Radiology: Imaging Cancer

REVIEW

A Review of Theranostics: Perspectives on Emerging Approaches and Clinical Advancements

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Theranostics is the combination of two approaches—diagnostics and therapeutics—applied for decades in cancer imaging using radiopharmaceuticals or paired radiopharmaceuticals to image and selectively treat various cancers. The clinical use of theranostics has increased in recent years, with U.S. Food and Drug Administration (FDA) approval of lutetium 177 (^{177}Lu) tetraazacyclododecane tetraacetic acid octreotate (DOTATATE) and ^{177}Lu–prostate-specific membrane antigen vector-based radionuclide therapies. The field of theranostics has imminent potential for emerging clinical applications. This article reviews critical areas of active clinical advancement in theranostics, including forthcoming clinical trials advancing FDA-approved and emerging radiopharmaceuticals, approaches to dosimetry calculations, imaging of different radionuclide therapies, expanded indications for currently used theranostic agents to treat a broader array of cancers, and emerging ideas in the field.

Background

Radionuclide therapy refers to the application of an unstable nuclide, coupled with a targeting vector, to selectively deliver therapeutic radiation to cancer cells. The molecular targeting mechanism and the type of ionizing radiation emission vary for different radiopharmaceuticals and may have important implications for the benefits and limitations of these agents.

Theranostics is a concept related to radionuclide therapy, but it specifically refers to the use of a pair of radiopharmaceuticals containing radionuclides for imaging (diagnostics) and/or therapy (therapeutics) (1). Radionuclides can be attached to a vector (eg, small molecule, peptide, antibody, particle) through a linker molecule, and the vector, also referred to as a *ligand*, binds to a target (eg, cell surface receptor). The radiopharmaceutical location can be imaged using a SPECT or PET scanner, with the standardized uptake value used as a measure of the amount of radiopharmaceutical in each location of the body. Ideally, the radiopharmaceutical is mostly bound to the target (minimal off-target binding) or has exited the body, with trace amounts circulating in the blood. These images allow the visualization of the target for diagnosis and staging, the selection of patients whose tumors express the target, confirmation of therapeutic delivery to all intended targets in a patient, the calculation of effective radiation delivered to the target (ie, dosimetry), and follow-up treatment monitoring (Fig 1) (2). The term *theragnostics* (from the Greek word *gnosis*, meaning knowledge), which combines the words *therapy* and *diagnosis*, is sometimes used (3), but the term *theranostics* is now more common.

This concept has been used for many decades in nuclear medicine, starting with the use of radioiodine pharmaceuticals for thyroid cancer in 1946 (4). Ideally, the diagnostic and therapeutic radiopharmaceuticals are structurally identical (a perfect theranostic pair), but this is often not the case. Most radiopharmaceuticals lack emission properties suitable for both diagnostic imaging and therapy, thus necessitating a diagnostic agent and therapeutic agent pair that bind to the same molecular target but are composed of two different molecular structures and radionuclides. Even slight differences in chemical structure from different radionuclides can lead to differences in biodistribution to target tumors, off-target binding, and clearance.

Radionuclides: Particle Emission and Relevant Types of Radiation

The types of emission from a given radionuclide are critical to understanding that radionuclide's potential therapeutic role.

β-Particle emission occurs primarily in radionuclides with a neutron excess undergoing β-minus decay and is the most used mechanism in radionuclide therapy because of the high availability of these radionuclides (eg, radioiodine). β Particles have a negative charge, low linear energy transfer (LET, approximately 0.2 keV/μm), and a long travel distance of approximately 2–12 mm (20 to 120 cell lengths) (5,6). Clinically used radionuclides that emit a β particle include lutetium 177 (^{177}Lu), iodine 131 (^{131}I), and yttrium 90 (^{90}Y), listed from lowest to highest maximum energy emission and path length (7).

An α particle is positively charged and is almost three orders of magnitude bigger than a β particle. As a result, α particles have a much higher LET (80 keV/μm) compared with that of β particles and travel a much shorter distance of 50–100 μm (one to three cell lengths) (6).

Auger electrons are low-energy electrons emitted by radionuclides when they decay by electron capture and,

Abbreviations

DOTATATE = tetraazacyclododecane tetraacetic acid octreotate, FAP = fibroblast activation protein, FAPI = FAP inhibitor, FDA = U.S. Food and Drug Administration, LET = linear energy transfer, mCRPC = metastatic castration-resistant prostate cancer, MIBG = metaiodobenzylguanidine, MIRD = Medical Internal Radiation Doses, NET = neuroendocrine tumor, PSA = prostate-specific antigen, PSMA = prostate-specific membrane antigen, SSR = somatostatin receptors

Summary

Emerging approaches to theranostics, including investigational radiopharmaceuticals, expanded indications for current radionuclide therapies, and posttreatment imaging, are active areas of innovation with potential to transform clinical practice.

Essentials

- Theranostics is a concept related to radionuclide therapy that specifically refers to the use of a pair of radiopharmaceutical agents containing radionuclides used for imaging (diagnostics) and/or therapy (therapeutics).
- α Particles have high linear energy transfer and enable increased precision in radiation delivery, which theoretically decreases collateral damage to adjacent healthy tissues and may facilitate more focused targeting of small tumors and micrometastasis relative to the same dose of β-particle emitters required to achieve similar cytotoxic effects.
- The imaging of theranostic agents can potentially serve multiple independent purposes, including patient selection for therapy, confirmation of delivery to tumors, dosimetry calculation, and treatment response assessment.
- Both tetraazacyclododecane tetraacetic acid octreotate (or, DOTATATE)– and prostate-specific membrane antigen–coupled agents that now have regulatory approval for clinical use in neuroendocrine tumors and prostate cancer, respectively, are being investigated for expanded indications in other tumor classes.

Keywords

Molecular Imaging, Molecular Imaging–Cancer, Molecular Imaging–Clinical Translation, Molecular Imaging–Target Development, PET/CT, SPECT/CT, Radionuclide Therapy, Dosimetry, Oncology, Radiobiology

in doing so, eject an electron from an electron orbit around the nucleus. Auger electrons travel an extremely short distance, in the nanometer to micrometer range. They are a form of β-particle emission; however, the electron is not emitted from the nucleus.

Biologic Effects of Radiation Types

Radiopharmaceuticals can exert antitumoral biologic effects through multiple mechanisms, such as direct effects via DNA damage to a targeted cell, crossfire effects to adjacent tumor cells, and indirect effects to adjacent tumor cells through generation of reactive oxygen species and/or induction of immunogenic cell death. Relative to α particles, the longer travel distance of β particles results in a crossfire effect that is advantageous in large tumor masses with intralesional heterogeneity, allowing for irradiation of all tumor cells, even those that do not express the radiopharmaceutical target (5). β Particles exert their therapeutic effects through the generation of reactive oxygen species that cause DNA damage via single-strand DNA breaks. Such damage can elicit a cell death response or be repaired via DNA repair mechanisms. As this mechanism is dependent on the presence of oxygen, β particles potentially have lower efficacy in the treatment of ischemic tumors because of hypoxemia-induced cellular defense mechanisms (Table 1, Figs 2–4) (5). In contrast, α particles are more cytotoxic than β particles because they cause irreparable double-strand DNA breaks. Moreover, α particles incite a stronger antigen T-cell immune response (abscopal effect), are oxygen independent, and generate greater ionization events and reactive oxygen species compared with β particles (8). The high LET of α particles and increased precision of radiation delivery theoretically decrease collateral damage to adjacent healthy tissues and may facilitate more focused targeting of small tumors and micrometastasis relative to the same dose of β emitters required to achieve similar cytotoxic effects. Furthermore, the therapeutic efficacy of α-particle therapy is less dependent on the presence of oxygen, implying a theoretical advantage in hypoxic tumor microenvironments (Table 1, Figs 2–4) (6). Auger electrons travel a very short distance, on the order of the size of the cell nucleus, and could theoretically be highly lethal to tumor cells if incorporated into the cell DNA. This short range may be particularly suited for small tumors in sensitive locations, when restricting toxicity to adjacent normal tissue is especially critical (9). Despite these theoretical advantages, there has not been widespread adoption of this class of radionuclide therapy outside of limited preclinical studies, likely because of its need to reach the cell nucleus to cause DNA damage and achieve lethal cytotoxic effects.

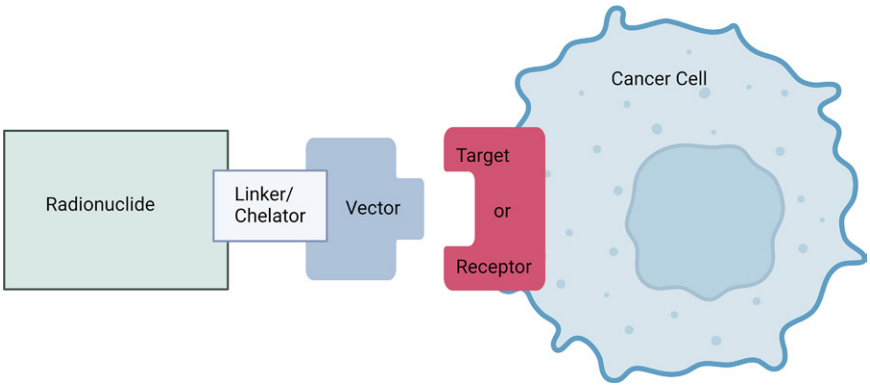

Figure 1: Radionuclide therapy schematic. A radionuclide held in a chelator or cage or bound covalently is attached to a vector by a linker molecule. The vector binds to a molecular target to enable visualization of the target for diagnostic or treatment purposes and selective delivery of radiation therapy to the target. Alternatively, a free radionuclide ion can, in some circumstances, be used to target tumors or cancer cells, as with iodine 131, alastine 211, and radium 223. Created with BioRender.com.

