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Review

The applications of radioisotopes in modern medicine: a review of diagnostic, therapeutic, and research advancements

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ABSTRACT

This review explores the vital role of radioisotopes in contemporary healthcare. Radioisotopes, atoms with unstable nuclei emitting ionizing radiation, have become invaluable tools in modern medicine. Their unique properties allow for diagnosing and treating a wide range of diseases, revolutionizing healthcare and improving patient outcomes. This review explores the most commonly used radioisotopes, their characteristics, and their diverse applications in the diagnosis and treatment of different medical cases, highlighting the diagnostic techniques such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) that have since revolutionized imaging by enabling detailed visualization of metabolic activities and anatomical structures. Furthermore, it highlights the therapeutic application of targeted radionuclide therapy (TRT), which leverages the precision of radioisotopes to deliver radiation directly to diseased cells, minimizing damage to healthy tissues. Finally, the challenges facing the use of radioisotopes are explored, along with the need for continued innovation and research to fully realize the potential of radioisotopes in healthcare.

Keywords: Radioisotopes, Positron emission tomography, Single-photon emission computed tomography, Targeted radionuclide therapy, molecular imaging.

1-Introduction

Radioisotopes are unstable atoms with nuclei that emit radiation, which have revolutionized medicine. Initially known for their destructive potential, these radioactive elements have been crucial in diagnosis, treatment, and research, leading to improved patient outcomes and a deeper understanding of human health. The first medical application of radioisotopes came in 1938 with the use of iodine-131 to diagnose thyroid function. This pioneering discovery paved the way for various diagnostic techniques, including positron emission tomography (pet) and single-photon emission computed tomography (spect), which utilize radioisotopes to visualize organ and tissue's metabolic activity and structure. Radioisotopes offer several advantages over traditional imaging techniques. Their ability to be incorporated into specific molecules allows them to target specific organs and tissues, providing detailed information about their function and potential abnormalities. This information is invaluable in diagnosing various diseases, including cancer, heart disease, neurological disorders, and infectious diseases (fassbender, 2020). Beyond diagnosis, radioisotopes also play a critical role in disease treatment. Targeted radionuclide therapy uses radioisotopes to deliver radiation directly to diseased cells, minimizing damage to surrounding healthy tissue. This approach has proven effective in treating various cancers, including thyroid, lymphoma, and prostate. Radioisotopes are also essential tools in medical research. Scientists use them to track biological processes, understand disease progression, and develop new drugs and treatment strategies. Their potential to shed light on the complex disease mechanisms holds significant promise for future medical advancements. While the benefits of radioisotopes in medicine are undeniable, there are challenges to consider. Exposure to radiation, even in small doses, carries potential risks. Therefore, carefully selecting radioisotopes, precise dosing, and strict safety protocols are essential to minimizing these risks. Additionally, the production and transport of certain radioisotopes can be complex and costly, limiting their accessibility in some regions (de lima, 1998).

1.1. definition and characteristics of radioisotopes

Radiopharmaceuticals, also known as radioisotopes, are drugs composed of two key components: pharmaceutical carriers and radioactive isotopes (özgenç et al., 2021). Radioactive isotopes undergo decay, emitting various forms of radiation, including alpha, beta, and gamma rays. This decay process ultimately leads to the stabilization of the isotope's nucleus. A crucial aspect of radiopharmaceuticals is their half-life, representing the time it takes for half of the radioactive atoms within a sample to decay. This characteristic is vital in determining a specific radioisotope's suitability for diagnostic and therapeutic medical applications (radioisotopes and their biomedical applications | enhanced reader, n.d.-a).

1.2. Types of radioisotopes used in medicine

Radioisotopes constitute a potent armamentarium in contemporary medical practice. Over 100 unique isotopes, each possessing distinctive decay characteristics, facilitate diverse diagnostic and therapeutic procedures. Technetium-99m (99mtc) reigns supreme in nuclear medicine, dominating approximately 80% of all procedures. Iodine-131 (131i) is crucial in diagnosis and therapy, notably in thyroid-related conditions. Fluorine-18 (18f) fuels positron emission tomography (PET) scans, enabling visualization of metabolic processes. Iodine-123 (123i) offers a shorter-lived alternative to 131i, which is particularly advantageous for pediatric imaging. Gallium-67 (67ga) is key in infection and inflammation imaging, guiding diagnosis and treatment management. This selection merely highlights the vast potential of radioisotopes in modern medicine, with each isotope offering unique properties to advance diagnosis, therapy, and research across diverse medical specialties (alsharef et al., 2020).

