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Theranostics: Leveraging Molecular Imaging and Therapy to Impact Patient Management and Secure the Future of Nuclear Medicine

Running Title: The Future of Theranostics

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ABSTRACT

Nuclear medicine is experiencing a renaissance with recent United States Food and Drug Administration (FDA) approval of theranostic agents and a wide variety of such agents soon to impact patient care significantly in the era of precision medicine. The NETTER-1 trial demonstrated the therapeutic effect of a theranostic agent in markedly improving progression free survival in patients with metastatic gastroenteropancreatic neuroendocrine tumors. Predominantly retrospective studies have demonstrated a significant response to ^{177}Lu-labeled agents targeting PSMA in patients with prostate cancer. At least two prospective clinical trials involving ^{177}Lu-PSMA agents are under way that will likely pave the way for FDA approval in the United States. A significant upside to theranostics is that patients tend to tolerate those agents better than chemotherapy. Theranostic compounds are likely to impact many cancers in the near future, not only through improvements in quality of life but also in terms of survival. This manuscript provides an overview of already approved agents as well as those on the horizon. It is important that as these agents are clinically onboarded that nuclear medicine physicians have the expertise to deploy theranostics safely and efficiently, ensuring that these agents attain and maintain their positions as leading lines of therapy in managing patients with cancer as well as an important aspect of nuclear medicine practice in the future.

Key Words: SSTR, PSMA, ^{177}Lu, ^{131}I, endoradiotherapy

NOTEWORTHY

Theranostic agents are likely to play a prominent role as patient care strategies become more precision-oriented.

Recent FDA-approved theranostics have a significant impact on patient outcomes.

Nuclear medicine physicians are positioned to lead in the administration of FDA-approved theranostics and introduction of new agents into the clinical arena.

MAIN TEXT

INTRODUCTION

"Theranostics" is one of the oldest sub-fields within nuclear medicine, tracing it roots to the original application of iodine-131 (^{131}I) for the treatment of thyroid disease (*1, 2*). ^{131}I-based therapy for thyroid cancer is the quintessential example of the theranostic principle. ^{131}I was discovered by Seaborg and Livingood in 1938. Following his observations on animal studies, Saul Hertz used ^{131}I as the first theranostic agent in 1941 for treating a patient with hyperthyroidism. For decades ^{131}I remained the sole, commonly-used example of a radiotracer capable of both diagnosis and therapy. With eventual easier accessibility to the diagnostic radionuclide ^{123}I, ^{123}I/^{131}I became the first theranostic pair to find widespread clinical adoption in nuclear medicine. Ultimately, radioiodine therapy provided an important proof-of-principle, although it was many years before new therapeutic radionuclides and theranostic agents became available (Table 1).

Confirming the presence of a target with molecular imaging and then utilizing that target to deliver radiation in a precise manner is an intuitive approach with applications far beyond thyroid disease. Radiolabeled antibodies have been utilized for targeted endoradiotherapy in lymphoma (*3, 4*) and solid tumors (*5*). However, it has been the introduction of multiple small-molecule theranostic pairs in recent years that has revitalized the nuclear medicine community. With the United States Food and Drug Administration (FDA) approval of ^{177}Lu-DOTATATE (Lutathera®) and ^{131}I-MIBG (Azedra®), a renaissance in theranostics is now world-wide and gaining momentum.

In the era of precision medicine, theranostics are likely to become increasingly important in patient care. The use of advanced diagnostics to select patients for targeted therapy is the very essence of precision medicine. Nuclear medicine physicians are uniquely equipped, and have a responsibility, to shepherd these valuable new agents to clinical care, working collaboratively with referring providers to determine at what point in the patient's treatment

pathway such agents should be deployed. Here we provide an overview of the current state of therapy in nuclear medicine, and highlight future directions.

UNITED STATES FDA-APPROVED THERANOSTIC AGENTS

High Specific Activity ^{131}I-MIBG (Azedra®)

^{131}I-MIBG has been used off-label in association with chemotherapy to treat metastatic neuroblastoma and pheochromocytoma for years (*6, 7*). MIBG is a substrate for the norepinephrine uptake transporter and localizes to neuroendocrine cells. That allows for diagnosis/follow-up assessment (using ^{123}I-MIBG or ^{131}I-MIBG) or treatment (using ^{131}I-MIBG) of tumors.

Indications for therapy are non-resectable, metastatic pheochromocytoma/ paraganglioma, neuroblastoma, and recurrent metastatic medullary thyroid cancer (*8*). Possible side effects include nausea and vomiting, as well as more long-term effects such as hypothyroidism and myelosuppression, that must be monitored closely during treatment. Although rare, hematologic malignancies may occur after treatment (*9, 10*).

