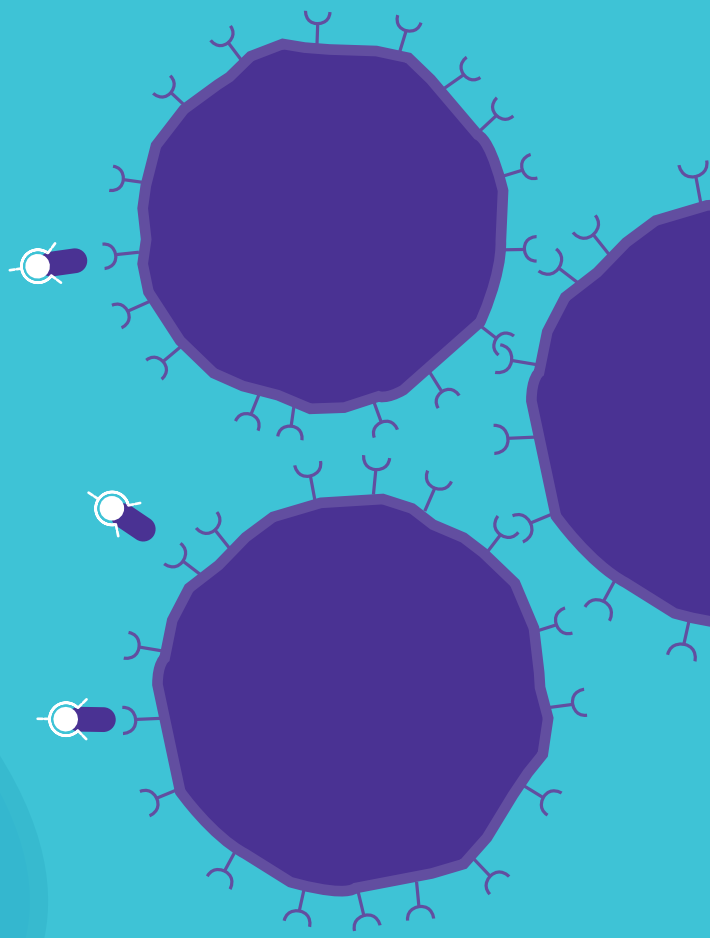
Radioligand therapy

REALISING THE POTENTIAL OF TARGETED CANCER CARE



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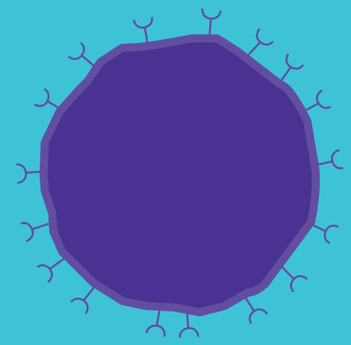
The Health Policy Partnership
[research, people, action]



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With many thanks to our steering committee members:

- Dr Josep Maria Borras, Director, Catalonia Cancer Strategy, Spain
- Dr Jaroslaw Cwikla, Professor, Department of Radiology, University of Warmia and Mazury in Olsztyn, Poland
- Professor Ken Herrmann, Director, Clinic for Nuclear Medicine, University Hospital Essen, Germany
- Nikie Jervis, Specialist Nurse: Patient Support, Information & Education, NET Patient Foundation, UK

Additional thanks to:

- Dr Annibale Versari, Director, Oncology and Advanced Technologies, ASMN Reggio Emilia, Italy
- Dr Harald Lahner, Deputy Director, ENETS Center of Excellence, University Hospital Essen, Germany
- Dr Jamshed Bomanji, Head of Clinical Department, Institute of Nuclear Medicine, University College London Hospital, UK
- Dr John Buscombe, President, British Nuclear Medicine Society, UK
- Dr Valentina Ambrosini, Associate Professor of Nuclear Medicine, University of Bologna, Italy

About this report

This policy report has been drafted by The Health Policy Partnership, an independent research organisation, with input from a multi-stakeholder steering committee. Its aim is to create greater awareness of radioligand therapy as an innovative component of cancer care. The steering committee had full editorial control over content, which reflects consensus among the group. All members provided their time for free. The outputs of this project are intended for educational purposes only and do not relate to any particular product.

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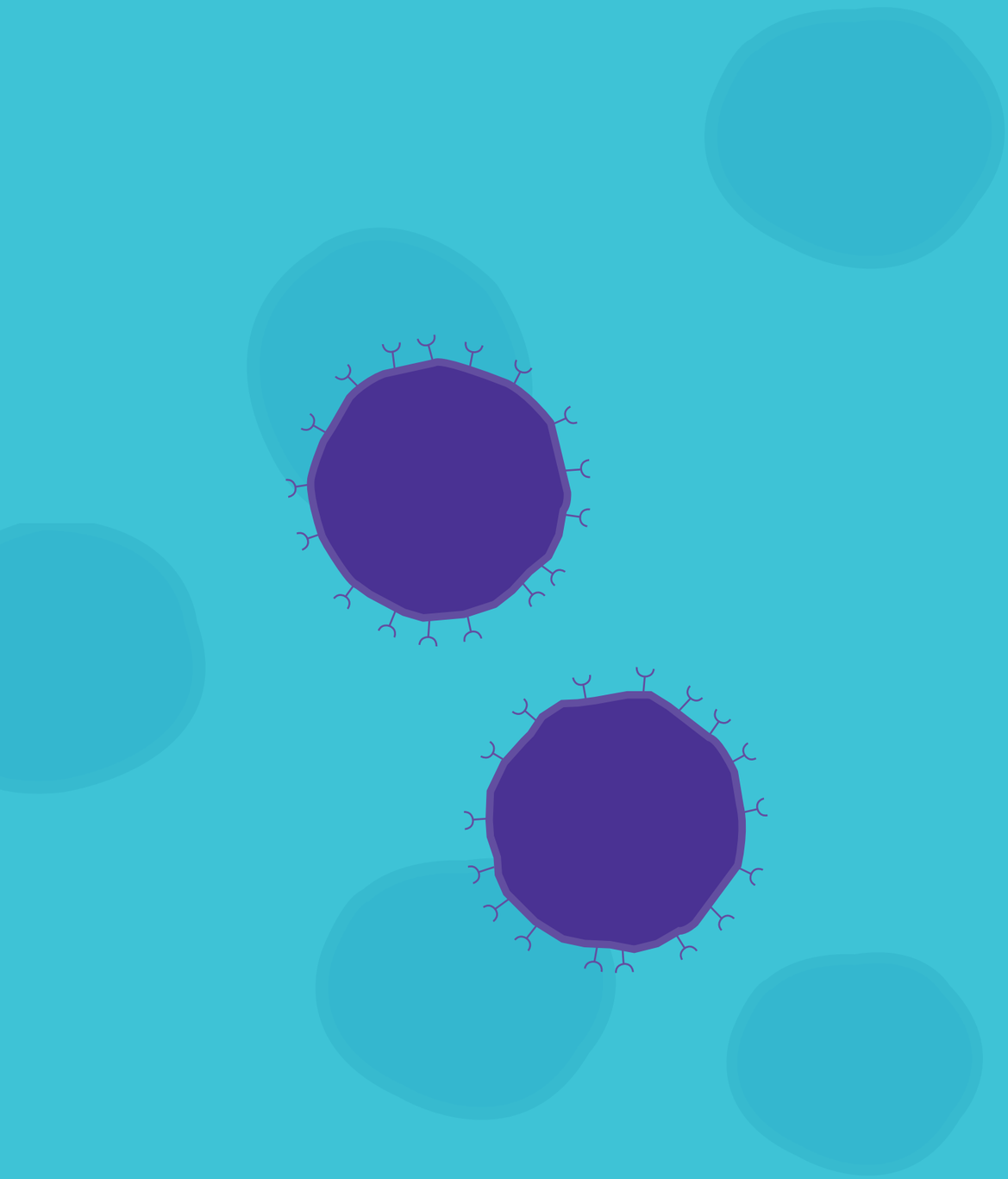