Table 1: Properties of Targeted β- and α-Particle Radionuclide Therapies

Property	β-Particle Therapy	α-Particle Therapy
LET	Low LET (0.2 keV/μm)	High LET (50–230 keV/μm)
Tissue range	Long tissue range (2–12 mm)	Short tissue range (50–100 μm)
DNA damage	Less complex Isolated DNA damage, SS and DS breaks (more repairable) Occurs along a linear tract	More complex Clusters of DNA damage, predominantly DS breaks (less repairable) Occurs along a linear tract
Cytotoxic effects	Less likely	More likely (mitotic arrest, apoptosis, necrosis)
Immunogenic effects	Less likely	Possibly more likely to induce T-cell response and immunogenic cell death (abscopal effect)
Off-target effects	Can cause injury to healthy cells near the target cell	High LET with potential to dissociate from conjugate vector and emit radiation in an off-target location

Note.—DS = double-strand, LET = linear energy transfer, SS = single-strand.

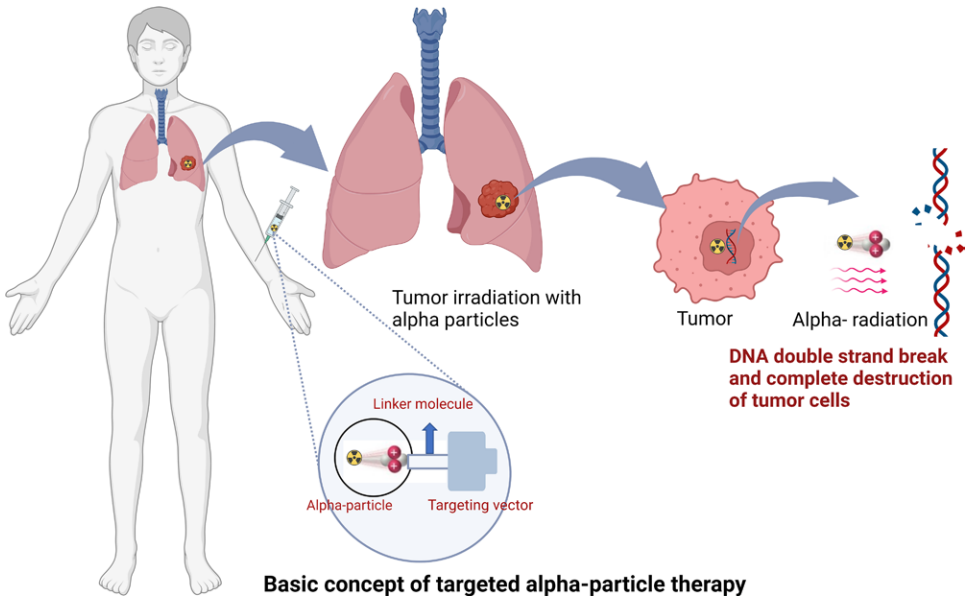

Figure 2: Targeted α-particle therapy schematic. The radionuclide therapy is intravenously infused and binds to the tumor through a vector linked to the radionuclide. While bound to the tumor, α-particle emission occurs, selectively delivering radiation to the tumor. α Particles are more cytotoxic than β particles because they cause irreparable double-strand DNA breaks, resulting in cell death. Created with BioRender.com.

Patient-specific Dosimetry

Radiation dosimetry is the science by which the amount of radiation energy deposited per unit mass in tissues can be calculated. By determining the biodistribution of a radiopharmaceutical and dose delivered to healthy tissues, dose calculations can be used to establish radiopharmaceutical safety (10). Dosimetry calculations could also be applied in the posttreatment setting to verify the activity delivered to the targeted tumors and record the dose to critical organs. A critical organ is the organ most susceptible to the effects of a specific radiopharmaceutical and may be the dose-limiting factor in the amount of therapeutic radionuclide activity administered (11).

Internal dosimetry methods have been described in detail by the Medical Internal Radiation Dose (MIRD) Committee and rely on the use of a time-integrated function incorporating the source organ activity, target organ mass, cumulated activity in each source organ, and the fraction of source organ energy emission that is absorbed by target organs. Calculation of the energy absorbed by target organs can be simplified with S-factors based on computational phantoms (10,11).

A relatively simple dosimetry example is the calculation of the minimal administered activity of therapeutic sodium iodide ($Na^{131}I$) for remnant ablation following thyroidectomy. This approach involves administering a trace amount of $Na^{131}I$, serial imaging with a γ camera or SPECT at multiple time points to produce a time-activity curve for a region of interest including the thyroidectomy bed, deriving the effective half-life for the thyroid remnant, and determining the initial activity in the lesion. These parameters could be used in a formula to calculate the minimum activity of $Na^{131}I$ needed to deliver 300 Gy to the

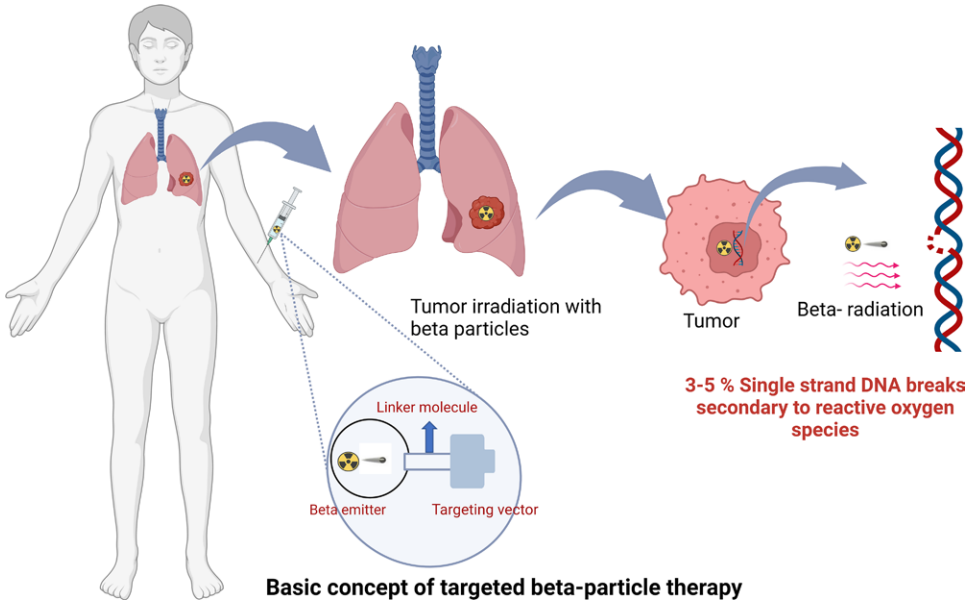

Figure 3: Targeted β-particle therapy schematic. While bound to the tumor, β-particle emission occurs, selectively delivering radiation to the tumor. β Particles exert therapeutic effects through reactive oxygen species, causing DNA damage via single-strand DNA breaks that may result in cell death if not repaired via DNA repair mechanisms. Created with BioRender.com.

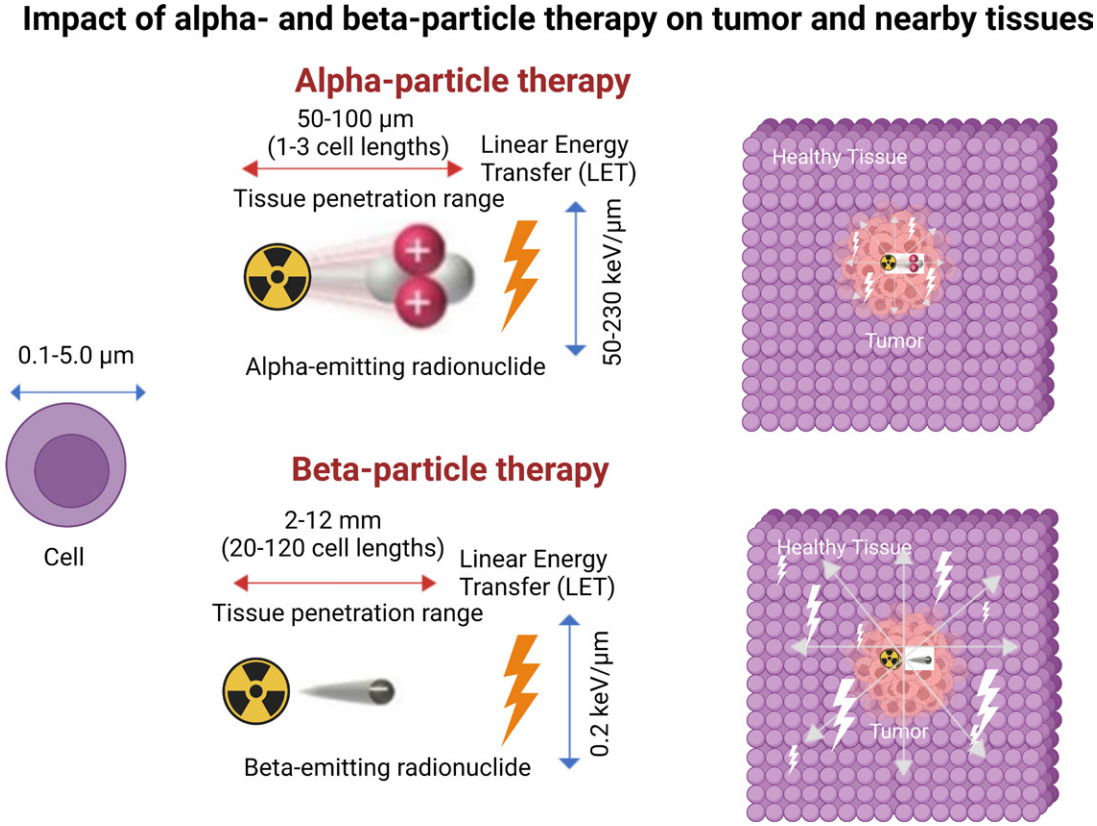

Figure 4: Targeted α-particle and β-particle therapy comparison. Illustration shows the characteristic features of α and β particles. α Particles are positively charged particles composed of two protons and two neutrons, essentially the nucleus of a helium atom, and β particles are negatively charged particles, essentially electrons. α Particles have much greater mass, higher linear energy transfer (LET), travel a much shorter distance in tissue, and are more cytotoxic than β particles. The illustration includes specific values of these characteristics for reference but is not to scale. Created with BioRender.com.

thyroid remnant (the minimum required for adequate ablation), allowing the calculation of a personally optimized dose (12,13).