Recently, the FDA approved a high-specific-activity formulation of ^{131}I-MIBG (tradename Azedra®). The difference between the high-specific-activity formulation and the conventional ^{131}I-MIBG regimen is that the level of non-radiolabeled MIBG in the therapeutic dose is significantly less, resulting in higher specific activity. High levels of non-radiolabeled MIBG may increase risk of hypertensive crisis during or immediately after the infusion (*11, 12*). Therefore, high-specific-activity radiopharmaceutical administration is likely to reduce peri-treatment complications and allow for greater treatment effect with a lower infusion dose. Pryma et al. recently published phase II results for patients with metastatic pheochromocytoma or paraganglioma and showed that the treatment was safe and effective (Figure 1), resulting in sustained control of

catecholamine-induced hypertension in 25% of patients and sustained anti-tumor effect in 22% of patients (*13*). The study reported no hypertensive complications during the infusion period.

^{131}I-MIBG therapy may also be considered for other neuroendocrine tumors demonstrating sufficient uptake of radiotracer on diagnostic imaging. A retrospective analysis of 25 patients with neuroendocrine tumors treated with conventional ^{131}I-MIBG therapy following a positive ^{123}I-MIBG scan demonstrated symptomatic control in 80% of patients, hormonal response in 55%, and tumor response in 48% of patients (*14*). Limited assessment is available for the efficacy of ^{131}I-MIBG therapy in patients with medullary thyroid cancer. Castellani et al. reported on their experience in this patient population. Thirteen patients with medullary thyroid cancer were treated with conventional ^{131}IMIBG therapy with four patients demonstrating partial disease response and four patients having stable disease after therapy (*15*). A phase II trial for neuroblastoma examining the utility of conventional ^{131}I-MIBG therapy showed an objective response rate of 36%, which is promising in light of these patients having heavily pretreated disease (*16*). 34% had stable disease for a median of 6.2 months with a large proportion of patients reporting pain relief (*16*). A phase IIa trial for HSA ^{131}I-MIBG was published yielding promising results in terms of safety and efficacy in the treatment of refractory neuroblastoma (*17*). Further studies are required to assess benefit compared to the conventional formulation of ^{131}I-MIBG and whether there is an overall survival benefit. (*14-16, 18*)

^{177}Lu-DOTATATE (Lutathera®)

Although ^{177}Lu-labeled somatostatin analog therapy has been available in Europe for decades, ^{177}Lu-DOTATATE (trade name Lutathera®) was only approved in the United States by the FDA in 2018. It is a tool for the treatment of progressive, metastatic neuroendocrine tumors (NETs). Those tumors most commonly arise from respiratory epithelium, pancreas, or gastroenteric tissue (*19*). It is important to note that the FDA did not approve ^{177}Lu-DOTATATE

for use in patients with primary pulmonary NETs. NETs may histologically be well-differentiated or poorly-differentiated; ^{177}Lu-DOTATATE binds to somatostatin receptor II.. To ensure that the treatment is indicated, patients generally undergo a ^{68}Ga-DOTATATE PET/CT to document radiotracer-avid disease.

There are multiple therapeutic options for patients presenting with metastatic NETs including somatostatin analogs, chemotherapy, and radioembolization of liver lesions. However, the NETTER-1 trial data suggests that ^{177}Lu-DOTATATE may offer patients with progressive, metastatic disease the best option for improved progression-free survival (*20*). The two arms of the NETTER-1 trial consisted of patients who either received a high dose, long-acting octreotide formulation (60 mg) or a ^{177}Lu-DOTATATE regimen with low dose, long-acting octreotide (30 mg). Median progression-free survival was not reached in the ^{177}Lu-DOTATATE group and was 8.4 months in the high dose octreotide group. Although the follow-up period was short, interim analysis suggests that the risk of death was 60% lower in the group receiving ^{177}Lu-DOTATATE (*21*). Although the NETTER-1 trial only included patients with mid-gut neuroendocrine tumors, there is significant retrospective data supporting the use of PRRT in neuroendocrine tumors of other origins including bronchial and hindgut (*22*).

When to administer the drug in a patient's disease course is not well-delineated at present (*23*). First-line therapy options are dependent on tumor origin, grade, and patient condition *(23-26)*. In our experience, PRRT is most often considered as a second line agent and beyond. A minority of patients who respond will demonstrate complete regression of disease following therapy, but most patients will have stable to minimally regressed disease on follow-up imaging (Figure 2). There is no set standard for when to re-image patients following therapy. The literature has suggested that in patients with low grade disease less frequent surveillance imaging and laboratory assessment are required, while those with high grade disease may benefit from more frequent assessment (*21, 27*). Imaging during therapy is generally not indicated as true response may be masked by pseudoprogression (*28*). Imaging during therapy

can be considered in patients with aggressive histologic disease or suspicion of progression based on clinical evaluation (*29*). There are also no prospective data examining the benefit of retreatment of patients with ^{177}Lu-DOTATATE should they progress. Retrospective data suggests that some patients may benefit from retreatment, having improved progression-free survival (*30*).