Contents

Glossary

This glossary provides definitions of terms used throughout this report.[1-3]

Biomarker is a naturally occurring molecule or other characteristic by which a particular disease or physiological process can be identified or monitored.

Chemotherapy slows or stops tumour growth with anti-cancer drugs.

Computed tomography (CT) scans use X-rays to create images of the body at different angles. A computer uses these images to develop a 3D image. X-rays are good at imaging bones and tissue changes caused by cancer or other disease.

Gene therapy utilises genes and genetic modification to treat cancer.

Hormone therapy is effective for cancers that use hormones for growth. Therapies either block the body's ability to produce hormones or change how hormones function.

Immunotherapy utilises the immune system in a variety of ways. Approaches include directly attacking the cancer (such as monoclonal antibodies) or supporting the immune system to work against the cancer (such as vaccines, cytokines or interferons).

Ligand is a molecule that selectively binds to a different molecule. Examples are antigens binding to an antibody, or a hormone binding to a receptor on a cell.

Magnetic resonance imaging (MRI) uses magnetic fields and radiofrequency waves to take images of different parts of the body. It is good at imaging soft tissues, particularly the brain.

Metastatic cancer occurs when a cancer has spread to different parts of the body from where it originated.

Neuroendocrine cancers are a group of cancers, sometimes referred to as neuroendocrine neoplasms (NENs) – which includes neuroendocrine tumours (NETs) and neuroendocrine carcinomas (NECs) – that occur in neuroendocrine cells.

Positron-emission tomography (PET) scans use radioactive tracers to produce 3D images of the inside of the body. The scan shows how organs and tissues function, and also can provide evidence of the presence or absence of cancer.

Radioiodine or radioiodine 131 is a radioactive form of iodine that is used to treat thyroid cancer.

Radioisotope is an unstable form of a chemical element that emits radiation as it breaks down to a stable form. Radioisotopes may occur naturally or be made in a laboratory.

Radioligand is a cancer-targeting molecule, or ligand, attached to a radioisotope. By choosing different radioisotopes to attach to the same type of ligand, the process can be tailored to either diagnose or treat certain types of cancer.

Radiotherapy uses internal or external radiation to kill or reduce the size of a tumour. Radiotherapy only affects the tumour and surrounding tissue.

Radiotracer is a radioisotope that emits gamma rays and is used for diagnostic purposes.

Single-photon emission computed tomography (SPECT) combines a CT scan with a radiotracer, showing how blood and other fluids move through the body to organs and tissues. It can be used to investigate metabolism and organ function.

Targeted therapy is a category of cancer treatment that exploits differences between normal and cancerous cells, and includes targeting and killing cancer cells (such as radioligand therapy) and stopping cancer growth (such as tyrosine kinase inhibitors).

Theranostics treats cancer using highly targeted and personalised therapy based on specific diagnostic tests.

Tumour antigen is a substance such as proteins, glycoproteins, glycolipids, or carbohydrates expressed on the surface of tumour cells that elicits an immune response. They may be restricted to tumour cells only, or present on both tumour cells and normal cells.

Tumour board is a meeting of the cancer care team that plans and assesses treatment. It may include medical and radiation oncologists, surgeons, pathologists, nurses and other healthcare professionals. It may also be called a multidisciplinary tumour board.

Executive summary

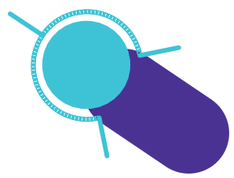
Despite progress in many areas of cancer care, important gaps remain. Many people do not have effective treatment options, particularly for aggressive or rare forms of cancer,[4] and new strategies are needed to improve not just survival, but quality of life.[5] One such emerging treatment modality is called radioligand therapy.

Radioligand therapy delivers radiation directly to select types of cells, and it is gradually emerging as an important component of cancer care. It has been shown to improve overall survival and quality of life for many people with neuroendocrine cancers and castration-resistant prostate cancer that has metastasised to the bone.[5-9] However, it has only recently been introduced into cancer care guidelines for these types of tumours.[10-19]

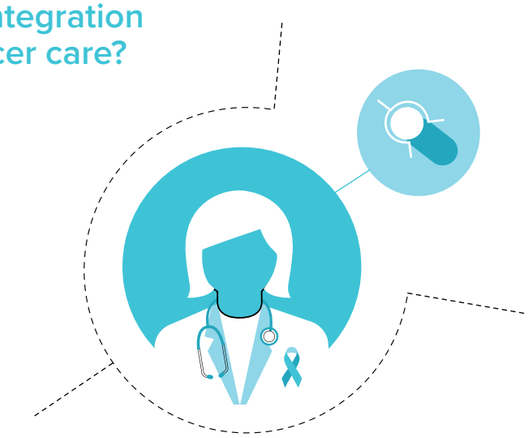
How does radioligand therapy work?

