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Beek, E.T. te; Burggraaf, J.; Teunissen, J.J.M.; Vriens, D.

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Erik T. te Beek[1,*], Jacobus Burggraaf[2], Jaap J. M. Teunissen[1] and Dennis Vriens[3]

The combined use of diagnostic and therapeutic radioligands with the same molecular target, also known as theranostics, enables accurate patient selection, targeted therapy, and prediction of treatment response. Radioiodine, bone-seeking radioligands and norepinephrine analogs have been used for many years for diagnostic imaging and radioligand therapy of thyroid carcinoma, bone metastases, pheochromocytoma, paraganglioma, and neuroblastoma, respectively. In recent years, radiolabeled somatostatin analogs and prostate-specific membrane antigen ligands have shown clinical efficacy in the treatment of neuroendocrine tumors and prostate cancer, respectively. Several candidate compounds are targeting novel theranostic targets such as fibroblast activation protein, C-X-C chemokine receptor 4, and gastrin-releasing peptide receptor. In addition, several strategies to improve efficacy of radioligand therapy are being evaluated, including dosimetry-based dose optimization, multireceptor targeting, upregulation of target receptors, radiosensitization, pharmacogenomics, and radiation genomics. Design and evaluation of novel radioligands and optimization of dose and dose schedules, within the complex context of individualized multimodal cancer treatment, requires a multidisciplinary approach that includes clinical pharmacology. Significant increases in the use of these radiopharmaceuticals in routine oncological practice can be expected, which will have major impact on patient care as well as (radio)pharmacy utilization.

The recent marketing authorization of several radioactive drugs for oncological imaging and therapy by the US Food & Drug Administration (FDA) and European Medicines Agency (EMA) reflects the significant advances of theranostics with radiopharmaceuticals in the last few years. Furthermore, several other novel theranostic agents, targeting some highly prevalent cancer types, are at various stages of clinical development.[1,2] With late-stage clinical trial successes, several candidate ligands underway, and the potential for widespread application in oncology, there is increasing recognition within healthcare and pharmaceutical industry of the utility of theranostic radiopharmaceuticals in molecular imaging and precision medicine, particularly regarding diagnosis and treatment of metastatic cancer. The design, evaluation, and use of novel radioligands and optimization of dose and dose schedules, within the complex context of individualized multimodal cancer treatment, requires a multidisciplinary approach that includes clinical pharmacology. When appropriate regulatory approvals and reimbursement policies are established, the use of diagnostic and therapeutic radiopharmaceuticals will likely increase significantly, with resultant increasing demand on radionuclide production and supply chain. Introduction of these radiopharmaceuticals into routine oncological practice will have major impact on patient care as well as (radio)pharmacy utilization. This article aims to provide a concise overview of the current status of clinical theranostics and highlight some trials with potential novel agents and other areas of ongoing research.

THERANOSTICS

Theranostics, a portmanteau of the words *therapeutics* and *diagnostics*, is essentially the combined use of diagnostic and therapeutic (radio)ligands with the same molecular target, enabling accurate patient selection, targeted therapy, and prediction of treatment response.[3] Ligands linked to radioactive nuclides emitting γ-radiation or β^+-particles (positrons) that target specific pathophysiologic processes or cell surface molecules in malignant tissues can be visualized *in vivo* with gamma cameras and positron emission tomography (PET) scanners, respectively. Analysis of their biodistribution allows detection of primary cancer and metastatic sites, thus enabling diagnostic imaging and staging. Similar ligands linked to nuclides emitting β^--or α-particles will also target those tissues and deliver cytotoxic ionizing radiation capable of inducing several types of DNA damage in the target tumor cells. This may include base damage, single-strand breaks, and double-strand breaks, either by direct ionization or by interaction of free radicals. Accordingly, highly localized therapeutic irradiation of multiple tumor sites can be achieved simultaneously, with only minimal radiation of the surrounding normal tissues.[4] Visualization of the diagnostic radioligand can confirm presence and anatomic location of a specific molecular target in order to select patients for targeted therapy with the therapeutic radioligand and to exclude patients who are unlikely to have a response to such therapy, thereby avoiding exposure to potentially toxic (and often costly) therapies.

[1]Department of Nuclear Medicine, Reinier de Graaf Hospital, Delft, The Netherlands; [2]Centre for Human Drug Research, Leiden, The Netherlands; [3]Department of Radiology, Section of Nuclear Medicine, Leiden University Medical Center, Leiden, The Netherlands. *Correspondence: Erik T. te Beek (e.tebeek@rdgg.nl)

Received February 9, 2022; accepted March 23, 2022. doi:10.1002/cpt.2598

The concept of theranostics is not new. Combinations of diagnostic and therapeutic iodine isotopes ^{123}I and ^{131}I have been used for decades in the treatment of hyperthyroidism (including Graves' disease, toxic adenoma, and multinodular goitre) and differentiated thyroid cancer. Also, the radioligands ^{123}I-mIBG and ^{131}I-mIBG have been used for many years in the diagnosis and treatment of pheochromocytoma, paraganglioma, and neuroblastoma. In recent years, theranostic ligands targeted against neuroendocrine tumors and prostate cancer have shown clinical efficacy, and several other ligands are at various stages of clinical development. With a few exceptions, most theranostic radioligands are composed of a radionuclide coupled to a carrier molecule, either covalently bound or linked with a bifunctional chelator, to direct the radionuclide to the molecular target *in vivo*.[5] Therapeutic radioligands thus combine specificity of molecular targeting with cytotoxicity of ionizing radiation. However, unlike external beam radiotherapy, radioligand therapy can be delivered systemically and, unlike targeted drugs, radioligand therapy is far less dependent on a detailed understanding of the involved downstream signaling pathways.[4] Delivery of significant levels of radioactivity is possible even at very low amounts of injected radioligand molecules. Pharmacodynamic effects of the radioligand at the theranostic target are generally far below measurable thresholds. Common nuclides for use in diagnostic radioligands include γ-emitters ^{99m}Tc (technetium-99m), ^{111}In (indium-111), ^{123}I, and positron-emitters ^{11}C (carbon-11), ^{18}F (fluorine-18), ^{64}Cu (copper-64), ^{68}Ga (gallium-68), ^{89}Zr (zirconium-89), and ^{124}I (**Table 1**). Nuclides suitable for therapeutic ligands include β^--emitters ^{89}Sr (strontium-89), ^{90}Y (yttrium-90), ^{131}I, ^{153}Sm (samarium-153), ^{166}Ho (holmium-166), ^{177}Lu (lutetium-177), ^{186}Re (rhenium-186), and ^{188}Re and α-emitters ^{211}At (astatine-211), ^{213}Bi (bismuth-213), ^{223}Ra (radium-223), and ^{225}Ac (actinium-225) among others. The most commonly used radionuclides for radioligand therapy by far are β^--emitting radionuclides, partly because of their wide availability.[4] Several therapeutic radionuclides emit both β^--particles and γ-radiation simultaneously, which allows imaging directly after administration of therapy. When feasible, post-therapy imaging is used for confirmation of radioligand delivery and evaluation of absorbed radiation in the target tissues and organs at risk. In recent years, encouraging results of ^{223}Ra-dichloride for treatment of bone metastases[6] has stimulated interest in α-emission radioligand therapy. An α-particle has higher linear energy transfer than β^--particles (leading to more irreparable double-strand DNA breaks in tumor cells), while the tissue range is shorter (limiting normal tissue toxicity).[4]

In addition to diagnostic imaging and therapeutic radiation, another potential application of theranostic ligands is radioguided surgery, which refers to the use of hand-held radiation detection probe systems for detection of radioligands during surgical procedures. Accumulation of radioligands in surgical targets, such as primary tumor or metastatic sites, can be detected with γ- or β^+-probes, providing real-time information on location, extent of disease, and evaluation of surgical margins. Intraoperative radioligand detection may be especially useful for identification and resection of small lesions with inconspicuous morphology or atypical location and during re-operation for recurrent or persistent disease after incomplete resection with positive margins, which can be challenging due to scar formation and altered anatomy. Radiation exposure to surgeons and other operating room personnel during these procedures remains well within annual limits for occupational workers.

Table 1 Radionuclides for diagnosis and therapy

Nuclide	Primary emission	Half-life
^{11}C	β^+	20.39 minutes
^{18}F	β^+	109.77 minutes
^{64}Cu	β^+ and β^-	12.7 hours
^{68}Ga	β^+	67.71 minutes
^{89}Sr	β^-	50.53 days
^{90}Y	β^-	64.1 hours
^{89}Zr	β^+	78.41 hours
^{99m}Tc	γ	6.02 hours
^{111}In	γ	2.8 days
^{123}I	γ	13.27 hours
^{124}I	β^+	4.18 days
^{131}I	β^- and γ	8.02 days
^{153}Sm	β^-	46.5 hours
^{166}Ho	β^-	26.8 hours
^{177}Lu	β^- and γ	6.65 days
^{186}Re	β^-	3.72 days
^{188}Re	β^-	17.0 hours
^{212}Pb	β^-	10.64 hours
^{213}Bi	α and β^-	45.59 minutes
^{211}At	α	7.21 hours
^{223}Ra	α	11.43 days
^{225}Ac	α	10.0 days

^{225}Ac, actinium-225; ^{211}At, astatine-211; ^{213}Bi, bismuth-213; ^{11}C, carbon-11; ^{64}Cu, copper-64; ^{18}F, fluorine-18; ^{68}Ga, gallium-68; ^{166}Ho, holmium-166; ^{123}I, iodine-123; ^{124}I, iodine-124; ^{131}I, iodine-131; ^{111}In, indium-111; ^{177}Lu, lutetium-177; ^{212}Pb, lead-212; ^{223}Ra, radium-223; ^{186}Re, rhenium-186; ^{188}Re, rhenium-188; ^{153}Sm, samarium-153; ^{89}Sr, strontium-89; ^{99m}Tc, technetium-99m; ^{90}Y, yttrium-90; ^{89}Zr, zirconium-89.

RADIOIODINE

Thyroid follicular cells accumulate iodine for thyroid hormone synthesis through sodium-iodide symporters expressed at the basolateral membrane, stimulated by thyrotropin (TSH). Most differentiated papillary and follicular thyroid cancer cells retain functional expression of sodium-iodide symporters.[7] Iodine uptake in thyroid cells allows diagnostic imaging with ^{123}I or ^{131}I and therapy with ^{131}I. Iodine scintigraphy for the detection of metastases or local recurrence of differentiated thyroid cancer is performed with low amounts of ^{131}I, usually 40–185 MBq. Treatment is performed with higher amounts of ^{131}I, usually 1.1 to 7.4 GBq, either as adjuvant ablative therapy following thyroidectomy or as therapy of advanced metastasized or recurrent disease (**Figure 1**).[8,9] Stimulation of ^{131}I uptake by high levels of TSH prior to radioiodine administration can be achieved by either withdrawal of levothyroxine use or by administration of recombinant human TSH (rhTSH). Short-term adverse effects include