^{177}Lu-DOTATATE therapy is likely to play a role in the treatment of other malignancies. Pheochromocytomas/paragangliomas may demonstrate significant uptake on ^{68}Ga-DOTATATE PET imaging due to somatostatin receptor expression. PRRT has been shown in a retrospective study to be efficacious for the treatment of unresectable pheochromocytoma/paraganlioma. Although follow up time was limited, Kong et al. demonstrated regression or stabilization of disease based on morphologic imaging as well as reduction in hypertension medications in more than half of the patients (*31*). Meningiomas are also known to express somatostatin receptors. Although meningiomas are in most cases benign and slow-growing, a small percentage may be atypical or malignant. Tumors with more aggressive histologic features have a high recurrence rate following resection (*32*). A trial of 29 patients with recurrent meningioma having exhausted all therapy options, explored the efficacy of ^{90}Y-labeled -somatostatin analog therapy and found that it may slow progression of disease (*33*). A combination of external beam radiotherapy and PRRT has shown some promise in these patients. A study of 10 patients with nonresectable meningioma treated with PRRT and external beam radiotherapy reported no morphologic tumor progression with mild side effects (*34*). Further prospective studies are needed. Additional disease states that demonstrate high somatostatin receptor expression may benefit from PRRT – for example, medullary thyroid cancer, solid cancers with neuroendocrine differentiation, and merkel cell cancer (potentially in combination with immunotherapy) (*31, 33-39*).

Radium-223 Dichloride Therapy (Xofigo®)

Radium-223 (^{223}Ra) dichloride (marketed as Xofigo®) (technically not a theranostic agent, but a therapy agent within the arsenal of treatment options in nuclear medicine) is a calcium mimic and α-particle emitter that targets areas of increased bone turnover (*40-42*). As elevated bone turnover commonly occurs in osseous metastases, ^{223}Ra has been developed as a targeted therapy for symptomatic bone metastases in prostate cancer, a common cause of morbidity and mortality in patients with metastatic disease (*43*). Following multiple phase II studies (*44-46*), a phase III randomized, double-blind, placebo-controlled study of 921 patients with metastatic castration-resistant prostate cancer (mCRPC) with isolated osseous metastases provided the primary evidence based on which patients are now treated clinically with ^{223}Ra (*47*). The primary endpoint was overall survival, with multiple secondary endpoints including time to increase in serum prostate specific antigen (PSA) (*47*).

^{223}Ra therapy was found to be both safe and effective in improving overall survival, with a 30% reduction in mortality in the treatment group compared to placebo (median overall survival of 14.0 months in the ^{223}Ra group and 11.2 months in the placebo group) (*47*). That finding was consistent across all patient subgroups. All secondary endpoints also favored ^{223}Ra over placebo, including a significantly longer time to a symptomatic skeletal event, defined as a fracture, need for targeted radiation therapy, orthopedic intervention for skeletal metastasis, or spinal cord compression (*47*). The safety profile of ^{223}Ra was also demonstrated, with rates of all adverse events higher in the placebo group. For instance, in mild symptomatic mCRPC patients, which have been chemotherapy-naïve and afflicted with predominant tumor burden in the skeleton, ^{223}Ra plus abiraterone acetate plus prednisone/prednisolone was compared to placebo plus abiraterone acetate plus prednisone/prednisolone. In the ^{223}Ra arm, an increased excess fracture and death rate was noted and thus, this phase III trial has been unblinded early (*48, 49*). Nonetheless, the safety profile of ^{223}Ra is favorable, and it is a viable therapeutic option for men who meet the FDA-approved indication (i.e., in men with mCRPC, symptomatic

bone metastases, and no known visceral metastases) (*50*). In regards to castration-sensitive prostate cancer, there is also emerging evidence and that men with bone metastases can benefit from therapy with ^{223}Ra (*51, 52*); and this continues to be actively investigated (for example, NCT03304418). However, the risk-benefit profile of ^{223}Ra in certain prostate cancer clinical scenarios may propel the adoption of ^{177}Lu-PSMA therapy (discussed below; e.g. a recently published, single-center, prospective phase-II trial (LuPSMA trial), reported high response rates, low toxic effects, and reduction of pain in men afflicted with progressive mCRPC after treatment with PSMA-targeted therapy (*53*)).

Even if ^{177}Lu-PSMA comes to play a prominent role in prostate cancer, ^{223}Ra may find clinical applicability in other malignancies. ^{223}Ra appears to be safe, well-tolerated, and biologically active in patients with breast cancer and predominantly bone metastatic disease (*54*). The combination of ^{223}Ra with therapy targeted against vascular endothelial growth factor decreases bone turnover markers and led to objective response rates in a subset of patients with bone-metastatic renal cell carcinoma (*55*). The utility of ^{223}Ra therapy in non-prostate cancers, either alone or in combination with other therapies, remains to be elucidated but is under active investigation (for example, ClinicalTrials,gov identifier NCT02283749).