1.3. Properties that make radioisotopes suitable for medical applications

Radionuclides, unstable atomic nuclei with excess energy, undergo radio-decay, converting to stable nuclei while emitting radiation (β-, γ-, or α-particles). This process, characterized by a specific "half-life" (t1/2), allows diverse biomedical applications, including cancer and tumor treatment: targeted radiation therapy. Imaging: for visualizing physiological processes and anatomical structures. Biochemical tests: quantifying biomolecules and their interactions. Biological labeling: tracking molecules in biological systems. Sterilization: eliminating microorganisms from medical equipment and materials. Clinical diagnostics: diagnosing various diseases using radiolabeled tracers. Radioactive dating: determining the age of geological and archaeological objects. Thus, radionuclides offer a powerful toolset in biomedicine with diverse applications (radioisotopes and their biomedical applications | enhanced reader, n.d.-b).

1.4. Historical evolution of radioisotope usage in medicine

Radiopharmaceuticals, pharmaceutical formulations incorporating radioisotopes for diagnosis or therapy, emerged alongside the discovery of radioactivity. While early attempts at therapeutic radiotracer applications existed, their practical realization awaited advancements. Cyclotrons paved the way, enabling particle acceleration and radioisotope production, followed by nuclear reactors offering higher yields. Radioiodine (iodine-131), employed in 1946 for treating thyroid cancer, remains the gold standard for both hyperthyroidism and thyroid cancer management. Initially, reactors primarily served to produce radioisotopes, highlighting the significance of medical applications. Today, research reactors remain crucial for generating radioisotopes for medical and industrial needs, with molybdenum-99 (for technetium-99m production), iodine-131, phosphorus-32, and other isotopes playing pivotal roles in medical diagnostics and therapy (iaea safety standards for protecting people and the environment radiation protection and safety of radiation sources international basic safety standards 2011 edition general safety requirements part 3 no. Gsr part 3, 2011).

2 . Diagnostic imaging with radioisotopes

2.1. Role of radioisotopes in diagnostic nuclear medicine

Radioisotopes exhibit diverse properties that have been harnessed for clinical applications. Specific gamma-emitting radionuclides are utilized in diagnostic nuclear medicine due to their high penetrability into tissues. This facilitates visualization of dynamic physiological and biochemical processes within complex, interconnected living systems. This approach allows for non-invasive evaluation of organ function and identification of pathological changes, providing valuable insights into disease progression and treatment response (saji, 2015).

2.2. Commonly used diagnostic radiopharmaceuticals

This study investigates the multifaceted applications of various radiopharmaceuticals in clinical diagnosis. Technetium-99m is crucial in identifying cardiac amyloidosis, while 51-chromium aids in diagnosing pernicious anemia. Additionally, fluorine-18 facilitates evaluating metabolic changes in glucose within the brain and cancerous tissues through positron emission tomography. Holmium-166 proves valuable in diagnosing liver cancer, while iodine-125 is a critical tool for assessing glomerular filtration rate. These findings highlight radiopharmaceuticals' diverse and impactful roles in modern diagnostics (alsharef et al., 2020).

2.3. Imaging techniques

Positron emission tomography (pet) and single-photon emission computed tomography (spect) are nuclear medicine techniques utilizing radiotracers to investigate various physiological and pathological processes. Pet employs positron-emitting tracers, enabling functional imaging of metabolic processes, blood flow, chemical absorption, and regional composition. Spect utilizes gamma-emitting tracers, allowing diagnosis of infections, strokes, seizures, and bone diseases by measuring blood flow and radiotracer distribution within tissues and organs (crişan et al., 2022).

2.4. Advances in molecular imaging with radioisotopes

In vivo, molecular imaging enables non-invasive visualization and quantification of biological processes at the molecular and cellular levels. This review highlights probes emitting radiation, fluorescence, bioluminescence, and NMR signals for visualizing processes like protein interactions and gene expression. Due to its deep tissue penetration, radiation offers the most sensitive and quantitative signal. Consequently, nuclear medical molecular imaging, employing tracers like 198au, 186re, 192ir, 117msn, and 99mo/99mtc, has found widespread applications in preclinical research (e.g., Alzheimer's disease) and clinical diagnosis (konefał et al., 2022; Ueda, 2021).