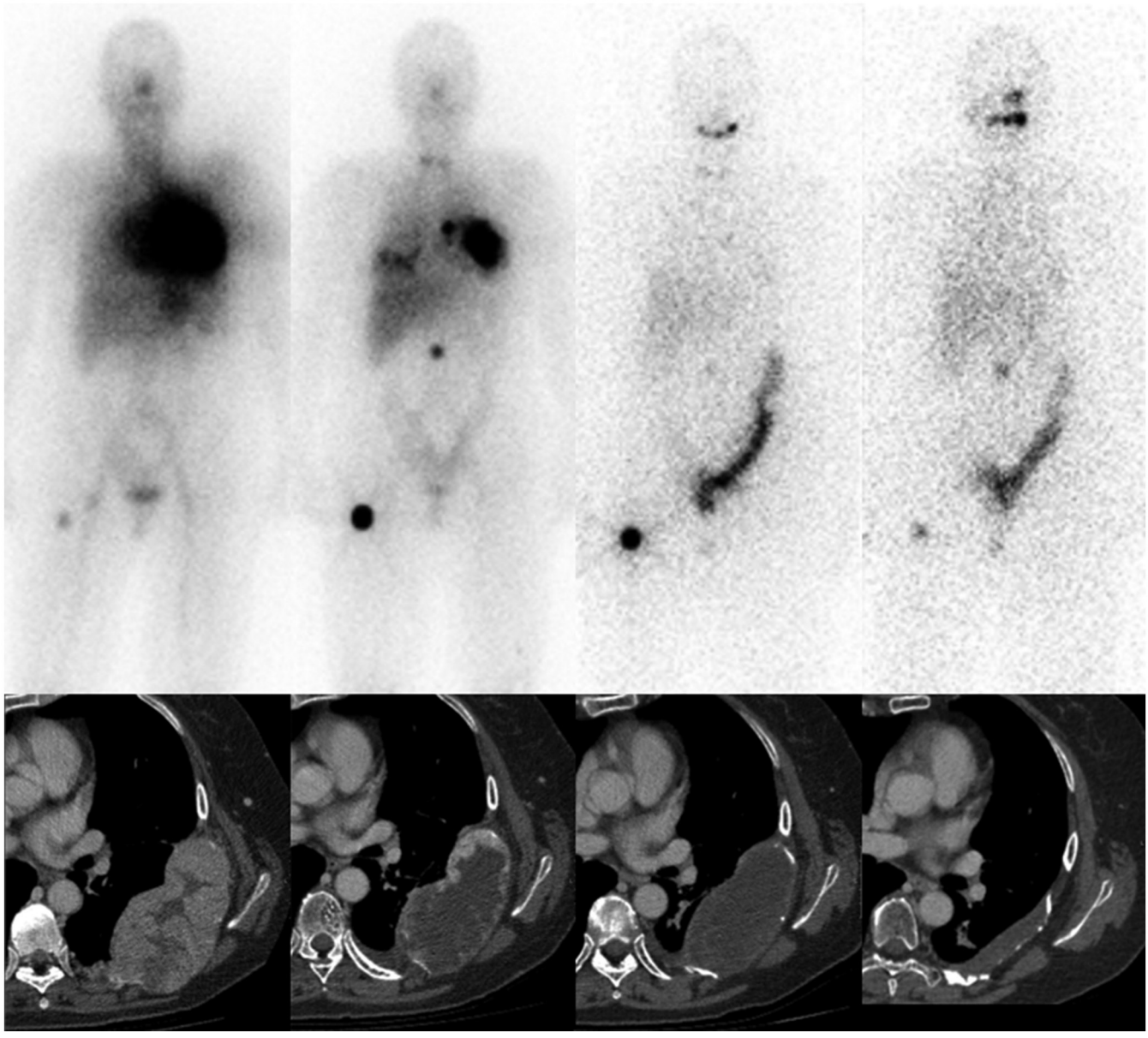

Figure 1 Example of ^{131}I imaging and therapy. A 55-year-old woman with follicular thyroid carcinoma pT3R1NxM1 with skeletal and pulmonary metastases. Total thyroidectomy and laminectomy with fixation of C7 was performed, followed by external beam radiotherapy of a metastasis in the sixth left rib. Subsequently, multiple therapies with ^{131}I were administered. Successive post-therapy scintigrams and CT scans demonstrate regression of the rib lesion. Also, a metastatic lesion in the right femur is visible, which demonstrates only minimal ^{131}I accumulation at the first therapy, likely due to competition with the extreme ^{131}I uptake in the rib lesion. At the second therapy, the femur lesion showed improved ^{131}I uptake, with clear regression at subsequent post-therapy scans. Thyroglobulin levels decreased from 6112 μg/L at first therapy to 58.9 μg/L at fourth therapy. The scans also show physiological activity in salivary glands, liver, bowels, and bladder. CT, computed tomography; C7, cervical vertebra 7; ^{131}I, iodine-131.

sialoadenitis, gastrointestinal symptoms, and radiation thyroiditis if large remnants of thyroid tissue are present.

Treatment with ^{131}I is often administered as adjuvant therapy after thyroidectomy for ablation of residual thyroid tissue following gross surgical resection, to decrease the risk of persistent or recurrent disease and to facilitate surveillance and early detection of disease recurrence by measurement of serum thyroglobulin. Postoperative thyroid remnant ablation improves overall survival in high-risk patients,[10] but survival benefit in low-risk patients has not been unequivocally demonstrated. Randomized controlled trials proving treatment efficacy on outcomes of low-risk thyroid cancer are lacking, and long-term observational studies have demonstrated inconsistent findings.[11] Current American Thyroid Association (ATA) guidelines recommend remnant ablation after thyroidectomy in high-risk patients, but not routinely in low-risk patients.

In advanced stages, treatment with ^{131}I has been shown to be an effective therapy for metastasized or recurrent disease

and can potentially achieve curation or long-term remission especially in young patients.[9,12] However, following further dedifferentiation and loss of functional sodium-iodide symporter expression, thyroid cancer may become refractory to ^{131}I therapy.

BONE-SEEKING RADIOPHARMACEUTICALS

Radiolabeled biphosphonates and ^{18}F-fluoride accumulate in bone, reflecting local blood flow and mineralization due to osteoblast activity. Bone scintigraphy with ^{99m}Tc-labeled biphosphonates, such as ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) or ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HDP), has been widely used for decades for the detection and monitoring of skeletal metastases.[13] PET imaging with the positron-emitting ^{18}F-NaF has superior contrast and spatial resolution to bone scintigraphy, but is also more costly.

The β^--emitting radiopharmaceuticals ^{89}Sr-dichloride, ^{153}Sm-EDTMP (ethylenediamine tetramethylene phosphonic acid) (also known as ^{153}Sm-lexidronam), ^{186}Re-HEDP (1-1-hydroethylidene diphosphate) and ^{188}Re-HEDP have also been used for many years in the palliation of metastatic bone cancer. ^{89}Sr dichloride acts as a calcium mimetic *in vivo*, whereas ^{153}Sm, ^{186}Re and ^{188}Re are coupled to the biphosphonates EDTMP and HEDP to achieve high affinity for hydroxyapatite *in vivo* (**Figure 2**). Pain response rates vary between 40% and 95%, usually starting 1–4 weeks after treatment and continuing for several months.[14] Adverse effects include transient pain flare and myelosuppression with thrombocytopenia or neutropenia, which is generally mild and reversible.

The α-emitter ^{223}Ra-dichloride, which also acts as a calcium mimetic *in vivo*, has been shown to be efficacious in the treatment of bone metastases of prostate cancer. A prospective, randomized, and placebo-controlled phase III trial (the ALSYMPCA trial) in

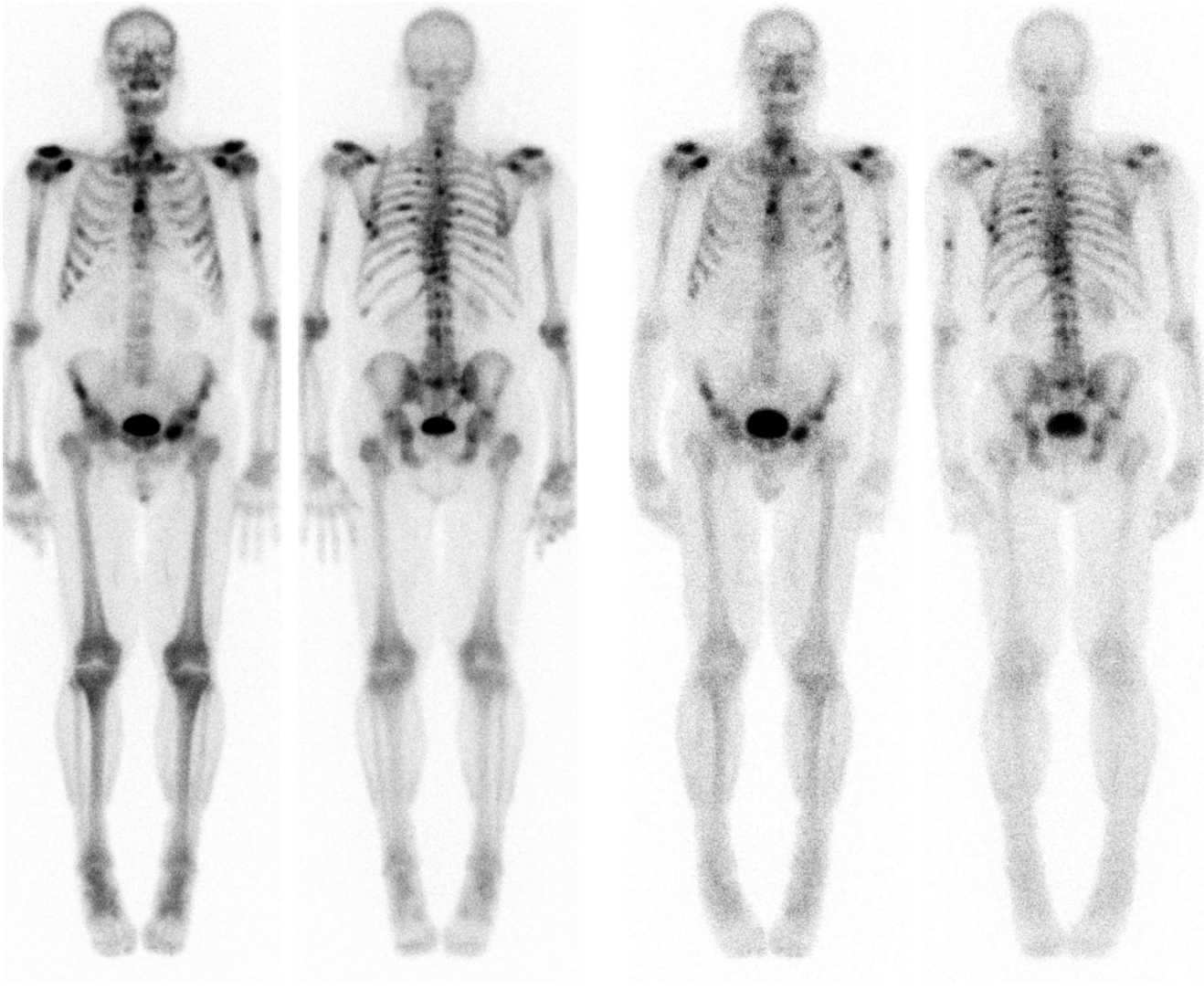

Figure 2 Example of imaging and therapy with bone-seeking radiopharmaceuticals. A 79-year-old man with castration-resistant prostate cancer with lymph node and skeletal metastases. The left panel shows anterior and posterior views of diagnostic ^{99m}Tc-HDP scintigraphy, demonstrating multiple skeletal metastases in left humerus, sternum, ribs, multiple vertebrae, and pelvis. The right panel shows anterior and posterior views of post-therapy scintigraphy after administration of ^{153}Sm-EDTMP therapy, demonstrating similar biodistribution. ^{153}Sm-EDTMP, samarium-153 ethylene diamine tetra methylene phosphonate; ^{99m}Tc-HDP, technetium-99m–hydroxymethylene diphosphonate.

patients with progressive castration-resistant prostate cancer with symptomatic bone metastases demonstrated that treatment with ^{223}Ra-dichloride significantly prolongs overall survival (median 14.0 vs. 11.2 months) and the time to first skeletal event (median 15.6 vs. 9.8 months).[6] Treatment with ^{223}Ra-dichloride was associated with a low incidence of myelosuppression with grade 3 or 4 anemia, neutropenia, and thrombocytopenia in 13%, 3%, and 7% of patients, respectively. ^{223}Ra-dichloride was approved by the FDA and EMA in 2013 for the treatment of castration-resistant prostate cancer with symptomatic bone metastases and absence of visceral metastases.

NOREPINEPHRINE ANALOGS

Catecholamine-secreting tumors such as pheochromocytoma, paraganglioma, and neuroblastoma originate from neural crest cells with abundant norepinephrine transporters on their surface, which can take up the norepinephrine analog *meta*-iodobenzylguanidine (mIBG) labeled with ^{123}I or ^{131}I, and store in noradrenergic neurosecretory granules. Scintigraphy with ^{123}I-mIBG has been used for many years in the diagnostic workup of primary or metastatic pheochromocytoma.[15] In recent years, however, PET–computed tomography (CT) imaging with other radioligands such as 6-[^{18}F]fluoro-L-dihydroxyphenylalanine (^{18}F-DOPA) has been shown to be superior to ^{123}I-mIBG scintigraphy,[16] although availability is more limited. Also, ^{18}F-labeled *meta*-fluorobenzylguanidine (^{18}F-mFBG) is being evaluated as novel PET tracer.