ON THE FDA HORIZON: ^{177}Lu-PSMA RADIOLIGAND THERAPY

Prostate-specific membrane antigen (PSMA) is expressed in prostate cancer with increased expression in mCRPC (*56*). The first small-molecule radioligand targeting PSMA for therapeutic purposes was ^{131}I-MIP-1095, although ^{177}Lu-based agents (including ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T), collectively referred to here as ^{177}Lu-PSMA, have seen more clinical use (*57*). ^{177}Lu-PSMA ligands are β-particle emitters that target PSMA-expressing tumors and have primarily been used in mCRPC (*58*).

A 2016 study by Kratochwil, et al demonstrated the safety and efficacy of ^{177}Lu-PSMA therapy in a small cohort of 30 patients with mCRPC, each of whom received 1-3 cycles (*59*). Thirteen of 30 patients experienced a PSA decrease of more than 50% following therapy with no significant decline in renal or liver function during the study period. Myelotoxicity, including leukopenia, anemia, and thrombocytopenia, occurred infrequently and most often in patients with baseline diffuse bone marrow metastases.

A larger 2016 study by Baum, et al included 56 patients with mCRPC who each received 2-4 cycles of ^{177}Lu-PSMA radioligand therapy (*60*). A PSA reduction was seen in 80% of patients, while a PSA reduction of >50% was reported in 59%. Additionally, 33% of patients reported decreased pain following treatment. Adverse events were infrequent and mild, with no significant nephrotoxicity or hematotoxicity.

A 2017 retrospective multicenter study conducted by Rahbar, et al involved 145 patients with mCRPC from 12 centers, all of whom had received at least one cycle of ^{177}Lu-PSMA therapy with further therapies 8-12 weeks apart (*61*). The primary study endpoint was biochemical response defined as a PSA decline of >50%. In total, 45% of patients had a biochemical response to therapy. Grade 3 or 4 hematologic events were uncommon and were seen in 18 patients (12%). Mild to moderate xerostomia occurred in 11 patients (8%), and nausea was reported in 6% of patients.

Based on studies demonstrating the safety and efficacy of ^{177}Lu-PSMA therapy, the German Society of Nuclear Medicine issued consensus recommendations in 2016 detailing the indications for use of these agents, which currently includes patients with mCRPC with detectable PSMA uptake on ^{68}Ga-PSMA PET/CT and evidence of biochemical or radiologic disease progression on standard therapy. Nonetheless, ^{177}Lu-PSMA therapy remains investigational. To determine the overall survival benefit of this therapy in patients with metastatic prostate cancer, a standardized, prospective trial of ^{177}Lu-PSMA radioligand therapy

is ongoing across multiple centers in the United States and Europe (ClinicalTrials.gov identifier NCT03511664). Secondary objectives of this trial include radiographic progression free survival, response evaluation criteria in Solid Tumors (RECIST) response, and time to first symptomatic skeletal event. If a survival benefit can be found, ^{177}Lu-PSMA may become an integral therapy in the treatment of patients with advanced prostate cancer.

Further prospective studies are also needed to elucidate the appropriate timing of PSMA-targeted endoradiotherapy in prostate cancer as well as to ascertain any role these agents may have in treating non-prostate malignancies with epithelial or endothelial PSMA expression (*62*). Additionally, more potent PSMA-targeted endoradiotherpeutics labeled with α-emitting radionuclides such as ^{225}Ac, are being investigated and can elicit profound responses in patients with advanced prostate cancer (*63*). However, the toxicity profile, particularly quality-of-life-altering xerostomia, of the PSMA-targeted, α-emitting agents may limit the adoption of these compounds into the clinic (*64*).

EMERGING THERANOSTIC AGENTS

^{177}Lu-Pentixather

Mesenchymal or marrow-derived stromal cells constantly secrete the chemokine stromal cell-derived factor-1 (SDF-1/CXCL12), which in turn attracts cancer cells by interacting with its cognate receptor, CXCR4 (*65*). CXCR4, a cell surface protein, plays a pivotal role in tumorigenesis, chemotaxis, and migration of metastatic tumor cells (*66*). CXCR4 has been observed in 75% of tumor entities, including pancreatic, breast, lung, prostate, and colorectal cancer (*67, 68*). Recent efforts have focused on the SDF-1/CXCR4 axis, e.g., the FDA-approved small-molecule CXCR4 antagonist plerixafor (Mozobil) for stem cell mobilization (*67, 69, 70*). Similar to plerixafor, the CXCR4 antagonist balixafortide demonstrated favorable results in combination with eribulin chemotherapy in patients with heavily-pretreated, relapsed metastatic

breast cancer (*71*).

