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From Bench to Bedside—The Bad Berka Experience With First-in-Human Studies

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Precision oncology is being driven by rapid advances in novel diagnostics and therapeutic interventions, with treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations. Inherent in the theranostics paradigm is the assumption that diagnostic test results can precisely determine whether an individual is likely to benefit from a specific treatment. As part and integral in the current era of precision oncology, theranostics in the context of nuclear medicine aims to identify the appropriate molecular targets in neoplasms (diagnostic tool), so that the optimal ligands and radionuclides (therapeutic tool) with favorable labeling chemistry can be selected for personalized management of a specific disease, taking into consideration the specific patient, and subsequently monitor treatment response. Over the past two decades, the use of gallium-68 labeled peptides for somatostatin receptor (SSTR)-targeted PET/CT (or PET/MRI) imaging followed by lutetium-177 and yttrium-90 labeled SSTR-agonist for peptide receptor radionuclide therapy has demonstrated remarkable success in the management of neuroendocrine neoplasms, and paved the way to other indications of theranostics. Rapid advances are being made in the development of other peptide-based radiopharmaceuticals, small molecular-weight ligands and with newer radioisotopes with more favorable kinetics, potentially useful for theranostics strategies for the clinical application. The present review features the Bad Berka experience with first-in-human studies of new radiopharmaceuticals, for example, prostate-specific membrane antigen ligand, gastrin-releasing peptide receptor, neurotensin receptor 1 ligand, novel SSTR-targeting peptides and nonpeptide, and bone-seeking radiopharmaceuticals. Also new radioisotopes, for example, actinium (^{225}Ac), copper (^{64}Cu), scandium (^{44}Sc), and terbium (^{152}Tb/^{161}Tb) will be discussed briefly demonstrating the development from basic science to precision oncology in the clinical setting.

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Over the last two decades, THERANOSTICS of neuroendocrine neoplasms (NENs) using Ga-68 labeled tracers for diagnostics and Lu-177 and Y-90 as radionuclides for peptide receptor radionuclide therapy (PRRT) applying the same peptide has created a paradigm with rapidly expanding clinical application.[1] PRRT lends a significant benefit in

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progression-free survival as well as in overall survival in metastasized and/or progressive NENs as compared to other treatment modalities and regardless of previous therapies. Quality of life is also significantly improved.[2-4]

At the THERANOSTICS Center at Zentralklinik Bad Berka (ZBB), Y-90 DOTATOC and/or Lu-177 DOTATATE and DOTATOC (in use at our center since 2004) as well as other radiolabeled somatostatin analogues have been applied alone or in combination since over 20 years (in Germany, the first neuroendocrine tumor patient was treated in July 1997 at Frankfurt University Hospital and in 1998 in Bad Berka by RPB). The Bad Berka neuroendocrine tumor center group was also the first to use Y-90 DOTATATE as well as Lu-177 DOTATOC in a large patient group with progressive NETs. The Bad Berka neuroendocrine tumor center group pioneered the systematic use of a combination of Lu-177 and Y-90 (DUO PRRT) and, just recently, Ac-225 DOTATOC in sequence and concurrently, taking the heterogeneity of patients presented with tumors of various sizes and inhomogeneous distribution of somatostatin receptor (SSTR) into account, as well as intra-arterial PRRT and the diagnosis and treatment with SSTR antagonists, which opened a new horizon (Table).

There has been a tremendous increase in the number of studies with Ga-68 since its first clinical use for PET/CT imaging at our center in July 2004. A highly efficient NaCl-based Ga-68 labeling procedure has been developed in our institutional radiopharmacy[5,6] according to good manufacturing practices (GMP) regulations. A GMP compliant, fully automated click and start cassette-based synthesis system with easy handling, is available for the daily routine production of Ga-68 labeled radiopharmaceuticals. The Bad Berka group was also the first to use in humans, a Ga-68 labeled gastrin-releasing peptide receptor (GRPR) selective bombesin analogue DO3A-CH2CO-G-4-aminobenzoyl-Q-W-A-V-G-H-L-M-NH2 (AMBA) and the GRPR antagonist Sarabesin 3[7] for imaging of metastatic breast, lung, and prostate cancers (PCs). Many other Ga-68 radiopharmaceuticals have been used by our group as first-in-human studies, such as Ga-68 labeled macroaggregates (MAA) for lung perfusion PET/CT in 2008,[8] Ga-68 labeled JR10 antagonist for SSTR imaging in 2009, Ga-68 DOTA-alpha-MSH (melanocyte-stimulating hormone) in a patient with metastatic ocular melanoma in 2010,[9] and Ga-68 labeled affibody molecule targeting HER2 (human epidermal growth factor receptor 2).[10]

Besides the introduction of novel radiopharmaceuticals, more improvement of pharmacokinetic properties, approaches for clinical routine, circulating biomarkers and gene cluster analysis, and personalized and predictive dosimetry have continuously evolved. The existence of theranostic pairs of radionuclides of the same element (ie, radioisotopes) allows the preparation of chemically identical radiopharmaceuticals for diagnostic and therapeutic purposes. In this regard, radioiodine presents an excellent example, as it has been used successfully to diagnose (I-123/I-124) and treat (I-131) differentiated thyroid cancer for several decades. Indeed, this was the first theranostic application of matched radionuclides in nuclear medicine. Recently, with the increasing focus on optimizing targeted personalized approach following theranostic strategies, interest in the development of new radioisotopes is expanding, particularly using matching isotope pairs for imaging and therapy. There have been a number of radiometals potentially useful for radiotheragnostics, among those matched pairs of copper (Cu-64/Cu-67), scandium (Sc-43/Sc-44/Sc-47), terbium (Tb-152/Tb-155/Tb-149/Tb-161), lead (Pb-203/Pb-212), yttrium (Y-86/Y-90), among others.

