demanding service, the necessary skill base to perform the required SIRT treatments will not be available. This is especially pertinent in HCC because these treatments need to be performed in hospitals/trusts that have both experience treating HCC and the required hepatology support.

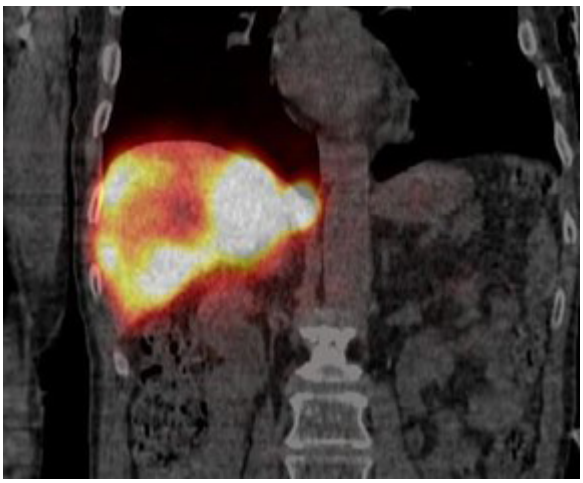


Figure 1. Tc-99m MAA SPECT-CT image used to predict the distribution of Y-90 SIRT.

Xofigo (Ra-223 Dichloride)

This alpha-particle emitter is an analogue of calcium and, like calcium, is incorporated into bones during bone growth. There is remodelling of bone around bone metastases especially in prostate cancer. On bone scintigraphy, the site of these bone metastases appear as 'hot spots' on the scan (Figure 2). Clinical trials have shown a survival benefit if radium-223 is given to men with metastases in the bones only arising from their prostate cancer who have progressed despite hormonal and chemotherapy treatments. The standard treatment is six cycles four weeks apart and is given by a simple intravenous injection.

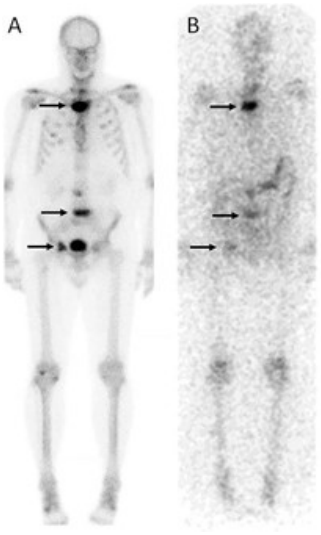


Figure 2. Anterior gamma camera images of [A] 99mTc-methyl diphosphonate distribution (A) and 223-Ra distribution (B). Corresponding sites of increased uptake are indicated. Note the excretion of 223-Ra via the intestines.

1.4.2 Lutathera (Lu-177 DOTATATE)

Lu-177 DOTATATE is the first true radioactive theragnostic treatment since radioiodine. It is used to treat patients with pancreatic and mid-gut neuroendocrine tumours (NETs) who have progressive or persistent symptomatic disease despite somatostatin analogue therapy (Figure 3). The decision to treat depends largely on functional imaging using the same ligand as therapy but with a diagnostic rather than therapeutic radionuclide. At present, most diagnostics are performed using Tc- 99m or In-111 labelled somatostain analogues, but the best method is Ga-68 DOTATATOC/DOTATATE PET.[6–8] Despite NHS England funding since 2020 the method of scanning is only available in a few centres. Those centres with a Ga-68 service are not necessarily those with a specialist NET service where patients would ideally receive all their required diagnostics and treatment. The standard treatment is four cycles eight weeks apart. Lu-177 DOTATATE is given by a 40–60 minute intravenous infusion.

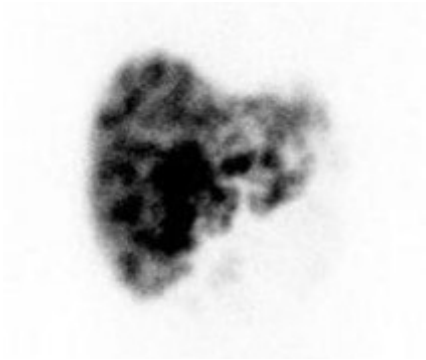


Figure 3. Anterior whole-body image performed 48 hours after administration of a therapeutic dose of Lu-177 DOTATATE (lutathera) showing uptake only within the tumour metastases in the liver with minimal uptake in other tissues. This demonstrates how well targeted this treatment is.

2. Survey of current molecular radiotherapy practice

2.1 Survey methodology

A survey was distributed via the BNMS, RCR and IPEM to members in all four nations of the UK; questions are available at Appendix A). The survey primarily asked each hospital/trust whether or not the three molecular radiotherapy services were offered and if so how many patients had been treated in the last 12 months. In addition, if these treatments were not offered, questions asked about the main reasons why not. Centres that offered any of the three treatments were asked about the capacity for increasing the number of treatments at that site. The survey was sent up to three times over a two-month period between May and July 2020.

2.2 Looking to the future

One of the motivations for this survey was the need to look at the future provision of molecular radiotherapy. At present a limited number of patients are treated, either because of the limited indications for the treatment or the rarity of the cancer to be treated. Within the next two years it is expected that an additional molecular radiotherapy treatment will become available.[9,10] This will be based on the theragnostics of prostate specific membrane antigen (PSMA). A phase III trial of a diagnostic PSMA (Ga-68 PSMA PET-CT) and a therapeutic (Lu-177 PSMA) have been completed and licensing alongside potential NICE approval is expected within a 12–18-month time frame. [11–13] This treatment will be suitable for selected patients with metastatic disease of the prostate who have not responded to hormonal treatment and chemotherapy. The number of patients eligible for the treatment will be greater than for the currently funded molecular radiotherapy treatments using Radium-223. Therefore, a final question in the survey asked whether centres were planning to start PSMA theragnostics and, if so, how they planned to manage the introduction of this new therapy.

2.3 Results of the survey

Replies were received from 49 hospitals or NHS trusts, some of which covered multiple sites. Of these, 43 sites employed medical staff who held an ARSAC certificate for Y-90 SIRT, Ra-223 or Lu-177 DOTATATE. In some sites, despite having trained staff, no patients had been treated over the past 12 months.

Reviewing the number of patients treated over the past 12 months across the UK, it is clear that very few patients receive Y-90 SIRT. Ra-223 is more widely available and the provision of Lu-177 DOTATATE is mixed, with a significant London-centric service provision (Table 1).

Table 1. Use of the three forms of molecular radiotherapy funded in England by the cancer drug fund and by national governments in 2019/2020

Region/nation	Y-90 SIRT patients per year	Y-90 SIRT number of sites	Ra-223 patients per year	Ra-223 number of sites	Lu-177 DOTATATE patients per year	Lu-177 DOTATATE number of sites
Scotland	4	1	40	1	–	–
Northern Ireland	–	–	–	–	–	–
Wales	–	–	20	1	18	1
London	17	3	160	2	193	6
South East	10	1	78	4	40	1
South West	9	1	123	4	49	2
East of England	3	1	54	2	15	1
East Midlands	–	–	77	4	–	–
West Midlands	3	1	54	2	17	1
Yorks and Humber	–	–	12	1	20	1
North East	29	1	38	2	23	1
North West	24	1	93	3	53	2
TOTAL	99	10	749	–	428	16

The varying population density of the separate regions should be taken into account. Table 2 shows the number of patients given each treatment per million population, based on the population estimates provided by the United Nations and the Office for National Statistics estimates published in 2017.[14] These data are also shown in Figures 4–6.