Dosimetry calculations could also be performed in the pretreatment planning phase to maximize the therapeutic radionuclide activity that can safely be administered, within the dose limits to critical organs. ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) therapy is another example of radionuclide therapy dosimetry adopted in clinical practice. Dosimetry is required for ^{131}I-MIBG therapy for metastatic pheochromocytomas and paragangliomas in the U.S. Food and Drug Administration (FDA) package insert. If critical organ dose estimates are above threshold, based on MIRD calculations from images after the initial dose, reductions in the administered activity are made for the second dose (14).

The biodistribution of a therapeutic radiopharmaceutical can differ between patients because of the variable size and location of tumors, which accumulate radionuclides and emit radiation. Despite this variability, many of the radionuclide therapies discussed in this article are administered in a set quantity in clinical practice. This framework substantially differs from the treatment model of external beam radiation therapy or brachytherapy delivery, where treatment planning is the standard of care and patient-specific dosimetry is used to estimate the absorbed dose to the targeted treatment field and to organs at risk (10). Dosimetry calculation is more complex for radionuclide therapy than for external beam radiation therapy because of a heterogeneous biodistribution of the radiopharmaceuticals, varied pharmacokinetics, and different mechanisms of particle-associated cytotoxicity (10,11,15). As a result, highly accurate dosimetry for longer-lived radiopharmaceuticals may require imaging at time points over multiple days. Calculation accuracy is also strongly dependent on the calibration of equipment, including dose calibrators and imaging systems (SPECT and PET), which have quantitative capabilities that are heavily influenced by reconstruction parameters and corrections for attenuation and scatter.

Radionuclide Therapy: Current Clinical Practice and Future Directions

In current clinical practice, several theranostic pairs are widely used. Thyroid cancer is treated with Na^{131}I and imaged with iodine 123 (^{123}I) or technetium 99m (^{99m}Tc) pertechnetate, both relying on the Na-I symporter as the target that transports the radiopharmaceuticals into cells (16). Osteoblastic metastases in prostate cancer can be imaged with ^{99m}Tc-medronate or fluorine 18 (^{18}F)–sodium fluoride (ie, NaF), which rely on affinity for hydroxyapatite and increased bone turnover, and treated with radium 223–dichloride (^{223}RaCl$_2$), strontium 89–chloride (ie, ^{89}SrCl), or samarium 153–ethylenediaminetetramethylene phosphonate (ie, ^{153}Sm–EDTMP), which do not target cancer cells directly but instead target the environment of the tumor in the bone (17). Norepinephrine transporter–expressing neuroendocrine neoplasms, including paraganglioma and pheochromocytoma, can be treated with ^{131}I-MIBG and imaged with ^{123}I-MIBG (18).

In recent years, the use of targeted radionuclide therapy in clinical practice has greatly expanded. The recent regulatory approval of multiple radionuclide therapies indicates that this is an area with momentum toward growing clinical adoption, which has found success in the setting of multiple types of malignancies.

^{223}RaCl$_2$ Therapy

In 2013, ^{223}RaCl$_2$ became the first α particle–emitting radiopharmaceutical to be granted FDA approval for clinical use and was indicated for patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease (19). ^{223}RaCl$_2$ is a calcium analog that binds avidly to bone matrix with high bone turnover and osteoblastic activity. The naked, unstable radionuclide incorporates into the extracellular environment, and the α particle emission in the tumor microenvironment suppresses abnormal bone formation and induces cell death (20). The phase 3 ALSYMPCA (or, ALpharadin in SYMPtomatic Prostate CAncer) trial demonstrated that ^{223}RaCl$_2$ was well tolerated and improved median overall survival to 14.9 months in the treatment arm versus 11.3 months in the placebo arm (30% risk reduction; hazard ratio, 0.70 [95% CI: 0.58, 0.83]; $P < .001$); it also improved the median time to first symptomatic skeletal event to 15.6 months in the radium arm versus 9.8 months in the placebo arm (34% risk reduction; hazard ratio, 0.66 [95% CI: 0.52, 0.83]; $P < .001$) (19).

Somatostatin Receptor–targeted Radionuclide Therapy

Somatostatin receptors (SSR), particularly SSR2a, expressing neuroendocrine tumors (NETs) of the pancreas and midgut can be imaged with gallium 68 (^{68}Ga) DOTA peptides (DOTATATE [tetraazacyclododecane tetraacetic acid octreotate], DOTANOC [tetraazacyclododecane tetraacetic acid sodium triiodide octreotide], and DOTATOC [tetraazacyclododecane tetraacetic acid D-phenylalanine 1 tyrosine 3 octreotide]), indium 111 (^{111}In) octreotide, or ^{99m}Tc-octreotide and treated with ^{177}Lu-DOTA-peptides or yttrium 99 octreotate (21) as a theranostic pair. The pivotal Neuroendocrine Tumors Therapy (NETTER)–1 phase 3 trial of ^{177}Lu-DOTATATE in patients with advanced midgut NETs demonstrated increased progression-free survival at 20 months of 65.2% versus 10.8% in the control, as well as a significantly increased tumor response rate with ^{177}Lu-DOTATATE (22). In 2018, FDA approval of ^{177}Lu-DOTATATE for NETs represented a major addition to the treatment options for patients with these tumors (21). Subsequently, the NETTER-1 trial did not demonstrate a statistically significant increase in overall survival at 5 years, complicated by high crossover within the randomized control group (36% of the controls subsequently received SSR-coupled radionuclide therapy) (23). Further research and innovation in radionuclide therapy are merited for patients with advanced midgut NETs.

Emerging SSR-targeted radionuclide therapies are under investigation. A recent phase 2 clinical trial investigated the use of an SSR-targeted α-particle therapy using actinium 225 (^{225}Ac) DOTATATE, demonstrating promising response and progression-free survival outcomes for gastroenteropancreatic NETs.

Table 2: Example Emerging Molecular Targets in Clinical Trials

Molecular Targeting Mechanism	Trial Registration No. and Agents	Type of Tumor
Somatostatin receptor antagonist	NCT02609737: ^{68}Ga-DOTA-JR11/^{177}Lu-DOTA-JR11	Neuroendocrine tumors
	NCT02592707: ^{68}Ga-OPS202/^{177}Lu-OPS201	Neuroendocrine tumors
	NCT04997317: ^{177}Lu-satoreotide	Meningiomas
	NCT05017662: ^{177}Lu-IPN01072	Neuroendocrine tumors, long-term surveillance for secondary malignancies
	NCT05359146: ^{161}Tb-DOTA-LM3	Neuroendocrine tumors
Bombesin family G protein–coupled receptor ligands	NCT03872778: ^{68}Ga-NeoB/^{177}Lu-NeoB	Multiple solid tumors (breast, lung, prostate, GBM, GIST)
	NCT05283330: ^{212}Pb-DOTAM-GRPR1	Solid GRPR-expressing tumors (prostate, breast, colorectal, cervical, melanoma, lung cancer)
Fibroblast activation protein inhibitor	NCT04849247: ^{68}Ga-DOTA-FAPI/^{177}Lu-DOTA-FAPI	Various
	NCT05432193: ^{68}Ga-PNT6555/^{177}Lu-PNT6555	Various
HER2 ligand	NCT04467515: CAM-H2	HER2-positive breast and gastric or gastroesophageal junction cancers
Cholecystokinin-2 receptor ligand (gastrin analog)	NCT02088645: ^{177}Lu-PP-F11N	Medullary thyroid cancer
STEAP1 receptor	NCT01774071: ^{89}Zr-DFO-MSTP2109A PET, targeted STEAP1 therapies in development	Prostate cancer

Note.—Search terms used on ClinicalTrials.gov on September 8, 2022, were the following: "radionuclide therapy/target/targeted/targeting," "bombesin," "FAPI," and "fibroblast activation protein inhibitor." Search results were manually reviewed for emerging agents used for therapy in a new (not yet recruiting), recruiting, or completed trial. Terminated or withdrawn trials were not included. DFO = deferoxamine, DOTA = tetraazacyclododecane tetraacetic acid, FAPI = fibroblast activation protein inhibitor, GBM = glioblastoma, GIST = gastrointestinal stromal tumor, GRPR = gastrin-releasing peptide receptor, HER2 = human epidermal growth factor receptor 2, IPN01072 = satoreotide tetraxetan, OPS = satoreotide trizoxetan, STEAP1 = six transmembrane epithelial antigen of the prostate 1.