From Bench to Bedside—Peptides/Ligands

Ga-68 and Lu-177 Labeled Prostate-Specific Membrane Antigen Ligand—Prostate-Specific Membrane Antigen I&T

The cell surface enzyme prostate-specific membrane antigen (PSMA), also known as glutamate carboxypeptidase II or *N*-acetyl-L-aspartyl-L-glutamate peptidase, is highly expressed on PC cells, and that further correlates with the malignancy of the disease, whereas with low or no PSMA expression in the normal prostate.[11-13] These characteristics make PSMA a promising target for molecular imaging and for targeted radionuclide therapy of PC. PSMA-specific PET/CT with Ga-68 or F-18 labeled radioligands, and PSMA-radioligand therapy (PRLT) with a beta emitter like Lu-177 or an alpha-emitter like Ac-225, offer a new and unique theranostic possibility by using similar PSMA ligands.[11]

To this aim, the diagnostic or therapeutic PSMA ligand DOTAGA-(I-y)fk(Sub-KuE), also called PSMA I&T, for "imaging and therapy" was developed. It was found that substitution of D-Phe by D-3-iodo-Tyr in the linker does have beneficiary influence in significantly improving PSMA affinity of the PSMA I&T constructs.[14-16] Preclinically compared with other promising PSMA-directed probes, Ga-68 and Lu-177 PSMA I&T both show a tissue distribution pattern comparable to that of Ga-68 PSMA-HBED-CC.[14,17] PRLT with Lu-177 PSMA-I&T could achieve high tumor-to-background ratios of mean absorbed doses.[15]

On the basis of the promising preclinical data obtained for Ga-68/Lu-177 PSMA I&T, initial proof of concept in humans was explored. In a first patient with metastatic castration-resistant prostate cancer (mCRPC) with multiple metastases, Ga-68 PSMA I&T PET/CT revealed multiple bone, abdominal lymph node, and a liver metastasis with high contrast.[14] The primary prostate tumor, as well as periprostatic tissue and urinary bladder invasion, was not concealed by radioactivity in the bladder. The liver lesion was not known before PET scanning. Further, a sclerosis in a sternal lesion, which had been barely visible in the CT image, exhibited a high Ga-68 PSMA I&T uptake with an SUVmax of 76.4. Two patients with mCRPC and multiple metastases in bone and lymph nodes were treated with Lu-177 PSMA I&T. The administered mass of PSMA I&T was 142 and 200 mg, and the administered activity was 5.7 and 8.0 GBq, respectively. Tumors exhibited a high uptake of Lu-177 PSMA I&T on posttherapy planar and SPECT/CT images. Therapy was well tolerated, and no significant fall in blood counts, renal function (serum creatinine, tubular extraction rate), or any of the laboratory parameters

Table Radiopharmaceuticals First Used at the Bad Berka THERANOSTICS Center

Radiopharmaceutical	First Use (Month/Year)	Principle	Clinical Indication
Ga-68 DOTANOC	07/2004	SSTR targeting (agonist)	NETs
Ga-68 gastrin	12/2006	Gastrin receptor targeting	Medullary carcinoma of thyroid
Ga-68 AMBA	08/2006	Bombesin analogue—GRP and NMB receptor targeting	Carcinomas of breast, prostate, colon
Ga-68 tyrosine	08/2008	Amino acid uptake by tumor cells	Brain tumors (gliomas)
Ga-68 BPAMD	02/2009	Biphosphonate—binding to hydroxyapatite structure of bone	Skeletal metastases
Ga-68 MAA	09/2008	Mechanical trapping of MAA (macroaggregated albumin) in the capillary bed	Pulmonary thromboembolism, visualization of the perfusion pattern before selective intra-arterial therapy (eg, internal radiation using Y-90 for hepatic metastases)
Ga-68 glucose	05/2009	Tumor hypermetabolism	Similar to the use of ^{18}F-FDG in tumors
Ga-68 demobesin	07/2009	GRP receptor antagonist	Carcinomas of breast, prostate, colon
Ga-68 JR10	05/2009	SSTR targeting (antagonist)	NETs
Ga-68 alpha-MSH	05/2010	Cell surface receptor targeting of melanocytes	Melanoma
Ga-68 sarabesin-6	08/2011	GRP receptor antagonist	Carcinomas of breast, prostate, colon
Ga-68 RGD	09/2011	Integrin/ alpha-v beta-3 targeting (antagonist)	Investigation and monitoring of neoangiogenesis and invasiveness of cancers like breast, colon, prostate, lung, etc
Ga-68 HER-2 affibody	12/2005	HER-2 targeting	Prognostication in carcinoma breast (investigation of HER-2 status before herceptin therapy)
Ga-68 SHAL	05/2010	Selective high affinity ligand for B-cell lymphoma	B-cell lymphoma
Tc-99m demobesin	11/2009	GRP receptor antagonist	Carcinomas of breast, prostate, colon
Scandium-44 DOTATOC	02/2009	SSTR targeting (agonist)	Pretherapeutic dosimetry before PRRT in NETs
Ga-68 NODAGA SOMscan	05/2012		
Ga-68 NODAGA GHRH	06/2012		
Ga-68 DOTA SOM	10/2012		
Ga-68 JR11	11/2012	SSTR targeting (antagonist)	
Ga-68 TRAP-RGD	03/2013		
Ga-68 CXCR4	03/2013		
Ga-68 neurotensin antagonist	07/2013	NTR1 targeting	
Cu-64 Chlorid	01/2015		
Ga-68 MCR1	05/2017		
Ga-68 PSMA-ALB-06	05/2017	anti-PSMA inhibitors	
Ga-68 TUM-788	06/2017		
Ga-68 LM3		SSTR targeting (antagonist)	SSTR-positive tumors
Cu-64 PSMA-617	03/2015	anti-PSMA inhibitors	Prostate
Ga-68 PSMA TO-1	05/2018	anti-PSMA inhibitors	
Ga-68 rhPSMA	07/2018	anti-PSMA inhibitors	
Tb-152 DOTATOC	05/2016	SSTR targeting	SSTR-positive tumors
Tb-152 PSMA-617	09/2016	anti-PSMA inhibitors	Prostate
Lu-177 DOTATATE	08/2004	SSTR targeting	PRRT in NETs
Combined Y-90 and Lu-177 labeled somatostatin analogues		TANDEM SSTR targeting	TANDEM-PRRT in NETs