3. Radioisotopes in nuclear cardiology

3.1. Myocardial perfusion imaging with technetium-99m

Technetium-99m (tc-99m) is the best radioisotope for cardiac perfusion tracers because it has good nuclear properties and a wide range of coordination chemistry. However, commercially available tc-99m radiopharmaceuticals, such as tc-sestamibi, tc-tetrofosmin, and tc-teboroxime, fall short of the ideal characteristics for myocardial perfusion imaging. Despite widespread clinical use, tc-sestamibi and tc-tetrofosmin exhibit limitations like high liver uptake and suboptimal first-pass extraction fraction. Tc-teboroxime, while possessing unique features, was clinically abandoned due to its rapid myocardial washout and high liver uptake. The ideal myocardial perfusion radiotracer should exhibit high myocardial uptake, a high and stable target-to-background ratio, a high first-pass extraction fraction, fast blood clearance, and a linear relationship between coronary blood flow and radiotracer uptake. Although achieving all these properties in one radiotracer remains a challenge, scientific research continuously strives to develop molecules that closely approach ideality, leading to improved diagnosis and management of cardiovascular diseases (emília de sousa et al., 2022).

3.2. Role of thallium-201 in cardiac imaging

Several studies have investigated the potential of rest-redistribution thallium-201 single photon emission computed tomography (spect) for predicting adverse outcomes in patients with mild-to-moderate left ventricular dysfunction (LVD) and ischemia. These studies consistently demonstrate that rest-redistribution spect provides valuable prognostic information, with the number of severe irreversible defects emerging as a potent predictor of adverse events, particularly acute myocardial infarction, and cardiac death. This emphasizes the utility of rest-redistribution spect in risk stratification and guiding clinical management in this patient population (perrone-filardi et al., 2009).

3.3. Pet radiotracers in cardiac applications

Clinical translation remains elusive despite the promising potential of fluorine-18-labeled radiotracers for net imaging due to their compatibility with pet technology. Existing radiotracers have limitations, such as complex radiolabeling procedures and suboptimal in vivo kinetics. This study investigated the biodistribution and net affinity of the novel radiotracer [18f]af78 in rats, demonstrating favorable properties and highlighting a crucial structure-activity relationship for future design of net-specific radiotracers with improved characteristics (chen et al., 2020).

3.4. Evaluating cardiac function and viability

A multitude of radioisotope techniques exist for cardiac function and viability evaluation. Amongst these, cardiac magnetic resonance imaging (CMR) surpasses echocardiography in detecting segmental wall motion abnormalities (swma). Moreover, cmr's superior spatial resolution facilitates the assessment of extracardiac findings and concomitant cardiac abnormalities. In conjunction with abnormal swma, CMR is a valuable tool for assessing myocardial viability, providing insights into cardiac contractile reserve (hussein et al., 2013). Muga scanning, also known as gated erna or rvg, comprehensively evaluates the heart's structure and function. This non-invasive imaging technique utilizes images captured throughout the cardiac cycle, generating a composite film depicting two-dimensional representations of various cardiac phases. This allows for the assessment of specific cardiac parameters at rest or stress. Muga employs several methods, including spect, first-pass, and erna. The first-pass technique involves administering a radioactive isotope bolus and imaging the labeled blood's initial passage through the heart, proving valuable for assessing intracardiac shunts and calculating right ventricular ejection fraction (hacker et al., 2006).

4. Therapeutic applications of radioisotopes:

4.1. Overview of radioisotope therapy

Radiotherapy combined with chemotherapy and surgery has established its efficacy in cancer treatment. Recent advancements in targeted internal and systemic radiation therapy offer significant improvements in effectiveness and reduced damage to healthy tissue. However, efficient delivery of radiation sources necessitates the development of cancer cell targeting platforms. Recent advances in nanoscience and nanotechnology highlight the potential of nanomaterials as multifunctional carriers for delivering therapeutic radioisotopes for tumor-targeted radiation therapy. These nanomaterials can also facilitate delivery monitoring and track the tumor's response to treatment, offering a promising avenue for improved cancer therapy (zhang et al., 2010).