Preclinical and early clinical studies have suggested that SSR2 antagonists may have greater receptor binding density, greater tumor-to-background ratio, and greater lesion detection compared with that of agonists (24,25). The ability of the antagonists to bind more receptors may facilitate increased sensitivity and allow treatment of tumors with lower receptor density (24). Table 2 lists five example registered trials using investigational theranostic pairs based on SSR antagonists for SSR-expressing NETs and meningiomas, an active area of innovation in radionuclide therapy. The investigational use of SSR-coupled radionuclide therapy earlier in the treatment course is also an area of interest. The NETTER-2 trial will assess ^{177}Lu-DOTATATE as an upfront treatment by randomizing untreated patients with metastatic grade 2–3 NETs to treatment with ^{177}Lu-DOTATATE plus long-acting octreotide or high-dose long-acting octreotide alone, and accrual goals were met in October 2022 (26).

Prostate-specific Membrane Antigen–targeted Radionuclide Therapy

Prostate-specific membrane antigen (PSMA)–coupled radiopharmaceuticals target PSMA, a transmembrane protein expressed in prostate cancer. The phase 2 TheraP trial of ^{177}Lu-PSMA-617 demonstrated higher prostate-specific antigen (PSA) response compared with that of cabazitaxel for progressive, metastatic castration-resistant prostate cancer (mCRPC) (27). Subsequently, the landmark phase 3 VISION trial (ClinicalTrials.gov no. NCT03511664) showed that participants receiving ^{177}Lu-PSMA-617 had increased progression-free survival (based on imaging) and overall median survival (15.3 months vs 11.3 months) compared with participants receiving standard-of-care treatment alone (28). ^{177}Lu-PSMA-617 was recently FDA approved for mCRPC, paired with diagnostic imaging using ^{68}Ga-PSMA-11 PET. ^{18}F-DCFPyL PET has also been used in the clinical research setting as the PSMA-targeted diagnostic pair (29,30).

PSMA-coupled radionuclide therapy is an area of active clinical innovation. Strong interest in developing PSMA-coupled targeted α-particle therapy has emerged, supported by an initial report in 2016 demonstrating a dramatic treatment response by using ^{225}Ac-labeled PSMA ligands (^{225}Ac-PSMA-617) in patients with mCRPC (31). Figure 5 shows a clinical example of a patient with mCRPC responding dramatically to ^{225}Ac-PSMA-617 following progression with multiple treatment modalities, including the α-particle therapy $^{223}RaCl_2$. Since the initial report of ^{225}Ac-PSMA-617 therapy (31), multiple studies have suggested that ^{225}Ac-PSMA-617 is an efficacious and safe treatment option. A recent systematic review and meta-analysis comprising 256 patients treated with ^{225}Ac-PSMA-617 showed overall biochemical response in 62.8% (95% CI: 53.4%, 71.7%) of patients, molecular response at ^{68}Ga-PSMA-11 PET/CT in 74% (95% CI: 50.1%, 92.1%) of patients, and pooled estimates of median progression-free survival and overall survival of 9.1 months

Table 3: Example α-Particle Therapy Trials

α-Particle–Emitting Radionuclide	Trial Registration No. and Agents	Type of Tumor
Actinium 225	NCT00672165: ^{225}Ac-labeled humanized anti-CD33 monoclonal antibody HUM195	Leukemia Myelodysplastic syndrome
	NCT05204147: ^{225}Ac-DOTA-anti-CEA monoclonal antibody M5A	Advanced colorectal carcinoma
	NCT05363111: ^{225}Ac-DOTA-daratumumab	Multiple myeloma
	NCT05496686: ^{225}Ac-MTI-201	Uveal melanoma
	NCT04644770: ^{225}Ac-labeled antibody targeting human kallikrein-2 (JNJ-69086420)	Advanced prostate cancer
	NCT03705858: ^{225}Ac-lintuzumab	Acute myeloid leukemia
	NCT05902247: ^{225}Ac-PSMA-I&T	Metastatic castration-resistant prostate cancer
	NCT04576871: ^{225}Ac-J591	
	NCT03746431: ^{225}Ac-FPI-1434	Various advanced solid tumors
	NCT05595460: RYZ101	Gastroenteropancreatic neuroendocrine tumors
Astatine 211	NCT04461457: ^{211}At-MX35 F(ab')2	Ovarian cancer
	NCT03670966: ^{211}At BC8-B10 monoclonal antibody (anti-CD45)	Bone marrow transplant Hematologic malignancies
	NCT05275946: ^{211}At NaAt	Thyroid cancer
	NCT00003461: ^{211}At antitenascin human-mouse chimeric 81C6 (^{211}At MAb 81C6)	Brain and central nervous system tumors Metastatic cancer Neuroblastoma
	NCT04466475: ^{211}At anti-CD38 monoclonal antibody OKT10-B10	Plasma cell myeloma
Bismuth 213	NCT00014495: ^{213}Bi monoclonal antibody M195	Leukemia Myelodysplastic syndromes Myelodysplastic or myeloproliferative neoplasms
Lead 212	NCT05283330: ^{212}Pb-DOTAM-GRPR1	Cervical cancer Metastatic prostate cancer Breast cancer Colon cancer Non–small cell lung cancer Cutaneous melanoma
	NCT01384253: ^{212}Pb-DOTAM-trastuzumab	Breast neoplasms Peritoneal neoplasms Ovarian neoplasms Pancreatic neoplasms Stomach neoplasms
	NCT03466216: ^{212}Pb-DOTAMTATE (^{212}Pb-octreotide analog)	Neuroendocrine tumor
	NCT05636618: ^{212}Pb-VMT-α-NET	
Thorium 227	NCT03724747: ^{227}Th-labeled immunoconjugate, specific for PSMA (BAY2315497)	Metastatic castration-resistant prostate cancer
	NCT03507452: ^{227}Th-labeled antibody-chelator conjugate, specific for mesothelin (BAY2287411)	Advanced recurrent epithelioid mesothelioma Serous ovarian cancer Metastatic or locally advanced pancreatic ductal adenocarcinoma
	NCT04147819: ^{227}Th-labeled antibody-chelator conjugate, specific for HER2 (BAY2701439)	Cancers with HER2 expression
	NCT02581878: ^{227}Th-labeled antibody-chelator conjugate, specific for CD22 (BAY1862864)	Lymphoma, non-Hodgkin

Note.—Search terms used on ClinicalTrials.gov on September 18, 2022, were the following: "actinium," "^{225}Ac," "^{225}Ac," "astatine," "^{211}At," "lead 212," "212-Pb," "bismuth," "^{213}Bi," "radium 223," "thorium 227," and "thorium." Terminated or withdrawn trials were not included. CD22 = cluster of differentiation 22, CD33 = sialic acid binding lg-like lectin 3, CD38 = cluster of differentiation 38, CEA = carcinoembryonic antigen, DOTA = tetraazacyclododecane tetraacetic acid, DOTAM = tetra-carbamoyl-methyl-cyclododecane, GRPR = gastrin-releasing peptide receptor, HER2 = human epidermal growth factor receptor 2, PSMA = prostate-specific membrane antigen.