Scintigraphy with ^{123}I-mIBG is also used for target confirmation and treatment planning prior to therapy with ^{131}I-mIBG (**Figure 3**). In metastasized pheochromocytoma and paraganglioma, therapy with ^{131}I-mIBG has demonstrated a significant effect on tumor volume (disease stabilization in 52%, partial response in 27%, and complete response in 3%) and on catecholamine excess (stable disease in 21%, partial response in 40%, and complete response in 11%).[17] Adverse effects include hematological toxicity with grade 3–4 neutropenia and thrombocytopenia occurring in up to 87% and 83% of treatments, respectively. More recently, a high-specific-activity preparation of ^{131}I-mIBG was developed.[18] In conventional low-specific-activity preparations of ^{131}I-mIBG using inefficient labeling procedures, more than 99% of the mIBG molecules are not labeled with ^{131}I and compete with the few ^{131}I-labeled mIBG molecules for uptake by norepinephrine transporters, thus lowering uptake of therapeutically active ^{131}I-mIBG. The primary end point of the trial was a reduction of 50% or more in baseline antihypertensive medication lasting at least 6 months, which occurred in 25% of patients. Among the patients with evaluable disease, 69% had stable disease and 23% had partial response. High-specific-activity ^{131}I-mIBG received marketing authorization from the FDA in 2018.

SOMATOSTATIN ANALOGS

Somatostatin is a peptide hormone produced by the hypothalamus, pancreas, gastrointestinal tract, and other tissues that inhibits the release of growth hormone and many other hormones and secretory proteins. Most neuroendocrine tumors and carcinoids overexpress somatostatin receptors (mostly the SSTR2 receptor subtype) on their surface.[19] Also, the majority of pheochromocytomas, paragangliomas, and meningiomas strongly express somatostatin receptors. Several somatostatin analog peptides conjugated with DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) have been developed that can be labeled with positron emitters for diagnostic imaging and with β^-- or α-emitters for therapy, including DOTA-Phe1-Tyr3-Octreotide (DOTATOC), DOTA-NaI3-Octreotide (DOTANOC), and DOTA-Tyr3-Octreotate (DOTATATE).

Diagnostic PET-CT imaging with somatostatin analogs has demonstrated high sensitivity for detection of primary and metastatic neuroendocrine tumors (**Figure 4**), superior to conventional imaging including ^{111}In-pentetreotide scintigraphy, CT, and magnetic resonance imaging.[20,21] Currently, no clinically relevant

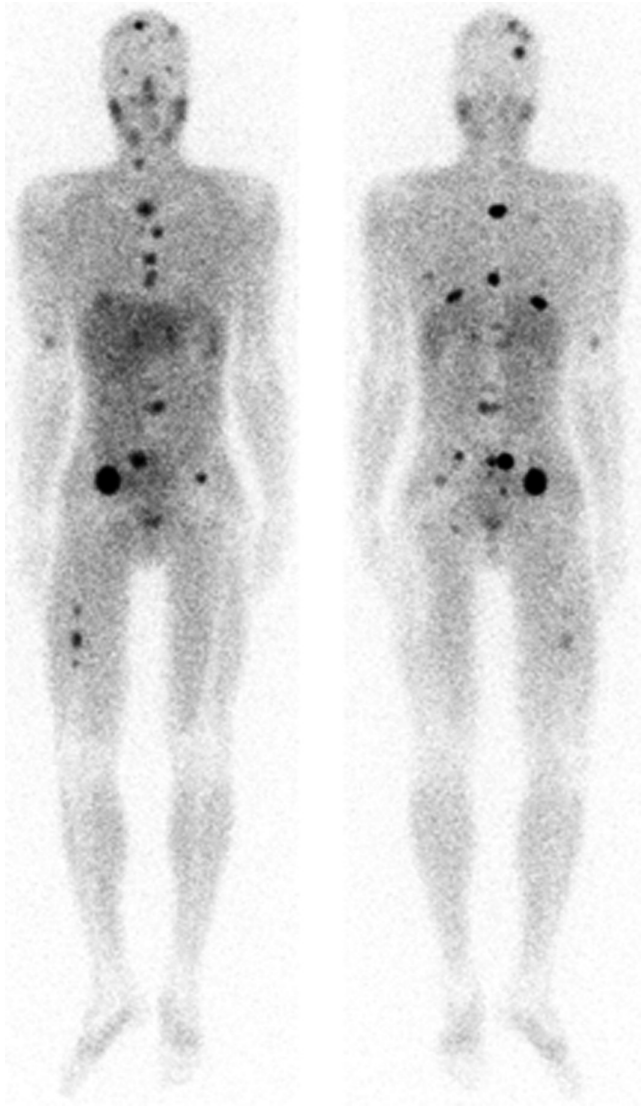

Figure 3 Example of ^{123}I-mIBG imaging. A 21-year-old man with a SDHB-mutated catecholamine-secreting para-aortic paraganglioma with lymph node metastases and skeletal metastases. The scan also shows physiological activity in salivary glands, liver, spleen, skeletal muscle, and bladder. ^{123}I-mIBG, iodine-123 *meta*-iodobenzylguanidine; SDHB, succinate dehydrogenase B subunit.

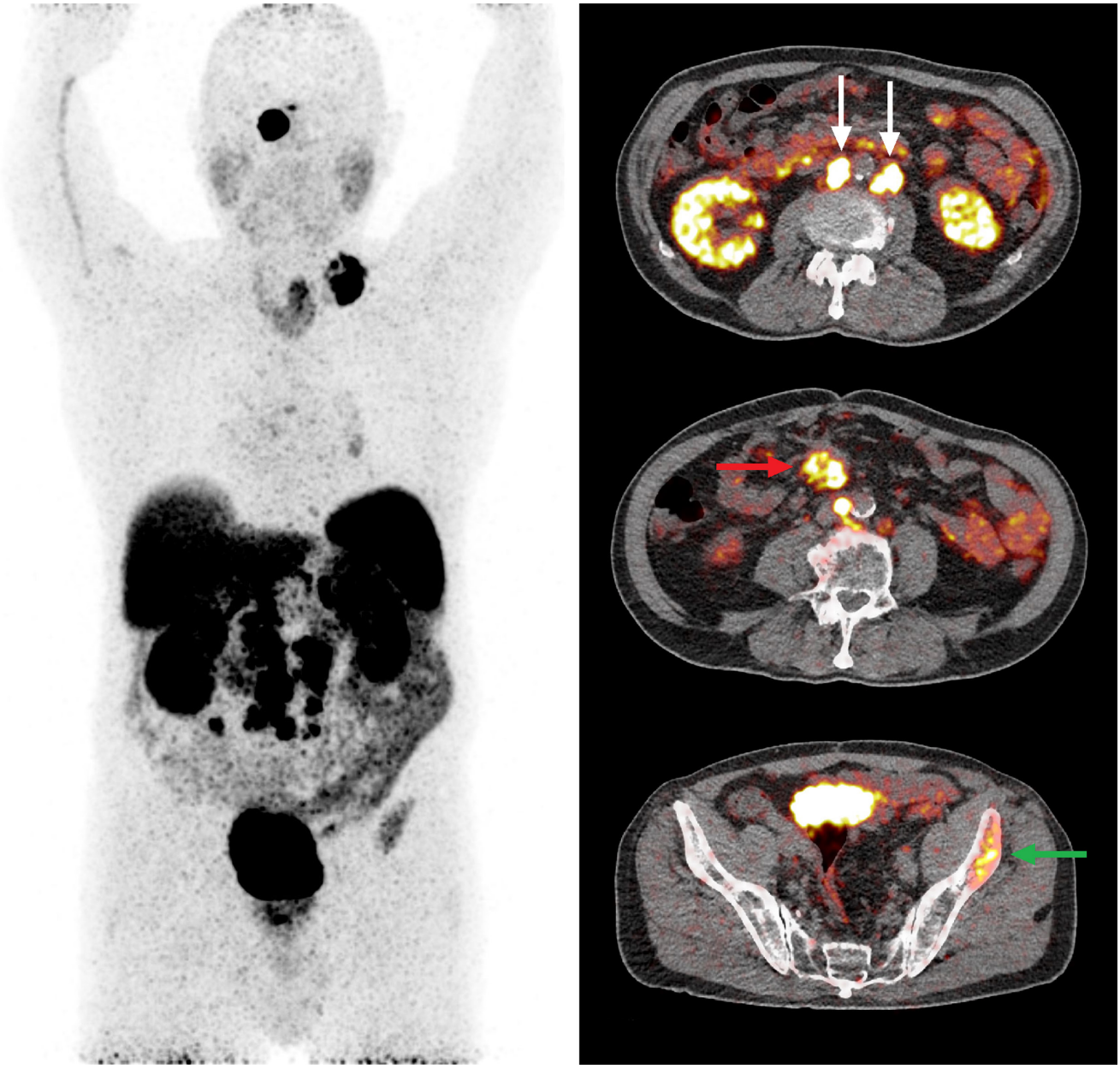

Figure 4 Example of ^{68}Ga-DOTATOC imaging. An 80-year-old man with a grade 1 neuroendocrine tumor. PET-CT imaging demonstrates the primary lesion in the small intestine (*red arrow*) with para-aortic (*white arrows*) and supraclavicular lymph node metastases and an osseous metastasis in the left iliac bone (*green arrow*). Also, an intracranial lesion is visible, probably a meningioma. The scan also shows physiological activity in pituitary gland, salivary glands, thyroid gland, liver, spleen, kidneys, adrenal glands, bowels, and bladder. ^{68}Ga-DOTATOC, gallium-68-DOTA-Phe1-Tyr3-Octreotide; PET-CT, positron emission tomography–computed tomography. [Color figure can be viewed at wileyonlinelibrary.com]

differences in detection rates between the different somatostatin analog tracers have been demonstrated. PET-CT imaging with ^{68}Ga-DOTATATE has also demonstrated high sensitivity for detection of metastatic pheochromocytoma and paraganglioma.[22] The diagnostic ligands ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, and ^{64}Cu-DOTATATE have been approved for detection of neuroendocrine tumors by the FDA in 2016, 2019, and 2020, respectively.