Table (*Continued*)

Radiopharmaceutical	First Use (Month/Year)	Principle	Clinical Indication
Systematic use of sequential Y-90 and Lu-177 labeled somatostatin analogues		DUO SSTR targeting	DUO-PRRNT in NETs
Intra-arterial Y-90 DOTATATE		SSTR targeting	Selective internal radiation therapy in NETs
Lu-177 AMBA		Bombesin analogue—GRP and NMB receptor targeting	Radionuclide therapy of metastatic carcinoma breast
Lu-177 RGD		integrin/ alpha-v beta-3 targeting (antagonist)	Anti-angiogenesis therapy
I-131 Phenylalanine (ACD-101)	04/2009		Endoradiotherapy in brain tumor (glioma)
Lu-177 BPAMD	07/2009	Biphosphonate—binding to hydroxyapatite structure of bone	Radionuclide therapy and pain palliation of skeletal metastases in carcinoma prostate
Lu-177 demobesin	12/2009	GRP receptor antagonist	Radionuclide therapy in carcinoma breast
Lu-177 sarabesin-6	04/2011	GRP receptor antagonist	Radionuclide therapy in carcinoma prostate
Lu-177 PMSA Minibody J591	08/2012	anti-PSMA inhibitors	
Lu-177 HA-DOTATATE	07/2013	SSTR targeting	
Lu-177 PSMA I&T	05/2013	anti-PSMA inhibitors	Radioligand therapy in prostate cancer
I-131 Pentixafor (CXCR4)	01/2014		
Lu-177 Pentixafor (CXCR4)	11/2014		
Lu-177 Neurotensin 1	02/2015	NTR1 targeting	
Bi-213 PSMA	12/2016	anti-PSMA inhibitors	
Bi-213 DOTATOC	12/2016	SSTR targeting	
Lu-177 MCR1	05/2017		
Lu-177 PSMA-HSA-06	07/2017	anti-PSMA inhibitors	
Lu-177 Zoledronat	07/2017		
Lu-177 LM3	08/2017	SSTR targeting (antagonist)	PRRT in SSTR-positive tumors
Lu-177 avb3 Integrin	09/2018		
Ac-225 PSMA	02/2018	anti-PSMA inhibitors	
TANDEM Ac-225 + Lu-177 PSMA-617	02/2018	Tandem Alpha-Beta radioligand therapy anti-PSMA inhibitors	Tandem Alpha-Beta radioligand therapy in prostate cancer
Tb-152 DOTATOC		SSTR targeting	PRRT in SSTR-positive tumors
Ac-225 DOTATOC	10/2018	SSTR targeting	PRRT in SSTR-positive tumors

was found. There was no adverse or clinically detectable pharmacologic effect. During early follow-up, no side effects were observed, particularly no dry mouth caused by radioactivity in salivary glands.

Further, we analyzed the safety and efficacy of the Lu-177 labeled PSMA I&T in a larger cohort of 56 mCRPC patients (125 cycles of Lu-177 PSMA I&T treatment) between May 2013 and June 2015.[18] The patient group was heterogeneous, with wide variations in the SUVmax on Ga-68 PSMA PET before PRLT, in tumor load, and in the distribution of metastases. All patients were clinically monitored during therapy and for 2-4 days thereafter as inpatients for possible side effects (such as nausea, vomiting, breathlessness, and fatigue). Vital parameters were recorded during therapy. A structured questionnaire was used to document any delayed complication (such as xerostomia). Laboratory analysis was performed before and after therapy. Dosimetry was performed in 30 patients in accordance with Bad Berka Dose Protocol established from more than 1,000 NEN patients undergoing PRRT.[19] Molecular and morphologic responses were evaluated in accordance with European Organization for Research and Treatment of Cancer criteria[20] and RECIST 1.1,[21] respectively. Lu-177 PSMA I&T showed high, specific, and rapid tumor uptake, high absorbed tumor doses (median, 3.3 mGy/MBq) compared with the levels in normal organs. The long effective half-lives in both skeletal and soft-tissue metastases resulted in high mean absorbed tumor doses, with the maximum doses obtained in bone and lymph node metastases of 260 and 468 Gy, respectively. Lu-177 PSMA I&T exhibited suitable targeting and retention characteristics for successful radioligand therapy for end-stage progressive mCRPC patients.