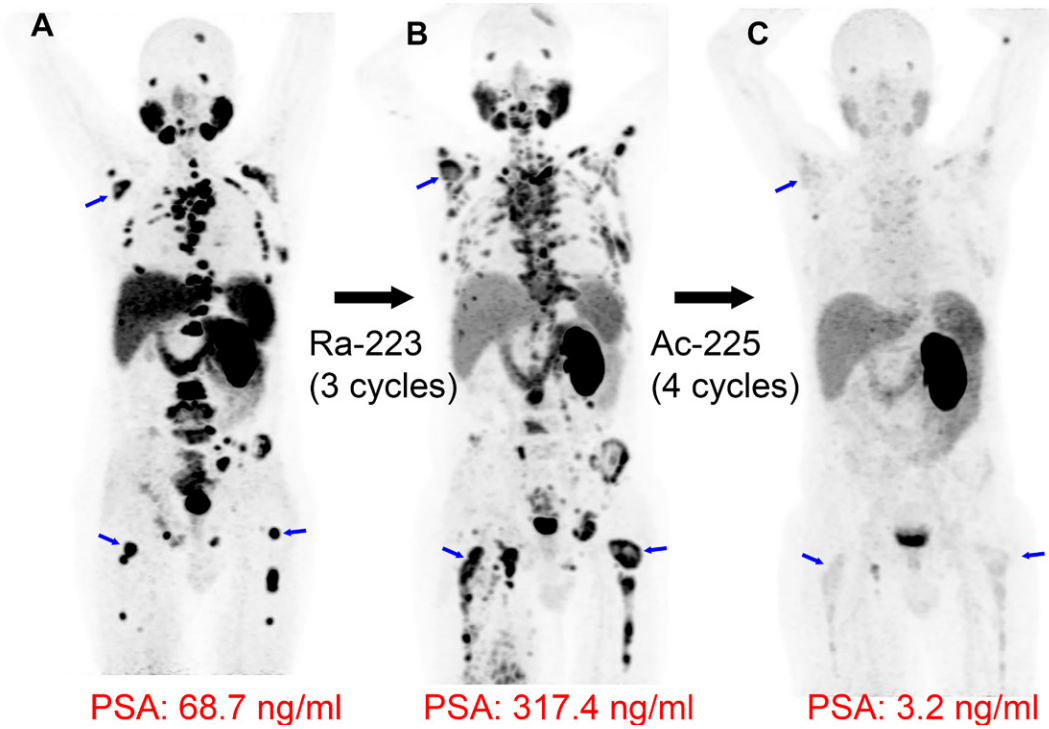

Figure 5: Targeted α-particle therapy: radium 223 dichloride ($^{223}RaCl_2$) followed by actinium 225 (^{225}Ac) prostate-specific membrane antigent (PSMA)–617. Images in a 66-year-old man with widely metastatic prostate cancer, with a Gleason score of 8 (4 + 4), that progressed following androgen deprivation, chemotherapy, and pelvic radiation. **(A)** Baseline gallium 68 (^{68}Ga) PSMA-11 PET/CT image demonstrates intense PSMA uptake in numerous metastatic lesions (blue arrows indicate examples in the right scapula and both femurs). **(B)** ^{68}Ga-PSMA-11 PET/CT image following three cycles of $^{223}RaCl_2$ (a targeted α-particle therapy that incorporates within osteoblastic lesions but does not directly bind to cancer cells) shows progression of many osseous metastases (blue arrows), and the prostate-specific antigen (PSA) value increased. **(C)** Lutetium 177 (^{177}Lu) PSMA-617 and ^{225}Ac-PSMA-617 were both considered as treatment options. Following multidisciplinary discussion and shared decision-making with the patient, four cycles of ^{225}Ac-PSMA-617 (a targeted α-particle therapy with affinity for PSMA) were administered 6 weeks apart, demonstrating dramatic response in the metastatic lesions, with near resolution of PSMA uptake at ^{68}Ga-PSMA-11 PET/CT (blue arrows in the location of previous lesions) and a corresponding dramatic reduction in PSA.

(95% CI: 3.6, 14.5) and 12.8 months (95% CI: 4.5, 21.0), respectively (32). Future randomized controlled trials are needed to further prove the therapeutic efficacy and survival benefit of ^{225}Ac-PSMA-617. Ongoing phase 1 and 2 trials and registry data are currently active and recruiting patients (Table 3). Currently, ^{225}Ac-PSMA-617 does not have FDA approval, has risks of adverse effects such as substantial xerostomia (31), and has not yet been investigated in a phase 3 trial. Other α-particle emitters investigated in preclinical and clinical studies, each offering different advantages and disadvantages, are summarized in Table 3 (6). While ^{177}Lu-PSMA-617 has regulatory approval for patients with mCRPC, its investigational treatment of local-regional disease in the neoadjuvant setting has been evaluated in the recently completed LuTectomy trial (ClinicalTrials.gov registration no. NCT04430192). This trial and future clinical studies using radionuclide therapy for ablation of the primary tumor site will be informative about the potential for this targeted treatment at earlier stages of disease.

Imaging in Theranostics

Imaging theranostic agents can potentially serve multiple independent purposes, including patient selection for therapy, confirmation of delivery to tumors, dosimetry calculation, and treatment response assessment.

Patient Selection

For a theranostic pair of agents, imaging of the diagnostic agent is used to visualize the treatment target for patient selection purposes and confirm that the tumor expresses the target (33). For example, ^{68}Ga-DOTATATE PET/CT is used to identify SSR-expressing disease in metastatic NETs. The degree of uptake is assessed with a Krenning score to select appropriate patients for ^{177}Lu-DOTATATE radionuclide therapy (34). Similarly, ^{68}Ga-PSMA-11 PET/CT is used to confirm PSMA-avid targets prior to initiation of ^{177}Lu-PSMA-617 therapy. PET images are also carefully reviewed to confirm that all known or suspected live tumors express the target and show uptake.

Imaging to Monitor Therapy Response

Following treatment with radionuclide therapy, current guidelines support the use of anatomic imaging for response assessment with anatomic imaging modalities (35–37). Importantly, anatomic imaging may characterize tumors that do not express the radionuclide therapy target. For gastroenteropancreatic NETs following treatment with ^{177}Lu-DOTATATE, anatomic imaging every 3–12 months is recommended by the National Comprehensive Cancer Network, using CT of the abdomen and pelvis with intravenous contrast media, CT of the chest with or without contrast media, and MRI of the liver

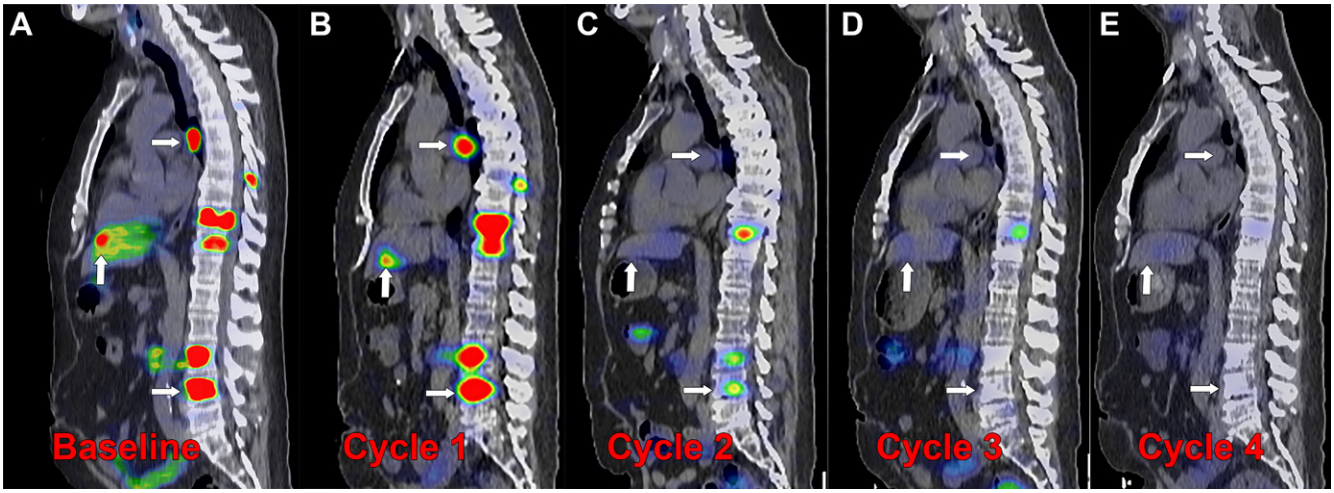

Figure 6: Posttherapy monitoring of index lesions with SPECT/CT imaging. Fused SPECT/CT sagittal images in a 56-year-old man with prostate-specific membrane antigen (PSMA)–avid metastatic prostate cancer undergoing lutetium 177 (^{177}Lu) PSMA-617 therapy. **(A)** Baseline fluorine 18 (^{18}F) carboxy-fluoro-pyridine-carbonyl-amino-pentyl-ureido-pentanedioic acid (DCFPyL) PET/CT image demonstrates intense PSMA uptake in nodal, osseous, and hepatic metastases (arrows). **(B–E)** Post-therapy SPECT/CT image with ^{177}Lu-PSMA-617 was performed approximately 24 hours after infusion of the therapeutic radiotracer after each of four cycles administered 6 weeks apart, demonstrating localization of the therapeutic radiopharmaceutical to the metastases. Index lesions in lymph node, bone, and liver (arrows) demonstrate decreased intensity of uptake with each cycle of therapy. **(C)** After cycle 2, the hepatic and nodal metastases were no longer conspicuous, and **(E)** after cycle 4, the spine metastasis was no longer conspicuous. Imaging the therapeutic radionuclide enables confirmation of effective delivery to the sites of cancer and detection of treatment response over the course of therapy, demonstrated by the changes in the imaged index lesions over time.

for hepatic-dominant disease. Guidelines support the use of molecular imaging with SSR-targeted PET for tumor response assessment in limited scenarios, including when other evidence of progression is present, to evaluate equivocal anatomic imaging findings, and in the setting of stable disease 9–12 months after ^{177}Lu-DOTATATE therapy completion (38). For metastatic prostate cancer treatment with ^{177}Lu-PSMA-617 and other systemic therapies, current guidelines support the use of anatomic imaging with CT or MRI and/or ^{99m}Tc-medronate bone scans for restaging (35). Consensus recommendations for PSMA-ligand PET/CT for response assessment have emerged recently (37). Following radionuclide therapy, scintigraphy of ^{177}Lu-PSMA-617 performed 0–3 days after administration is recommended to confirm delivery of the therapeutic radionuclide to the targeted tumors (39). The response to therapy can also potentially be assessed with "therapy-monitoring" imaging of the therapeutic radionuclide with each cycle of therapy. For example, SPECT/CT imaging of ^{177}Lu-PSMA-617 at approximately 24 hours after infusion can demonstrate changes in tumor uptake of the therapeutic radionuclide (Fig 6).

A ^{177}Lu-PSMA-617 and NOX66 combination trial (LuPIN) found that quantitative assessment of changes in radioactive total tumor volumes between baseline imaging and cycle 3 of posttherapy SPECT/CT are predictive of progression-free survival (40). This technique has the potential to generate useful quantitative biomarkers for predicting response to radionuclide therapy and may be applied to other theranostic pairs. Unanswered questions remain regarding the use of additional cycles of therapy following tumor progression or complete response as assessed with posttherapy SPECT/CT. Evidence supporting clinical benefit of ^{177}Lu-PSMA-617 therapy is based on the VISION trial, which used a regimen of four to six cycles (28) with no SPECT/CT imaging; however, some patients may experience an early complete response (Fig 7), and at present, the benefit of completing further cycles of therapy remains uncertain.