4.2. Targeted radionuclide therapy in cancer treatment

Targeted radionuclide therapy leverages the selective accumulation of radiolabeled pharmaceuticals in tumors to deliver localized radiation doses. This targeted approach maximizes cancer cell destruction while minimizing harm to healthy tissues. This translates to the potential for a highly therapeutic medication with an infinitely high therapeutic index, offering both high efficacy and minimal toxicity. The selection of appropriate radionuclides is crucial for trnt success. Ideally, the chosen radionuclide should exhibit high cytotoxicity toward cancer cells while minimizing damage to biomolecules. This targeted effect is primarily mediated by reactive oxygen species generated through water radiolysis.

Radionuclides emitting α-particles or β-particles, which exhibit higher relative biological effectiveness than x-rays and γ-radiation, are optimal due to their enhanced destructive potential within biological systems. Despite initial promise, auger electron emitters have shown limited efficacy in clinical trials. Bmitting radionuclides 131i and 90y dominate the trnt landscape, accounting for approximately 90% of clinical applications (gudkov et al., 2015).

4.3. Lodine-131 therapy for thyroid disorders

Radioactive iodine (rai) therapy effectively reduces the risk of thyroid cancer recurrence and treats metastatic disease. Administered orally as tablets or liquid, rai selectively targets thyroid cells, including cancerous ones, due to their unique iodine uptake mechanism. This targeted radiation destroys cancer cells, leading to long-term remission. Pre-treatment with mits (molecular iodine imaging and thyroid scintigraphy) assists in treatment planning and ensures optimal therapeutic efficacy (wang et al., 2021).

4.4. Strontium-89 and samarium-153 for bone pain palliation

Strontium-89 (89sr) and samarium-153-ethylenediamine tetramethylene phosphonate (153smedtmp) are radiopharmaceuticals used for pain palliation in bone metastases. 89sr, with a 50.5-day half-life, emits beta particles with an average energy of 0.58 MeV and a maximum of 1.46 MeV. Its recommended dosage is 150 mbq every 90 days. 153sm-dump, with a 1.9-day half-life, emits beta particles with an average energy of 0.32 MeV and a maximum of 0.81 MeV. Its suggested dosage is 37 mbq/kg. 89sr accumulates in the bone due to its similarity to calcium, achieving 10 times higher concentration at metastasis sites than normal bone. 153sm, however, lacks natural bone affinity and is combined with edtmp, which selectively targets areas of bone turnover. Both 89sr and 153sm-edtmp are commercially available after receiving marketing authorization (murray & du, 2021).

5. Quality control and safety measures

5.1. Radiopharmaceutical quality control processes

Activity measurements using a long-lived check source demonstrated high accuracy and repeatability in the short term. The chamber's response was linear for 99mtc. Long-term stability tests were initiated. The relative response to a 57co or 137cs check source was measured under 99mtc calibration settings using three rncs. The long-lived rnc reference check sources were 20 ml of resin in 27 ml polyethylene vials containing 137cs (7.1 mbq) and 57co (2.7 mbq). Accuracy was determined by comparing the activity measured with each rnc to the reference activity. Long-term stability was assessed by monitoring the response to the long-lived check sources over time. Short-term reproducibility was assessed through a relative standard deviation of ten back-to-back activity measurements of the 57co check source. Linearity was evaluated using the decay method for different 99mtc activity ranges (živanović et al., 2022).

5.2. Radiation safety protocols in medical applications

The iaea's 2006 fundamental safety principles (sf-1) outline the core safety objectives and principles of radiation protection. The international basic safety standards provide specific requirements to address these principles (gsr part 3, 2014). This safety guide assists in fulfilling gsr part 3 requirements related to ionizing radiation use in medical settings. It encompasses three exposure categories: medical exposure (patients undergoing procedures, caregivers, comforters, and research participants), occupational exposure (health professionals performing procedures), and public exposure (safety standards | iaea, n.d.)

Ionizing radiation exposure risks necessitates robust protection programs (rpps) (iaea, 2014). These programs include creating radiation safety committees, developing standardized operating procedures (sops), and implementing engineering controls like shielding and ventilation. Utilizing dosimeters for regular radiation level monitoring helps assess worker exposure and confirm adherence to recommended dose limits, ensuring workplace safety. (iaea, 2014a).