Transferring the concept of the SDF-1/CXCR4 interaction to molecular imaging, CXCL12 conjugates have been labeled with radioisotopes, including the cyclic pentapeptide ^{68}Ga-pentixafor (*72*). That imaging agent is the most extensively investigated CXCR4 radioligand to date (*72, 73*). Its theranostic twin, pentixather, radiolabeled with either ^{177}Lu or ^{90}Y, has also been studied (*74-76*) (Table 2). Due to physiologic expression of CXCR4 in the bone marrow, and substantial retention of radioactivity in renal parenchyma, side effects include myelosuppression and deterioration in renal function. Consequently, peri-therapeutic dosimetry is highly recommended (*72*) (Figure 3). To achieve maximum tumor bone marrow ablation, endoradiotherapy with 177Lu pentixather has been performed as an add-on to a conventional chemotherapy and conditioning regimen prior to autologous or allogeneic stem cell transplantation (*72*). For instance, Lapa et al. reported on absorbed tumor doses of 30-70 Gy in intra- or extramedullary lesions in multiple myeloma, along with complete remission in 1/8 and partial remission in 5/8 subjects (*75*). To further corroborate those promising findings, the COLPRIT trial (Eudra-CT 2015-001817-28) will investigate this theranostic approach in multiple myeloma and lymphoma prospectively (*72*). Future assessments may also focus on solid tumors, such as neuroendocrine neoplasias, small cell lung cancer, or adrenal cortical carcinoma (*77-79*), although this theranostic approach may need to be utilized with care in patients who are not planned to undergo stem cell transplanation as part of therapy, given the significant myelosuppression that can occur. Nonetheless, as there is a increasing body of evidence on relevant hematotoxicity, which may even result in bone marrow ablation, autologous stem cell support is essential prior the CXCR4-directed endoradiotherapy (*77, 80*).

^{131}I-IMTO (iodometomidate)

With an annual incidence of 0.7 – 2.0 cases per one million inhabitants, ACC is a rare but extremely aggressive disease (*81*). Hahner et al. have investigated radiolabeled iodometomidate

theranostics of ACC (Table 2). In a feasibility study, 11 patients with non-resectable ACC, which demonstrated sufficient uptake on ^{123}I-IMTO SPECT, underwent a total of 19 treatment cycles (1.6 – 20 GBq 131I-IMTO per cycle, one to three cycles). Transient bone marrow depression was noted in up to 11% of patients. According to RECIST 1.1, best response was classified as partial response in one case, stable disease in 5 patients, and progressive disease in the remaining patients. In the six cases demonstrating controlled disease, overall survival was 13 months (range, 0.35 – 33 months) (*82*). However, IMTO is rapidly inactivated by endogenous esterases, which in turn may hamper diagnostic accuracy and therapeutic efficacy. Thus, Hahner and colleagues have recently introduced the theranostic pair ^{123}I/^{131}I-azetidinylamide (IMAZA), which has a comparable degree of inhibition of CYP11B enzyme activity, but shows higher metabolic stability *in vitro* compared to its predecessor, IMTO. Target-to-background ratios increased dramatically, enabling dosimetry-based tumor doses of up to 180 Gy administered to three patients (*83*).

^{177}Lu-3BP-227

Neurotensin plays a role in lipid ingestion, stimulation of pancreatic, biliary and gastrid acid secretion, and small-bowel motility. Among three subtypes, NSTR1 is a promising target for cancer treatment, as it is overexpressed in breast cancer (91%), in ductal pancreatic adenocarcinomas (75%), prostate cancer cells, and lung adenocarcinoma (60%) (*84*). Baum et al. described three patients with ductal pancreatic adenocarcinoma who underwent radionuclide therapy with ^{177}Lu-3P-227 (range, 5.1 – 7.5 GBq) (Table 2). In that feasibility study all patients showed clear uptake in tumor lesions up to 96 h post-injection, with the kidney as the dose-limiting organ. One patient, who received three intraperitoneal administrations at 8-10 week intervals, demonstrated favorable results with imaging-based partial response and significant reduction of pain along with

improved quality of life (Figure 4). This initial report provides evidence of the feasibility of ^{177}Lu-3P-227 in pancreatic adenocarcinoma, along with a high safety profile (reversible grade 2 anemia) (*85*).

TRAINING REQUIREMENTS FOR NUCLEAR MEDICINE PRACTITIONERS

The increased use of theranostics for the diagnosis and treatment of multiple tumor entities has created a need for nuclear medicine practitioners with substantial training in the field of radionuclide therapy. Thus, skills beyond "conventional" radioisotope imaging are of utmost importance to face the challenges of performing endoradiotherapies in clinical practice (*86*). These challenges include, but are not limited to dedicated administration protocols, understanding of the underlying biological pathways and complex kinetics of a radiotherapeutic agent, the appropriate use of dosimetry in different clinical scenarios and addressing acute or delayed therapeutic side effects (*86, 87*). We, as a nuclear medicine community cannot lose this momentum presented to us to further enrich the practice of nuclear medicine and to deliver on the theranostic promise for the sake of our (often palliative) patients afflicted with cancer.