Radioligand therapy with somatostatin analogs, often designated as peptide receptor radioligand therapy, mostly using the β^--emitter ^{177}Lu has been shown to be an effective therapy. Initial clinical studies of ^{177}Lu-DOTATATE in patients with metastasized gastroenteropancreatic neuroendocrine tumors demonstrated favorable tumor response rates and progression-free survival, compared with the limited number of alternative treatment modalities, with few adverse effects.[23,24] Median overall survival was 63 months and median progression-free survival was 29 months, significantly longer than in historical controls. Complete or partial response was obtained in 39% and stable disease in 43%. Adverse effects included grade 3 or 4 hematologic toxicity in 9.5% of patients, acute leukemia in 0.7%, and myelodysplastic syndrome in 1.5%. Subsequently, ^{177}Lu-DOTATATE was evaluated in a prospective randomized phase III trial (the NETTER-1 trial) in patients with

inoperable locally advanced or metastasized well-differentiated grade 1 and 2 midgut neuroendocrine tumors, who were randomly assigned to receive treatment with ^{177}Lu-DOTATATE or high dose octreotide long-acting release (LAR).[25] Treatment with ^{177}Lu-DOTATATE was administered as intravenous infusions of 7.4 GBq every 8 weeks, with a total of four cycles. Expression of somatostatin receptors on target lesions was confirmed with somatostatin receptor imaging prior to randomization. Treatment with ^{177}Lu-DOTATATE resulted in markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR with clinically significant myelosuppression occurring in <10% of patients. At the time of data cutoff for primary analysis, the primary end point progression-free survival was 65.2% in the ^{177}Lu-DOTATATE group and 10.8% in the control group.[25] Based on these phase III results, ^{177}Lu-DOTATATE received marketing authorization from the EMA in 2017 and from the FDA in 2018. Long-term follow-up results were recently published, which confirmed a favorable safety profile.[26] In total, 2% of patients developed myelodysplastic syndrome after receiving ^{177}Lu-DOTATATE treatment and no cases of acute myeloid leukemia were reported. In contrast to the markedly longer progression-free survival, the final overall survival did not differ significantly between the study groups (median 48.0 months in the ^{177}Lu-DOTATATE group and 36.3 months in the control group), but confounding factors included a high rate of crossover (36% of control patients received ^{177}Lu-DOTATATE treatment in the follow-up phase of the trial), subsequent use of other anticancer treatments (24% of patients received further antineoplastic agents), and missing data (20% of patients were censored because of consent withdrawal or loss to follow-up). Nevertheless, an arguably clinically relevant difference of 11.7 months in median overall survival was recorded.[26]

The NETTER-2 study is an ongoing phase III trial evaluating ^{177}Lu-DOTATATE as a first-line treatment of inoperable locally advanced or metastasized well-differentiated grade 2 and 3 gastroenteropancreatic neuroendocrine tumors (NCT03972488, **Table 2**). Other ongoing phase III trials are comparing ^{177}Lu-DOTATOC with everolimus (COMPETE trial, NCT03049189) or best standard of care (COMPOSE trial, NCT04919226). Radiolabeled somatostatin analogs may also have efficacy as neoadjuvant therapy prior to surgery. A retrospective study of ^{177}Lu-DOTATATE as neoadjuvant therapy in locally advanced unresectable gastroenteropancreatic neuroendocrine tumors to decrease tumor size demonstrated that 26% of tumors became resectable.[27] A prospective phase II trial of neoadjuvant ^{177}Lu-DOTATATE therapy prior to surgery of pancreatic neuroendocrine tumors at high risk of recurrence is currently ongoing (NCT04385992). The use of somatostatin analogs for radioguided surgery was evaluated in a prospective study in surgical candidates with gastroenteropancreatic neuroendocrine tumors, pheochromocytoma, and paraganglioma, which demonstrated that radioguided surgery with ^{68}Ga-DOTATATE is feasible and highly sensitive for intraoperative lesion detection.[28] Another phase I study evaluating radioguided surgery using ^{68}Ga-DOTATATE is underway (NCT03623984). Several studies, mostly small retrospective series and case reports, have suggested that ^{177}Lu-DOTATATE may also be effective in

Table 2 Overview of currently ongoing clinical trials with theranostic radioligands

Radioligand	Trials
Somatostatin analogs	
^{177}Lu-DOTATATE	NCT03972488, NCT04385992, NCT03206060
^{177}Lu-DOTATOC	NCT03049189, NCT04919226, NCT04276597
^{177}Lu-satoreotide tetraxetan	
^{212}Pb-DOTAMTATE	NCT03466216
PSMA ligands	
^{68}Ga-PSMA	NCT04987086, NCT05170555, NCT04750473, NCT03857087, NCT03903419, NCT05006326, NCT04310540, NCT04762888, NCT04801264
^{18}F-DCFPyL	NCT04573231, NCT03811899, NCT05095519
^{177}Lu-PSMA-617	NCT04689828, NCT04720157, NCT04343885, NCT04443062, NCT04430192
^{177}Lu-PSMA-I&T	NCT04647526, NCT04297410, NCT04291300
^{225}Ac-PSMA-617	NCT04597411
FAP inhibitors	
^{68}Ga-FAPI-04	NCT05003427, NCT04441606
^{68}Ga-FAPI-46	NCT04457232, NCT04147494, NCT04457258, NCT04459273, NCT05172310
^{68}Ga-FAPI-2286	NCT04621435
^{177}Lu-FAP-2286	NCT04939610
^{68}Ga- and ^{177}Lu-FAPI (specific inhibitor unknown)	NCT04554719, NCT05034146, NCT04849247
CXCR4 ligands	
^{68}Ga-pentixafor	NCT04504526, NCT05093335, NCT03335670, NCT04561492
GRPR ligands	
^{68}Ga-NOTA-RM26	NCT05001204
^{68}Ga-DOTA-NeoBOMB1	NCT03698370
^{177}Lu-NeoBOMB1	NCT03872778
Radioguided surgery	
^{68}Ga-DOTATATE	NCT03623984
^{111}In-PSMA-I&T	NCT04300673
^{99m}Tc-PSMA-I&S	NCT03857113, NCT04857502, NCT04832958
Dosimetry	
^{177}Lu-DOTATATE	NCT02743741
^{177}Lu-DOTATOC	NCT04917484
Multireceptor targeting	
^{68}Ga-PSMA-617, ^{68}Ga-DOTATATE and ^{18}F-FDG	NCT04000776

(Continued)

Table 2 (Continued)

Radioligand	Trials
Receptor upregulation	
^{131}I	NCT03244956, NCT04619316, NCT04554680, NCT04462471, NCT04858867, NCT02152995
^{68}Ga-PSMA	NCT04391556
^{18}F-PSMA-1007	NCT03876912
Radiosensitization	
^{223}Ra-dichloride	NCT03574571, NCT04090398, NCT03317392, NCT04109729
^{177}Lu-DOTATATE	NCT02736448, NCT04086485, NCT04375267, NCT05053854, NCT04750954, NCT04525638
^{177}Lu-DOTATOC	NCT04194125
^{177}Lu-PSMA-617	NCT03874884, NCT03658447
Radiation genomics	
^{177}Lu-DOTATATE	NCT03667092

^{225}Ac, actinium-225; CXCR4, chemokine receptor 4; FAP, fibroblast activation protein; ^{18}F, fluorine-18; ^{68}Ga, gallium-68; GRPR, gastrin-releasing peptide receptor; ^{177}Lu, lutetium-177; ^{212}Pb, lead-212; ^{223}Ra, radium-223; DCFPyL, 2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid; DOTATATE, DOTATyr^3-Octreotate; DOTATOC, DOTA-Phe^1-Tyr^3-Octreotide; FDG, fluorodeoxyglucose; PSMA, prostate-specific membrane antigen.

treatment of metastatic and locally advanced pheochromocytoma and paraganglioma.[29] Prospective phase II trials evaluating ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC treatment in pheochromocytoma and paraganglioma (NCT03206060, NCT04276597) are currently ongoing.

Several other candidate compounds targeting somatostatin receptors are being evaluated. A modification of ^{177}Lu-DOTATATE with an extended biological half-life and increased bioavailability, ^{177}Lu-DOTA-EB-TATE, has shown increased tumor-absorbed radiation dose with acceptable hematotoxicity.[30] Also, the use of antagonists instead of agonists has been proposed, because some antagonists can bind to somatostatin receptors in both active and inactive states and thus show higher tumor uptake than agonists, which can only bind to receptors in active state. The diagnostic somatostatin receptor antagonists ^{68}Ga-satoreotide tetraxetan (also known as ^{68}Ga-OPS202), ^{68}Ga-NODAGA-LM3, and ^{68}Ga-DOTA-LM3[31,32] have shown favorable biodistribution and high tumor uptake, while the first clinical studies with the therapeutic antagonists ^{177}Lu-satoreotide tetraxetan and ^{177}Lu-DOTA-LM3 have shown encouraging response rates.[33,34] Also, α-emitting somatostatin analogs are currently being evaluated. Preliminary short-term results of ^{225}Ac-DOTATATE therapy in a small group of neuroendocrine tumor patients who were stable or refractory to previous ^{177}Lu-DOTATATE therapy indicate high response rates, low toxicity profile, and significant improvements in quality of life, while long-term results are pending.[35] Similarly promising results were obtained with ^{225}Ac-DOTATATE therapy in a small series of patients with advanced-stage paraganglioma, including patients with prior ^{131}I-mIBG or ^{177}Lu-DOTATATE therapy, with similarly encouraging results.[36] A clinical phase I trial with the somatostatin analog ^{212}Pb–DOTAMTATE is currently ongoing (NCT03466216). The nuclide ^{212}Pb (lead-212) decays by β^- emission into the α-emitters ^{212}Bi and ^{212}Po (polonium-212). Preliminary results of this ongoing trial suggest that ^{212}Pb-DOTAMTATE is well tolerated with objective radiological response rate of 80%.[37]

PROSTATE-SPECIFIC MEMBRANE ANTIGEN LIGANDS

Prostate-specific membrane antigen (PSMA), also known as glutamate carboxypeptidase II, is a type II transmembrane protein found in the normal prostate, proximal renal tubules, small intestine, salivary glands, lacrimal glands, and astrocytes. PSMA is significantly overexpressed in most prostate cancer cells, increasing with higher tumor grade and hormone-refractory disease.[38] In recent years, PSMA has emerged as a key target for molecular imaging and radioligand therapy of prostate cancer. In addition, PSMA is also expressed in several other cancer types, including salivary gland cancer (especially adenoid cystic carcinoma and salivary duct carcinoma), glioblastoma, thyroid cancer, hepatocellular carcinoma and renal cell carcinoma, mostly in neovascular endothelial cells.[39]

Several diagnostic PSMA ligands have been developed, including the ^{68}Ga-labeled compounds PSMA-11 (also known as PSMA-HBED-CC) and PSMA-I&T and the ^{18}F-labeled compounds 2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid (DCFPyL) and PSMA-1007. The utility of PET-CT imaging with PSMA ligands has been evaluated in many studies that have demonstrated high accuracy for identifying pelvic nodal or distant metastatic disease at primary staging of high-risk prostate cancer and high rates of lesion detection at biochemical recurrence (**Figure 5**), far superior to conventional CT imaging and bone scintigraphy.[40–44] A meta-analysis found no significant differences in detection rates between the different PSMA tracers, at least in the biochemical recurrence setting.[45] The diagnostic ligands ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL were approved by the FDA in 2020 and 2021, respectively.

Radioligand therapy with PSMA ligands has mostly been performed with ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T. Initial clinical studies evaluated patients with progressive metastatic castration-resistant prostate cancer who were treated on a compassionate use basis. Biochemical response was demonstrated in 36–45% of patients with a favorable safety profile.[46,47] The therapeutic ligand ^{177}Lu-PSMA-617 was evaluated in a prospective phase II trial (the LuPSMA trial) in patients with metastatic castration-resistant prostate cancer with progressive disease after standard treatment (including taxane-based chemotherapy and second-generation anti-androgens).[48] Prior to treatment, ^{68}Ga-PSMA-11 imaging was performed to confirm high PSMA expression at metastatic sites. Treatment with ^{177}Lu-PSMA-617 resulted in a PSA decline of 50% or more in 57% of patients, with a low toxicity profile, and improved quality-of-life parameters, especially in patients with pain. Another phase II trial (the TheraP trial) compared ^{177}Lu-PSMA-617 with cabazitaxel in patients with metastatic castration-resistant prostate cancer with progressive disease after treatment with docetaxel.[49] Reductions in PSA levels larger than 50% were more frequent in the ^{177}Lu-PSMA-617 group than in the cabazitaxel group (66% vs. 37% by intention to treat and 66% vs. 44%