Effective radiation safety protocols rely heavily on comprehensive training and education initiatives. These programs equip individuals with the necessary knowledge and skills to implement safe handling techniques, adhere to regulatory frameworks (iaea, 2014), and manage emergencies effectively. Furthermore, ongoing awareness campaigns promote a safety culture by enhancing risk comprehension and fostering the adoption of best practices. Consequently, continuous learning through refresher courses and professional development programs ensures optimal radiation safety performance. (iaea, 2014b).

5.3. Regulatory guidelines for radioisotope use

Motivated by the inherent risks associated with radioisotope utilization, the Nuclear Regulatory Commission (NRC), in conjunction with the agreement states, has been tasked with safeguarding public health and safety. This mission is achieved through comprehensive inspections of radioisotope applications across diverse domains, encompassing medicine, academia, and industry. Additionally, rigorous oversight of users' practices ensures safe and responsible radioisotope handling, mitigating the potential for unforeseen contingencies and minimizing the impact of hidden risks. By adopting such a proactive approach, the nrc and the agreement states strive to guarantee the responsible use of radioisotopes, thereby maximizing societal benefits while minimizing public health and environmental risks.("the regulation and use of radioisotopes in today's world," 2011).

The utilization of radioisotopes necessitates adhering to stringent licensing and authorization protocols established by international bodies (iaea) and national regulatory agencies (nras) (iaea, 2018). These safeguards guarantee proper expertise and infrastructure for handling radioactive materials responsibly. The licensing process typically requires a detailed application outlining intended use, radioisotope type, and quantity, and implemented safety measures (NRC, 2018). Radiation safety remains paramount during radioisotope use. Regulatory mandates require comprehensive radiation safety programs to shield personnel and the environment from harmful radiation exposure (mundigl, 2015). These programs encompass radiation monitoring: continuous monitoring of radiation levels in work areas and around sources to assure compliance with safety limits. Personal protective equipment (ppe): Provide appropriate ppe like gloves, lab coats, and respirators to minimize internal and external exposure risk. Training and education: regular training programs for personnel using radioisotopes to enhance their understanding of radiation safety principles and practices. Emergency preparedness: establishing procedures to respond to potential radiation accidents and mitigate their consequences effectively. Waste management: the generated radioactive waste requires proper management to prevent environmental contamination. Regulatory guidelines mandate the classification, storage, treatment, and disposal of radioactive waste based on its radioactivity level. (iaea, 2018).

6. Advancements and Future Directions

6.1. Emerging radioisotopes in medical research

The unique power of isotope tracers lies in their ability to differentiate atoms of the same element based on their origins and pathways within intricate systems. The exceptional sensitivity of modern detection techniques further enhances this. Combining these qualities, radioactive isotopes excel as tracers, and their application is anticipated to expand due to increased availability through cyclotron bombardment. However, stable isotopes like 13c, 15n, and 18o are gaining traction for several reasons. First, their nonradioactive nature eliminates environmental and sample contamination concerns, particularly in biological studies. Second, their infinite shelf life allows for extended research durations. Despite their past high cost and limitations in detection sensitivity (requiring expensive or imprecise techniques like optical devices or mass spectrometers), progress is being made. Lower detection limits (well below the parts-per-million threshold) are now achievable, paving the way for wider adoption of stable isotopes as powerful tracers (glubrecht, n.d.).

6.2.Technological innovations in radioisotope production

For over 60 years, research reactors (rrs) have been instrumental in driving advancements in nuclear power, radioisotopes, medicine, materials science, computer modeling, elemental analysis, and capacity building. However, with over half of the 243 operational rrs (2016) exceeding 40 years old, aging infrastructure, underutilization, and fuel cycle concerns pose significant challenges. Conversely, demand for rr-based research and applications is growing, particularly amongst iaea member states embarking on nuclear power and technology programs. These states look to the iaea for guidance and support in establishing their first rr and building their technological and safety infrastructure (iaea, 2010).