CONCLUSIONS

Performing endoradiotherapy infusion procedures is not a trivial task and requires considerable medical knowledge and astute decision-making on the part of the nuclear medicine physician. ^{177}Lu-PSMA therapy will almost certainly be FDA-approved in the near future, potentially opening the floodgates of endoradiotherapy in the United States, and helping to further widespread acceptance of this technique. Going forward, nuclear medicine training must emphasize acquiring the necessary skills for carrying out these important procedures. We have likely only begun to scratch the surface of potential applications of theranostic agents, and this active area of research and burgeoning clinical care can drive the field of nuclear medicine to

unprecedented levels. As a field, we must do everything possible to leverage this unique opportunity.

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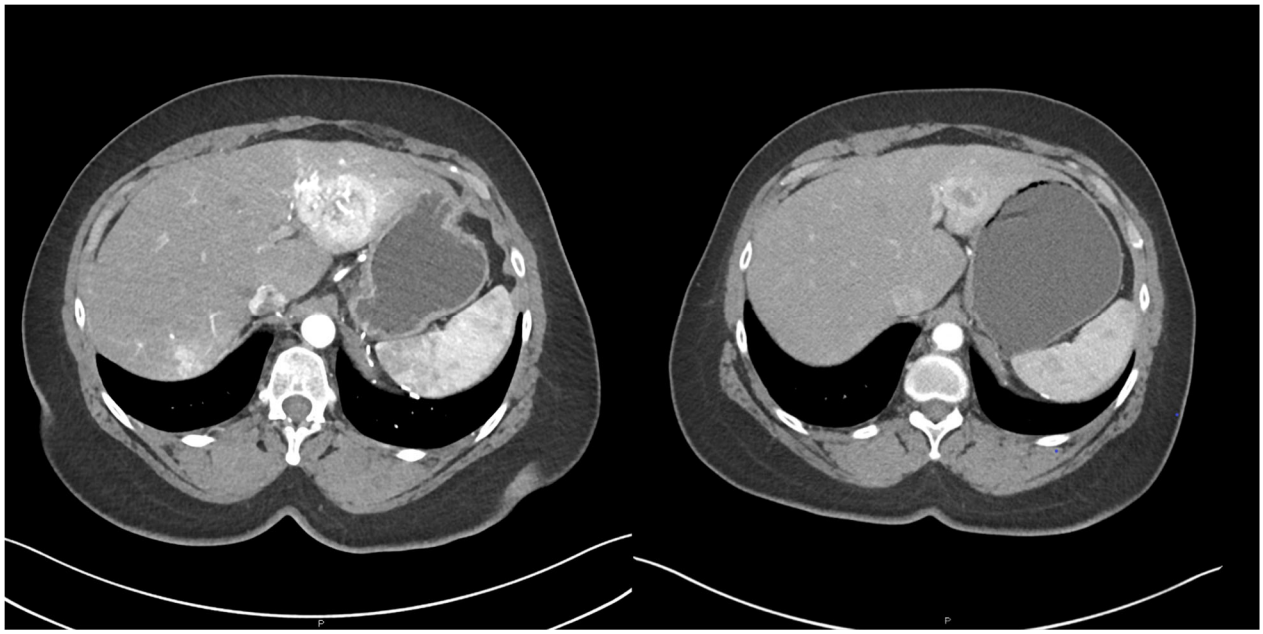
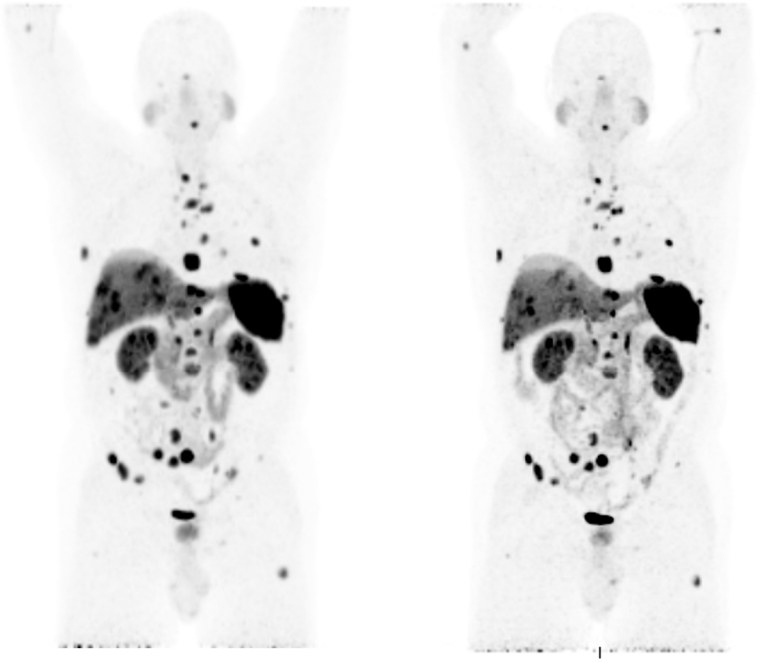
Figure 1.



Axial contrast enhanced CT scans through the liver in a patient with metastatic paraganglioma demonstrating significant response to high-specific-activity I131 MIBG therapy.