Expanded Indications to Other Classes of Tumors for Currently Available Targeted Radioligand Therapies

While radioligand therapies binding new molecular targets or using more efficacious radionuclides will be necessary for the field of theranostics to reach its full potential, the most direct route for growth in this field is by identifying additional uses for currently available radiopharmaceuticals. Both DOTATATE- and PSMA-coupled radiopharmaceuticals that now have regulatory approval for clinical use in NETs and prostate cancer, respectively, are being investigated for expanded indications for other classes of tumors.

^{177}Lu-DOTATATE Therapy

SSRs are expressed in a variety of neoplasms other than gastrointestinal NETs, as well as nonneoplastic processes (41). While the investigation of therapeutic intervention has lagged behind that of imaging studies, ongoing clinical trials are using ^{177}Lu-DOTATATE for the treatment of malignancies as diverse as glioblastoma, esthesioneuroblastoma, breast cancer, small cell lung cancer, and Merkel cell carcinoma. Paraganglioma and meningioma, two areas of substantial interest for ^{177}Lu-DOTATATE therapy, are discussed below.

Paragangliomas and pheochromocytomas.— Paragangliomas and pheochromocytomas express SSRs, are ^{68}Ga-DOTATATE avid at PET, and may be a treatment target for DOTATATE-coupled radionuclide therapies (Fig 8) (42,43). Treatment options for both entities are limited in patients with metastatic and inoperable tumors. ^{123}I-MIBG and ^{131}I-MIBG have been used as

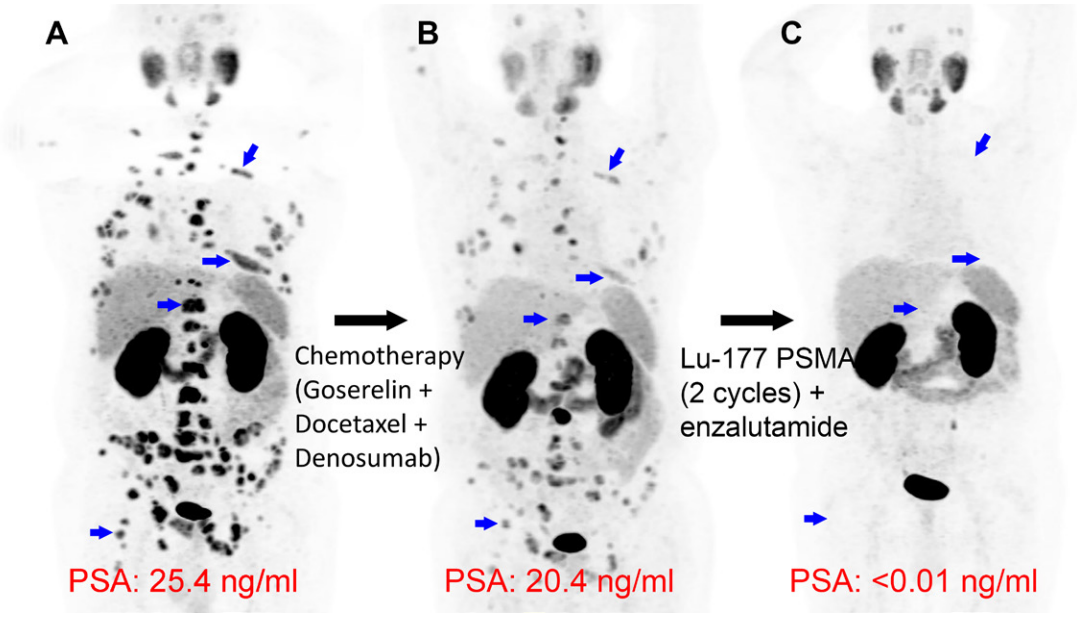

Figure 7: Complete treatment response after two cycles of lutetium 177 (^{177}Lu) prostate-specific membrane antigen (PSMA)–617 therapy. Images in a 63-year-old man with widely metastatic prostate cancer, with a Gleason score of 9 (4 + 5). **(A)** Gallium 68 (^{68}Ga) PSMA-617 PET/CT maximum intensity projection image demonstrates widespread metastatic disease, such as numerous bone lesions (blue arrows indicate select examples). **(B)** Following chemotherapy and hormonal therapy, persistent PSMA-avid metastatic lesions are observed on ^{68}Ga-PSMA-11 PET/CT image, with slight reduction in prostate-specific antigen level. **(C)** Following two cycles of ^{177}Lu-PSMA-617, there is complete resolution of metastatic PSMA uptake, with undetectable PSA. Blue arrows in the expected location of previous nodal uptake show the resolved lesions on ^{68}Ga-PSMA-11 PET/CT image.

a theranostic pair in combination with systemic chemotherapy for paragangliomas and pheochromocytomas, but this regimen has often failed to result in sustained remission, and bone marrow suppression is a critical disadvantage. Several relatively small clinical studies have investigated targeted radioligand therapies, including ^{177}Lu- or ^{90}Y-DOTATATE and -DOTATOC, in paragangliomas of the head, neck, abdomen, and urinary bladder (43–48). These early clinical studies have predominantly included inoperable paragangliomas, documenting stable disease and treatment response in many patients. SSR-targeted radionuclide therapies are reasonable therapies in such patients with limited alternative options, and ^{177}Lu-DOTATATE is a recommended treatment in the National Comprehensive Cancer Network guidelines for metastatic paragangliomas and pheochromocytomas (49). Future studies will need to examine the efficacy of this therapy in larger cohorts, such as the forthcoming ^{177}Lu-DOTATATE in Therapy of Inoperable Pheochromocytoma/Paraganglioma study (ClinicalTrials.gov no. NCT03206060). Further studies are also needed to determine the long-term outcomes of ^{177}Lu-DOTATATE, assess the impact of molecular subtypes of paragangliomas on treatment response, compare different radionuclides, and compare the therapy with other treatment modalities. For example, ^{177}Lu-DOTATATE may be better suited for small and medium-sized tumors, whereas ^{90}Y-peptide–receptor radionuclide therapy may be preferred for larger tumors (7,50). Recently, a high specific activity formulation of ^{131}I-MIBG (iobenguane) has become available that is thought to have an improved adverse effect profile compared with older formulations and has received FDA approval for use in unresectable, metastatic pheochromocytomas and paragangliomas (14,51). Based on expert consensus, ^{177}Lu-DOTATATE may be favored in patients with poor bone marrow reserve because of differences in toxicity, and high specific activity ^{131}I-MIBG may be favored in patients at greater risk for catecholamine crisis (51). Comparative studies between these agents will be needed in the future (14). At present, a theranostic strategy may inform the choice of radionuclide therapy on a case-by-case basis by using the diagnostic agent pair to assess the degree of binding of MIBG compared with that of DOTA-based peptides.

Meningiomas.— Meningiomas are classically ^{68}Ga-DOTATATE avid and potentially serve as an ideal treatment target for radionuclides coupled to DOTATATE. Treatment of meningiomas with β-emitting SSR-targeted radiopharmaceuticals has been described in numerous reports of treatment-refractory meningiomas (52–54). These preliminary reports suggest that treatment is well tolerated and appears to have some antitumor activity. Forthcoming clinical trials (ClinicalTrials.gov nos. NCT03971461 and NCT04082520) will provide future information about the efficacy of this treatment strategy.

^{177}Lu-PSMA-617 Therapy

Despite its name, PSMA expression is not truly prostate-specific and is observed in many other neoplasms. For many of these tumors, PSMA expression is found in the associated neovasculature rather than in the tumor cells themselves (55). However, a few other nonprostate tumors, such as adenoid cystic carcinoma, a salivary gland neoplasm, show high PSMA expression on tumor cells (56). A phase 2 clinical trial assessing ^{177}Lu-PSMA-617 treatment of advanced salivary gland cancers