A cancer cell has specific molecules on its surface which may not be present on healthy cells. Radioligand therapy utilises this structural difference to deliver radiation directly to cancer cells, regardless of where they are in the body.[20-22] Radioligands are made of two parts: a ligand, which finds cancer cells that have a particular surface molecule; and a radioisotope, which provides radiation.[20] By choosing different radioisotopes to attach to the same type of ligand, the process can be used to either diagnose or treat certain types of cancer.[20-23] As the radiation works over very short distances and can be directed specifically to cancer cells, the treatment is generally well tolerated with self-limiting side effects.[20 21 24 25]

Radioligand therapy may contribute to ongoing efforts to provide personalised and targeted treatments to cancer patients. It can be targeted to the unique characteristics of the cancer being treated, which may help improve the efficacy of treatment.[23]



What are potential barriers to integration of radioligand therapy into cancer care?



Radioligand therapy is a relatively new treatment approach and its integration into clinical practice will require strengthening and alignment of a number of factors. Many oncologists, radiation oncologists and even some nuclear medicine specialists, who are typically those who prescribe radioligand therapy, may not be fully aware of the many applications of radioligands,[26-28] while patients may have preconceived negative perceptions around the use of radioactive substances.[22 26 29 30]

There are very few healthcare professionals trained in radioligand therapy,[22 27] which restricts use of the approach to a small number of specialist centres[27 28] and may limit their ability to participate in all relevant multidisciplinary care teams and tumour boards.[27 28 31 32]

The regulatory frameworks for radioligands must also evolve to suit this emerging treatment modality. This may affect who provides treatment, and how.[29 33 34] Other policy advances are needed in terms of supply of radioisotopes and nuclear waste; some radioisotopes do not require significant specialist waste collection or storage, while others do,[35] so a ‘one size fits all’ nuclear waste disposal policy is not appropriate.

Finally, the limited availability of representative clinical and economic data on radioligand therapy poses challenges.[26 30 32 36-38] These barriers contribute to variations in availability of radioligand therapy across Europe and must be overcome if this treatment modality is to become available to all people who may benefit from it.

What can decision-makers do to ensure integration of radioligand therapy into cancer care?

There are many actions that can be taken to build radioligand therapy into cancer care plans and encourage its appropriate utilisation in practice. These will require concerted action by decision-makers, nuclear medicine and the broader cancer clinical community, hospital managers, patient organisations, researchers and industry. Actions include:

- **Increase** awareness of radioligand therapy and the role of nuclear medicine among decision-makers, people with cancer and the clinical cancer community.
- **Harmonise** education and training standards across Europe for nuclear medicine specialists and all members of the multidisciplinary cancer team.
- **Ensure** that nuclear medicine specialists have adequate capacity to participate in multidisciplinary cancer care processes.
- **Develop** clear processes and patient pathways for care in each national context.
- **Ensure** adequate hospital capacity and resources for delivery of radioligand therapy to meet current and future demand.
- **Incorporate** radioligand therapy into national, regional and local cancer plans.
- **Establish** clear, consistent regulatory frameworks for the use of radioisotopes spanning approval, funding and reimbursement.
- **Ensure** continued supply and appropriate disposal policies.
- **Invest** in real-world data on radioligand therapy to better understand patient outcomes and cost-effectiveness.
- **Identify and share** best practices to optimise and standardise care.

Introduction

Despite progress in many areas of cancer care, too many people still do not have effective treatment options, particularly those with aggressive or rare forms of cancer.[4] New strategies are needed to improve not just survival, but quality of life.[5] Cancer is the second leading cause of death globally.[39] In Europe there were almost 4.3 million new cases in 2018, and incidence and mortality rates are set to rise significantly in the future.[40]

Our growing understanding of the biology of cancer has led to new opportunities for increasingly precise, targeted and effective treatment.[20] Greater knowledge of the differences between tumour cells and normal cells has allowed the development of treatments that can target tumour cells directly, minimising damage to healthy cells[9] with greater efficacy and less toxicity for patients.

One such example is radioligand therapy, which delivers radiation directly to specific cells. Targeted radiation has existed for decades. For example, radioiodine was first used to treat overactive thyroid glands and subsequently thyroid cancer in the 1940s.[41-44] Because the thyroid absorbs significantly more iodine than any other organ, radioiodine is taken directly to the thyroid and delivers radiation to kill cancerous cells. Radioiodine remains a mainstay of treatment for thyroid cancer today. This principle of targeted radiation has evolved from organ-level precision to cellular-level precision in line with scientific advances; radioligands bind to certain types of cancer cells wherever they are located in the body and can therefore be used for targeted diagnosis and treatment.

Radioligand therapy is currently used in a small number of cancers, but the approach looks promising in other cancer and non-cancer conditions as well. It is frequently used for metastatic neuroendocrine cancers and bone metastases in castration-resistant prostate cancer (mCRPC),[20 33 45] and has been shown to improve overall survival and quality of life for many patients.[5-9] People with these types of cancers typically have limited therapeutic options, and radioligand therapy presents a new opportunity for treatment. Researchers are also exploring how the approach could be utilised in other conditions, but further data are needed to understand its full potential.

The integration of radioligand therapy into clinical practice requires new models of care, potentially more than other new treatment modalities. Because it uses radioactivity delivered into the bloodstream that can reach cells across the whole body, radioligand therapy raises specific issues for patient education, as well as hospital capacity, infrastructure and nuclear waste disposal. Integrating radioligand therapy into clinical practice requires revision of the traditional multidisciplinary team to ensure inclusion of relevant specialists for both diagnostic and therapeutic discussions. These potential barriers must be understood and overcome if this treatment modality is to become available to all people with cancer who may benefit.

This report aims to provide decision-makers around Europe with a grounding in radioligand therapy, offering evidence-based recommendations on how to create an enabling environment for its wider integration into cancer care. Based on a literature review and expert consultation, this report will first explain what radioligand therapy is and how it is used, and then explore some of the challenges and opportunities for decision-makers and other stakeholders to ensure this treatment modality is made available to all patients who need it.

What is radioligand therapy?

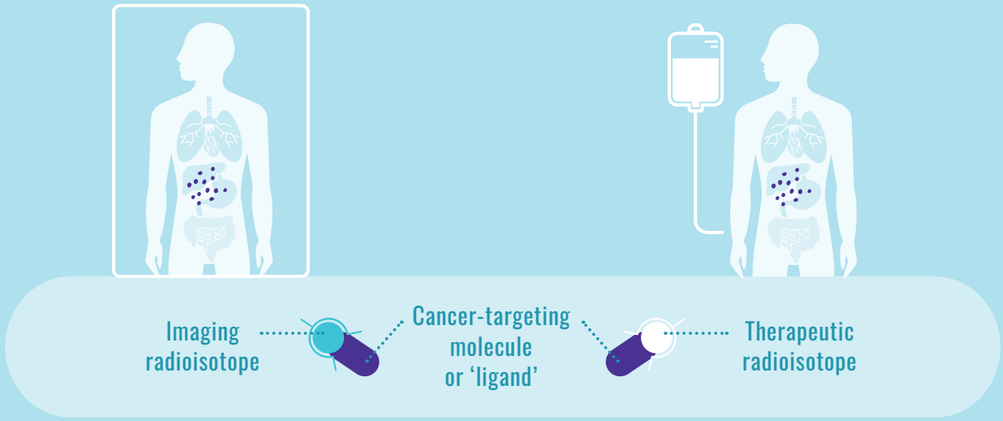
Radioligand therapy is an innovative approach to cancer treatment that delivers radiation directly to select types of cells.