Table 2. Regional and national populations estimated for 2017 with treatment rates per million the three forms of molecular radiotherapy. This has been obtained by looking at the total number of patients treated in the UK divided by the total population and then multiplied by the population of that nation or region

Region	Population Estimate 2020 (millions)	Y-90 SIRT rate per million	Radium-223 rate per million	Lu-177 DOTATATE rate per million
Scotland	5.5	0.7	7.3	0
Northern Ireland	1.9	0	0	0
Wales	3.1	0	6.4	5.8
London	8.2	1.9	17.8	21.4
South East	9.2	1.1	8.5	4.4
South West	5.6	1.6	22	8.7
East of England	6.2	0.5	8.7	2.4
East Midlands	4.8	0	6	0
West Midlands	5.9	0	9.1	2.9
Yorks and Humber	5.5	0	2.2	3.6
North East	2.7	10.7	14.1	8.5
North West	7.4	3.2	12.6	7.2
Total for UK	68	1.5	11	6.3

Figure 4. Map showing population-based provision of Y-90 SIRT compared to national average of 1.5 treatments/million in 2019/20

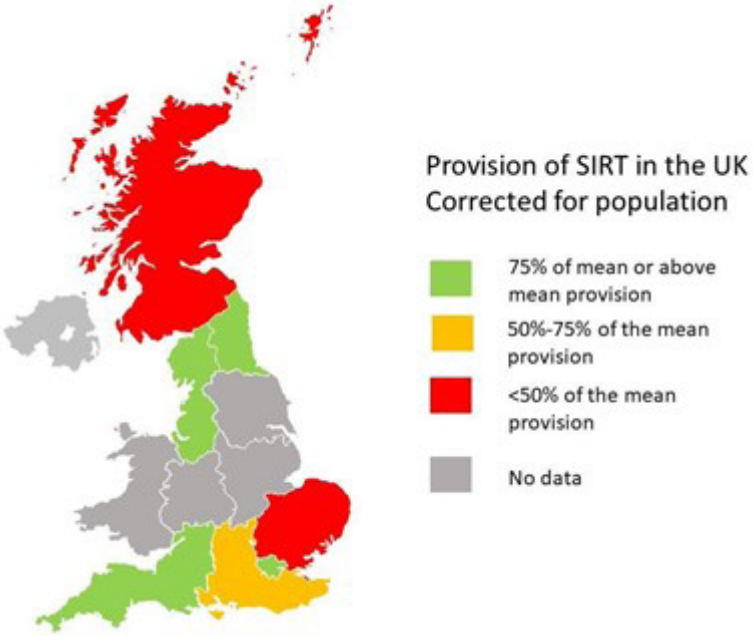


Figure 5. Map showing population-based provision of Ra-223 (Xofigo) compared to national average of 11 treatments/million in 2019/20

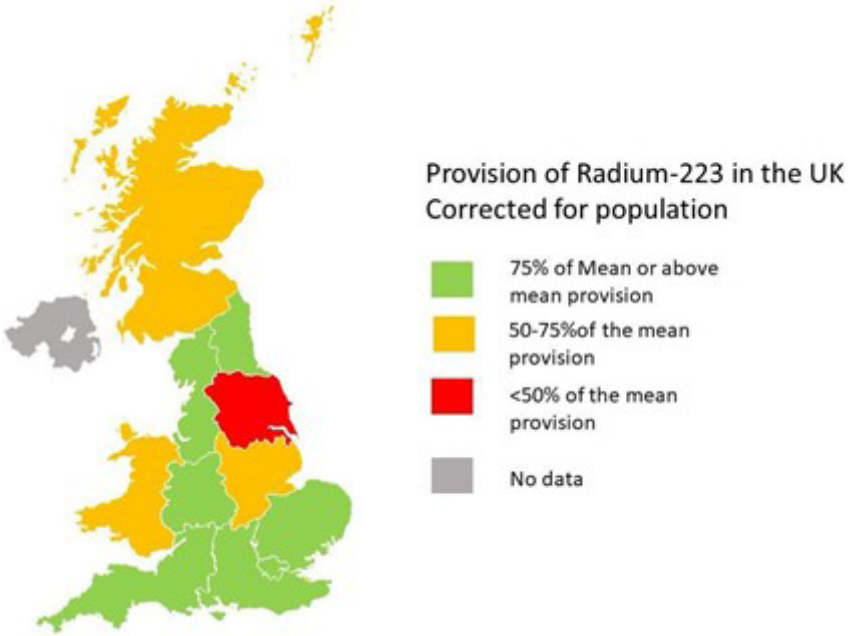
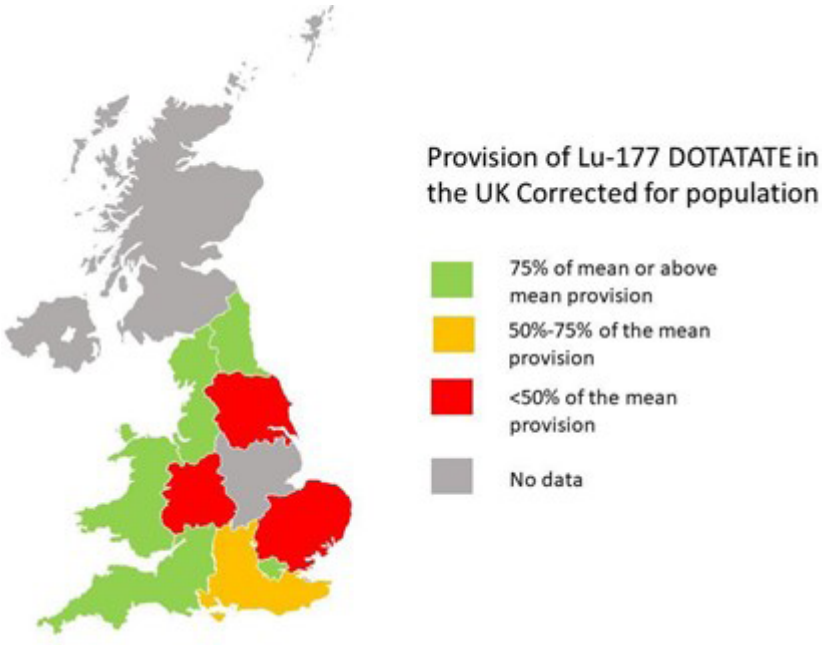


Figure 6. Map showing population-based provision of Lu-177 DOTATATE (Lutathera) compared to national average of 6.3 treatments/million in 2019/20



Significant differences in treatment rates are observed across the UK, with some areas delivering no treatments at all while others have much higher treatment rates. This can be partially explained by referral of patients from one region into another. This may for example explain the London centric figures for Lu-177 DOTATATE especially from the southern part of the East Midlands and East of England and northern South East (which comprises the 'home counties'), where referral patterns from the former Thames regions may still exist. However, this does not explain the disparate treatment rates in regions more distant from London.

2.3.1 Y-90 SIRT (SIRTEX and Theraspheres)

A single hospital trust in the North East provided the most Y-90 SIRT treatments over the period investigated (10.7 treatments/million/year). The second highest number of treatments per head of population was reported in the North West, delivered at a regional cancer hospital. Nevertheless, this compares favourably with the rest of the UK. In London, the South East and the South West the treatment rate is fewer than two treatments/million; most other regions that offer the service deliver less than one treatment/ million/year.

Table 3. Reasons for not performing SIRT

Number of hospitals/trusts per region or nation replying to the question	Lack of trained staff	Oncologist not convinced of utility	Offered at local hospital	Lack of reimbursement
Yorks and Humber 1	x	x		x
London 1			x	
South East 1	x			
East Midlands 1			x	x
North West 1	x	x		
Wales 1			x	
North East 1	x	x	x	
West Midlands 1			x	
Yorks and Humber 2			x	x
South West 1			x	
London 2				x
West Midlands 2				x
East Midlands 1		x		
London 3			x	
West Midlands 3		x	x	
South East 1	x	x		x
London 4	x	x	x	x
Wales 2				x
Total	6	7	10	8

Y-90 SIRT is considered to be a highly specialised service and as such is only offered within some cancer networks. In their responses to the survey, many centres noted that hepatic-based interventional radiology – which is not always available – is essential for Y-90 SIRT. Lack of reimbursement was an issue, primarily with NHS England. This will need to

be solved with the agreement to fund the treatment of HCC. Some oncologists were not convinced of the efficacy of SIRT, which reflects the pre-2021 NICE guidance.[4] Lack of trained staff is also reported as a major barrier to implementation of a SIRT service.

2.3.2 Radium-223 dichloride (Xofigo)

The provision of Radium-223 treatment is more evenly spread; only Northern Ireland is either not delivering a Radium-223 service or not providing an answer to the survey. There is, however, great variation in service delivery rates across the rest of the UK. This is not easily explained as prostate cancer is a common cancer and there is no evidence for a great variation in the incidence of castrate resistant prostate cancer with mainly bone metastases. The national average rate of treatment is 11/million/year. The South West delivers the highest rate of treatments at 22/million/year followed by London (17.8/million/year), the North East (14.1/million/year) and the North West (12.6/million/year). Other regions offer less than the national average. The reason for the poor uptake of radium-223 in Yorkshire and Humber cannot be based solely on the number of patients with prostate cancer being higher in the South West; the population demographic and social situation in the North East and North West is similar to Yorkshire and Humber and they have higher rates of treatment. Therefore a different explanation must be found.

Table 4. Reasons for not offering Ra-223 service.