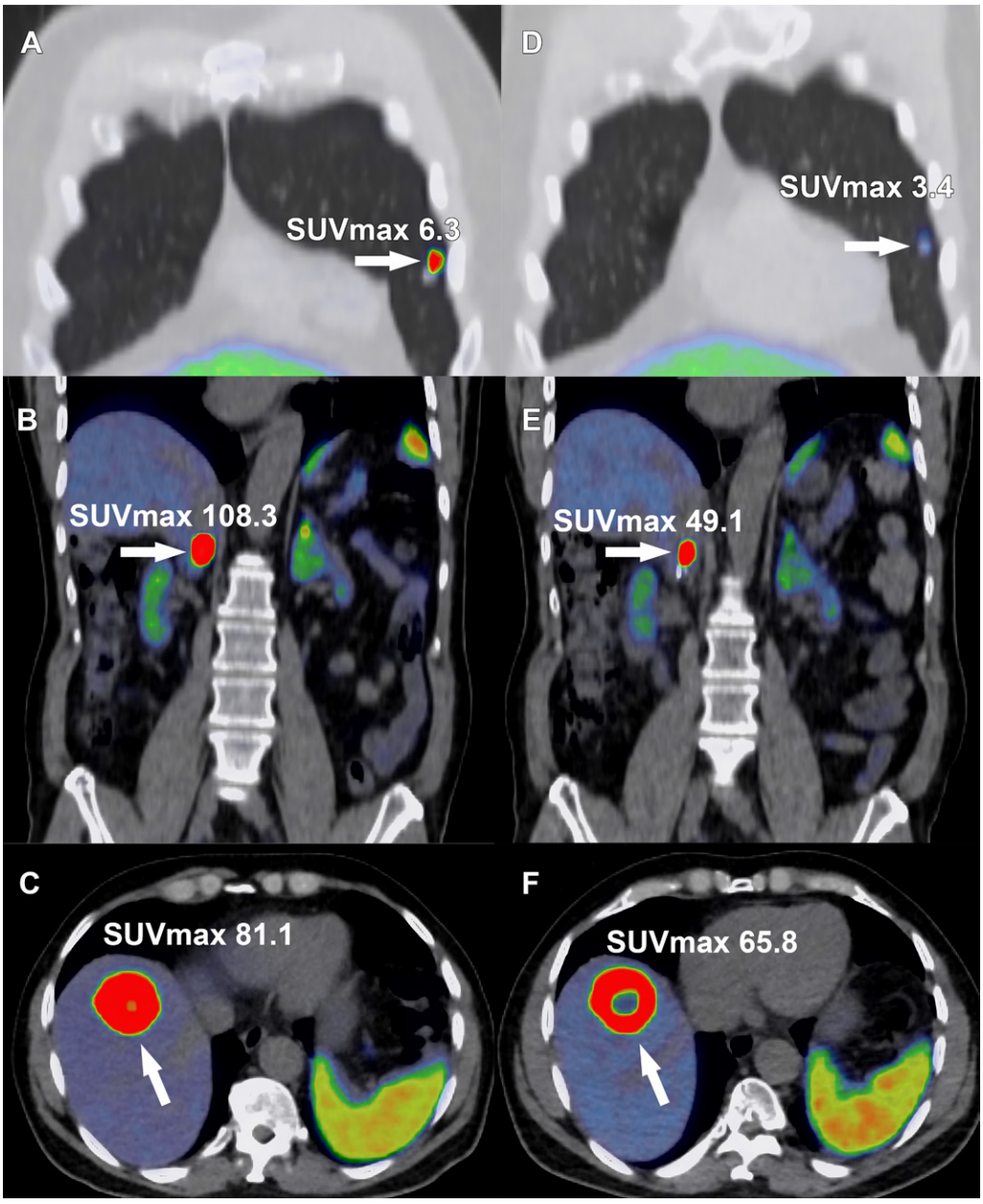

Figure 8: Images in a 68-year-old man with metastatic pheochromocytoma treated with four cycles of lutetium 177 (^{177}Lu) tetraazacyclododecane tetraacetic acid octreotate (DOTATATE). A right adrenal pheochromocytoma was resected 2 years previously, with subsequent development of hepatic, osseous, and pulmonary metastasis and inferior vena cava (IVC) tumor thrombus. Selected gallium 68 (^{68}Ga) DOTATATE PET/CT fusion images show a DOTATATE-avid **(A)** pulmonary metastasis (arrow), **(B)** IVC tumor thrombus (arrow), and **(C)** hepatic metastasis (arrow). Following completion of off-label ^{177}Lu-DOTATATE therapy, **(D)** the pulmonary metastases (arrow), **(E)** IVC tumor thrombus, and **(F)** hepatic metastasis decreased in radiotracer uptake level. Central photopenia indicating tumor necrosis increased with the treated hepatic metastasis (**E**, arrow). SUV_{max} = maximum standardized uptake volume.

(ClinicalTrials.gov no. NCT04291300) is currently enrolling patients, and a small of number of patients treated with ^{177}Lu-PSMA-617 thought to be targeting neovascular PSMA expression in glioblastoma, thyroid cancer, and hepatocellular carcinoma have been reported (57–60).

Re-treatment

The official FDA labeling for ^{177}Lu-DOTATATE therapy consists of a fixed four-dose series, each dose separated by 8 weeks. Similarly, the regimen for ^{177}Lu-PSMA-617 is up to six doses separated by 6 weeks each. However, even after completion of a standard course of therapy, clinicians have re-treated patients off-label with encouraging results that have been described in multiple retrospective series for ^{177}Lu-DOTATATE (61–64). A systematic meta-analysis of ^{177}Lu-DOTATATE re-treatment in patients with NETs included 13 studies. The median progression-free survival time was 12.52 months, and median overall survival was 26.78 months. Only two patients with therapy-

related myeloid neoplasms were reported (65). Overall, in patients with favorable responses to initial ^{177}Lu-DOTATATE for NETs, repeat treatment appears to be a reasonable option in the absence of alternatives, albeit based on mostly retrospective data. For ^{177}Lu-PSMA-617, a phase 2 trial re-treated 30% of the patients with subsequent progression of PSMA-positive disease, of which 73% experienced a PSA decline of 50% or greater with few grade 3 or 4 adverse events (66).

Investigational Uses of Dosimetry in Radionuclide Therapy

Dosimetry has potential investigational applications for ^{177}Lu-coupled radiopharmaceuticals. ^{177}Lu gives off a β-particle emission, which is used to kill cancer cells, but also gives off a γ-photon emission and thus can be imaged. As demonstrated in some reports, multiple-time-point imaging of ^{177}Lu-DOTATATE with planar whole-body γ-camera protocols and SPECT/CT can provide quantitative assessments of the radionuclide distribution within individual patients over time, permitting personalized dosimetry calculations for tumors and critical organs (eg, kidney). In theory, knowledge of the dose delivered could be used to appropriately adjust the activity of subsequent cycles and predict outcomes.

A notable example in the literature is the use of sodium–iodine 124 (^{124}I) PET imaging for thyroid cancer lesional dosimetry calculations to predict which patients would respond to Na^{131}I radioablation following sensitization with selumetinib (67). Other studies of Na^{124}I for thyroid cancer dosimetry have shown that the maximal dose could be increased using this approach (68); however, Na^{124}I does not have FDA regulatory approval and has not been implemented for routine clinical use.

^{177}Lu-DOTATATE Dosimetry

^{177}Lu-DOTATATE dosimetry is not yet routinely performed in clinical practice. ^{177}Lu-DOTATATE is typically administered as a fixed-activity regimen of 7.4 MBq (200 mCi) in four therapeutic infusions (or cycles of therapy) in patients able to tolerate the full dose, regardless of the radionuclide distribution. ^{177}Lu-DOTATATE could be imaged during each cycle of therapy, and dosimetry can be used to extrapolate an optimal injected activity for the subsequent cycle. A ^{177}Lu-DOTATATE dose response has been observed from the analysis of dosimetry data (69); however, no dosimetry data were reported or used to guide treatment in the landmark NETTER-1 prospective trial (22), and some smaller trials using dosimetry to guide therapy have not achieved significant correlation between tumor response outcomes and the delivered activity (70). The forthcoming COMPETE trial of ^{177}Lu-DOTATOC (ClinicalTrials.gov no. NCT03049189) will include dosimetry data from a large cohort, which may inform the use of this technique, and the forthcoming DOBATOC trial (ClinicalTrials.gov no. NCT04917484) will evaluate the use of dosimetry for guiding treatment dose compared with standard fixed-dose regimens. As experience with SSR-targeted radionuclide therapy has grown, more complex scenarios are arising, such as the use of extended or repeated cycles. One study used dosimetry to extend cycles of ^{177}Lu-DOTATATE until patients reached a threshold renal dose (23 Gy) or had other reasons to discontinue, such as bone marrow toxicity or progression. Response and survival outcomes were improved in those able to continue to higher doses, although selection bias was a notable limitation (71). Dosimetry may have a promising role in modulating dose regimens in the future and predicting patients likely to respond from further cycles of therapy—a gap in the existing literature that remains to be addressed in future targeted radionuclide therapy trials for NETs and other malignancies.

^{177}Lu-PSMA-617 Dosimetry

As with ^{177}Lu-DOTATATE, ^{177}Lu-PSMA-617 is administered using a fixed activity regimen in current clinical practice. Dosimetry may have prognostic value for prostate cancer radionuclide therapy. ^{177}Lu-PSMA-617 dosimetry has been performed with each cycle in the trial setting and shown to be predictive of PSA response. However, dosimetry has not been used to guide dose administration for prostate cancer radionuclide therapy or been reported in the major prospective TheraP or VISION trials (27,28).

Much-needed efforts to standardize dosimetry methods for radiopharmaceutical therapies are underway. Specifically, joint European Association of Nuclear Medicine and MIRD society guidelines on the dosimetry of ^{177}Lu with quantitative SPECT have been issued (72) and applied in the clinical trial setting. Dosimetry is often required for clinical use of external beam radiation, and there are emerging requirements for dosimetry for radiopharmaceuticals in some countries. However, whether dosimetry calculations should be required in the clinical use of ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 and the degree of benefit of using dosimetry to modify therapeutic dose in a patient-specific manner remains under debate.

An additional challenge of radionuclide therapy dosimetry is that α-particle emitters cannot be imaged successfully. An estimate of dosimetry is in fact still possible with a diagnostic surrogate radionuclide that emits γ rays, while acknowledging that the change in radionuclide may affect the biodistribution. For example, either ^{111}In or ^{225}Ac can be chelated in the same radiopharmaceutical, thus the version with ^{111}In can be used to calculate dosimetry with SPECT/CT (10). These measurements may assist in tailoring treatment by maximizing the dose-response relationship within safe limits of toxicity to critical organs. Ongoing work to establish the impact of dosimetry on patient outcomes and establish standardized methods to increase the feasibility of performing dosimetry at various centers is needed to realize the potential benefits.

Auger Electron Therapy

Proof of concept of Auger electron therapy has been shown preclinically, and the therapy has been used in very few clinical studies of cancer treatment (9), including pilot studies of iodine 125 (^{125}I) deoxyuridine and ^{131}I-deoxyrudine for metastatic colon cancer (73), ^{111}In-DTPA-octreotide for NETs (74,75), ^{111}In-DTPA-hEGF for breast cancer (76), and ^{125}I-murine anti–epidermal growth factor receptor monoclonal antibodies for glioblastoma (77).