6.3. Integration of artificial intelligence in radioisotope imaging

In recent years, nuclear medicine has witnessed a burgeoning integration of artificial intelligence (ai). This has translated into a diverse range of applications, encompassing image analysis, pre- and post-processing, treatment-associated adverse events prediction, and disease staging optimization. This rapid advancement underscores the transformative potential of ai in furthering nuclear medicine's diagnostic and therapeutic capabilities(tamam & tamam, 2022). Artificial intelligence (ai) is rapidly transforming the field of nuclear medicine, impacting workflows across the imaging spectrum, from planning and acquisition to interpretation. This review highlights the potential of AI to improve diagnostic accuracy, personalize patient care, and streamline clinical workflows. Addressing technological challenges and enhancing image analysis capabilities, AI offers significant opportunities to reduce radiation exposure, shorten acquisition times, and improve image quality. Additionally, AI-powered automated disease classification and image reading free up physicians' time, enabling them to focus on personalized patient care. This collaborative approach between ai and human expertise holds promise for the future of nuclear medicine, offering enhanced image quality, personalized reporting, and, ultimately, improved patient outcomes (seifert et al., 2021). This study implements AI-based techniques to achieve faster pet/ct image acquisition, significantly improving the efficiency of tumor lesion segmentation. The results demonstrate the potential of ai in revolutionizing nuclear medicine imaging, leading to faster diagnoses and improved patient care (chakravarty & chakraborty, 2021). This study investigates the potential of artificial intelligence (ai) to improve clinical practice through enhanced decision-making, documentation, and quality control in medical imaging. We highlight specific applications of ai techniques, including tumor volume measurement, pathological foci segmentation and classification, and micrometastasis detection. By leveraging AI, we aim to improve clinical efficiency and accuracy, ultimately leading to better patient outcomes (seifert et al., 2021).

6.4. Potential applications of novel radioisotopes in medicine

Nuclear medicine utilizes radiopharmaceuticals' unique properties to explore the human body's metabolic, physiological, and pathological landscape. This powerful imaging modality excels at detecting abnormalities at the earliest stages of the disease, enabling prompt initiation of treatment. Its unparalleled strength lies in the ability to monitor in vivo anatomical and physiological processes, a capability unmatched by other contemporary imaging techniques like CT, MRI, or ultrasound. Additionally, nuclear medicine offers a spectrum of therapeutic applications, effectively managing diverse conditions such as hyperthyroidism, rheumatoid arthritis, Hodgkin's disease, and a range of cancers (liver, colon, lung, breast, ovarian, prostate). Notably, it has been extensively employed in treating leukemia, cardiac diseases, and the debilitating pain associated with metastatic bone cancer (das, n.d.). Future research may focus on differentiating metastatic tumor volume by organ system to assess tumor heterogeneity and varying metastatic aggressiveness. This involves longitudinally tracking individual metastasis volume, potentially in response to therapy.

Additionally, combining tracers like fdg and psma pet, or fap pet and psma pet, could help evaluate intralesional tumor heterogeneity in vivo. Furthermore, dynamic pet acquisitions (4d pet) could provide valuable insights as whole-body pet scanners become more widespread. Finally, image denoising techniques will be crucial to enable "ultra-low-dose" pet acquisitions (seifert et al., 2021).

7. Conclusion

Radioisotopes are vital and versatile in medicine, offering invaluable benefits in diagnosis, treatment, and research. Regarding diagnostic applications, radioisotopes, like technetium-99m, are used in numerous imaging techniques like PET scans and bone scans to diagnose various conditions, including cancer, heart disease, and neurological disorders. These scans provide detailed information about the structure and function of organs, enabling early detection and accurate diagnosis. Furthermore, radioisotopes are commonly used in therapeutic applications. Iodine-131 is used to treat hyperthyroidism and thyroid cancer, while others like yttrium-90 are used to treat certain types of cancer, including liver and prostate cancer. These isotopes target and destroy diseased cells with minimal damage to healthy tissue, offering effective treatment options. On the other hand, the risks of radiation exposure from radioisotopes can have potential side effects, including nausea, fatigue, and increased risk of cancer, although these could be minimized with proper procedures and dosages. Access to certain radioisotopes, especially those with short half-lives, can be limited due to production and transport challenges, impacting availability and affordability in some regions. Overall, the benefits of radioisotopes in medicine outweigh the limitations. They offer safe, effective, and non-invasive methods for diagnosis and treatment. Further research is ongoing to develop new radioisotopes with targeted effects and even shorter half-lives, minimizing radiation exposure and expanding the range of applications.

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