Axial CT scan images before and 12 months after initiation of high-specific-activity ^{131}I-MIBG therapy demonstrate marked decrease in size of left lobe of liver metastatic lesions and resolution of right lobe of liver metastatic lesion in a patient with metastatic paraganglioma.

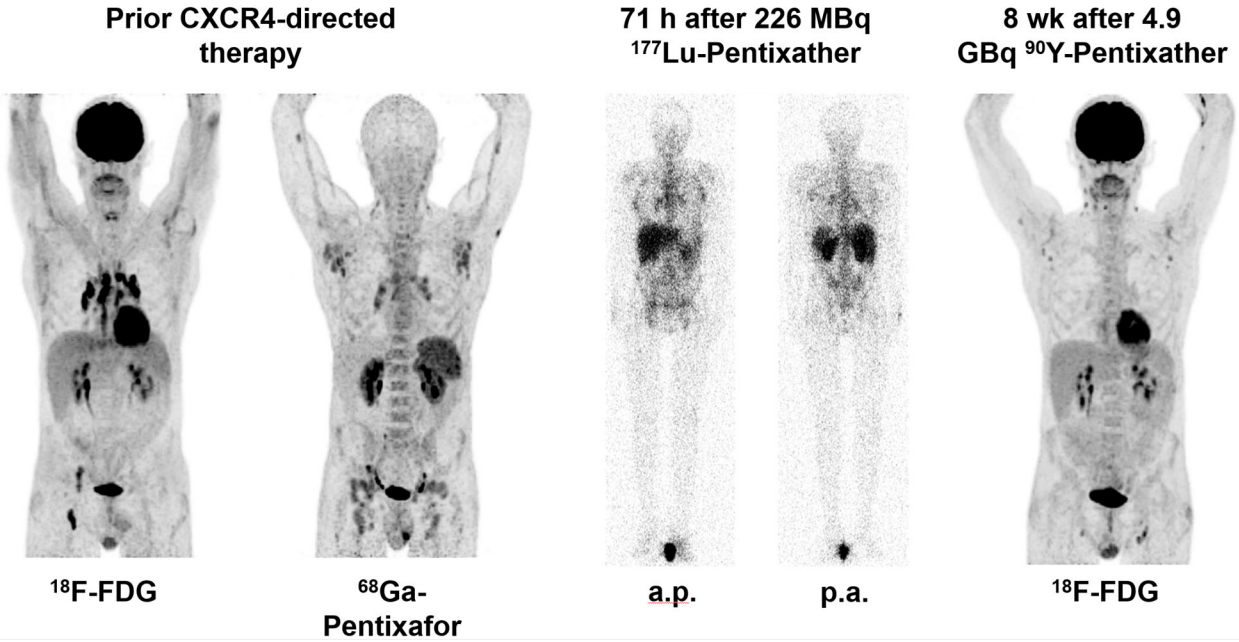
Figure 2.



^{68}Ga-DOTATATE PET/CT Pre therapy **^{68}Ga-DOTATATE PET/CT Post therapy**

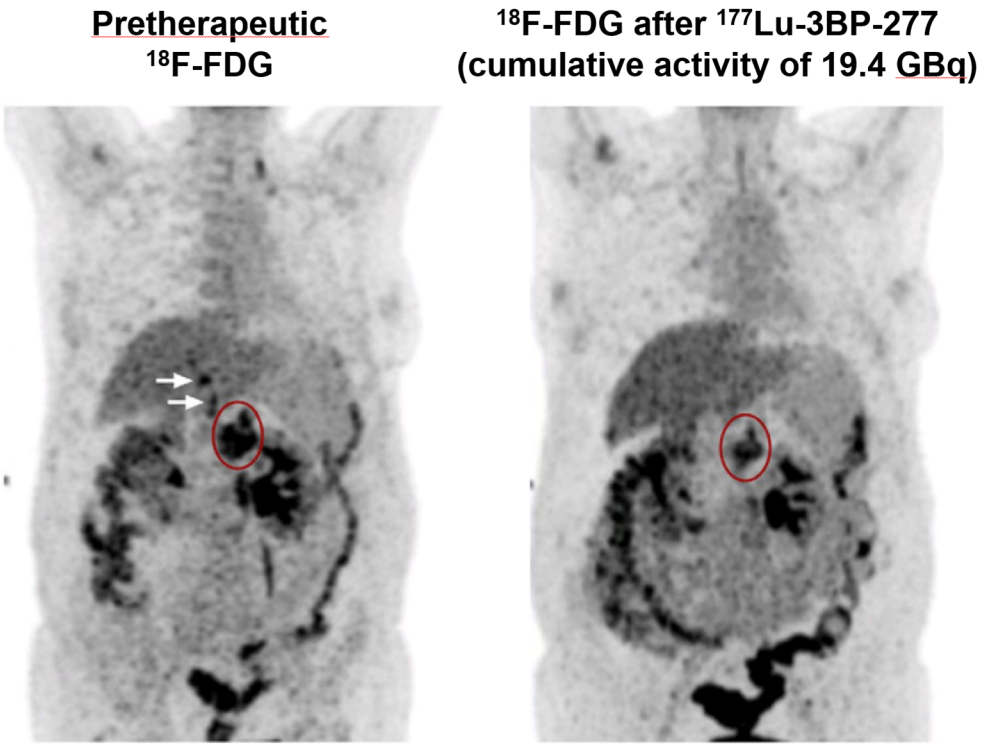
70 year old male with metastatic bronchial carcinoid who underwent Lutathera therapy. Pre treatment scan demonstrates marked metastatic disease in orbit, lungs, and bones which had been progressing on chemotherapy. Subsequent ^{68}Ga-DOTATATE scan demonstrates mild decrease in tumor volume 6 months following treatment completion (arrested disease).