Cancer cells have particular molecules on their surface which may not be present on healthy cells or are over-expressed in cancerous cells. Radioligand therapy utilises this structural difference to deliver treatment. Radioligands are made of two parts: a ligand, which is able to find cancer cells with a particular tumour target, and a radioisotope for treatment (*Figure 1*).[20] The ligand finds cells that present the tumour target and delivers radiation directly to these cancerous cells, regardless of where they are in the body.[20-22] At present, radioligand therapy is typically given to people with metastatic, often progressive cancer who have undergone other types of cancer treatment without success.[9]

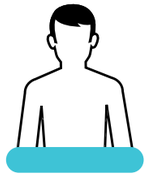
Radioligands can be used for both imaging and treatment.

Different radioisotopes have different properties; some can be used for imaging, others for therapy and some have applications for both.[46] By choosing different radioisotopes to be attached to the same type of ligand, the process can be tailored to either diagnosing or treating certain types of cancer.[20-23] Combining these processes is known as theranostics.[9 47] *Box 1* and *Box 2* outline key aspects of imaging and treatment with radioligands; *Box 3* describes different types of radiation and their properties.

FIGURE 1. Radioligand therapy is an evolution of technology from imaging to therapy



Radioligand therapy may contribute to ongoing efforts to provide increasingly personalised and targeted treatments to cancer patients.



It can be adapted to the unique characteristics of the cancer being treated, for example by choosing different therapeutic radioisotopes, or altering dosing or the number of treatment cycles.[6 22 23 48 49] This can help improve the efficacy of treatment.[23]

BOX 1. **Radioisotopes** can often improve the accuracy of diagnosis

During diagnosis, a person undergoes scans to differentiate between cancerous and non-cancerous tissue. Scans may include positron-emission tomography (PET), computed tomography (CT), single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI).[50]

PET scans use radioisotopes, or radiotracers, that emit gamma radiation to show how the cells in the body function. They can detect processes such as metabolism and blood flow to diagnose different health conditions.[51] To diagnose certain cancers, a ligand is attached to the radioisotope to find cancer cells wherever they are in the body.[51] The resulting images provide a complex view of the cancer, allowing healthcare professionals to diagnose and stage the cancer and see the extent of metastases.[21 51 52]

Improving our understanding of tumour metabolism and cancer biology through imaging may help treat cancers in an increasingly personalised way. In some situations, PET scans can be more sensitive than conventional imaging with CT, SPECT and MRI, and the additional functional information PET provides may help with planning subsequent treatment with greater confidence.[9 53-57] The images may even be used as a biomarker to predict who might benefit from treatment or to monitor treatment response.[58]

BOX 2. **Radioligand therapy** is an emerging treatment modality for metastatic and resistant cancers

Once the cancer has been detected and characterised with a PET scan, a therapeutic radioisotope is attached to the same type of ligand and used to kill the cancer cell by damaging its DNA.[22] As the highly targeted alpha or beta radiation works over short distances, the treatment is generally well tolerated with self-limiting side effects.[20 21 24 25]

The systemic and targeted nature of radioligand therapy provides an opportunity to treat metastatic cancers,[59] which are responsible for up to 90% of cancer-related mortality.[60] They tend to be difficult to treat because tumours are found in multiple locations around the body, so treatment options such as surgery and external beam radiotherapy are less effective.[59]

Radioligand therapy may also be an effective treatment option for cancers that are resistant or unresponsive to other treatment approaches, such as chemotherapy.[61]

BOX 3. **Different radioisotopes** emit radiation with various useful properties

As radioisotopes decay, they give off radiation with different levels of energy that are effective over different distances. It is this energy that is harnessed to either diagnose a cancer or kill cancer cells. There are three types of radiation:[46 62]

- **Alpha** has very high energy and a short range – approximately the width of 1–3 cells.
- **Beta** has a lower energy and longer range.
- **Gamma** has the lowest energy and longest range.

Diagnostics typically use gamma radiation because its longer range allows detection by scanners.[63] Treatment generally utilises alpha and beta radiation because the high energy is emitted over a short range, meaning surrounding cells receive less radiation.[20]

Regardless of radiation type, every radioisotope has a characteristic half-life, which denotes how long the atoms will remain radioactive:[64]

- **A longer half-life** means the radioisotope can be produced in a specialised, central location and subsequently delivered to hospitals and clinics. However, this means that the radioactivity will be detectable for longer.
- **A shorter half-life** means the radioisotopes must be prepared closer to the time and site of treatment.

There are various terms used for radioligand therapy, including peptide-receptor radionuclide therapy (PRRT), systemic radiation therapy, targeted radionuclide therapy, targeted radiotherapy and molecular radiotherapy. Sometimes the ligand is an immune cell, in which case the approach is known as radioimmunotherapy. This report uses the term radioligand therapy.

How do radioligand therapy and nuclear medicine fit in with other treatments?

The history of radioligand therapy provides a strong foundation for the modern cohort of therapies that are beginning to enter into clinical practice. As mentioned previously, the use of radioiodine to treat people with thyroid cancer is well established;[42-44] this approach has inspired wider applications of radioligands for imaging and therapy.