Ga-67, Ga-68, In-111, and Lu-177 Labeled GRPR Antagonist—SB3, NeoBOMB1

GRPR is a member of the G protein-coupled receptor family of bombesin receptors.[22,23] The high-density expression of GRPR in various types of human tumors including PC, mammary carcinoma, colorectal cancer, small cell lung cancer, head and neck squamous cell tumors, gastric carcinoma, and gastrointestinal stromal tumors and gliomas[24-27] makes it an attractive target for molecular imaging and therapy. The first-generation radiopeptides developed for such purposes were GRPR agonists derived from C-terminal fragments of the amphibian tetradecapeptide bombesin (BBN)[23,28-31] or the respective human 27mer peptide GRP.[32-34] However, BBN-like receptor agonists showed suboptimal pharmacokinetics in vivo and would induce undesirable effects in patients.[7] This finding limited the translational prospects of radioagonists despite their ability to internalize in cancer cells, a property initially proposed for prolonged lesion retention. Later, interest shifted from GRPR agonists to the second-generation GRPR-antagonist-based radiopeptides.[35] Several studies have shown that noninternalizing radioantagonists can successfully target and be sufficiently retained in GRPR-expressing cancer lesions while rapidly clearing from physiological organs in both animal models and humans.[26,36-39] The superior pharmacokinetics of radiolabeled GRPR antagonists over agonist in combination with their higher inherent biosafety has attracted the development of new improved GRPR antagonist candidates for clinical translation.

Following this rationale, we have initially developed Tc-99m labeling demobesin 1, a GRPR antagonist radioligand for SPECT imaging, containing the [DPhe6,Leu-NHEt13,des-Met14]BBN(6-14) peptide fragment.[35,40] Demobesin 1 carries a tetraamine chelator and is unsuitable for labeling with bi/trivalent radiometals. It can only be labeled with Tc-99m. Then we introduced GRPR antagonist, SB3 (DOTA-p-aminomethylaniline-diglycolic acid-DPhe-Gln-Trp-Ala-Val-Gly-His-Leu-NHEt), which is the corresponding DOTA (instead of N4) carrying conjugate that can be labeled with bi/trivalent radiometals, such as Ga-68, In-111, and Lu-177. We evaluated Ga-68 SB3 as a PET tracer first in animals and eventually in patients with prostate and breast cancer for imaging.[7] First clinical data with Ga-68 SB3 PET/CT in patients with disseminated PC and breast cancer showed encouraging results, which favors the application of radionuclide labeled SB3 as an attractive tool for prostate and breast cancer imaging, and eventually patient stratification for radionuclide therapy with GRPR antagonist.

Interestingly, it was found that the respective In-111 and Lu-177 labeled radioligands, in addition to showing less affinity for GRPR, turned out to be less stable in the biological milieu.[41] As a result, GRPR targeting of xenografts in animal models with In-111 and Lu-177 SB3 was found inferior to Ga-68 SB3, restricting the theranostic application options of SB3 in the clinic (not found). In the quest of radioligands with higher stability, by replacing the C-terminal-His^{12}-Leu13NHEt of SB3 by -His12-NH-CH[CH2-CH(CH3)2]2, we produced NeoBOMB1,[23] and labeled it with different radionuclides for both imaging and therapy. In a preclinical study, we used human androgen-independent prostate adenocarcinoma PC-3 cells expressing the GRPR for in vitro assays, and PC-3 xenograft-bearing mice to investigate in vivo radioligand stability and biodistribution. Ga-67/Ga-68/In-111/Lu-177 NeoBOMB1 radiopeptides, showing a remarkably preserved GRPR affinity and cell binding, high in vivo stability, and an ability to target PC xenografts in mice independent of radiometal used.[23] These features highlight the promising theranostic prospects of NeoBOMB1 as compared with SB3.

We subsequently explored the clinical utility of NeoBOMB1 in patients. First translational evidence of the Ga-68 NeoBOMB1 efficacy as a PET tracer was acquired in PC patients. Four patients with prostate adenocarcinoma underwent Ga-68 NeoBOMB1 PET/CT at our center. All patients were studied before by conventional imaging modalities (eg, MRI, F-18 choline PET, and Tc-99m methylene diphosphonate bone scanning). Ga-68 NeoBOMB1 was well tolerated by all subjects, and no side effects were reported after the administration. Furthermore, the new radiopeptide strongly localized in primary prostate-confined disease but also in the metastases. Impressively, Ga-68 NeoBOMB1 exhibiting a high diagnostic sensitivity, including evident uptake in a liver micrometastasis not visualized on the arterial phase of CT but later confirmed on follow-up angiography, and was able to detect lymph node metastases down to 5 mm in size, normally considered negative on conventional imaging. Further clinical studies using radiolabeled GRPR antagonist in other tumor types are ongoing.

Ga-68 and Lu-177 Labeled Novel SSTR Antagonist—LM3

Radiolabeled SSTR agonists have been used clinically for diagnosis, such as Ga-68 labeled DOTATOC, DOTATATE, DOTANOC, as well as their theranostic pairs Lu-177 or Y-90 labeled SSTR-agonist (DOTATATE or DOTATOC) for PRRT.[42] Preclinical studies have indicated that radiolabeled SSTR antagonists bind to significantly more receptor sites than agonists as targeting agents, and better tumor visualization than agonists, despite the lack of internalization.[43,44] Therefore, imaging probes based on SSTR antagonists have been explored and several SSTR antagonist-based PET tracers have been investigated in the clinic. The first clinical studies with SSTR antagonist (DOTA-BASS, DOTA/NODAGA-JR11) based PET/CT imaging have reported the feasibility and higher tumor detection rates in patients with gastroenteropancreatic neuroendocrine tumors than the currently used SSTR agonists.[45,46]

We applied a novel SSTR-targeting PET tracer, the Ga-68 labeled SSR-antagonist LM3 [p-Cl-Phe-cyclo(D-Cys-Tyr-D-4-amino-Phe(carbamoyl)-Lys-Thr-Cys)D-Tyr-NH_2] conjugated to the chelator NODAGA (1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid) for human SSTR-expressing solid tumors, and compare it qualitatively as well as quantitatively with the SSTR-agonist Ga-68 DOTATOC PET/CT, followed by a therapeutic compound Lu-177 DOTA-LM3 for PRRT in patients with SSTR-expressing tumors.