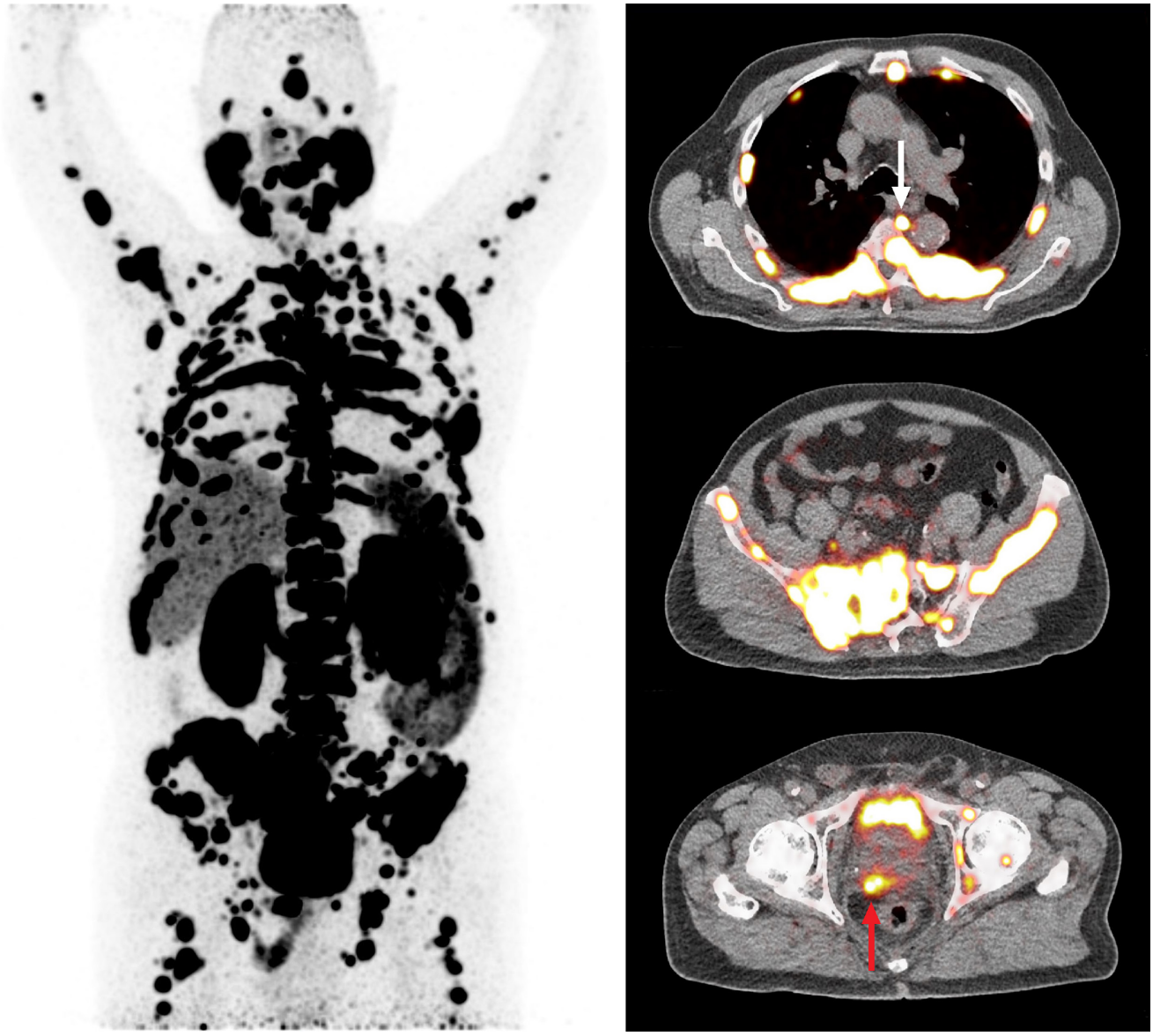

Figure 5 Example of ^{68}Ga-PSMA-11 imaging. A 72-year-old man with Gleason 8 prostate cancer and a PSA level of 847 μg/L. PET-CT imaging demonstrates the primary lesion in the prostate (*red arrow*), multiple lymph node metastases (*white arrow*), and extensive skeletal metastases. The scan also shows physiological activity in lacrimal glands, salivary glands, liver, spleen, kidneys, small bowels, and bladder. ^{68}Ga-PSMA-11, gallium-68-prostate-specific membrane antigen 11; PET-CT, positron emission tomography–computed tomography; PSA, prostate-specific antigen. [Color figure can be viewed at wileyonlinelibrary.com]

by treatment received) with fewer grade 3 or 4 adverse events. Subsequently, ^{177}Lu-PSMA-617 was evaluated in a prospective randomized phase III trial (the VISION trial) in patients with metastatic castration-resistant prostate cancer with progressive disease after anti-androgen therapy and taxane regimens, who were randomly assigned to receive treatment with ^{177}Lu-PSMA-617 or best standard of care.[50] Treatment with ^{177}Lu-PSMA-617 was administered as intravenous infusions of 7.4 GBq once every 6 weeks, with a total of 4–6 cycles. Expression of PSMA on target lesions was confirmed with ^{68}Ga-PSMA-11 imaging prior to randomization. Treatment with ^{177}Lu-PSMA-617 significantly prolonged overall survival (median 15.3 vs. 11.3 months) and radiographic progression-free survival (median 8.7 vs. 3.4 months). Adverse events of grade 3 or higher were more frequent after ^{177}Lu-PSMA-617 treatment (52.7% vs. 38.0%), but quality of life was not adversely affected. The most common adverse effects after ^{177}Lu-PSMA-617 treatment included fatigue, xerostomia, and nausea, nearly all of grade 1 or 2, while adverse events higher than grade 3 included fatigue, anemia, thrombocytopenia, lymphopenia, leukopenia, and back pain.[50] In March 2022, ^{177}Lu-PSMA-617 was approved by the FDA for treatment of PSMA-positive metastatic castration-resistant prostate cancer who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.

A phase III study with the therapeutic ligand ^{177}Lu-PSMA-I&T, also known as ^{177}Lu-PNT2002, is currently ongoing (SPLASH

trial, NCT04647526). Also, several studies are evaluating efficacy of ^{177}Lu-PSMA-617 at earlier disease stages, such as taxane-naïve (NCT04689828), hormone-sensitive metastatic (NCT04720157 and NCT04343885), and oligometastatic (NCT04443062) stages. A pilot study of ^{177}Lu-PSMA-617 in low-volume hormone-sensitive metastatic prostate cancer demonstrated a PSA response of more than 50% in half of the patients.[51] Radiolabeled PSMA ligands may also have efficacy as neoadjuvant therapy prior to surgery. Several studies are evaluating ^{177}Lu-PSMA-617 (NCT04430192) or ^{177}Lu-PSMA-I&T (NCT04297410) as neoadjuvant therapy prior to prostatectomy. The use of PSMA ligands for radioguided surgery was evaluated in several studies in surgical candidates with prostate cancer, which demonstrated that radioguided surgery with ^{111}In-PSMA-I&T and ^{99m}Tc-PSMA-I&S is feasible and highly sensitive for intraoperative lesion detection.[52,53] Further phase I and II studies evaluating radioguided surgery using ^{111}In-PSMA-I&T (NCT04300673) and ^{99m}Tc-PSMA-I&S (NCT03857113, NCT04857502, NCT04832958) are underway. Several ongoing trials are evaluating PSMA imaging of renal cell carcinoma (NCT04987086 and NCT05170555), breast cancer (NCT04750473 and NCT04573231), ovarian cancer (NCT03857087 and NCT03811899), glioblastoma (NCT03903419), hepatocellular carcinoma (NCT05006326, NCT04310540, NCT05095519 and NCT04762888), and adenoid cystic carcinoma of the salivary gland (NCT04801264). Also, a phase II clinical trial evaluating ^{177}Lu-PSMA-I&T therapy in advanced salivary gland carcinoma (NCT04291300) is underway.

Treatment with α-emitters may have the potential to overcome β^--resistance after ^{177}Lu-PSMA therapy and limit hematologic toxicity in patients with extensive skeletal metastases and diffuse bone marrow infiltration. Initial clinical experience with the α-emitting ligands ^{225}Ac-PSMA-617[54,55] and ^{225}Ac-PSMA-I&T[56] in heavily pretreated patients, including some patients with failure after several cycles of ^{177}Lu-PSMA, indicates a PSA decline of 50% or more in 50–70% of patients, although xerostomia may be more severe. A prospective clinical phase I trial with ^{225}Ac-PSMA-617 (NCT04597411) is currently ongoing.

FIBROBLAST ACTIVATION PROTEIN INHIBITORS

Fibroblast activation protein is a type II transmembrane glycoprotein expressed on the surface of cancer-associated fibroblasts that plays a complex role in modulating stromal components of various tumors.[57] Emerging evidence suggests a potentially widespread application in oncology for radiolabeled inhibitors of the fibroblast activation protein (FAPIs). Diagnostic PET-CT imaging with the fibroblast activation protein inhibitor ^{68}Ga-FAPI-04 has demonstrated remarkably high uptake of the ligand in several solid cancers, including breast, esophageal, lung, pancreatic, head and neck, and colorectal cancer.[58] Tumor-to-background ratios in PET-CT imaging with FAPI ligands is superior to imaging with ^{18}F-fluorodeoxyglucose (FDG), which may result in superior diagnostic efficacy, specifically for regions with physiologically high ^{18}F-FDG background activity, such as liver and brain.[59,60] Currently, many early-phase clinical trials evaluating PET imaging with FAPI ligands for diagnosis and staging of several different cancer types are ongoing (NCT04554719, NCT05034146, NCT04457232, NCT04147494, NCT04457258, NCT05003427, NCT04621435, NCT04459273, NCT04441606, and NCT05172310).

Clinical studies of radioligand therapy with FAPIs are currently limited to small series of patients with progressive and metastasized cancers without other treatment options. Clinical studies of radioligand therapy with ^{177}Lu-labeled FAPI-04, FAP-2286, and FAPI-46[61–63] have demonstrated feasibility and a favorable toxicity profile, but obviously studies in larger cohorts are needed to determine efficacy and toxicity. Phase I clinical trials with ^{177}Lu-DOTA-FAPI (NCT04849247) and ^{177}Lu-FAP-2286 (NCT04939610) in various tumors are underway.

NOVEL THERANOSTIC TARGETS

Other biological targets under clinical investigation include neurotensin receptors, B7-H3, and integrin receptors, and a variety of candidate compounds are being evaluated as novel theranostic radioligands, including small molecules, peptides, and antibodies.[1,2] Compounds that have progressed from preclinical phase to early-phase clinical studies include ligands of C-X-C chemokine receptor 4 and the gastrin-releasing peptide receptor. A variety of radiolabeled antibodies are being investigated, including girentuximab and trastuzumab, and more recently daratumumab in patients with multiple myeloma.[64]

The C-X-C chemokine receptor 4 (CXCR4) is a G protein–coupled receptor that mediates cellular migration and chemotaxis and is overexpressed in several cancer types. PET-CT imaging with the diagnostic CXCR4 ligand ^{68}Ga-pentixafor has shown promising results in assessment of newly diagnosed multiple myeloma.[65] The therapeutic CXCR4 ligands ^{177}Lu-pentixather and ^{90}Y-pentixather have been administered in a small number of patients with advanced multiple myeloma[66] and diffuse large B-cell lymphoma[67] demonstrating feasibility, although response duration was rather short, probably reflecting the selection of very advanced and highly treatment-refractory lymphoma patients. Further phase I and II studies with ^{68}Ga-pentixafor (NCT04504526, NCT05093335, NCT03335670, and NCT04561492) are currently ongoing.

The gastrin-releasing peptide receptor (GRPR) is expressed at high density in frequently occurring cancers, such as prostate and breast cancer. Pilot studies of PET imaging with the bombesin analog GRPR ligands ^{68}Ga-RM2 and ^{68}Ga-RM26 demonstrated high uptake in putative and biopsy-proven sites of recurrent prostate cancer[68,69] and breast cancer.[70] A first-in-human dosimetry study with ^{177}Lu-RM2 indicated high uptake in tumor sites.[71] A phase I trial with ^{68}Ga-NOTA-RM26 for imaging of gastrointestinal stromal tumors (GISTs) is currently ongoing (NCT05001204). PET-CT imaging with another GRPR ligand ^{68}Ga-NeoBOMB1 also demonstrated rapid and high-contrast visualization of pathologic lesions in a small number of prostate cancer patients[72] and a subset of patients with GISTs.[73] Phase II clinical trials with ^{68}Ga-DOTA-NeoBOMB1 for imaging of prostate cancer and other solid tumors are ongoing (NCT03698370 and NCT03872778). A phase I clinical trial with ^{177}Lu-NeoBOMB1 in patients with advanced solid tumors, including breast cancer, lung cancer, prostate cancer, GIST, and glioblastoma, is also underway (NCT03872778).