Number of hospitals/ trusts per region or nation replying to the question	Treatment offered at local hospital	Lack of reimbursement	Oncologists unsure of efficacy	COVID issues
London 1	x			
West Midlands 1	x			
South West 1	x			
London 2		x		
West Midlands 2	x			
North West 1		x	x	
London 2		x		
London 3				x
Norther Ireland 1		x		
Total	4	4	1	1

The primary reason given for not offering Ra-223 was that this service was being offered at another 'local' hospital; in some cases that local hospital was over two hours' journey away. Lack of reimbursement was another reported reason for not offering a Radium-223 service, despite having the necessary trained staff. These centres felt NHS England had frustrated the delivery of a locally based service. One site in London reported that they had stopped Ra-223 treatments due to the COVID-19 pandemic despite the BNMS having provided advice on COVID-19-secure service delivery.

NICE has revisited its advice and to state that as Ra-223 therapy is not immunosuppressive it should be considered before chemotherapy (such as taxanes) in vulnerable patients. Oncologists at one site were unsure of the efficacy of treatment with Ra-223.

There was reported to be a problem with reimbursement of Ra-223 in Northern Ireland.

2.3.3 Lu-177 DOTATATE

The geographic provision of Lu-177 DOTATATE is more complex than the other therapies. Neuroendocrine tumours (NETs) are rare and complex forms of cancer. Patients with NETs have tended to be seen in 'centres of excellence' indicating that they have gravitated to these centres for other aspects of their clinical care. These centres are generally located in London, the North West and Yorkshire and Humber and have tended to deliver the highest rate of Lu-177 DOTATATE therapies.

Therefore the Lu-177 DOTATATE treatment rate of 21.4/million/year in London may reflect continuing inward referrals for treatment. There is a question regarding whether this is providing the best care to patients, for who long journey times may be difficult due to their symptoms. Outside of London, only the South West, North East and North West deliver more treatments per year than the national average of 6.3/million/year.

Table 5. Reasons for not offering Lu-177 DOTATATE

Number of hospitals/trusts per region or nation replying to the question	Lack of reimbursement	Lack of trained staff	Lack of facilities	Offered at a local hospital
South East 1	x			
Yorks and Humber 1		x		
East Midlands 1		x		
North West 1				x
South West 1	x			
London 1	x			
East Midlands 2		x		
North East 1		x	x	x
West Midlands 2		x		
North West 2	x			
London 2				x
East Midlands 2				x
South West 2				x
Scotland 1	x			
Wales 1	x			
South East 2	x			
Northern Ireland 1	x			
Total	8	5	1	5

The most common cause for not offering Lu-177 DOTATATE therapy is the lack of reimbursement. This involves not only NHS England but also devolved national health offices in Wales (though it is understood this is under review), Scotland and Northern Ireland. Whilse many centres state that services are offered in local hospitals the distance to these sites can vary from a few miles to nearly 200 miles. The complex nature of NETs and their need for a multidisciplinary treatment approach means that these patients should be managed by an appropriate specialist MDT. This may necessitate patients travelling to a central hub for treatment. However, in these days of electronic communication it should be possible to offer some specialist services locally with the expert opinion of the NET specialists available through teleconferencing. As seen with other molecular radiotherapy techniques, lack of trained staff is a significant issue. Not shown in the table, two centres in their survey reply stated that levels of radioactive discharge set by the Environmental Agency of England and Wales was an issue. In the survey the problem of radioactive discharge impacted a single site in London who were performing about 25% of all Lu-177

DOTATATE treatments in the UK. Because of these discharge limits they could not treat more patients . These restrictions on effluent discharge are somewhat misleading because they assume local discharge when in fact, as previously noted, patients are returning home after therapy which can be 200 miles from the treatment centre.

If the radioactive discharges required could be shared among more centres this would be an argument for there to be more centres being reimbursed by NHS England and the devolved nations if they have trained staff and a neuroendocrine MDT.

No additional reasons for not offering or expanding a service were provided. However, two centres reported concerns about reimbursement from NHS England. One centre reported that NHS England withdrew reimbursement and then returned it making forward planning and resourcing difficult.

2.3.4 Reasons stated for this variation.

The most common stated reasons why some centres did not offer a particular service were lack of reimbursement and lack of trained staff. While the latter is understandable it would appear that some centres have trained staff who are not utilised, primarily because NHS England and the devolved national governments will not reimburse treatment at those particular sites. This means patients suffer prolonged travel distances and times not because of a lack of local resources but because of central bureaucracy (Tables 3–5).

2.4 Changes over the past decade

This is not the first of this type of survey to be performed. A British Institute of Radiology survey performed in 2009 counted the number of centres providing treatment but not the number of patients.[15] At that time Ra-223 and Lu-177 DOTATATE were not available.

More recently the Internal Dosimetry Users Group (IDUG) published a review of the use of molecular radiotherapy up to 2017. They used a different methodology and their review showed that the number of patients being treated with molecular radiotherapy methods has consistently doubled over the past eight years giving an average growth rate of 12% per year.[1] Their most recent report, published in 2019, shows that while use of some treatments such as Stronium-89, Samarium-153 and I-131 mIBG has decreased over ten years, there has been significant growth in the use of Ra-223 and Lu-177 DOTATATE. The result is sustained growth in the use molecular radiotherapy overall. The outlier is Y-90 SIRT; the number of patients treated rose and fell related to changes in reimbursement through the Commissioning through Evaluation (CtE) scheme and subsequently NICE approval. The recommendation by NICE that SIRT can be used to treat advanced HCC will likely increase demand. It is expected that the number of patients treated with molecular radiotherapy will continue on its present upward trajectory especially after the expected introduction of Lu-177 PSMA in 2022.

3. How prepared is the UK for a new molecular radiotherapy agent such as Lu-177 PSMA?

3.1. What is PSMA therapy?

Prostate specific membrane antigen (PSMA) is expressed on the surface of prostate cancer cells in a much higher concentration than non-cancer cells. The name is a misnomer as it can be present on other cancer cells but it has found its greatest utility in prostate cancer.[16,17,18]

Originally, small molecules called ligands were found which bound to the PSMA. They were labelled with a radioactive metal gallium-68 (Ga-68) which enables the tumour to be seen using positron emission tomography (PET). It was soon discovered that there was a significant advantage over bone scanning since metastases could be found in soft tissues as well as bones (Figure 7).[19–29] Using the theragnostic principle that 'if you can see it you can treat it' many researchers, primarily in Germany and Australia have changed the imaging isotope, for example, Ga-68 to the therapeutic isotope Lu-177. Phase 1 and phase 2 trials are now complete and a major multicentre phase 3 trial has just reported increased survival compared to second line chemotherapy.[13] A March 2021 press release by the sponsors of the trial suggested that Lu-177 PSMA will be useful in treating metastatic prostate cancer when chemotherapy has stopped working.[12]

Therefore, it is likely the product will be licenced and possible approved by NICE for use in the UK. If this is the case the number of patients who would benefit from treatment would be greater than all those that receive Y-90 SIRT, Radium-223 and Lu-177 DOTATATE combined.

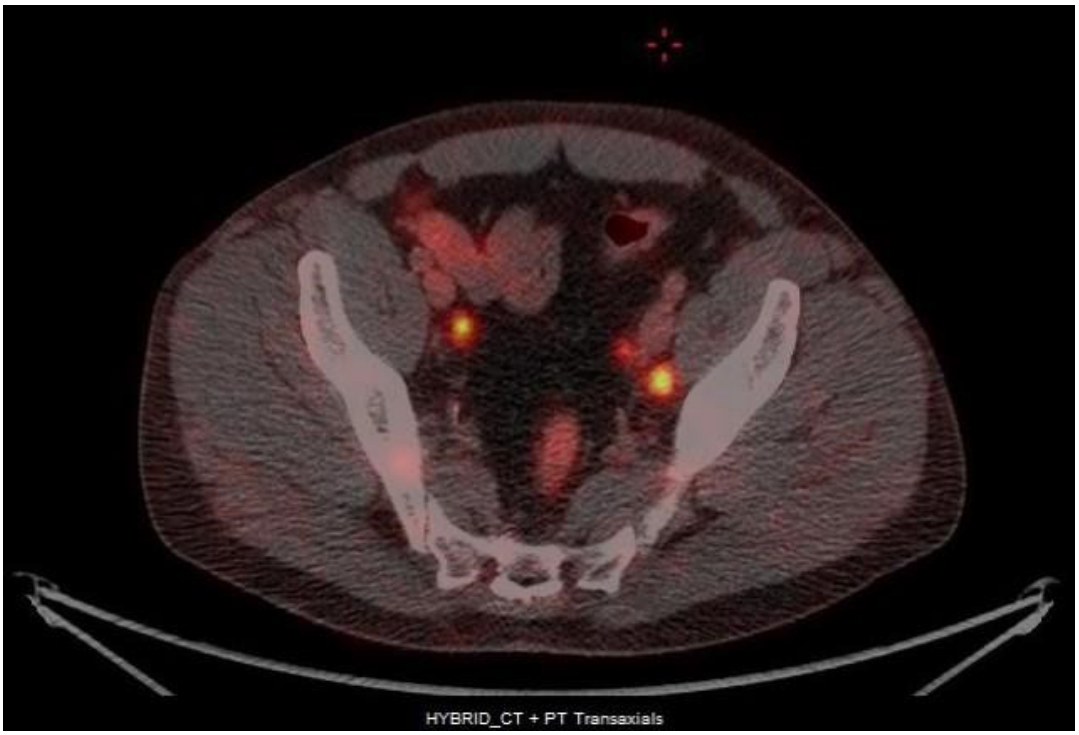


Figure 7. A Ga-68 PSMA PET-CT scan showing uptake in three lymph nodes within the pelvis. It would be possible to treat patients with metastases that take up Ga-68 PSMA with Lu-177 PSMA the so called 'theragnostic principle'.