Radioligands are gradually emerging as an important component of cancer care. However, their use as a therapy has recently been introduced into cancer care guidelines for NETs[10-14] and mCRPC[15-19] (*Figure 2*). The approach is also currently being explored both as a standalone treatment approach and in combination with other treatment modalities:

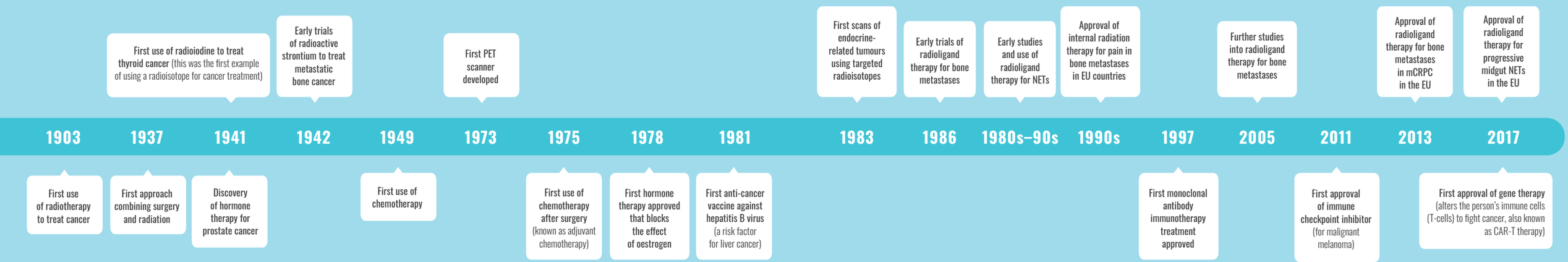
- Combining different radioisotopes with the same type of ligand could be extremely beneficial. Radioisotopes with varying ranges could potentially treat both small and large tumours at the same time and may improve survival.[65 66]
- Using radioligand therapy in conjunction with other therapies, for example radiotherapy, chemotherapy or certain targeted therapies, may be a promising way to enhance efficacy of both treatments,[7 22] especially for aggressive cancers.

Appropriate integration of radioligand therapy into clinical cancer care will require close collaboration and clear workflows across numerous specialists and disciplines involved in cancer care.[22 29 34 35] A multidisciplinary team includes healthcare professionals specialising in different disciplines. In cancer care this can include oncologists, radiation oncologists, surgeons, nuclear medicine physicians and other oncology and non-oncology specialties such as urology or endocrinology. Despite the fact that radioligand therapy is typically administered by nuclear medicine specialists, the specialism does not always play an active role in multidisciplinary cancer care teams or therapeutic tumour boards. Through its applications to both diagnostics and therapy, nuclear medicine will have a growing role in cancer care,[67] and the greater integration of radioligand therapy into clinical cancer care requires far more emphasis on multidisciplinary working. Such an approach is particularly important as radioligand therapy is unlikely to become the sole therapeutic approach for people with cancer.[30]

The newest applications of radioligands focus on NETs and bone metastases in mCRPC, with research ongoing in many other conditions. *Appendices i–iii* highlight how the approach is used in these different diseases.

To integrate radioligand approaches in cancer care, there are many potential challenges that need to be addressed. The next sections outline some of these barriers and potential solutions.

FIGURE 2. Timeline of major advances in radioligand therapy and cancer care[41 42 68-81]



What are the barriers to integration of radioligand therapy into cancer care?

Radioligand therapy as a modality has developed rapidly in recent years but its integration into clinical practice will require a number of factors to align, including: greater understanding and awareness among patients and healthcare professionals; coordination and collaboration between medical oncologists, nuclear medicine physicians and other specialties involved in delivering cancer care; hospital capacity planning – both physical and human resources – to deliver radioligand therapy safely and effectively; and effective nuclear waste disposal protocols tailored to the different types of therapy.[34 35 82]

Understanding of radioligand therapy

Limited understanding of radioligand therapy among healthcare professionals may lead to fewer referrals of eligible patients.

Many oncologists, radiation oncologists, and even some nuclear medicine specialists may not be fully aware of the many applications of radioligands.[26-28] Referring clinicians may also be concerned about potential side effects of radioligand therapy, may prefer other approaches with which they are more familiar, or may fear losing their patients to the care of other specialists and hospitals.[22 26 32 36]

Patients, too, may not fully understand what radioligand therapy is and have preconceived negative perceptions around its use of radioactive substances.[22 26 29 30]

Despite nuclear medicine approaches being generally safe and well tolerated, negative perceptions may make people wary of their use. Furthermore, people may confuse radioligand therapy with radiotherapy, not fully understanding what the approach involves.[30] More time and educational materials are needed to properly explain to patients what radioligand therapy is and describe its relative risks and benefits.[30 36]

Professional capacity, training and workforce planning

Professional training is an important area for development.

There are very few healthcare personnel appropriately trained in radioligand therapy,[22 27] which restricts use of this approach to a small number of specialist centres.[27 28] Educating the multidisciplinary team on radioligand therapy is also important; however, there seem to be few consistent educational initiatives appropriate to the whole cancer care team. Furthermore, as radioligand therapy and the discipline of nuclear medicine continue to evolve, education must be updated.[30] The existing cohort of trained and experienced personnel needs to grow, especially if new types of radioligand therapy are approved and their clinical use increases. Limited numbers of specialists, and healthcare professionals more broadly, could become a significant barrier to care in the future.

Limited capacity and resources may restrict multidisciplinary working and integration of radioligand therapy into clinical practice.

The lack of consistent processes and resources for multidisciplinary working in hospital settings can limit implementation of multidisciplinary teams in cancer care.[31 38] There can be confusion as to the roles and responsibilities of different members of the multidisciplinary team[29 83] or how to include nuclear medicine specialists in tumour boards in non-specialist hospitals. In addition, new processes around radioligand therapy may be disruptive to current cancer care pathways, which may be a barrier in itself.[22] In some hospitals, the limited number of nuclear medicine specialists may simply mean there is not enough capacity for them to participate in every multidisciplinary tumour board.[27 28 31 32] These workforce issues may compound the gaps in training described above.[36]

Models of care

Providing radioligand therapy requires intensive planning with clear workflows and processes.[22 27 34 35] However, a lack of harmonised, up-to-date guidelines and standardised treatment protocols is a challenge to providing consistent care in line with the latest scientific advances.[84 85] Furthermore, different countries and even different hospitals often have disparate ways of organising the delivery of radioligand therapy and composition of multidisciplinary teams.[26 36 38 49] For example, the nuclear medicine physician is a core member of the multidisciplinary team in accredited centres for neuroendocrine tumours,[32] but protocols and patient pathways for delivering treatment vary considerably between different centres.[36]

Physical capacity and resourcing

Healthcare systems may not be adequately prepared for greater utilisation and integration of radioligand therapy. There are significant geographical variations in access to care, as centres that provide radioligand therapy tend to be concentrated in a small number of metropolitan areas or in certain regions.[27 28 38] As a result, people often travel significant distances, and even across countries, for treatment.[22] The approach is frequently provided as an inpatient procedure, which may require isolation of patients in lead-lined rooms. As the number of people eligible for radioligand therapy grows and demand increases, existing treatment centres may not have sufficient capacity to provide inpatient care. For example, there may be additional requirements for equipment or storage facilities for contaminated materials.[26 36] Such resource challenges may cause delays in making the approach accessible to patients.