STRATEGIES TO IMPROVE EFFICACY OF RADIOLIGAND THERAPY

Notwithstanding the encouraging results of the NETTER-1 and VISION phase III trials, a significant number of patients unfortunately show insufficient or absent response to radioligand therapy, despite previously confirmed tissue expression of the theranostic target. In addition to development of novel ligands, several other strategies to enhance efficacy of radioligand therapy have been proposed, including dosimetry-based dose optimization, multireceptor targeting, upregulation of target receptors, and radiosensitization.[74,75] Also, pharmacogenomics and radiation genomics may represent a novel potential strategy to personalize radioligand therapy in order to maximize efficacy and avoid adverse effects.

Dosimetry-based dose optimization

The NETTER-1 and VISION phase III trials used fixed activity regimens (in GBq) of ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617. At fixed administered ligand activity, the absorbed amount of radiation to both target tissues and critical dose-limiting organs (kidney and bone marrow) can be highly variable and some patients may be relatively undertreated. As an alternative strategy, dose schedules may be personalized based on individual dosimetry in order to allow increases in the administered radiation dose with increased tumor radiation without exceeding toxicity thresholds of critical organs. In a prospective phase II trial, cycles of 7.4 GBq ^{177}Lu-DOTATATE were repeated until the absorbed radiation to the kidneys reached the preset limit of 23 Gy based on dosimetry calculated from post-therapy scans, or until other reasons prohibited further therapy, thus varying the total number of cycles per patient. Patients in whom the renal-absorbed radiation reached 23 Gy had longer progression-free and overall survival than patients in whom this limit was not reached.[76] Another prospective phase II trial used dosimetry to individualize the amount of administered activity per cycle, instead of varying the total number of cycles, by standardizing the renal-absorbed radiation. The first activity dose was calculated from the estimated glomerular filtration rate and body surface area. Subsequent doses were titrated based on the renal-absorbed radiation calculated from the post-therapy scan of the previous dose administrations. Initial results suggest that this strategy allows higher cumulative tumor-absorbed radiation in 85% of patients, with similar toxicity profile compared with fixed-activity regimens.[77] Several other trials are also evaluating dosimetry-based individualized dose schedules (NCT02743741 and NCT04917484).

Targeting multiple receptors

Concomitant targeting of multiple receptor types may potentially increase sensitivity and specificity of diagnostic imaging and increase efficacy of radioligand therapy by (at least partially) overcoming tumor heterogeneity or changes in phenotype during disease progression.[78] Pharmacological approaches include the use of radioligands with dual or multireceptor affinity, coadministration of multiple ligands, and sequential administration of ligands.

Prostate cancer can show neuroendocrine differentiation, which correlates with poor prognosis, independently of the Gleason score. PET imaging in a small series of castration-resistant prostate cancer patients demonstrated uptake of ^{68}Ga-DOTATATE in all patients, which opens the possibility of combination treatment with both ^{177}Lu-PSMA and ^{177}Lu-DOTATATE.[79] A larger triple-tracer imaging study with ^{68}Ga-PSMA, ^{68}Ga-DOTATATE, and ^{18}F-FDG is ongoing to determine tumor heterogeneity and polyclonality on the basis of discordant multitracer imaging phenotypes and evaluate eligibility for associated radioligand therapy (NCT04000776).

As an extrapolation of multireceptor targeting, combinations of differently targeted radioligands may be used simultaneously to exploit their differences in pharmacokinetics and dosimetry. A significant number of neuroendocrine tumors show uptake of both somatostatin analogs and ^{131}I-mIBG. The dose-limiting organs for treatment with ^{90}Y-DOTATOC are the kidneys, whereas the dose-limiting organ for ^{131}I-mIBG is the bone marrow. Combining ^{90}Y-DOTATOC and ^{131}I-mIBG may significantly increase the total radiation dose on the tumor, with only relatively minor increases in total radiation dose on bone marrow and kidneys without exceeding dose limits for either one. This combined treatment was evaluated in a phase I trial, which demonstrated that the addition of ^{131}I-mIBG to ^{90}Y-DOTATOC resulted in tumor dose increases of 34–83%.[80]

Upregulation of target receptors

Upregulation of target receptors on the surface of tumor cells allows target engagement of a higher number of radioligand molecules per tumor cell, resulting in a proportionally higher dose of therapeutic radiation.

In thyroid cancer, progressive dedifferentiation can lead to loss of functional sodium-iodide symporter expression. As a result, thyroid cancer can become refractory to ^{131}I therapy. Several studies have explored pharmacological approaches to induce redifferentiation and increase the expression of the sodium-iodide symporter.[81] Expression of the gene encoding the sodium-iodide symporter is downregulated by activation of the mitogen-activated protein kinase (MAPK) signaling pathway in dedifferentiating thyroid cancer cells. Thus, pharmacological inhibition of the MAPK pathway with MEK or BRAF inhibitors may be effective in increasing sodium-iodide symporter expression. Several small pilot studies have evaluated the MEK inhibitor selumetinib and BRAF inhibitors dabrafenib and vemurafenib in previously iodine-refractory thyroid cancers, which indeed showed significant increases in iodine uptake.[82–84] Several early phase clinical trials with trametinib, dabrafenib, lenvatinib, and vemurafenib in iodine-refractory thyroid cancer (NCT03244956, NCT04619316, NCT04554680, NCT04462471, NCT04858867, and NCT02152995) are underway.

In prostate cancer, treatment with PSMA radioligands may similarly be improved by upregulation of PSMA expression in tumor cells. Androgens are known to downregulate the gene encoding PSMA (FOLH1) and consequently inhibit PSMA expression. Thus, pharmacological blockade of androgen receptors or inhibition of androgen synthesis may be effective in increasing PSMA expression. Small clinical studies with various types of androgen deprivation therapy in prostate cancer patients have yielded inconsistent results, but the majority of studies suggest that short-term therapy causes PSMA upregulation, whereas long-term therapy

decreases PSMA ligand uptake.[85,86] Larger studies to evaluate uptake of PSMA ligands after potentiation by short-term administration of a luteinizing hormone-releasing hormone (LHRH) antagonist (NCT04391556, NCT03876912) are ongoing.

Radiosensitization

Radiosensitization refers to co-administration of antineoplastic agents with radiation in order to augment the effectiveness of radiation to achieve additive or even synergistic effects while minimizing toxicity.[87] Potential methods for radiosensitization have been evaluated extensively in combination with external beam radiotherapy. The combination of conventional chemotherapies, such as cisplatin, 5-fluorouracil (5-FU), and temozolomide, with external beam radiotherapy has resulted in significant clinical improvements in many different tumor types, typically by adding to the DNA damage induced by radiotherapy, thereby increasing tumor cell death. Accordingly, concurrent chemoradiotherapy has become standard of care for several tumor types. However, these treatments are not specific for tumor cells and the benefits of these treatments are offset by an increase in normal tissue toxicity.[88] Alternative mechanisms for radiosensitization include inhibition of DNA damage repair, cell-cycle interference, inhibition of signal transduction pathways, and immune checkpoints.[89,90] These strategies for enhancing external beam radiotherapy may also potentiate efficacy of radioligand therapy, although their effects may not be directly translatable due to differences in radiobiological effects, dose rate, and duration of radiation exposure between external beam radiotherapy and different types of radioligand therapy.

Several small retrospective studies have evaluated the combination of ^{177}Lu-DOTATATE with conventional chemotherapies such as 5-FU, capecitabine, and temozolomide in patients with advanced progressive neuroendocrine tumors, which demonstrated that coadministration was safe and showed promising tumor response rates.[91,92] A retrospective cohort study suggested that adding capecitabine to ^{177}Lu-DOTATATE prolongs overall survival and progression-free survival compared with ^{177}Lu-DOTATATE alone.[93] Prospective phase II trials evaluating combinations of ^{177}Lu-DOTATATE plus capecitabine (NCT02736448) and ^{177}Lu-DOTATOC plus capecitabine and temozolomide (NCT04194125) are underway. Also, clinical trials evaluating the combination of ^{223}Ra-dichloride with docetaxel in prostate cancer patients (NCT03574571) and ^{223}Ra-dichloride with paclitaxel in breast cancer patients (NCT04090398) are underway.

Radiosensitization by inhibiting DNA repair mechanisms is currently being evaluated using inhibitors of poly ADP ribose polymerase (PARP) proteins, which are crucial elements of DNA damage response. Several early-phase trials of ^{177}Lu-DOTATATE in combination with the PARP inhibitors olaparib (NCT04086485, NCT04375267) and talazoparib (NCT05053854), ^{177}Lu-PSMA-617 in combination with olaparib (NCT03874884), and ^{223}Ra-dichloride in combination with olaparib (NCT03317392) are underway. Also, a clinical phase I trial is evaluating ^{177}Lu-DOTATATE in combination with the DNA-dependent protein kinase inhibitor peposertib (NCT04750954).

Radiosensitization by inhibiting the mammalian target of rapamycin (mTOR) signaling pathway, which regulates cell growth, proliferation, and apoptosis, was evaluated in a phase I trial of ^{177}Lu-DOTATATE with coadministration of the mTOR inhibitor everolimus, which demonstrated that the combination was safe with manageable and reversible toxicities.[94]

Radiosensitization by blocking immune checkpoints with programmed cell death protein 1 (PD-1) inhibitors was evaluated in a phase I study of ^{177}Lu-DOTATATE with coadministration of the PD-1 inhibitor nivolumab, which showed that the combination was well tolerated.[95] A phase II trial combining nivolumab and ^{177}Lu-DOTATATE is underway (NCT04525638). Also, early-phase trials are evaluating the combination of ^{223}Ra-dichloride and nivolumab (NCT04109729) and the combination of ^{177}Lu-PSMA-617 and the PD-1 inhibitor pembrolizumab (NCT03658447).

Pharmacogenomics and radiation genomics

Evaluation of the role of somatic mutations and genetic variants in the response of tumor cells to radioligand therapy and toxicity is an area of increasing relevance.[96] In the context of cancer, acquired somatic mutations in tumor cells can define the tumor subtype and associated treatment choice, while inherited germline genetic variation may affect pharmacokinetics and response to cancer pharmacotherapy (both efficacy and toxicity), independently of tumor type.[97] Polymorphisms in genes encoding drug-metabolizing enzymes can cause interindividual variability in efficacy outcome and toxicity of several drugs, requiring starting dose adaptations based on pretreatment genotyping. Similar to pharmacogenomics, somatic mutations and genetic polymorphisms involved in cellular response to radiation such as DNA repair, apoptosis, cell-cycle control, signal transduction, and tumor microenvironment modulation may predispose subjects to cancer development or influence their response to therapeutic radiation.[98] Evaluation of genetic determinants of radiation sensitivity and radioligand pharmacokinetics has great potential in enhancing efficacy and limiting toxicity of radioligand therapy. Central to the concept of theranostics is selection of patients with confirmed expression of the theranostic target, but a complementary predictive tool to identify radiosensitive patients, based on pharmacogenomic and radiogenomic factors, would allow even more personalized cancer treatment.[99] Pretreatment stratification of radiosensitivity and toxicity risk could then be used to individualize radioligand therapy protocols (i.e., emission type, dose, and frequency). Circulating gene transcript analysis of genes involved in growth factor signaling and metabolism has demonstrated high accuracy for predicting response of neuroendocrine tumors to radioligand therapy with ^{177}Lu-DOTATATE,[100] but no markers have yet been identified for prediction of toxicity. Further evaluation of transcript variation analysis for identification of potential biomarkers of radiosensitivity to ^{177}Lu-DOTATATE therapy is ongoing (NCT03667092). Pharmacogenomic data of PSMA radioligand therapy is currently limited to a few studies in small series of patients, evaluating possible associations of mutations in DNA damage-repair-associated genes and response to PSMA radioligand therapy, which yielded inconsistent results.[101,102] Systematic inclusion of pharmacogenomics in future prospective trials with large patient cohorts is needed for identification of

genomic changes predictive of response and toxicity for individual patient selection.

CONCLUSION

Recent prospective randomized clinical trials have shown that several theranostic radioligands have high accuracy in diagnostic imaging and efficacy as therapeutics to prolong progression-free and overall survival in several cancer types. Development of novel radioligands may expand the clinical indications for theranostics to include some highly prevalent cancer types. Thus, use of diagnostic and therapeutic radiopharmaceuticals is likely to increase significantly, resulting in increasing utilization of radiopharmacy infrastructure. A multidisciplinary approach, including clinical pharmacology, is required for both development and successful introduction of novel theranostics into routine clinical oncology practice, as well as the design of highly individualized combination treatments for further optimization of theranostics, focusing on dosimetry-based dose optimization, multireceptor targeting, upregulation of target receptors, radiosensitization, pharmacogenomics, and radiation genomics.