Emerging Molecular Targets

Numerous potential theranostic targets are under investigation (78). Table 2 summarizes examples of current trials in humans with promising approaches.

Molecular agents related to bombesin are under active development for diagnostic PET and theranostic applications, with recent and ongoing early clinical studies. Bombesin, named following isolation from the *Bombina bombina*, or fire-bellied toad, activates G protein–coupled receptors, including the gastrin-releasing peptide receptor highly expressed in multiple human malignancies. Initially, gastrin-agonist radioligands were investigated with associated growth stimulation and adverse effects related to receptor activation (79). Subsequently, gastrin-antagonists have been developed, such as ^{177}Lu-RM2 and ^{177}Lu-NeoBOMB1, with improved pharmacokinetics and decreased concern of receptor activation–related adverse effects (80,81). Other challenges of the initial investigational gastrin-releasing peptide receptor ligands, including suboptimal pharmacokinetics, dose-limiting uptake in the pancreas, and metabolic instability related to proteolytic degradation, are potentially improved with the newer gastrin-antagonists and with concurrent use of peptidase inhibitors (80).

Fibroblast activation protein (FAP) inhibitors such as quinolone-based ligands are also an important class of radionuclide therapies under active development. Fibroblast proliferation is associated with many malignancies, and these tumor-associated cells become part of the tumor volume. FAP overexpression has been observed in tumor-associated cells in up to 28 different types of tumors (82). ^{90}Y-FAP-inhibitor (FAPI)–04 was an early radiopharmaceutical in this class used in a theranostic application for metastatic breast cancer in two patients (83), demonstrating a reasonable safety profile. FAP-based radionuclides are characterized by relatively low background activity compared with common radiopharmaceuticals, an attractive feature for a theranostic candidate (84). Multiple small early clinical studies in ^{90}Y-FAPI-46, ^{177}Lu-FAP-2286, and ^{177}Lu-FAPI-46 have been well tolerated in treatment-refractory sarcomas, pancreatic cancer, breast cancer, colorectal cancer, ovarian cancer, prostate cancer, and other FAP-expressing cancers (85–87). Tracer uptake in normal organs has varied with different agents of this class, with expression in the salivary glands, thyroid, and oral mucosa presenting possible disadvantages of some agents, to be explored in larger clinical studies (88).

Other potential molecular targets, such as human epidermal growth factor receptor 2, or HER2, expressed in breast cancer and gastrointestinal cancers, cholecystokinin-2 receptor ligand expressed in medullary thyroid cancer, melanocortin receptor subtype 1 expressed in melanoma, and the six transmembrane epithelial antigens of the prostate 1, or STEAP1, receptor expressed in prostate cancer are currently being investigated in clinical trials as potential candidates for theranostic pair development (Table 2).

Investigational Combination Therapies

Combined Radionuclide Therapies

Some medical practices in countries where ^{225}Ac-PSMA-617 is a clinical option promote the use of the α-particle emitter in patients whose cancer progressed after treatment with the β-particle emitter ^{177}Lu-PSMA-617. One argument is that differences in the radiocytotoxic mechanism of action may facilitate benefits from α emitters in tumors that are resistant to β-particle emissions in sequence (Fig 9) (89). Similarly, ^{225}Ac-DOTATATE α-particle therapy has been used for NETs in patients previously treated with ^{177}Lu-DOTATATE (90). The safety and feasibility of ^{177}Lu-PSMA-617 after $^{223}RaCl_2$ (Fig 5) have been demonstrated in the recent Radium Lutetium (or, RALU) study (91). Further trials are needed comparing the effects of α- and β-particle emitters and studying the effects of using them simultaneously in combined regimens.

Radionuclide Therapy with Cytotoxic Chemotherapy and Other Systemic Agents

Tumor heterogeneity, in terms of varied tumor size, varied differentiation, and molecular features, especially in the setting of heavily treated metastatic disease, may ultimately benefit from a variety of combined treatment strategies relying on different mechanisms of action.

Low-dose cytotoxic chemotherapy is frequently used as a radiosensitizing agent in conjunction with external-beam radiation in a multitude of malignancies. This synergy might be expected to translate into enhancement of the antineoplastic effect of radionuclide therapy. Some phase 2 studies of ^{177}Lu-DOTATATE in combination with cytotoxic chemotherapy (92–94) have suggested additive efficacy; however, there are concerns of increased long-term hematologic toxicity and subsequent secondary malignancies related to repairable DNA damage using this investigational approach. Improvement in survival has not yet been shown with combined radionuclide therapy and cytotoxic chemotherapy.

Likewise, combining hormonal therapies with ^{177}Lu-PSMA-617 is an important consideration in the clinical management of metastatic prostate cancer. The landmark VISION trial of ^{177}Lu-PSMA-617 permitted standard-of-care hormonal treatments; however, the additive impact of this combination has not yet been systematically investigated (28).

Other agents of interest in combination with radionuclide therapy are in early investigational stages. For example, poly (adenosine diphosphate–ribose) polymerase inhibitors may radiosensitize by inhibiting DNA repair and immune checkpoint inhibitors, which may augment an abscopal response to radiation-induced cell death.

Conclusion

In this review, we summarized various theranostic radiopharmaceuticals and their clinical use against a variety of cancers. Overall, theranostics for cancer imaging and treatment is rapidly evolving. Various emerging molecular targets and radiopharmaceuticals with different forms of radiation emission, such as α-emitting therapies, have a high potential to emerge as next-generation theranostics. Current and continued efforts to better estimate the dosimetry of therapeutic radiopharmaceuticals and quantify and monitor treatment response are necessary steps in the direction of individualized precision medicine for theranostics. Additional work will be needed to refine the role

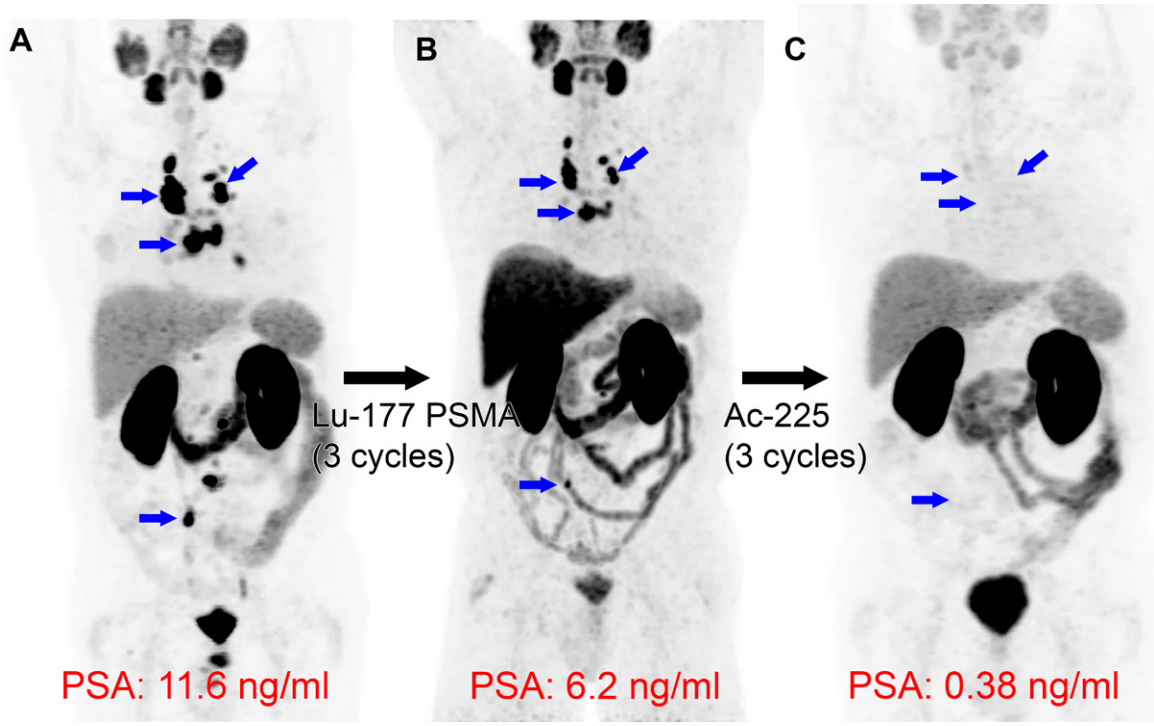

Figure 9: Actinium 225 (^{225}Ac) prostate-specific membrane antigen (PSMA) α-particle therapy following lutetium 177 (^{177}Lu) PSMA-617 β-particle therapy. Images in a 71-year-old man with widely metastatic prostate cancer, with a Gleason score of 7 (3 + 4), that progressed despite androgen deprivation therapy, taxane-based chemotherapy, and thoracic spine stereotactic radiation. **(A)** Baseline gallium 68 (^{68}Ga) PSMA-11 PET/CT image demonstrates intense PSMA uptake in many nodal metastases (blue arrows). **(B)** Following three cycles of the targeted β-particle therapy with ^{177}Lu-PSMA-617, the ^{68}Ga-PSMA-11 PET/CT image demonstrates persistent PSMA-avid disease (blue arrows), with a mild reduction in prostate-specific antigen (PSA). **(C)** Following three cycles of the targeted α-particle therapy with ^{225}Ac-PSMA-617, nearly complete resolution of uptake in the nodal metastases is observed (blue arrows in the location of previous nodal uptake), with a substantial reduction in PSA level.

of radionuclide therapy in combination with other modalities of cancer treatment.

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