Ensuring a consistent supply of radioisotopes can also be challenging. Most medical radioisotopes are created in a small number of nuclear reactors, which are becoming increasingly unreliable due to old age.[86-88] Reactors frequently shut for planned or unplanned maintenance, and there can be additional logistical difficulties in post-production processing and distribution to hospitals.[86-89] Such unpredictability in the global supply chain has directly impacted availability of diagnostic tests and medical procedures involving certain radioisotopes.[86 88] International, European and national decision-makers have been working to improve the reliability of medical radioisotope supply, but as demand for all types of radioisotopes continues to grow, sustained efforts are needed to secure their supply and delivery.[87-91]

Evolving legislation and policy

Given the recent introduction of radioligand therapy into cancer care, the regulatory and reimbursement frameworks used for it are not always clear or appropriate, and may need adapting. Radioligand therapy approaches are initially used in the context of research and clinical trials, and therefore under national legislation on use of experimental therapies.[49] Wider clinical use requires approval by the European Medicines Agency, and subsequent approval and reimbursement in each member state. However, both international and national regulatory frameworks developed for conventional medicines may need to be adapted to be appropriate for the evaluation of radioligand therapy and radioisotopes.[92] This is not unique to radioligand therapy, as the value frameworks embedded into health technology assessment and reimbursement processes may also require modification to be suitable for other non-medicinal approaches such as radiotherapy and surgery.[93]

Regulatory frameworks do not fully account for differences between radioisotopes. For example, regulatory evaluation processes may be particularly unsuitable for radioisotopes with a short half-life. Such rigid frameworks can therefore restrict the use of certain types of radioligand therapy or affect who provides treatment, and how.[29 33 34]

The categorisation and regulatory frameworks for approval of theranostics also need to evolve. Theranostics presents a crossover between diagnosis and treatment.[94] In some countries, the evaluation and approval process for radioligand imaging is different to that for radioligand therapy,[30 38] impeding use of theranostics and leading to variations in availability to patients.

Waste disposal policies also require careful planning, as different radioisotopes require different processes.[35] Although some radioisotopes do not require significant specialised waste collection or storage, these processes may be required in other cases – and a ‘one size fits all’ nuclear waste disposal policy is therefore not appropriate. As demand increases, there may be additional pressures on such processes.[26 36]

Data and research

The limited availability of representative clinical data on radioligand therapy also poses a challenge.[26 32 36-38 49] For example, analysis of existing clinical trial data may be hindered by the heterogeneity of patient groups with advanced cancer[9] and the retrospective nature of the data.[49] In the field of neuroendocrine tumours, the low number of people affected presents an additional barrier.[37] A further challenge is the absence of a clear or consistent understanding of what constitutes a response to radioligand therapy.[9 20 49 95] The absence of economic data on radioligand therapy may also pose a barrier for funding and reimbursement within healthcare systems;[26 30 36 38] hospitals may want data on budget impact before agreeing to fund radioligand therapy.[26]

These data challenges contribute to significant variability in availability of radioligand therapy across Europe.[20 22] As the use of radioligand therapy increases in cancer care there will be more real-world data reflecting longer-term experiences of patients.[36] This information will be important to support greater understanding of radioligand therapy's impact on patient outcomes and resource use, and guide future use.

Conclusions and recommendations

Radioligands are an innovation driven by our increasing understanding of the molecular biology of cancer and the role of radiation in cancer care. The use of radioligands for diagnostics is well established, with PET scanners being a mainstay in imaging departments across Europe. For people undergoing radioligand therapy, there are proven improvements in survival and quality of life.

Radioligand therapy is gradually becoming an important component of care for certain types of cancer. To ensure it can be appropriately embedded into cancer care and made available to patients – now and in the future – cancer plans and multidisciplinary teams must integrate and increase the visibility of nuclear medicine within cancer care, and work to ensure that radioligand therapy is included in appropriate cancer care processes.[30 34 35 82] A shift towards integrated multidisciplinary working and re-evaluation of discrete, independent health specialties is essential – not just for radioligand therapy but for all cancer treatment.

Efforts to strengthen integration and expand the use of radioligand therapy will require concerted action. The inclusion of radioligand therapy in future cancer plans and cancer-related policies will be essential, as well as proactively addressing hospital capacity issues to enable the provision of safe, high-quality care. While this therapy may be best delivered by centres of excellence, health system planning must ensure that such centres are reasonably distributed in order to minimise geographical inequities in care. European-level efforts may also help mitigate some of the existing challenges for radioligand therapy, particularly in terms of setting frameworks and guidelines for multidisciplinary working, care pathways and training standards. The EU also has an important role to play in fostering exchange of best practice and investing in research to address existing data gaps, securing supply of radioisotopes and clarifying regulatory issues.

Policy recommendations

We call on decision-makers at the European and national levels to integrate radioligand therapy as a potential treatment option into all cancer plans and relevant health policy frameworks.

There are 10 key actions that can be taken to overcome barriers to greater integration of radioligand therapy in clinical cancer care. These will require concerted action by multiple stakeholders including decision-makers, nuclear medicine and the broader cancer clinical community, hospital managers, patient organisations, researchers and industry.

Low awareness and understanding

ACTION NEEDED

- Increase awareness of radioligand therapy and the role of nuclear medicine among decision-makers, people with cancer and the clinical cancer community

Limited professional capacity, training and workforce planning

ACTION NEEDED

- Harmonise education and training standards across Europe for nuclear medicine specialists and all members of the multidisciplinary cancer team
- Ensure that nuclear medicine specialists have adequate capacity to participate in multidisciplinary cancer care processes

Unclear models of care

ACTION NEEDED

- Develop clear processes and patient pathways for care in each national context

Inadequate physical capacity and resourcing in hospitals

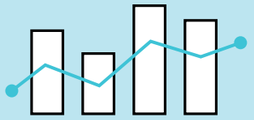
ACTION NEEDED

- Ensure adequate hospital capacity and resources for delivery of radioligand therapy to meet current and future demand

Evolving legislation, regulation and policy

ACTION NEEDED

- Incorporate radioligand therapy into national, regional and local cancer plans
- Establish clear, consistent regulatory frameworks for the use of radioisotopes spanning approval, funding and reimbursement
- Ensure continued supply and appropriate disposal policies