FUNDING

No funding was received for this work.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

1. Langbein, T., Weber, W.A. & Eiber, M. Future of theranostics: an outlook on precision oncology in nuclear medicine. *J. Nucl. Med.* **60**, 13S–19S (2019).
2. Herrmann, K. *et al*. Radiotheranostics: a roadmap for future development. *Lancet Oncol.* **21**, e146–e156 (2020).
3. Jadvar, H., Chen, X., Cai, W. & Mahmood, U. Radiotheranostics in cancer diagnosis and management. *Radiology* **286**, 388–400 (2018).
4. Sgouros, G., Bodei, L., McDevitt, M.R. & Nedrow, J.R. Radiopharmaceutical therapy in cancer: clinical advances and challenges. *Nat. Rev. Drug Discov.* **19**, 589–608 (2020).
5. Vermeulen, K., Vandamme, M., Bormans, G. & Cleeren, F. Design and challenges of radiopharmaceuticals. *Semin. Nucl. Med.* **49**, 339–356 (2019).a
6. Parker, C. *et al*. Alpha emitter Radium-223 and survival in metastatic prostate cancer. *N. Engl. J. Med.* **369**, 213–223 (2013).
7. Kogai, T. & Brent, G.A. The sodium iodide symporter (NIS): regulation and approaches to targeting for cancer therapeutics. *Pharmacol. Ther.* **135**, 355–370 (2012).
8. Gonzalez Carvalho, J.M. *et al*. Evaluation of ^{131}I scintigraphy and stimulated thyroglobulin levels in the follow up of patients with DTC: a retrospective analysis of 1420 patients. *Eur. J. Nucl. Med. Mol. Imaging* **44**, 744–756 (2017).
9. Reiners, C., Hänscheid, H., Luster, M., Lassmann, M. & Verburg, F.A. Radioiodine for remnant ablation and therapy of metastatic disease. *Nat. Rev. Endocrinol.* **7**, 589–595 (2011).
10. Jonklaas, J. *et al*. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. *Thyroid* **16**, 1229–1242 (2006).
11. Verburg, F.A., Flux, G., Giovanella, L., van Nostrand, D., Muylle, K. & Luster, M. Differentiated thyroid cancer patients potentially benefitting from postoperative I-131 therapy: a review of the literature of the past decade. *Eur. J. Nucl. Med. Mol. Imag.* **47**, 78–83 (2020).
12. Durante, C. *et al*. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J. Clin. Endocrinol. Metab.* **91**, 2892–2899 (2006).
13. Cook, G.J.R. & Goh, V. Molecular imaging of bone metastases and their response to therapy. *J. Nucl. Med.* **61**, 799–806 (2020).
14. Finlay, I.G., Mason, M.D. & Shelley, M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. *Lancet Oncol.* **6**, 392–400 (2005).
15. Wiseman, G.A. *et al*. Usefulness of ^{123}I-MIBG scintigraphy in the evaluation of patients with known or suspected primary or metastatic pheochromocytoma or paraganglioma: results from a prospective multicenter trial. *J. Nucl. Med.* **50**, 1448–1454 (2009).
16. Fiebrich, H.B. *et al*. 6-[F-18]fluoro-L-dihydroxyphenylalanine positron emission tomography is superior to conventional imaging with ^{123}I-metaiodobenzylguanidine scintigraphy, computer tomography, and magnetic resonance imaging in localizing tumors causing catecholamine excess. *J. Clin. Endocrinol. Metab.* **94**, 3922–3930 (2009).
17. van Hulsteijn, L.T., Niemeijer, N.D., Dekkers, O.M. & Corssmit, E.P.M. ^{131}I-MIBG therapy for malignant paraganglioma and phaeochromocytoma: systematic review and meta-analysis. *Clin. Endocrinol.* **80**, 487–501 (2014).
18. Pryma, D.A. *et al*. Efficacy and safety of high-specific-activity ^{131}I-MIBG therapy in patients with advanced pheochromocytoma or paraganglioma. *J. Nucl. Med.* **60**, 623–630 (2019).
19. Öberg, K.E., Reubi, J.C., Kwekkeboom, D.J. & Krenning, E.P. Role of somatostatins in gastroenteropancreatic neuroendocrine tumor development and therapy. *Gastroenterology* **139**, 742–753 (2010).
20. Sadowski, S.M. *et al*. Prospective study of ^{68}Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites. *J. Clin. Oncol.* **34**, 588–596 (2016).
21. Geijer, H. & Breimer, L.H. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. *Eur. J. Nucl. Med. Mol. Imag.* **40**, 1770–1780 (2013).
22. Janssen, I. *et al*. PET/CT comparing ^{68}Ga-DOTATATE and other radiopharmaceuticals and in comparison with CT/MRI for the localization of sporadic metastatic pheochromocytoma and paraganglioma. *Eur. J. Nucl. Med. Mol. Imag.* **43**, 1784–1791 (2016).
23. Kwekkeboom, D.J. *et al*. Treatment with the radiolabeled somatostatin analog [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate: toxicity, efficacy, and survival. *J. Clin. Oncol.* **26**, 2124–2130 (2008).
24. Brabander, T. *et al*. Long-term efficacy, survival, and safety of [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin. Cancer Res.* **23**, 4617–4624 (2017).
25. Strosberg, J. *et al*. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. *N. Engl. J. Med.* **376**, 125–135 (2017).
26. Strosberg, J.R. *et al*. ^{177}Lu-Dotatate plus long-acting octreotide vs. high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol.* **22**, 1752–1763 (2021).
27. Parghane, R.V. *et al*. Surgical feasibility, determinants, and overall efficacy of neoadjuvant ^{177}Lu-DOTATATE PRRT for locally advanced unresectable gastroenteropancreatic neuroendocrine tumors. *J. Nucl. Med.* **62**, 1558–1563 (2021).
28. El Lakis, M. *et al*. Radioguided surgery with gallium 68 dotatate for patients with neuroendocrine tumors. *JAMA Surg.* **154**, 40–45 (2019).
29. Mak, I.Y.F., Hayes, A.R., Khoo, B. & Grossman, A. Peptide receptor radionuclide therapy as a novel treatment for metastatic and invasive phaeochromocytoma and paraganglioma. *Neuroendocrinology* **109**, 287–298 (2019).

30. Liu, Q. *et al*. Peptide receptor radionuclide therapy of late-stage neuroendocrine tumor patients with multiple cycles of ^{177}Lu-DOTA-EB-TATE. *J. Nucl. Med.* **62**, 386–392 (2021).
31. Nicolas, G.P. *et al*. Sensitivity comparison of ^{68}Ga-OPS202 and ^{68}Ga-DOTATOC PET/CT in patients with gastroenteropancreatic neuroendocrine tumors: a prospective phase II imaging study. *J. Nucl. Med.* **59**, 915–921 (2018).
32. Zhu, W. *et al*. A prospective randomized, double-blind study to evaluate the safety, biodistribution, and dosimetry of ^{68}Ga-NODAGA-LM3 and ^{68}Ga-DOTA-LM3 in patients with well-differentiated neuroendocrine tumors. *J. Nucl. Med.* **62**, 1398–1405 (2021).
33. Reidy-Lagunes, D. *et al*. Phase I trial of well-differentiated neuroendocrine tumors (NETs) with radiolabeled somatostatin antagonist ^{177}Lu-satoreotide tetraxetan. *Clin. Cancer Res.* **25**, 6939–6947 (2019).
34. Baum, R.P., Zhang, J., Schuchardt, C., Müller, D. & Mäcke, H. First-in-human study of novel SSTR antagonist ^{177}Lu-DOTA-LM3 for peptide receptor radionuclide therapy in patients with metastatic neuroendocrine neoplasms: dosimetry, safety and efficacy. *J. Nucl. Med.* **62**, 1571–1581 (2021).
35. Ballal, S., Yadav, M.P., Bal, C., Sahoo, R.K. & Tripathi, M. Broadening horizons with ^{225}Ac-DOTATATE targeted alpha therapy for gastroenteropancreatic neuroendocrine tumour patients stable or refractory to ^{177}Lu-DOTATATE PRRT: first clinical experience on the efficacy and safety. *Eur. J. Nucl. Med. Mol. Imag.* **47**, 934–946 (2020).
36. Yadav, M.P., Ballal, S., Sahoo, R.K. & Bal, C. Efficacy and safety of ^{225}Ac-DOTATATE targeted alpha therapy in metastatic paragangliomas: a pilot study. *Eur. J. Nucl. Med. Mol. Imag.* **49**, 1595–1606 (2022).
37. Delpassand, E. *et al*. Targeted alpha-emitter therapy with ^{212}Pb-DOTAMTATE for the treatment of metastatic SSTR-expressing neuroendocrine tumors: first-in-human, dose-escalation clinical trial. *J. Nucl. Med.* (2022). Online ahead of print. https://doi.org/10.2967/jnumed.121.263230.
38. Maurer, T., Eiber, M., Schwaiger, M. & Gschwend, J.E. Current use of PSMA-PET in prostate cancer management. *Nat. Rev. Urol.* **13**, 226–235 (2016).
39. Uijen, M.J.M. *et al*. PSMA radioligand therapy for solid tumors other than prostate cancer: background, opportunities, challenges, and first clinical reports. *Eur. J. Nucl. Med. Mol. Imag.* **48**, 4350–4368 (2021).
40. Hofman, M.S. *et al*. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet* **395**, 1208–1216 (2020).
41. Hope, T.A. *et al*. Diagnostic accuracy of ^{68}Ga-PSMA-11 PET for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection. a multicenter prospective phase 3 imaging trial. *JAMA Oncol.* **7**, 1635–1642 (2021).
42. Fendler, W.P. *et al*. Assessment of ^{68}Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. *JAMA Oncol.* **5**, 856–863 (2019).
43. Jansen, B.H.E. *et al*. Pelvic lymph-node staging with ^{18}F-DCFPyL PET/CT prior to extended pelvic lymph-node dissection in primary prostate cancer – the SALT trial. *Eur. J. Nucl. Med. Mol. Imag* **48**, 509–520 (2021).
44. Morris, M.J. *et al*. Diagnostic performance of ^{18}F-DCFPyL-PET/CT in men with biochemically recurrent prostate cancer: results from the CONDOR phase III, multicenter study. *Clin. Cancer Res.* **27**, 3674–3682 (2021).
45. Crocerossa, F. *et al*. Detection rate of prostate specific membrane antigen tracers for positron emission tomography/computerized tomography in prostate cancer biochemical recurrence: a systematic review and network meta-analysis. *J. Urol.* **205**, 356–369 (2021).
46. Rahbar, K. *et al*. German multicenter study investigating ^{177}Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. *J. Nucl. Med.* **58**, 85–90 (2017).
47. Sadaghiani, M.S. *et al*. A systematic review and meta-analysis of the effectiveness and toxicities of Lutetium-177-labeled prostate-specific membrane antigen-targeted radioligand therapy in metastatic castration-resistant prostate cancer. *Eur. Urol.* **80**, 82–94 (2021).
48. Hofman, M.S. *et al*. [^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol.* **19**, 825–833 (2018).
49. Hofman, M.S. *et al*. [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet* **397**, 797–804 (2021).
50. Sartor, O. *et al*. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N. Engl. J. Med.* **385**, 1091–1103 (2021).
51. Privé, B.M. *et al*. Lutetium-177-PSMA-617 in low-volume hormone-sensitive metastatic prostate cancer: a prospective pilot study. *Clin. Cancer Res.* **27**, 3595–3601 (2021).
52. Rauscher, I. *et al*. Value of ^{111}In-prostate-specific membrane antigen (PSMA)-radioguided surgery for salvage lymphadenectomy in recurrent prostate cancer: correlation with histopathology and clinical follow-up. *BJU Int.* **120**, 40–47 (2017).
53. Maurer, T. *et al*. ^{99m}Technetium-based prostate-specifc membrane antigen-radioguided surgery in recurrent prostate cancer. *Eur. Urol.* **75**, 659–666 (2019).
54. Sathekge, M. *et al*. Predictors of overall and disease-free survival in metastatic castration-resistant prostate cancer patients receiving ^{225}Ac-PSMA-617 radioligand therapy. *J. Nucl. Med.* **61**, 62–69 (2020).
55. Feuerecker, B. *et al*. Activity and adverse events of Actinium-225-PSMA-617 in advanced metastatic castration-resistant prostate cancer after failure of Lutetium-177-PSMA. *Eur. Urol.* **79**, 343–350 (2021).
56. Zacherl, M.J. *et al*. First clinical results for PSMA-targeted α-therapy using ^{225}Ac-PSMA-I&T in advanced-mCRPC patients. *J. Nucl. Med.* **62**, 669–674 (2021).
57. Hicks, R.J., Roselt, P.J., Kallur, K.G., Tothill, R.W. & Mileshkin, L. FAPI PET/CT: will it end the hegemony of ^{18}F-FDG in oncology? *J. Nucl. Med.* **62**, 296–302 (2021).
58. Kratochwil, C. *et al*. ^{68}Ga-FAPI PET/CT: tracer uptake in 28 different kinds of cancer. *J. Nucl. Med.* **60**, 801–805 (2019).
59. Chen, H. *et al*. Comparison of [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG PET/CT for the diagnosis of primary and metastatic lesions in patients with various types of cancer. *Eur. J. Nucl. Med. Mol. Imag.* **47**, 1820–1832 (2020).
60. Giesel, F.L. *et al*. Head-to-head intra-individual comparison of biodistribution and tumor uptake of ^{68}Ga-FAPI and ^{18}F-FDG PET/CT in cancer patients. *Eur. J. Nucl. Med. Mol. Imag.* **48**, 4377–4385 (2021).
61. Baum, R.P. *et al*. Feasibility, biodistribution and preliminary dosimetry in peptide-targeted radionuclide therapy of diverse adenocarcinomas using ^{177}Lu-FAP-2286: first-in-human results. *J. Nucl. Med.* **63**, 415–423 (2022).
62. Kuyumcu, S. *et al*. Safety of fibroblast activation protein-targeted radionuclide therapy by a low-dose dosimetric approach using ^{177}Lu-FAPI04. *Clin. Nucl. Med.* **46**, 641–646 (2021).
63. Assadi, M. *et al*. Feasibility and therapeutic potential of ^{177}Lu-fibroblast activation protein inhibitor-46 for patients with relapsed or refractory cancers: a preliminary study. *Clin. Nucl. Med.* **46**, e523–e530 (2021).
64. Krishnan, A. *et al*. Identifying CD38+ cells in patients with multiple myeloma: first-in-human imaging using copper-64–labeled daratumumab. *Blood Adv.* **4**, 5194–5202 (2020).
65. Pan, Q., Cao, X., Luo, Y., Li, J., Feng, J. & Li, F. Chemokine receptor-4 targeted PET/CT with ^{68}Ga-pentixafor in assessment of newly diagnosed multiple myeloma: comparison to ^{18}F-FDG PET/CT. *Eur. J. Nucl. Med. Mol. Imag.* **47**, 537–546 (2020).
66. Herrmann, K. *et al*. First-in-human experience of CXCR4-directed endoradiotherapy with ^{177}Lu- and ^{90}Y-labeled pentixather in advanced-stage multiple myeloma with extensive intra- and extramedullary disease. *J. Nucl. Med.* **57**, 248–251 (2016).