3.2 Are centres ready for PSMA therapy?

The survey asked centres whether they were planning to offer PSMA therapy when it is licenced and reimbursed. Three response options were available:

- **Fully ready** – they were fully prepared and could start treatments as soon as the product was available (fully ready)
- **Additonal resources needed** – they had made some preparations but would need additional staff and/or facilities
- **Hoping to offer service in future** – they hoped to offer the treatment at some time point but were not yet prepared to treat patients.

Table 6. Preparedness for Lu-177 PSMA therapy

Hoping to offer service in future	Some preparations more facilities/staff needed	Ready to start
15	26	4

The results indicate that many centres had undertaken some level of preparation and had begun the process of determining what further resources may be required. Two of the four centres that said they were ready to give Lu-177 PSMA did not have experience with Lu-177 DOTATATE, so had not handled Lu-177 radiopharmaceuticals in volume before; this could be a cause for concern. One further centre stated they were near their Environment Agency limit for disposal of Lu-177 so it is unclear how they would be able to perform Lu-177 PSMA unless they stopped doing Lu-177 DOTATATE treatments.

A second survey with seven questions was distributed in January 2021 to all 45 centres which had stated they had an interest in providing a PSMA theragnostic service. Replies were obtained from 25 sites (54%).

The survey included questions about whether a relevant MDT existed, which MDT would review the cases that were being planned for PSMA therapy and who would attend such an MDT. The answers are listed in Tables 7, 8 and 9.

Table 7. Responses to whether a relevant MDT existed to review cases and decide who should have PSMA therapy

Such an MDT already exists	A new MDT or new section of an existing MDT would need to be set up	At present no plans are in place for such an MDT
16	8	1

Table 8. Responses to which MDT would review whether the patient should undergo PSMA therapy

Urological cancer/ prostate cancer MDT	Molecular therapy MDT	It is not yet known which MDT would review cases
18	3	3

Table 9. Responses to which clinicians would attend the MDT which decides on a patient receiving PSMA therapy. Any individual may have more than one role in which case each role is marked.

Attendee at MDT	Number of centres where that person would attend (n=25)	%
The patient's treating oncologist	23	92
ARSAC licence holder (clinical oncology)	16	64
Oncologist with a specialist knowledge concerning PSMA therapy	14	56
ARSAC licence holder (nuclear medicine/radiology)	13	52
Clinical nurse specialist in prostate cancer	13	52
Medical physics experts (MPE)	12	48
Nuclear medicine nurse	5	20
Clinical scientist not an MPE	2	8

It is clear that most centres have both thought about which MDT would decide on treatment but and who would attend. The approach is clearly multidisciplinary showing a good understanding of the skillsmix required. Significant concerns remain over the fact these MDTs do not all have clinical scientist and nursing input. Such input could be considered vital for good practice given the complex nature of molecular radiotherapy. Also, with the increasing use of virtual attendance at MDTs barriers to attendance of non-medical health care professionals/craft groups are now greatly reduced. It would be good practice for the MPE involved in these treatments to attend the MDT. This would fulfil the requirements under IR(ME)R 2017 that the MPE be closely involved in each patient's treatment.[30] The presence of experienced nursing staff and clinical scientist/MPEs will enable complex cases and those with significant co-morbidities and mobility/continence issues to be flagged and planned prior to treatment allowing a personalised risk assessment and amelioration to be put in place.

Further questions investigated the diagnostic provision required to determine whether a patient is suitable for PSMA molecular radiotherapy. At the time of writing there are two PET agents: Ga-68 PSMA and F-18 PSMA used in imaging prostate cancer and its metastases. Neither of these have product authorisation in the UK, but this is expected by 2022. A third imaging method uses standard gamma camera technology. This PSMA, labelled with Tc-99m, has product authorisation in the UK but reimbursement is not currently available.[31] The usefulness of the Tc-99m PSMA in the identification of small metastases is less than the PET agents but this may not be clinically relevant in patients receiving PSMA molecular radiotherapy as they will probably have bulk or widespread disease that has failed treatment with chemical castration and chemotherapy. It is also not known yet if the marketing approval for Lu-177 PSMA will require pre-imaging with only Ga-68 PSMA as this was the imaging modality used pre-treatment in all the clinical trials. As access to these agents at any one time may be limited, centres may plan to use more than one agent if they can or

send their patients to a centre that performs more than one form of PSMA imaging. The results of these questions are provided in Tables 10 and 11.

Table 10. Centres' plans for PSMA imaging

Plan for PSMA imaging	Number of centres (n=25)	%
PSMA imaging already performed	15	60
PSMA imaging will be started in the future using existing staff and facilities	5	20
PSMA imaging is already or will be performed at another		
hospital/trust and this has been agreed	2	8
PSMA imaging will be performed at another hospital/trust but this has not yet been agreed	2	8
We do not know where the PSMA imaging will take place	1	4

Table 11. Centres' current and planned use of PSMA agent/s (centres could indicate more than one form of PSMA imaging)

Form of PSMA imaging	Number of centres planning to use this method of imaging (n=25)
Ga-68 PSMA PET	16
F-18 PSMA PET	16
Tc-99m PSMA single photon imaging	2

It is concerning that so few centres are just in the stage of planning PSMA imaging. Setting up new imaging sites is complex. This may significantly limit access to PSMA molecular radiotherapy as patients can only be treated if they have a positive PSMA scan. Centres looking to deliver PSMA molecular radiotherapy will need to rely on other hospitals/trusts to perform PSMA imaging, potentially leading to 'bottle necks' in the patient pathway.

3.3 Readiness for patient-based dosimetry?

Part of good practice in molecular radiotherapy is the ability to perform patient-specific dosimetry.[30, 32–37] This is routine in most radiotherapy practice but is not always performed in molecular radiotherapy. The BNMS have stated that it is their aim to ensure all patients receiving molecular radiotherapy treatment should, if possible, have patient-based dosimetry.[38] In their February 2021 guidance notes, ARSAC require those applying for an ARSAC therapy licence to state which method of dosimetry they will use in patients treated with that particular agent.[39,40] This is even more important with new agents such as Lutetium-177 PSMA to help understand both how much treatment is required to obtain a significant anti-tumour effect but also to understand any possible toxicity. Unlike some agents such as Radium-223 and Yttrium-90, there is a small yield of gamma photons with Lutetium-177 allowing for post-therapy gamma camera imaging. These images can be used to calculate the radiation dose received both by the tumour and relevant normal organs. The provision of a dosimetry service requires clinical scientist input and relevant

software to enable results to be comparable across different treatment hospitals/trusts. The PSMA readiness survey included two questions concerning departments' readiness for such patient-based dosimetry (Tables 12 and 13). This included a question concerning any planned post-therapy imaging which was designed to test if the centres had a complete understanding of what would be required to perform patient-based dosimetry with PSMA therapy or if the centre had any desire to perform such a calculation.

Table 12. Centres' plans for post-therapy imaging

Post-therapy imaging/dosimetry planned	Number of centres (N=25)	%
No post-therapy imaging planned	2	8
Whole-body imaging after every treatment cycle	1	4
Whole-body imaging after some treatment cycles	2	8
*SPECT and **SPECT/CT imaging after every treatment cycle	7	28
SPECT and SPECT/CT imaging after some treatment cycles	7	28
Imaging with full organ and tumour dosimetry after each treatment cycle	6	24

**Single photon emission computed tomography*
*** Single photon emission computed tomography/computed tomography*

To perform the requisite patient-based dosimetry – which would include tumour- and organ-based dosimetric calculations – would ideally require SPECT and SPECT/CT with each treatment cycle.[41–45] This is because there is a degree of unpredictability in the bio-distribution of any injected agent and it cannot be assumed that the distribution of the agent is consistent between cycles. In fact, a change is desirable as this would mean a potential reduction in tumour size. SPECT and SPECT/CT after each cycle or full dosimetric assessment are the ideal answers and this was provided by 13 centres (54%). There is significant concern that the remaining centres are not considering dosimetry for each treatment cycle or in some cases any post-therapy imaging. This may impact on the ability of medical staff from those centres to acquire an ARSAC licence.