The radiolabeling of Ga-68/Lu-177 LM3 was performed in our radiopharmacy department in accordance with GMP. The safety, biodistribution profile, and dosimetry were analyzed, as well as a head-to-head comparison with SSTR agonist DOTATOC. From February to October 2017, Ga-68 NODAGA-LM3 PET/CT were performed in 40 patients with SSTR-expressing solid tumors (GEP-NEN, n = 16; lung/mediastinal-NEN, n = 8; paraganglioma/pheochromocytoma, n = 7; thyroid cancer, n = 3; renal cell carcinoma, n = 1; meningioma, n = 1; cervix MiNEN, n = 1; CUP-NEN, n = 1), as well as for establishing the initial diagnosis in the case of clinical suspicion of an NEN (n = 2). Before and after injection of Ga-68 NODAGA-LM3, safety data were collected, including the blood pressure, pulse, respiratory frequency, and temperature, and routine blood and urine tests, liver function, and renal function were examined. The acquired images obtained with radiolabeled LM3 were analyzed qualitatively (visually) and semiquantitatively (SUVmax). Out of these, 3 patients (P1, pancreas-NEN; P2, paraganglioma; P3, pheochromocytoma) had a Ga-68 DOTATOC PET/CT (TOC) within 3 months, for comparative analyses. In these patients, Ga-68 NODAGA-LM3 (mean activity = 285 MBq, radiochemical purity >97%, specific activity 20-50 MBq/nmol) was administered followed by PET/CT imaging at 50 minutes post injection (p.i.) No adverse events or serious adverse events occurred after Ga-68 NODAGA-LM3 injection for all the patients, and no obvious changes in vital signs or clinical laboratory tests were found during and after the injection. With respect to the clinical indication, Ga-68 NODAGA-LM3 was positive in 36 and negative in 7 studies, respectively. Where positive, Ga-68 NODAGA-LM3 demonstrated excellent image quality with high specific uptake in SSTR-expressing lesions. Despite the limited number of patients for direct comparison with Ga-68 DOTATOC, Ga-68 NODAGA-LM3 detected more SSTR-expressing lesions, which adheres to the recently reported results comparing radiolabeled SSTR-antagonists with agonists (Fig. 1). Compared to the agonists, it also provides a significant advantage of detecting more lesions in the liver due to the distinctively higher tumor-to-liver ratio. This first-in-human study indicates the safety and significant efficiency of a new type of SSTR antagonist PET radiotracer Ga-68 NODAGA-LM3. First-in-human study of Lu-177 labeled DOTA-LM3 for safety, biodistribution, pharmacokinetics, and dosimetry evaluation of Lu-177 labeled DOTA-LM3 were performed in patients with neuroendocrine tumors, demonstrating higher absorbed dose in the whole body, kidneys, spleen, and tumor lesions, as compared to the SSTR agonist Lu-177 DOTATOC (Fig. 2). Long-term efficacy and survival analysis of Lu-177 DOTA-LM3 PRRT are evaluated.

Ga-68 and Lu-177 Labeled Bone-Seeking Bisphosphonates—BPAMD, DOTA^{ZOL}

Bone-seeking radiopharmaceuticals are currently used for diagnostic and therapeutic purposes.[47] The increased metabolism of the bone material can be visualized via both SPECT and PET, for example, by using Tc-99m labeled bisphosphonate complexes or F-18 fluoride (NaF). For the treatment of disseminated bone metastases, there are two classes of therapeutic bone-seeking radiopharmaceuticals, including calcimimetic- and phosphonate-based radiopharmaceuticals. The simplest bone binding radiopharmaceuticals for palliative endoradiotherapy, belonging to the class of calcium mimetics, are Sr-89, P-32, and Ra-223, and their localization underlies the same mechanisms as calcium and, therefore, may be unpredictable.[48] The development of radiometal labeled bisphosphonate-based tracers requires the use of chelators for complexation of trivalent metals. Many research groups across the world are currently undertaking research into complexing bisphosphonate compounds to radionuclides using macrocyclic chelators and aim at identifying a labeled product that has high affinity for bone and offers a high thermodynamic and kinetic stability. One of these so-called macrocyclic bisphosphonates is BPAMD (4-[49]-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl)acetic acid), which was initially able to show a high potential in terms of high bone accumulation with Ga-68 labeling in preclinical study.[50]

We explored the possibility of diagnosing bone metastases using Ga-68 BPAMD as well as the application of Lu-177 BPAMD for therapy and the development of combination of novel bisphosphonates with macrocyclic chelators provides promising tracers for diagnosis, therapy, and also theranostics of bone metastases.[49,51-53] In the first human applications, the bisphosphonate revealed very high target-to-soft tissue ratios combined with fast renal clearance. Standardized uptake values were comparable with those of the ^{18}F-NaF scan, and some metastases even showed higher accumulation of the bisphosphonate. These promising diagnostic examinations finally led to the first therapeutic applications using the β^--emitter Lu-177 instead of Ga-68. Lu-177 BPAMD was performed in patients with widespread, painful skeletal metastases, presenting with progressive disease and refractory to conventional treatment (Fig. 3). The very long half-life of the radiopharmaceutical in the metastases (>80 hours), provided high tumor doses, ranging from 2.4 to 209 mGy/MBq (wide range due to different size of the lesions), which led to a significant reduction in osteoblastic activity of the bone metastases. A significant reduction in osteoblastic activity of the bone metastases was seen on the follow-up PET/CT using Ga-68 BPAMD or F-18 fluoride. Furthermore, the therapy did not cause any significant adverse effects. There were only mild-to-moderate changes in blood cell counts, and no significant alterations in serum creatinine/BUN or other lab parameters were observed.