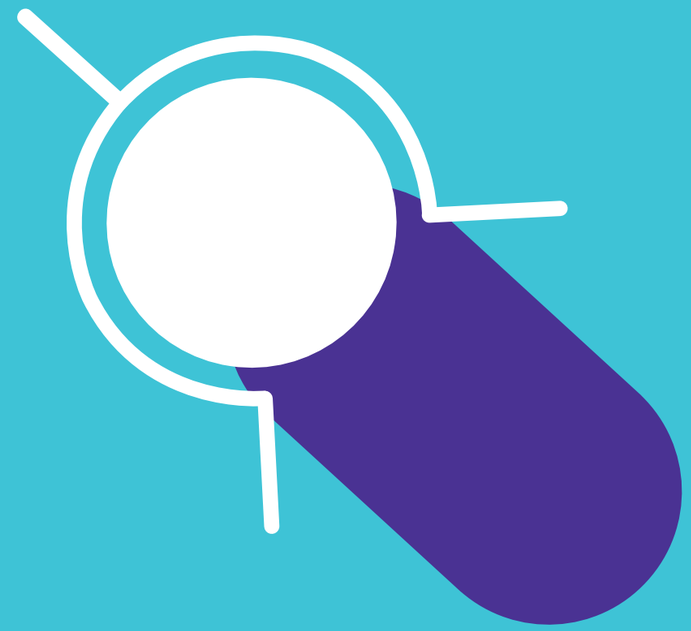
Lack of data and research

ACTION NEEDED

- Invest in real-world data on radioligand therapy to better understand patient outcomes and cost-effectiveness
- Identify and share best practices to optimise and standardise care

The mechanism of radioligand therapy suggests it may have wide applications and could become an important pillar of treatment for many types of cancers and other diseases. Further research and enhanced real-world data collection will help efforts to identify opportunities to use this highly personalised branch of medicine, as well as optimising current delivery.

Cancer is the second most frequent cause of mortality and morbidity in Europe, and it is expected that the burden of disease will continue to grow in the coming years. As our understanding of this complex and diverse group of diseases grows, it becomes increasingly clear that we must have a broad range of tools that are adaptable and can be personalised. Current cancer care often fails to meet the needs of people with rare, resistant or metastasised forms of cancer. Radioligand therapy may help to address this gap and provide life-enhancing treatment for people with limited therapeutic options, playing an important role in realising the potential of personalised, targeted healthcare. It is up to decision-makers to act now to ensure that every person with cancer receives appropriate and adaptable care as soon as they need it.



Appendix i. **Radioligand therapy for neuroendocrine cancers**

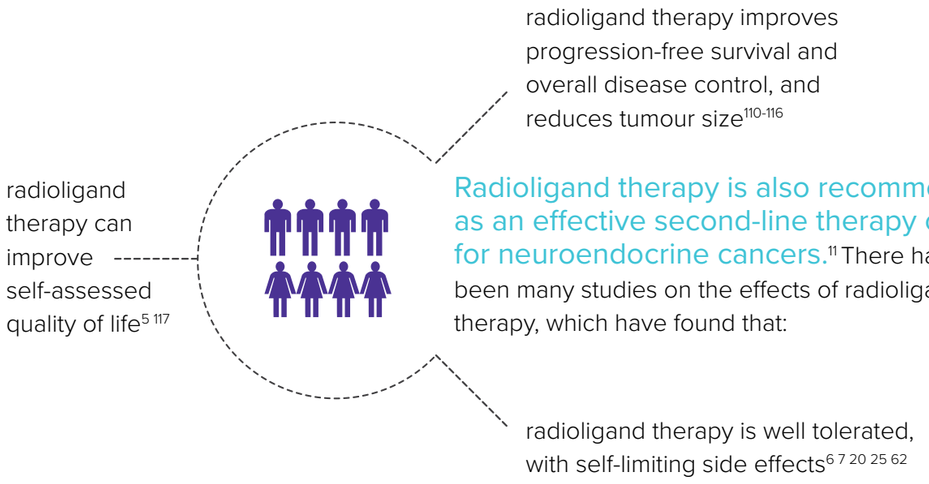
Neuroendocrine cancers are a diverse group of cancers affecting cells that produce and release hormones, frequently occurring in the gastrointestinal tract, pancreas and lungs, among other locations.[7 20 25 62 96] Neuroendocrine cancers, also known as neuroendocrine neoplasms (NENs), include both neuroendocrine tumours (NETs) and neuroendocrine carcinomas (NECs). These cancers differ depending on their site of origin. The majority of people are diagnosed with advanced metastatic cancer, for which the five-year survival rate is less than 50%.[7] However, some neuroendocrine cancers may be extremely slow to develop.[25 97 98] As these are rare cancers,[25 96] collecting epidemiological or clinical data across small populations can be extremely challenging.[22 25] However, the incidence is growing rapidly and they are gradually becoming less rare.[99-101]

The variability and rarity of neuroendocrine cancers present challenges in diagnosis and management. Many people remain asymptomatic for a long time and symptoms can be nonspecific, impeding referral and diagnostic pathways.[102-104] Furthermore, the rarity of these cancers means that healthcare professionals may have limited experience in recognising them.[31 32 36 37] As a result, the average time to diagnosis from symptom onset is more than four years,[102 104] and incorrect diagnoses are common.

It is difficult to run clinical trials in neuroendocrine cancers due to their rarity.[31] The impact of this may be mitigated through international collaborative research efforts such as those led by the European Neuroendocrine Tumor Society (ENETS) and European Reference Networks, which also offer opportunities for collection of real-world data across multiple countries.

Therapeutic options can be limited for many people with neuroendocrine cancers. The diversity of these cancers necessitates a variety of therapeutic approaches,[22 25] including surgery, targeted therapy, chemotherapy, interventional radiotherapy, hormone therapy, immunotherapy and radioligand therapy.[10 11 96 105-108] Not every person will be eligible for all treatment approaches; where possible, combinations of approaches are commonly used to optimise outcomes. For people with metastatic neuroendocrine cancers, surgery may not be a curative option, leaving them with extremely limited therapeutic options.[5 25]

Radioligands are becoming well established in the diagnosis and management of neuroendocrine cancers. The past 15 years have seen increasing uptake of radioligand therapy and official integration into care pathways and guidelines.[25] A PET/CT using radiotracers is now seen as the 'gold standard' in imaging for neuroendocrine cancers,[103] and is increasingly common across Europe.[109]



Radioligand therapy is also recommended as an effective second-line therapy option for neuroendocrine cancers.[11] There have been many studies on the effects of radioligand therapy, which have found that:

To expand and optimise the use of radioligands for neuroendocrine cancers, more research is needed. A number of guidelines for radioligand therapy exist but, as experience and evidence grow, these will need to be updated and consensus-driven standardised therapeutic protocols developed.[7 22 49 62] More evidence is needed to verify the impact of radioligand therapy through prospective randomised controlled trials.[85] Specific areas requiring further research and data include response predictors, effectiveness in different sites of disease or rates of growth, opportunities to utilise alpha-emitting radiation, and the combination of radioligand therapy with other approaches.[6 36 62 96]