Figure 3.



55-year-old male with a history of peripheral T cell lymphoma who was referred for evaluation of CXCR4-directed endoradiotherapy. The patient had experienced disease relapse in multiple lymph nodes two months after tandem high-dose chemotherapy and subsequent autologous stem cell transplantation. *Left:* At initial re-staging, both ^{68}Ga-Pentixafor-PET/CT as well as ^{18}F-FDG-PET/CT as standard of reference were performed with CXRC4-directed PET demonstrating more sites of disease than ^{18}F-FDG. *Middle:* Subsequent pre-therapeutic dosimetry with 226 MBq of ^{177}Lu-Pentixather confirmed persistent radiotracer accumulation and allowed for individualized activity calculation. *Right:* With the kidney as the dose-limiting organ, 4.9 Gbq of ^{90}Y-Pentixather could be administered and were combined with another cycle of high-dose chemotherapy with bendamustine (200 mg/m^2) and autologous stem cell transplantation. 8 weeks after therapy, a partial response could be recorded.

Figure 4.



^{18}F-FDG PET of a 59-year old female patient suffering from ductal pancreatic adenocarcinoma with metastases in the liver, lung, lymph nodes, and peritoneum. Pretherapeutic ^{18}F-FDG PET demonstrated the primary tumor (red oval) and liver metastases (indicated by the arrows). After 3 cycles of ^{177}Lu-3BP-277, a partial response with reduction in both size and metabolic activity of the primary (along with diminished liver lesions) was appreciated. Modified from Baum et al, (*85*) © by the Society of Nuclear Medicine and Molecular Imaging, Inc..

Table 1. Physical characteristics of common radionuclides used in radiotherapy (*88*).

Radionuclide	$T_{1/2}$ (hours)	E Max (keV)	Particle range max in soft tissue (mm)
^{177}L	162	β - (498), γ (208)	2
^{90}Y	64	β - (2250)	11
^{131}I	193	β - (610), γ (362)	2.9
^{225}Ac	240	6 MeV α particle	No clear range because of successive alpha emissions

Table 2. Overview of emerging theranostic twins.

Theranostic Twin	Subcellular Mechanism	Treated tumor entities	Organs at risk	Key Characteristics
^{68}Ga-Pentixafor / ^{177}Lu-Pentixather	SDF1 / CXCR4 axis	Multiple Myeloma	Bone marrow, kidneys	✓ Has been applied for the treatment of multiple myeloma (*74, 75*), with complete/partial remission in the majority of the subjects (*75*) ✓ Add-on to conventional chemotherapy and conditioning regimen prior to autologous or allogeneic stem cell transplantation (*72*) ✓ COLPRIT-Trial investigates CXCR4-directed endoradiotherapy in multiple myeloma and lymphoma at an early disease stage (*72*)
^{123}I-/^{131}I-IMTO	11ß-hydroxylase aldosterone synthase	ACC	Bone marrow, adrenal insufficiency	✓ Partial response in 1/11 and stable disease in 5/11 patients (*82*) ✓ The novel theranostic pair ^{123}I-/^{131}I-IMAZA may increase efficacy (*83*) ✓ The currently recruiting FAMIAN trial investigates the impact of 123I-IMTO for clinical management (*89*)
^{177}Lu-3BP-277	NTSR1	Ductal pancreatic adenocarcinoma	Kidney	✓ NTSR1 as a promising target with overexpression in breast cancer, pancreatic adenocarcinoma, prostate cancer and lung cancer (*84*) ✓ Feasibility study demonstrated partial response in a patient with pancreatic adenocarcinoma and extensive tumor burden (*85*) ✓ PET-guided strategies for risk stratification are needed (*90*)

^{123}I-/ ^{131}I-IMTO = ^{123}I-/ ^{131}I-metomidate, ACC = Adrenocortical cancer, ^{123}I-/^{131}I-IMAZA = ^{123}I/^{131}I-azetidinylamide, FAMIAN = "Combined ^{18}F-FDG PET and ^{123}I-IMTO Imaging for Adrenal Neoplasia" study, NTSR1 = neurotensin receptor 1.