Despite those promising clinical results, there is still much potential for improvements with regard to radiosynthesis, and raising the accumulation in bone metastases and reducing the uptake in healthy tissue. In addition to the well-established NOTA derivatives, there is another class of bifunctional chelators appropriate for labeling with Ga-68. These so-called DATA chelators are based on 6-amino-1,4-diazepine-triacetic acid and enable more rapid quantitative radiolabeling under milder conditions.[54] The combination of this chelator with next-generation bisphosphonates is also

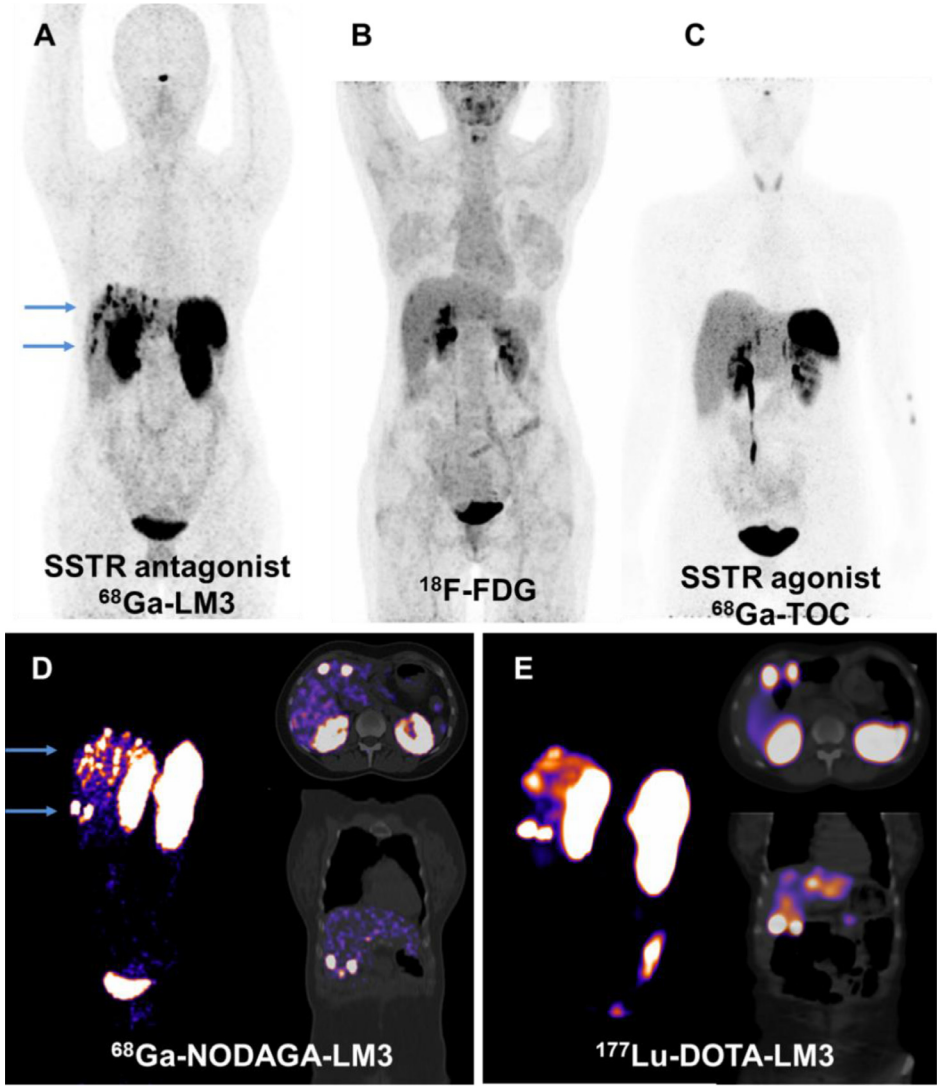

Figure 1 Disseminated liver metastasis detection by SSTR antagonist: theranostics approach using Ga-68/Lu-177 LM3 for imaging and intra-arterial PRRT. A 29-year-old woman was diagnosed in 2017 with a well-differentiated nonfunctional, pancreatic neuroendocrine neoplasm with hepatic metastases. The Ki-67 proliferation index (biopsy) was 15% for the inoperable primary tumor and 20% for hepatic metastases. Initial tumor classification pT2 pN0 (0/16) cM1 (HEP) G2 L0 V0 Pn0 R0, stage IV (World Health Organization 2017). The biomarkers chromogranin A, synaptophysin, and cytokeratin MNF116 were elevated. Multiple (at least 25) small, bilobar-distributed somatostatin receptor-positive liver metastases were detected by on PET/CT using antagonist Ga-68 NODAGA-LM3 (A), as compared to somatostatin receptor agonist (B) Ga-68 DOTATOC. (C) ^{18}F-FDG-PET/CT. (D) Somatostatin receptor expression in multiple liver metastases on Ga-68 NODAGA-LM3 PET/CT. (E) Post-therapy Lu-177 DOTA-LM3 (intra-arterial, 6.9 GBq) SPECT/CT.

conceivable and might provide a compound of high diagnostic efficiency, as well.

Another DOTA-conjugated zoledronate ($DOTA^{ZOL}$) labeled with Ga-68 and Lu-177[55] was also proven in clinical studies. In the same PC patient, both Ga-68 PSMA-11 and Ga-68 DOTAZOL detected multiple skeletal lesions in thoracic and lumbar vertebrae, as well as in the pelvis. Comparison of SUVs revealed an approximately three-fold higher uptake of the bisphosphonate in bone metastases and an approximately three-fold lower uptake in normal tissue organs, exemplifying the bisphosphonate's better target-to-background ratio. It is also advantageous for therapeutic applications due to reduced radiation dose for nontarget tissue. Thus, DOTAZOL for example may be a potent conjugate for theranostics of bone metastases.