To explore these issues more closely a question was included investigate perceived barriers to performing patient-based dosimetry; each centre could identify more than one reason.

Table 13. Reasons identified for not being confident undertaking patient-based dosimetry

Reason stated	Number of sites (n=25)
Lack of staff to perform dosimetry	18
Lack of experience in performing dosimetry	9
Lack of guidance on how to perform dosimetry	5
Lack of gamma camera availability to perform dosimetry	10
Lack of software to perform dosimetry	10

The responses demonstrated a significant skills shortage which – while it may not prevent centres starting PSMA therapy – will need to be addressed moving forward. Good cooperation between radiotherapy and nuclear medicine/radiology services will be required to find the necessary skilled staff and ensure the correct imaging equipment and software are available at each centre. It may also be necessary to outsource patient-based dosimetry and to include other hospitals/trusts or third parties in dosimetric calculations. In addition, it is important that dosimetry becomes a core competency in the training of clinical scientists, clinical oncologists and nuclear medicine physicians across the UK to help provide this service

3.4 Barriers to running a PSMA theragnostic service

Finally, the survey looked to identify any other barriers that might need to be overcome if PSMA theragnostics was to commence in these centres. Again, each centre may have more than one barrier and even those centres who felt they were ready for PSMA therapy may have some issues in dealing with the expected number of patients. The results are shown in Table 14 .

Table 14. Other issues that would need to be addressed before a PSMA theragnostic service could be provided

Issue	Number of sites (n=25)
There are no issues – we can treat patients as soon as it is authorised and reimbursed	9
We do not have sufficient physical facilities to perform PSMA theragnostics (this could include lack of radiopharmacy space, PET/CT or SPECT/CT scanning capacity or room in which to give PSMA therapy)	7
We do not have Environment Agency authorisation for holding and disposing of Lu-177	3
We are close to our Environment Agency limits for holding and disposal of Lu- 177	4
Our present staff will need additional training	13
We will need to employ additional staff to provide a PSMA theragnostic service	18
We are not confident that ARSAC will give our hospital a site licence for PSMA imaging and/or therapy	0
We are not confident that ARSAC will give our medical staff a licence for PSMA imaging and/or therapy	1
We are not sure what information we need to provide for the required business case for PSMA theragnostics	5
In addition to the above reasons we do not know what will be the expected demand for PSMA theragnostics	13

A wide range of issues were identified. Some of these can be solved by education which should be the joint responsibility of any company providing the products used in PSMA theragnostics, specialist societies and the individuals involved in providing a PSMA theragnostic service. Some of the issues are much more structural and will require significant input from hospital/trust management which may include a strategic review of the facilities and staff available. It is telling that 52% of the centres do not know what the demand for PSMA therapy will be. At this stage this is to be expected as the result of the phase III trials are still unknown and there is no guidance as to the type of patient who would either benefit from or be funded by the NHS for PSMA theragnostics. The development of clinical algorithms to show the placement of Lu-177 PSMA within the patient treatment journey would be very helpful. However, what is clear is that centres have thought about these issues and remain motivated to start a new molecular radiotherapy service despite these potential hurdles.

4. Possible new indications for currently available molecular radiotherapy agents and new molecular radiotherapy agents

4.1.1 Further molecular radiotherapy agents are being researched involving a variety of different cancers. Research covers additional indications for the agents currently used as well as new agents. Introduce these new agents across the UK will require extensive planning. A recent review of the clinical trials registered with the European Medicine Agency (EMA) and the United States Food and Drugs Administration (FDA) gives an indication of what is to come. This is a copy of a table recently published in Clinical Oncology (Table 15).[9]

Table 15. Multicentre trials using molecular radiotherapy products licenced with the food and drugs administration (FDA) or European Medicines agency (EMA) as of May 2020[10,46]

Radioisotope	Ligand	Disease	Administration	Phase
P-32	Silicon	Pancreatic cancer	Local	Phase II
Y-90	SIRT	Uveal melanoma in liver	Local	Phase II
Y-90	SIRT	Hepatocellular carcinoma	Local	Phase III
I-131	antibody 81C6	Glioma	Systemic and local	Phase II
I-131	mIBG*	Neuroblastoma	Systemic	Phase II
I-131	omburtomab	Neuroblastoma	Systemic	Phase II
I-131	omburtomab	Brain metastases	Systemic	Phase III
I-131	omburtomab	Peritoneal metastases	Local	Phase II
Ho-166	SIRT	hepatocellular carcinoma	Local	Phase II
Lu-177	DOTATATE	Neuroblastoma	Systemic	Phase III
Lu-177	DOTATATE	Liver mets from NETs	Local	Phase III
Lu-177	edotreotide	Neuroendocrine tumours	Systemic	Phase III
Lu-177	Satoreotide	Neuroendocrine tumours	Systemic	Phase II
Lu-177	3BP-220	Upper GI and pancreatic cancer	Systemic	Phase II
Lu-177	Lilitomab	Follicular NHL	Systemic	Phase II
Ra-223	chloride	Bone mets from thyroid cancer	Systemic	Phase II
Ac-225	Lintuzumab	Acute myeloid leukaemia	Systemic	Phase II

Radioisotope	Ligand	Disease	Administration	Phase
Th-227	BAY2287411	Ca Ovary, mesothelioma	Systemic	Phase II

Legend: mets=metastases, miBG= meta-iodobenzyl guanidine, GI=gastrointestinal, NHL=non Hodgkins lymphoma.

*Using new highly specific form of mIBG.

Even if only 50% of these agents make it to market, there will need to be a significant expansion in the delivery of molecular radiotherapy services. The old pattern of relying on service delivery via a few major centres is no longer sustainable. There needs to be and should be a much more sustainable provision of services across the UK so that patients who need molecular radiotherapy are able to access these services as required.

5. The argument for equitable access

5.1 Background

It is clear that molecular radiotherapy can no longer be seen as a niche, specialist service provided primarily by enthusiasts. This model has led to significant variability in service delivery across the UK, that is, a post code lottery. Once a treatment has been approved by NICE and is reimbursed, that treatment should be available to any patient for whom it is appropriate.

A four-nations strategy to deliver services to patients across the UK is required. For Northern Ireland, Scotland and Wales such a strategy may depend on their own local circumstances, including the need to deal with some significant journey times. Within England the logical way forward would be to ask each of the 11 radiotherapy Operational Deliver Network (ODNs).[47] to develop a strategy to deliver molecular radiotherapy to the patients within the area they cover. This strategy should include not only the molecular radiotherapy agents currently available but also be able to deliver potential future services across a range of cancer types including haematological and well as solid cancers. While it is understood that such a service is not set up at present, each radiotherapy ODN and nation should perform a gap analysis to see how their services compare to a required blueprint of service provision.

The four-nations strategy will need to ensure that local ODNs, cancer alliances, hospitals and trusts as well as commissioners are required to work together to deliver a standard which meets nationally set key performance indicators. It should also include a robust audit and feedback mechanism to ensure a high-quality service is provided across the UK. This would be similar to the quality-assurance programmes that were used in the roll out of PET-CT in England in the mid 2000s.[48,49]

5.2 A suggested blueprint of services

A suggested blueprint of the kind of services that will need to be provided to deliver molecular radiotherapy within each ODN and nation is provided. It may be that not every part of this blueprint is needed for each type of molecular radiotherapy treatment. It may also be the case for less frequently provided services nations and ODNs may pool resources .

5.3 The equitable delivery of molecular radiotherapy

It is important that each nation/radiotherapy ODN determines the best way to deliver molecular radiotherapy within their area. This may mean centralisation of services into a single specialised service, or more wider devolution of services. A single centralised service may not be appropriate and a general guide is that patients should receive their molecular radiotherapy at the same site as they receive the other specialised treatment for their cancer so they can remain with their normal care team. For example, it may be best to deliver Lu-177 DOTATATE therapy where they are seen within a specialist NET clinic. There may only be one such clinic per nation/ODN or a specialist clinic may be shared by more than one nation/ODN as this is a rare tumour. However, this idea should not be used to disrupt present working relationships. For example, it may be best for patients from North Wales to continue to be seen in the North West England region instead of having to take the longer journey to South Wales. Ra-223 is used in prostate cancer, which is much more common that NETS, therefore Ra-223 molecular radiotherapy should ideally be available more locally. The results of the survey indicate that this is already the case to some degree.