67. Lapa, C. *et al*. Feasibility of CXCR4-directed radioligand therapy in advanced diffuse large B-cell lymphoma. *J. Nucl. Med.* **60**, 60–64 (2019).
68. Minamimoto, R. *et al*. Prospective evaluation of ^{68}Ga-RM2 PET/MRI in patients with biochemical recurrence of prostate cancer and negative findings on conventional imaging. *J. Nucl. Med.* **59**, 803–808 (2018).
69. Zhang, J. *et al*. PET using a GRPR antagonist ^{68}Ga-RM26 in healthy volunteers and prostate cancer patients. *J. Nucl. Med.* **59**, 922–928 (2018).
70. Zang, J. *et al*. ^{68}Ga-NOTA-RM26 PET/CT in the evaluation of breast cancer: a pilot prospective study. *Clin. Nucl. Med.* **43**, 663–669 (2018).
71. Kurth, J., Krause, B.J., Schwarzenböck, S.M., Bergner, C., Hakenberg, O.W. & Heuschkel, M. First-in-human dosimetry of gastrin-releasing peptide receptor antagonist [^{177}Lu]Lu-RM2: a radiopharmaceutical for the treatment of metastatic castration-resistant prostate cancer. *Eur. J. Nucl. Med. Mol. Imag.* **47**, 123–135 (2020).
72. Nock, B.A. *et al*. Theranostic perspectives in prostate cancer with the gastrin-releasing peptide receptor antagonist NeoBOMB1: preclinical and first clinical results. *J. Nucl. Med.* **58**, 75–80 (2017).
73. Gruber, L. *et al*. MITIGATE-NeoBOMB1, a phase I/IIa study to evaluate safety, pharmacokinetics, and preliminary imaging of ^{68}Ga-NeoBOMB1, a gastrin-releasing peptide receptor antagonist, in GIST patients. *J. Nucl. Med.* **61**, 1749–1755 (2020).
74. Gill, M.R., Falzone, N., Du, Y. & Vallis, K.A. Targeted radionuclide therapy in combined-modality regimens. *Lancet Oncol.* **18**, e414–e423 (2017).
75. Chan, T.G., O'Neill, E.O., Habjan, C. & Cornelissen, B. Combination strategies to improve targeted radionuclide therapy. *J. Nucl. Med.* **61**, 1544–1552 (2020).
76. Garske-Román, U. *et al*. Prospective observational study of ^{177}Lu-DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. *Eur. J. Nucl. Med. Mol. Imaging* **45**, 970–988 (2018).
77. Del Prete, M. *et al*. Personalized ^{177}Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: initial results from the P-PRRT trial. *Eur. J. Nucl. Med. Mol. Imag.* **46**, 728–742 (2019).
78. Reubi, J.C. & Maecke, H.R. Approaches to multireceptor targeting: hybrid radioligands, radioligand cocktails, and sequential radioligand applications. *J. Nucl. Med.* **58**, 10S–16S (2017).
79. Gofrit, O.N., Frank, S., Meirovitz, A., Nechushtan, H. & Orevi, M. PET/CT with ^{68}Ga-DOTA-TATE for diagnosis of neuroendocrine differentiation in patients with castrate-resistant prostate cancer. *Clin. Nucl. Med.* **42**, 1–6 (2017).
80. Bushnell, D.L. *et al*. Addition of ^{131}I-MIBG to PRRT (^{90}Y-DOTATOC) for personalized treatment of selected patients with neuroendocrine tumors. *J. Nucl. Med.* **62**, 1274–1277 (2021).
81. Lamartina, L., Anizan, N., Dupuy, C., Leboulleux, S. & Schlumberger, M. Redifferentiation-facilitated radioiodine therapy in thyroid cancer. *Endocr. Relat. Cancer* **28**, T179–T191 (2021).
82. Ho, A.L. *et al*. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *N. Engl. J. Med.* **368**, 623–632 (2013).
83. Rothenberg, S.M., McFadden, D.G., Palmer, E.L., Daniels, G.H. & Wirth, L.J. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. *Clin. Cancer Res.* **21**, 1028–1035 (2015).
84. Dunn, L.A. *et al*. Vemurafenib redifferentiation of BRAF mutant, RAI-refractory thyroid cancers. *J. Clin. Endocrinol. Metab.* **104**, 1417–1428 (2019).
85. Rosar, F. *et al*. New insights in the paradigm of upregulation of tumoral PSMA expression by androgen receptor blockade: enzalutamide induces PSMA upregulation in castration-resistant prostate cancer even in patients having previously progressed on enzalutamide. *Eur. J. Nucl. Med. Mol. Imag.* **47**, 687–694 (2020).
86. Vaz, S., Hadaschik, B., Gabriel, M., Herrmann, K., Eiber, M. & Costa, D. Influence of androgen deprivation therapy on PSMA expression and PSMA-ligand PET imaging of prostate cancer patients. *Eur. J. Nucl. Med. Mol. Imag.* **47**, 9–15 (2020).
87. Seiwert, T.Y., Salama, J.K. & Vokes, E.E. The concurrent chemoradiation paradigm – general principles. *Nat. Clin. Pract. Oncol.* **4**, 86–100 (2007).
88. Higgins, G.S., O'Cathail, S.M., Muschel, R.J. & McKenna, W.G. Drug radiotherapy combinations: review of previous failures and reasons for future optimism. *Cancer Treat. Rev.* **41**, 105–113 (2015).
89. Le, Q.T., Shirato, H., Giaccia, A.J. & Koong, A.C. Emerging treatment paradigms in radiation oncology. *Clin. Cancer Res.* **21**, 3393–3401 (2015).
90. Begg, A.C., Stewart, F.A. & Vens, C. Strategies to improve radiotherapy with targeted drugs. *Nat. Rev. Cancer* **11**, 239–253 (2011).
91. Claringbold, P.G. & Turner, J.H. Pancreatic neuroendocrine tumor control: durable objective response to combination ^{177}Lu-octreotate-capecitabine-temozolomide radiopeptide chemotherapy. *Neuroendocrinology* **103**, 432–439 (2016).
92. Yordanova, A. *et al*. Peptide receptor radionuclide therapy combined with chemotherapy in patients with neuroendocrine tumors. *Clin. Nucl. Med.* **44**, e329–e335 (2019).
93. Ballal, S., Yadav, M.P., Damle, N.A., Sahoo, R.K. & Bal, C. Concomitant ^{177}Lu-DOTATATE and capecitabine therapy in patients with advanced neuroendocrine tumors: a long-term-outcome, toxicity, survival, and quality-of-life study. *Clin. Nucl. Med.* **42**, e457–e466 (2017).
94. Claringbold, P.G. & Turner, J.H. Neuroendocrine tumor therapy with Lutetium-177-octreotate and everolimus (NETTLE): a phase I study. *Cancer Biother. Radiopharm.* **30**, 261–269 (2015).
95. Kim, C. *et al*. Phase I study of the ^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate (lutathera) in combination with nivolumab in patients with neuroendocrine tumors of the lung. *J. Immunother. Cancer* **8**, e000980 (2020).
96. Scott, A.M. & Bodei, L. Pharmacogenomics in radionuclide therapy: impact on response to theranostics. *J. Nucl. Med.* **62**, 884–885 (2021).
97. Wheeler, H.E., Maitland, M.L., Dolan, M.E., Cox, N.J. & Ratain, M.J. Cancer pharmacogenomics: strategies and challenges. *Nat. Rev. Genetics* **14**, 23–34 (2013).
98. Borchiellini, D., Etienne-Grimaldi, M.C., Thariat, J. & Milano, G. The impact of pharmacogenetics on radiation therapy outcome in cancer patients. A focus on DNA damage response genes. *Cancer Treat. Rev.* **38**, 737–759 (2012).
99. Kerns, S.L., Ostrer, H. & Rosenstein, B.S. Radiogenomics: using genetics to identify cancer patients at risk for development of adverse effects following radiotherapy. *Cancer Discov.* **4**, 155–165 (2014).
100. Bodei, L. *et al*. Molecular profiling of neuroendocrine tumours to predict response and toxicity to peptide receptor radionuclide therapy. *Lancet Oncol.* **21**, e431–e443 (2020).
101. Privé, B.M. *et al*. Impact of DNA damage repair defects on response to PSMA radioligand therapy in metastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis.* **25**, 71–78 (2022).
102. van der Doelen, M.J. *et al*. Clinical outcomes and molecular profiling of advanced metastatic castration-resistant prostate cancer patients treated with ^{225}Ac-PSMA-617 targeted alpha-radiation therapy. *Urol. Oncol.* **39**, 729.e7–e16 (2021).