Neurotensin Receptor 1 Targeted Therapeutic Compound—Lu-177 3BP-227

Neurotensin receptor 1 (NTR1) has found to be involved in the growth of various tumors.[56,57] The high expression in ductal pancreatic adenocarcinoma but not in normal pancreatic tissue or chronic pancreatitis, and restricted expression in normal tissues, limited to the central nervous system and the intestinal tract,[58] makes NTR1 a promising target for radioligand therapy

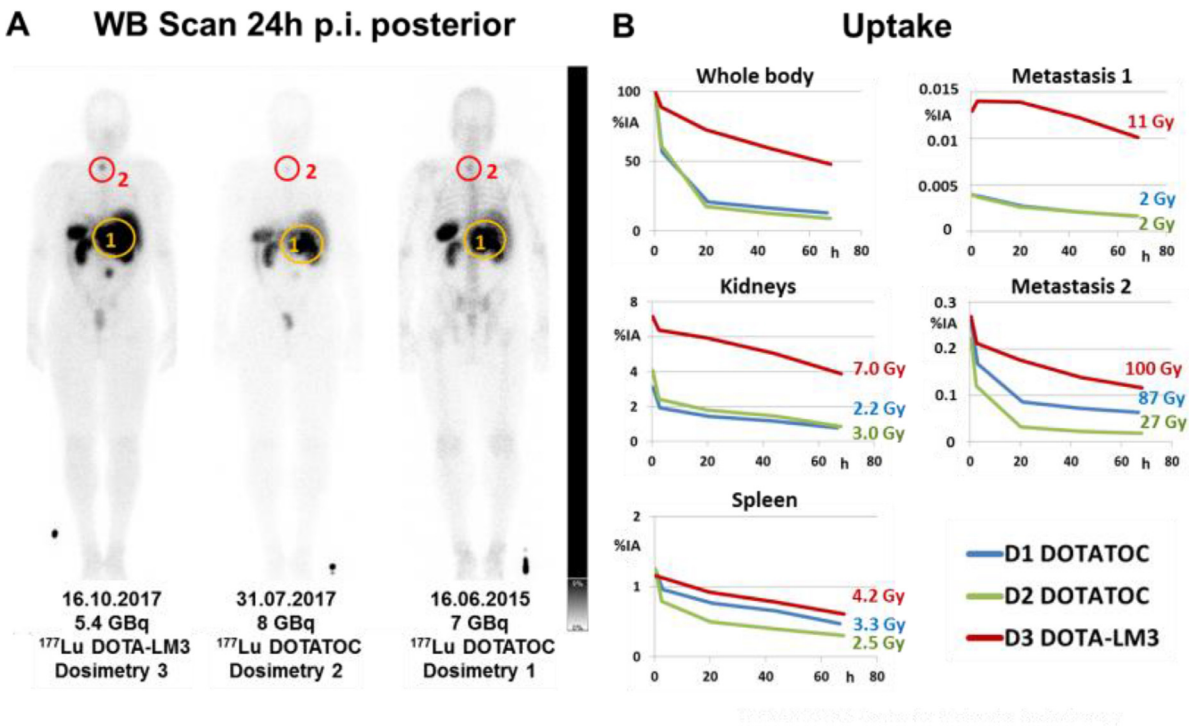

Figure 2 Dosimetry comparison: Lu-177 DOTA-LM3 vs Lu-177 DOTATOC in the same patient. (A) Whole-body anterior projection images of Lu-177 DOTA-LM3 and Lu-177 DOTATOC in the same patient. Lu-177 DOTA-LM3 demonstrated higher quality image with high TBR as well as high specific uptake in SSTR-expressing lesions. (B) Time-activity curves of whole body, kidneys, spleen, and target tumor lesions after administration of Lu-177 DOTA-LM3 and Lu-177 DOTATOC. Lu-177 DOTA-LM3 demonstrated higher absorbed dose in the whole body, kidneys, spleen, and target tumor lesions, as compared to the SSTR agonist Lu-177 DOTATOC.

of ductal pancreatic adenocarcinoma (which has an extremely poor prognosis). Additionally, the incidence of NTR1 expression and receptor density increases with higher malignancy of the pancreatic lesion, and hepatic metastases express NTR1 receptor with similar intensity to that of the primary tumor.[59]

DOTA-conjugated NTR1 antagonist 3BP-227 labeled with the radioisotope was developed on the basis of the previously described SR142948A. In early preclinical studies with animal models, the novel procedure significantly inhibited tumor growth and resulted in a 9-fold increase in tumor doubling time, as well as a tumor growth delay of more than 5 weeks.[60]