There may be other local factors for particular treatments such as SIRT which requires hepatic interventional radiology and hepatology services. These may only be available at one site within a network. A working example of this is London with SIRT is concentrated in the hospitals with regional liver units.

Other local factors may include the skillsmix available to deliver molecular radiotherapy within the nation/ODN. This will require hospitals/trusts to become more flexible in ensuring key staff are able to work at the correct site with sufficient time to deliver molecular radiotherapy even if this means sharing staff.

Consideration should be given to which site(s) can deliver any required nuclear medicine imaging in a timely manner. There may be a limited number of sites with sufficient physical facilities for safe administration of molecular radiotherapy agents. These sites would also need to have appropriate Environment Agency (EA) holding and disposal licences. The monthly limits defined in these EA licences may be constrained by factors outside the hospital's control. Decisions may need to be made that will allow some dispersal of services in the ODN/nation so no individual hospital site breaches their EA holding and dispersal limits. For this reason, in England the decision regarding which centre should provide a particular form of molecular radiotherapy must be made at radiotherapy ODN level and no longer centrally by NHS England.

5.4 The delivery of molecular radiotherapy skillsmix

Each nation/ODN will need to ensure they have a sustainable supply of trained staff to deliver molecular radiotherapy. This may mean employing new staff or training existing staff. Some skills will be legal requirements while others will be required for good practice. This is most suitably based around the MDT. This may be a local MDT or in a larger networked MDT as appropriate. The delivery of molecular radiotherapy requires MDT to include some individuals with very specific roles. Some of these roles are related to the legal framework in which molecular radiotherapy must be administered. Some centres have found it useful to create a molecular radiotherapy MDT to cover all aspects of molecular radiotherapy care.

5.5 Within each MDT/molecular radiotherapy team the following staff are a legal requirement:

5.5.1 ARSAC licence holder

The ARSAC licence holder will be a medically qualified person normally with a substantive consultant-level contract with the hospital/trust providing that particular molecular radiotherapy service. These licenses are very specific to both the molecular radiotherapy agent used and its indication. Any significant variation would need an additional license. It would be expected that the ARSAC licence holder is present on site or quickly available for each therapy. Their legal role would be to 'justify' the radiation exposure of the patient to the molecular radiotherapy agent. To perform this role they would need to have a background knowledge in radiation biology, aspects of dosimetry and the medium- and long-term effects of radiation. They would also have significant knowledge of the cancer that is being treated to enable them to advise if and when molecular radiotherapy treatment is indicated. They would know:

- The expected efficacy and acute and longer-term side-effects of the treatment.
- How to ensure safe delivery of that form of molecular radiotherapy and any other co-medicines needed for treatment

- How to manage any acute side-effects of treatment and ensure any appropriate onward care.

To ensure cover for planned and unplanned leave, it would be expected that there should be two ARSAC licence holders for each licenced treatment per hospital/trust. To obtain an ARSAC licence the applicant would need to show evidence of:

- General training in molecular radiotherapy (normally a certificate of completion of training (CCT) or certificate of eligibility for specialist registration (CESR) in clinical oncology or nuclear medicine is sufficient)
- Evidence of specific training in the type of molecular radiotherapy for which they are seeking a licence.

An ARSAC licence holder should attend the MDT relevant to that treatment.

5.5.2 Medical physics expert

Though an MPE is a legal requirement for any administration of ionising radiation under the IR(ME)R 2017 legislation,[30] an MPE covering molecular radiotherapy would be expected to have significant knowledge of the technique being used. The MPE would be a registered clinical scientist who has received the required extra training. The MPE is responsible for many of the aspects of any molecular radiotherapy treatment but their primary role would be to ensure the patient was as safe as achievable throughout the diagnostic and therapeutic procedures and in addition look to the safety of any comforters and carers. They may not need to be present for each treatment but should be readily available for consultation should the need arise. The involvement of the MPE should be commensurate with the hospital's experience delivering that particular therapy. The MPE will need to ensure that appropriate risk assessments and standard operating procedures are in place, accessible and kept up to date. If there any significant issues that could compromise patient safety, the MPE has a legal duty to advise the hospital/trust chief executive officer (CEO). It is also necessary to report any significant radiation event to the Care Quality Commission.[30]. Some of these duties overlap with those of the relevant radiation protection adviser and radiation protection supervisor. MPEs may hold contracts with single or multiple hospitals/ trusts or a third party.

5.6 Additional staff requirements which may vary from centre to centre. (A single individual may undertake more than one of these roles.)

5.6.1 Theragnostic diagnostic nuclear medicine physician/radionuclide radiologist

Treatments such Lu-177 DOTATATE and Lu-177 PSMA depend on very specific imaging. Diagnostic versions of the therapeutic are either a gamma emitter or positron emitter. Examples used alongside Lu-177 DOTATATE are gamma emitters such as Tc-99m DOTATATE or In-111 octreotide Alternatively the positron emitter Ga-68 DOTATC that uses PET technology can be used. The use of a Ga-68 label currently limits the number of centres which can use the Ga-68 DOTATOC but it is able to confirm 11% more patients are eligible for Lu-177 DOTATATE than the single photon techniques.

With PSMA imaging there is a gamma emitter, Tc-99m PSMA, and two agents using PET technology, Ga-68 PSMA and F-18 PSMA. None of the radiolabelled PSMAs currently have marketing authorisation and access is limited. There is also inconsistent funding and availability across the UK.

5.6.2 Clinical nurse specialist(s) (CNS):

The CNS is the key to successful molecular radiotherapy as they provide the essential links between the various diagnostic tests, the MDT and treatment planning for the patient. They also have a key role in follow-up, helping to ensure the patient follows the required schedule of post-therapy tests and blood tests. The CNS also co-ordinating with the patient's GP and local oncology team if the molecular radiotherapy is to be performed in a centre outside of the one providing the primary cancer care.

5.6.3 Clinical scientist

There should be input from a clinical scientist who may be the MPE or work closely with the MPE. There are many aspects of their work which will impact the safe delivery of a molecular radiotherapy treatment. The clinical scientist:

- Will be responsible for ensuring the correct activity of the radionuclide therapy is given
- Will perform and check any required dosimetric calculations needed to ensure the correct activity is administered
- May be responsible for the safe administration of the molecular radiotherapy agent, including reducing radiation exposure to themselves, other staff and the patient's comforters and carers.
- May need to advise ward staff of the procedures around in-patient molecular radiotherapy and ensure monitoring equipment and personal protective equipment (PPE) is available and working
- Will advise the patient on which precautions they will need to take upon discharge to reduce exposure to their family and the public and can advise concerning travel in the months following treatment
- Will supervise the cleaning of any rooms or spaces used by the patient once the patient has left the treatment centre
- Will ensure the correct safe holding and disposal of any radiation contaminated materials
- May have a responsibility to ensure that the parameters allowed by the Environment Agency in holding and disposing of radionuclides is not exceeded, working with the hospital/trust's radioactive waste adviser
- May be responsible for any post-treatment patient dosimetry calculations and recording.

5.6.4 Radiopharmacist

The radiopharmacist will have the responsibility of manufacturing and releasing/dispensing the diagnostic and therapeutic radiopharmaceuticals and any other pharmaceuticals required for treatment, such as the amino acids used in Lu-DOTATATE therapy. They may also have a role in administering the funding and ensuring any molecular radiotherapy drug is reimbursed.

5.6.5 Nuclear medicine radiography/technologist and nursing staff

The nuclear medicine staff will have a role in the safe administration of radiopharmaceuticals and pre- and post-therapy imaging. Their presence at the MDT may be useful if the patient has medical, social or mobility issues which may mean that operating procedures for safe administration of any theragnostic radiopharmaceutical and/or imaging

may need to be modified for the safety of the patient, the patient's carers and staff. Nuclear medicine technician staff will work very closely with the CNS and may deputise some CNS responsibilities where appropriate.

6. Obstacles and proposed solutions

6.1 Current obstacles

Unlike many forms of cancer treatment, molecular radiotherapy has no well-defined 'home' in present hospital practice. This may mean that the delivery of care will involve a mixture of departments and managerial divisions in a hospital/trust. Unless there is a clear lead and advocate for molecular radiotherapy it may be difficult to advocate for the service, especially if additional resources are required to run a theragnostic and molecular radiotherapy service.