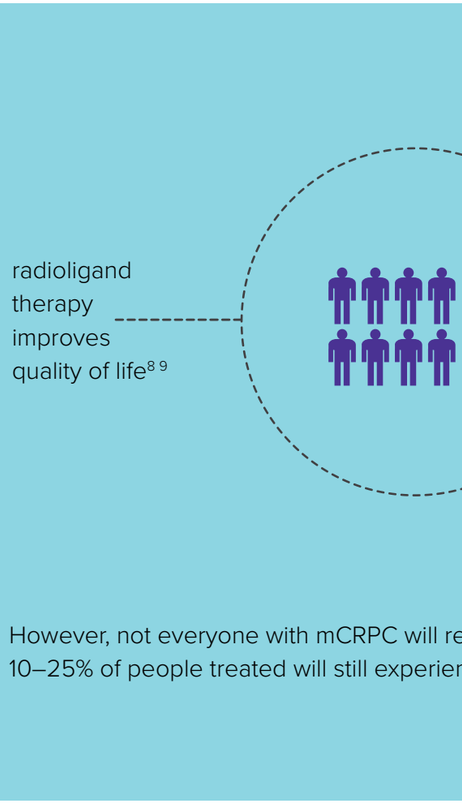
Appendix ii. **Radioligand therapy for metastatic castration-resistant prostate cancer**

Prostate cancer is the most commonly diagnosed cancer among men in Europe.[118] More than 1.5 million men live with the condition.[119] Recent years have seen a rapid increase in detection rates due to screening initiatives and awareness-raising efforts.[118] Despite this, prostate cancer remains the third most frequent cause of cancer mortality in men.[118]

mCRPC is a type of prostate cancer that does not need hormones to grow and so does not respond to hormone therapies. It frequently metastasises to bone, organs and soft tissue.[8 29] Bone metastases are particularly difficult to treat and can reduce mobility, quality of life and overall survival, and increase treatment costs.[8 29 120] It is estimated that in the UK there are 40,000 new cases of mCRPC each year, and the incidence of this type of cancer is increasing.[121]

Treatments for mCRPC are increasingly varied, requiring expert input. Options include chemotherapy, immunotherapy, external beam radiotherapy and radioligand therapy.[8 29] Clinical presentation of mCRPC can be so diverse that, despite the existence of clinical guidelines, it is not always clear which treatment options are most appropriate for each individual.[29]

Most people with prostate cancer receive radioligand therapy only after other treatments have been unsuccessful. Radioligand therapy is usually given to people with mCRPC and bone metastases under palliative conditions once other treatments, such as chemotherapy and other approaches, have failed.[9] However, more research is needed to understand the potential benefit of using radioligand therapy earlier in the treatment course for people with mCRPC and bone metastases.[29] To achieve this, we need further prospective data to better understand the impact and role of radioligand therapy in mCRPC,[9 33 48] as well as randomised head-to-head trials against other treatment options.[48]



However, not everyone with mCRPC will respond to radioligand therapy: it is estimated that 10–25% of people treated will still experience disease progression.[123]

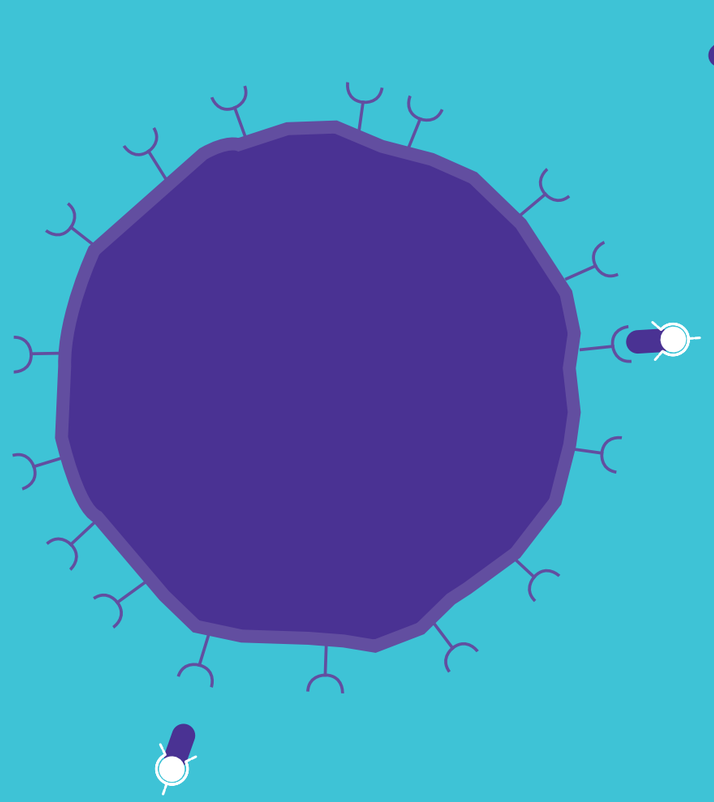
As experience grows of using radioligand therapy in prostate cancer, new care models and protocols will need to be developed. Urologists' and oncologists' awareness or experience of nuclear medicine approaches may be limited, hindering referrals or multidisciplinary working. Therefore, as radioligand therapy becomes more common in mCRPC, additional awareness-raising and multidisciplinary care models may be needed.[22 34]

Appendix iii. The potential of radioligand therapy in other disease types

Extensive research is underway to investigate the possible application of radioligands in a number of cancer and non-cancer conditions. *Table 1* outlines just some of the conditions under investigation.

TABLE 1. Conditions currently under investigation for use of radioligand imaging or therapy

CONDITION	DESCRIPTION
Lymphoma and non-Hodgkin's lymphoma[22 124]	A cancer that begins in lymphocytes, an immune system cell found in lymph nodes, bone marrow and other locations[125]
Breast cancer[126 127]	A cancer of the cells in the breast, typically in milk-producing glands or ducts[126]
Melanoma[33]	A type of skin cancer in cells called melanocytes[129]
Multiple myeloma[130]	A cancer that develops in bone marrow plasma cells[131]
Lung cancer and neuroendocrine cancers in the lungs[126]	A cancer in the lungs or airways[132]
Pancreatic cancer[133]	A cancer in the pancreas (a gland in the digestive system)[134]
Atherosclerosis[23]	A build-up of fat and other material inside arteries, which typically manifest as ischaemic heart disease, ischaemic stroke and peripheral artery disease[135]



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FOR MORE INFORMATION, PLEASE CONTACT

Christine Merkel at The Health Policy Partnership:
christine.merkel@hpolicy.com

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