6.2 Nuclear medicine/radiology

In most hospitals within the UK, nuclear medicine and often nuclear medicine physics lie in the department or division of radiology. This is because the vast majority of studies performed will be diagnostic studies. Therefore, when assessing workload, staffing and consultant job plans, most radiology departments rely on the number of diagnostic studies performed and reported to allocate resources. When viewed numerically, molecular radiotherapy patients will always appear as a smaller area of interest. Radiology management more accustomed to diagnostic services may find it difficult to understand that the time required to treat a single molecular radiotherapy patient may be many multiples of the time needed to read a bone scintigram. Also, requests by nuclear medicine medical staff to attend relevant outpatient clinics may be met by incomprehension and unresolvable cross-division issues concerning resource allocation. The training of radiologists who cover nuclear medicine –radionuclide radiologists – does not normally include molecular radiotherapy. Nuclear medicine physician higher specialist training does include comprehensive training in all aspects of theragnostics and molecular radiotherapy.[50] However, there are still areas of the UK where nuclear medicine trained physicians and radiologists have not been appointed, partly because of the emphasis of most radiology departments on imaging. Health Education England (HEE) has increased the number of additional radiology training posts, allowing those on radiology training schemes to receive an additional 12 months or more nuclear medicine training so they can become 'dual accredited'. This move may help to provide more specialists trained in all aspects of theragnostics.

6.3 Oncology

An alternate 'home' for molecular radiotherapy would be within oncology and while there are many aspects of synergy, the fit between molecular radiotherapy and oncology may not be ideal. The diagnostic aspects of theragnostic molecular radiotherapy is not routinely covered within oncological training. In addition, there are aspects of molecular radiotherapy used in benign conditions such as thyroid disease and joint diseases which do not sit comfortably in oncology. A further issue is that oncology tends to be systems based, with oncologists specialising in a small number of cancer sites such as lung or head and neck. This has some advantages in that the oncologist understands all non-surgical treatment modalities available to treat those cancer sites and their relative merits. However, molecular radiotherapy techniques tend to be more holistic and their use depends more on tumour function than the site of tumour origin. Within the clinical oncology curriculum, the requirement for training in molecular radiotherapy is vague and unless it becomes a special interest of that trainee they may not gain sufficient competence to obtain an ARSAC licence.[39,40,51] A range of potential new molecular radiotherapy agents are entering phase 2 and phase 3 trials involving a wide variety of cancers. This means that training and competence in molecular radiotherapy techniques needs to be rapidly changed from

being seen as a specialist area to a core competency. The profile of molecular radiotherapy remains low within organisations such as The Royal College of Radiologists. There is active and frequent engagement between the Faculty of Clinical Radiology and the diagnostic side of nuclear medicine but such interactions are fewer for therapy with the only formal multi-college link being the Intercollegiate Standing Committee on Nuclear Medicine (ICSCNM).

6.4 The need for a plan

The results of the surveys indicate that provision of molecular radiotherapy services across the UK is patchy and most centres feel they need additional training and resources before the introducing new molecular radiotherapy agents. Therefore, the time when it can be assumed that the required facilities can be provided in some organic way without intervention has passed. A plan is required which needs national direction but local implementation.

6.5 The lessons from the COVID-19 crisis

The UK was ill prepared for the COVID-19 crisis which has engulfed the NHS in 2020 and 2021. However, significant lessons were learnt which could be applied to the provision of a molecular radiotherapy service.

6.5.1 Cooperation works better than competition

Though this would appear to be obvious, for the last two decades the NHS has often run on a spirit of competition with providers vying to provide services. While giving the illusion of efficiency, this often resulted in significant wasted efforts on behalf of both medical staff and managers. The COVID-19 crisis showed that when the NHS works together it can quickly produce changes and that professionals, when cooperating and working in a task- and outcome- orientated fashion, will be able to deliver the required solutions to clinical problems.

6.5.2 Not everyone needs to be physically in the same place

While the administration of molecular radiotherapy treatment will require the presence of a medically qualified clinician who is either the ARSAC licence holder or their trained and competent deputy and the MPE or deputy as well as the required nursing and technical staff, other functions including MDTs can be undertaken remotely allowing the use of expertise from other sites. Likewise, images can be transferred electronically to allow for assessment by imaging experts or dosimetric assessment at another centre.

6.5.3 Facilities do not need to be fixed

During the COVID-19 pandemic, many hospitals used a range of temporary buildings to provide care outside of main hospital buildings to provide safe, COVID-19-free clinical zones. Similar facilities could be used to deal with the immediate need to expand treatment facilities. It may be possible that hospitals/trusts can share a mobile facility or that facilities could be provided by a third party.

6.5.4 Job plans do not need to be inflexible

Over the past 20 years there has been a process of increasing specialisation within medicine which accelerated after the changes introduced in the Modernising Medical

Careers programme.[52] The Royal College of Physicians has recognised that the loss of general medical skills may not have been ideal and has worked with the General Medical Council to enhance general internal medical training and skills. The COVID-19 crisis meant that many specialist medical staff were reassigned to look after sick patients in intensive treatment units (ITUs) and high-dependency units, demonstrating that specialists such as radiologists have good basic clinical skills.

During the pandemic, work plans became more flexible proving that it is possible to build job plans across departments and divisions.

6.5.5. Somebody needs to champion these changes

The COVID-19 pandemic confirmed that both individual staff and hospital management structures can become more flexible. However, there is a clear need for leadership. Within the UK we would recommend that each radiotherapy ODN or nation appoint a clinical oncologist or nuclear medicine physician to be the molecular radiotherapy lead. They will need sufficient managerial time and support to work with hospitals/trusts to ensure appropriate delivery of molecular radiotherapy.

6.5.6 Virtual training

At present, ARSAC requires evidence for training in both the theoretical and practical aspects of both diagnostic and therapeutic radiopharmaceuticals. For diagnostic radiopharmaceuticals this may be achieved by use of remote learning and scan reading. However, currently for therapeutic radiopharmaceuticals it is expected that there will be a period of observation at a site offering treatments as part of training. With COVID-19 restrictions likely to be in place for some time, methods for gaining practical experience with remote access need to be considered with agreements between ARSAC, the commercial companies and training organisations such as the Royal Colleges, BNMS and IPEM on how this can be achieved.

6.6 Overall plan

There is an urgent need for each national government to set out a programme that will direct the equitable provision of molecular radiotherapy across the UK. In England, the delivery of these services should be devolved to the cancer ODNs. NHS England would expect regular reporting from each network, matching the delivery of molecular radiotherapy against the national plan. The devolved nations' health ministries will also take on this role.

6.7 Research

Though the primary role of this report is the delivery of a molecular radiotherapy clinical service, it is vital that the molecular radiotherapy leads for each nation/ODN interact with research-based groups such as the radiotherapy clinical trials group (CTRad) and the National Institute for Healthcare Research (NIHR). This will make the UK an increasingly attractive site for academic and commercial phase 2 and phase 3 molecular radiotherapy trials.

6.8 Children's molecular radiotherapy

This report has not addressed the issue of molecular radiotherapy in children under the age of 18. The task group members are fully aware there is an urgent need for a similar review

of molecular radiotherapy services in children. The task group also recognises that the treatment of children with cancer may need specialist skills and would be best delivered within specialist centres.

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Appendix 1. Survey questions

Molecular radiotherapy questionnaire

1. Which NHS trust/hospital do you work at?
Free-text box

2. Do you work in:

- England
- Scotland
- Wales
- Northern Ireland

2a. If England, in which radiotherapy network do you primarily work?
Free-text box

3. Do you hold an ARSAC certificate for Y-90 SIRT, Radium-223 or Lu-177 DOTATATE?
Yes/No

If yes continue questionnaire at **Q4.**

3a. If no – does anyone hold an ARSAC certificate for Y-90 SIRT, Radium-223 or Lu-177 DOTATATE in your institution?
Yes/No

If no – go to **Q11.**

3b. If yes – please provide their name(s) and email(s) and end questionnaire.

This section concerns the use of selective internal radiotherapy of primary or secondary tumours in the liver using Y-90 SIRtex or Y-90 therapspheres.

4. Do you hold an ARSAC certificate for Y-90 SIRT?
Yes/No

4a. If yes – how many patients did you treat in the last 12 months?
Free-text

4b. Were there patients who you feel should have been treated but you were unable to?
Yes/No

4c. If Yes – what is preventing you from treating more patients at your institution? What was the reasons for this? Please tick ALL that apply.

- Lack of trained staff
- Oncologists unsure of efficacy
- Lack of reimbursement
- At or near disposal limit with Environment Agency licence for that isotope
- Patients who could benefit from this treatment do not live in my area
- We send these patients to another trust/hospital
  - Free-text – where?
- Other reason
  - Free-text box

4d. If no – if there are suitable patients in your area do you refer to another centre?
Yes/No

4e. If yes – where are they treated?
Free-text box

What is travel distance to that site?
Free-text box

What is travel time to that site?
Free-text box

4f. If no – why not?
Free-text box

Would you like to start SIRT treatment at your institution?
Yes/No

If yes – what is preventing you from doing SIRT please tick ALL that apply

- Lack of trained staff
- Oncologists unsure of efficacy
- Lack of reimbursement
- At or near disposal limit with Environment Agency licence for that isotope
- Patients who could benefit from this treatment do not live in my area
- Other reason
  - Free-text box

This section concerns the use of Radium-223 (Xofigo) in the treatment of bone metastases in castrate resistant prostate cancer.

5. Do you hold an ARSAC certificate for Radium-223?
Yes/No

5a. If yes – How many patients did you treat in the last 12 months?
Free-text box

5b. Were there patients who you feel should have been treated but you were unable to?
Yes/No

5c. If yes – what is preventing you from treating more patients at your institution? Please tick ALL that apply.

- Lack of trained staff
- Oncologists unsure of efficacy
- Lack of reimbursement
- At or near disposal limit with Environment Agency licence for that isotope
- Patients who could benefit from this treatment do not live in my area
- We send these patients to another trust/hospital
  - Free-text box– where?
- Other reason
  - Free-text box

5d. If no – if there are suitable patients in your area do you refer to another centre?
Yes/No

5e. If yes – where are they treated?
Free-text box

What is travel distance to that site? ~
Free-text box

What is travel time to that site?
Free-text box

5f. If no – why not?
Free-text box

Would you like to start Radium-223 treatment at your institution?
Yes/No

If yes What is preventing you from giving Radium-223? Please tick ALL that apply.

- Lack of trained staff
- Oncologists unsure of efficacy
- Lack of reimbursement
- At or near disposal limit with Environment Agency licence for that isotope
- Patients who could benefit from this treatment do not live in my area
- Other reason
  - Free-text box

This section concerns the use of Lu-177 DOTATATE (Lutathera) to treat metastatic pancreatic and mid-gut neuroendocrine tumours (NETs).

6.Do you hold an ARSAC certificate for Lu-177 DOTATATE?
Yes/No

6a. If yes – how many patients did you treat in the last 12 months?
Free-text box

Were there patients who you feel should have been treated but you were unable to?
Yes/No

If yes – what is preventing you from treating more patients at your institution? Please tick ALL that apply.

- Lack of trained staff
- Oncologists unsure of efficacy
- Lack of reimbursement
- At or near disposal limit with Environment Agency licence for that isotope
- Patients who could benefit from this treatment do not live in my area
- We send these patients to another trust/hospital
  - Free-text box – where?
- Other reason
  - Free-text box

6b. If No ¬– if there are suitable patients in your area do you refer to another centre?
Yes/No

If yes – where are they treated?
Free-text box

What is travel distance to that site?
Free-text box

What is travel time to that site?
Free-text box

If No – why not?
Free-text box

6c. Would you like to start Lu-177 DOTATATE treatment at your institution?
Yes/No

6d. If yes – what is preventing you from giving Lu-177 DOTATATE? Please tick ALL that apply.

- Lack of trained staff
- Oncologists unsure of efficacy
- Lack of reimbursement
- At or near disposal limit with
- Environment Agency licence for that isotope
- Patients who could benefit from this treatment do not live in my area
- Other reason
  - Free-text box

You may be aware that it is likely that Lu-177 PSMA therapy for hormone resistant metastatic prostate cancer will be available in the next 12–18 months. It is thought likely the demand for treatment could be ten times greater than for Lu-177 DOTATATE or Radium-223.

7. How prepared is your department for this new treatment? Please tick the option that applies to your institution.

- Fully prepared and ready to go
- Some preparations but some additional infrastructure/staff needed
- Not prepared but hope to offer service in the future
- Do not plan to offer this treatment in our centre
-

Appendix 2. Second survey concerning preparedness for PSMA therapy

Short six-question survey concerning your department's readiness for PSMA therapy.

Dear colleague recently you were sent a questionnaire concerning the state of molecular radiotherapy within the UK from the molecular therapy task and finish group set up jointly by the RCP London, the RCR, IPEM and the BNMS. In your answers you stated some interest in providing a PSMA therapy service when that became available. This short survey is to assess your level of readiness. Please complete one survey per trust/hospital. Information may be required from clinical oncology, nuclear medicine/radiology and medical physics. This survey consists of just six questions.

Before we start

- Hospital/trust in which you hope to offer the PSMA therapy service?
- Email address of person completing the form in case of queries.

1. It is expected ARSAC licensing will require any decision to treat to be decided by an MDT. How will this be achieved? Tick one
   - Such an MDT already exists
   - We will need to set up a new MDT or a new section of an existing MDT
   - We do not know how we will comply with this requirement yet
2. Wht type of MDT will make the decision be made to treat with PSMA?
   - A prostate/urological cancer MDT
   - A molecular radiotherapy MDT
   - We do not know yet
3. Who will attend the MDT who makes the decision to treat with PSMA? Please tick all that apply.
   - Patient's treating oncologist
   - An oncologist with specialist knowledge of PSMA therapy
   - ARSAC licence holder (nuclear medicine/radiology)
   - ARSAC licence holder (clinical oncologist)
   - Medical Physics Expert (MPE)
   - Clinical Scientist who is not an MPE
   - Nuclear medicine nurse
   - Oncology clinical nurse specialist.
4. PSMA therapy requires a thera(g)nostic approach using both PSMA imaging and PSMA therapy. What plans do you have for the PSMA imaging? Tick one:
   - We already perform PSMA imaging
   - We plan to commence PSMA imaging using existing staff and facilities
   - Patient will be scanned at another hospital/Trust and we already have an agreement
   - We plan to have the patient scanned at another hospital/Trust but this has not been agreed yet.
   - We do not yet know how we will perform PSMA imaging
5. If scanning with PSMA, which form of PSMA imaging will you perform? Please tick all that apply.

- Ga-68 PSMA
- F-18 PSMA
- Tc-99m PSMA

6. Do you plan on performing post therapy Lu-177 PSMA imaging?
   - No
   - Yes (whole body sweep after every fraction)
   - Yes (whole body sweep after some fractions)
   - Yes (SPECT and or SPECT/CT after every fractions)
   - Yes (SPECT and or SPECT/CT after some fractions)
   - Yes with organ and/or lesion dosimetry
7. ARSAC licensing requires detail of therapy verification with dosimetry. In your centre, which of the following may inhibit your ability to perform dosimetry (select all that apply).
   - Lack of staff to perform dosimetry
   - Lack of experience in performing dosimetry
   - Lack of guidance on how to perform dosimetry
   - Lack of scanner availability for additional dosimetry imaging
   - Lack of software for performing dosimetry
8. Concerning the provision of a PSMA service which we assume will be a primarily out-patient treatment, are there any issues that concern you? Please tick all that apply.
   - There are no issues we can treat patients as soon as it is authorised and reimbursed
   - We do not have the physical facilities needed to treat patients. This may include radiopharmacy space to make the imaging or therapy product, sufficient PET/CT or SPECT/CT capacity or room to give the actual therapy.
   - We do not have Environment Agency authorisation for holding and disposal of Lu-177
   - We are close to our Environment Agency limits for holding and disposal of Lu-177
   - Our present staff will need additional training before we can start PSMA therapy
   - We may need to employ additional staff to deliver PSMA imaging and therapy
   - We are not confident that ARSAC will give us a site certificate for PSMA imaging and/or therapy
   - We are not confident that ARSAC will give the medical staff involved a certificate for PSMA imaging and/or therapy
   - We are not sure what information we need to provide for a business case for delivery of PSMA imaging and/or therapy
   - In addition to those indicated, we have more difficulties as we do not know the expected demand for PSMA imaging and therapy
   - Any other issues (free text box)
   - How do you propose to solve any issues highlighted in this survey? (Free-text box).

Appendix 3. Disclosures of task and finish group members

Dr John Buscombe: Paid consultancy AAA Novartis, Paid lecturer BTG Compatibles, educational grant SIRTex. Unpaid consultancy Health Policy Partnership

Dr Jonathan Gear: Unpaid Chair of the European Association of Nuclear Medicine Dosimetry Committee

Dr Prakash Manoharan: Paid Consultancy and Lecturer, AAA Novartis Dr Shaunak Navilkissoor Paid Consultancy and Lecturer, AAA Novartis Dr Roger Staff. No disclosures

Dr Stefan Vöö: No disclosures

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