We explored initial experience of NTR1 targeted radioligand therapy using Lu-177 3BP-227 in patients with metastatic pancreatic adenocarcinoma after exhaustion of all other treatment options, as salvage therapy. Six patients with confirmed metastatic ductal pancreatic adenocarcinoma received Lu-177 3BP-227 intravenously. Planar whole-body scintigraphy and SPECT/CT was performed with to determine the tumor uptake and the patients' eligibility for treatment. The kinetics of Lu-177 3BP-227 was determined on the basis of studies at 5 time points after administration of the radiopharmaceutical. Dosimetry was calculated. The administered activity was individually chosen on the basis of uptake in the tumor lesions after infusion of 1.2-1.5 GBq of Lu-177 3BP-227. Treatment planning was based on the clinical condition of the patient, the patient's hematologic and renal function, and the practical guidance on PRRT.[61-63] If the patient's condition allowed, ^{18}F-FDG-PET/CT imaging was performed 8-12 weeks after therapy to determine treatment efficacy. Lu-177 3BP-227 targeted radioligand therapy was well tolerated by all patients, with the most severe adverse reaction a reversible grade 2 anemia. One patient experienced significant improvement of symptoms and quality of life-surviving 13 months from diagnosis and 11 months from the start of Lu-177 3BP-227 therapy. The kidneys were identified as the dose-limiting organ. However, none of the reported patients received a dose to the kidney that exceeded 23 Gy; the highest renal dose (22 Gy) was received by the patient obtaining a partial response. This study provides the first clinical evidence of the feasibility of treating ductal pancreatic adenocarcinoma using Lu-177 3BP-227.[64,65] The high uptake in metastatic tumor lesions and a promising toxicity profile warrant further investigation of Lu-177 3BP-227 in prospective clinical studies to systematically evaluate its safety and efficacy, and to define the patient population it will most benefit.

From Bench to Bedside—Radioisotope

Copper 64 (Cu-64)—PET Using Cu-64 Labeled PSMA

One of new generation radiotheranostics using the PET isotope copper Cu-64 and the therapeutic isotope Cu-67 may

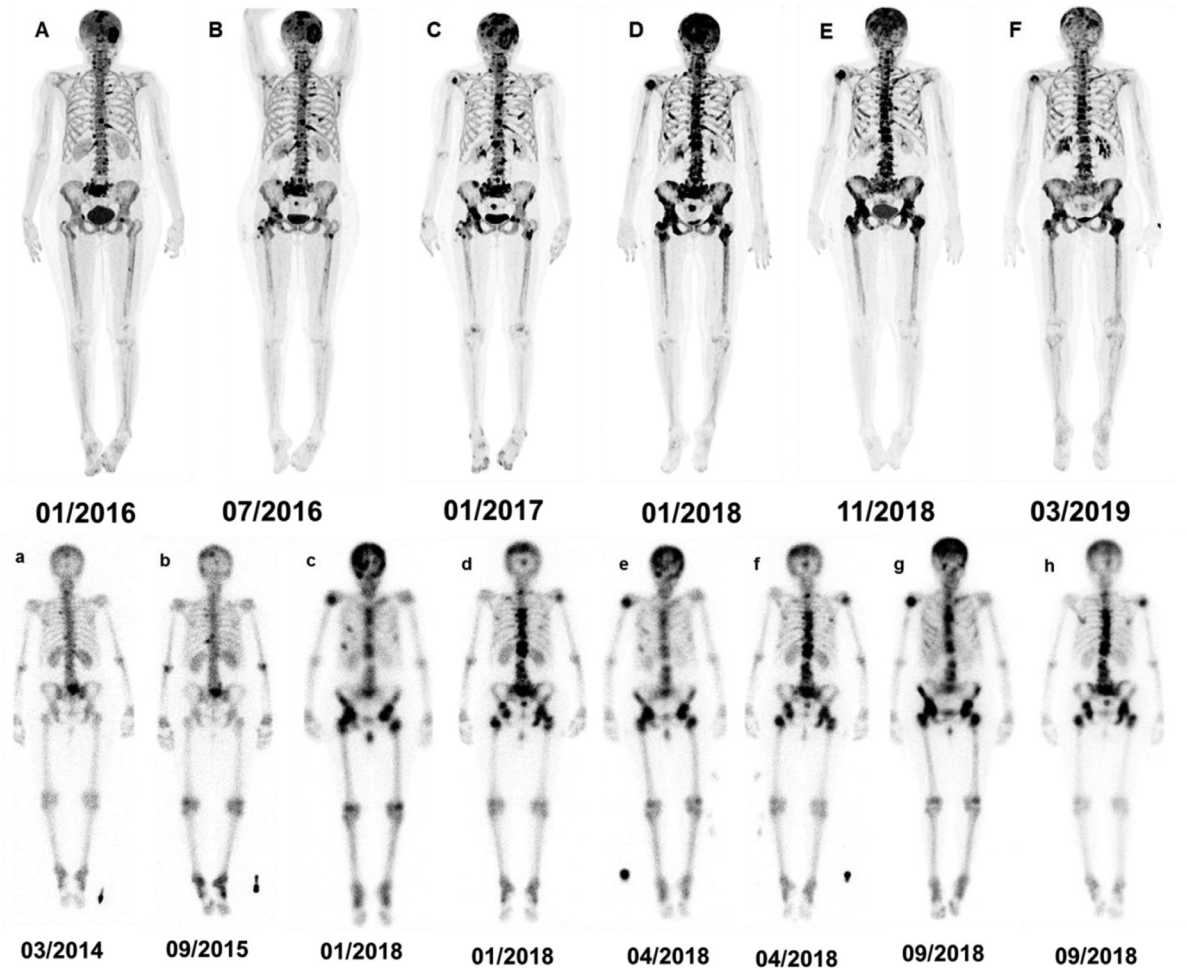

Figure 3 A 50-year-old woman with ductal adenocarcinoma of the breast and extensive bone metastases, with the initial tumor classification pT1c (G2) pN1 cM0, ER/PR positive, HER2 negative, underwent chemotherapy, radiotherapy, antihormonal therapy, and therapy with Anastrozole, Zometa, Faslodex, and XGEVA, and then significantly progressed in March 2014. The patient was treated with five cycles of Lu-177 BPAMD radioligand therapy between March 2014 and September 2015 with a cumulative administered radioactivity of 16.0 GBq (432 mCi) of Lu-177. There was partial remission of the disease evaluated in accordance with EORTC criteria and RECIST 1.1. (A-F) F-18 fluoride PET/CT was shown. The patient received three cycles of Lu-177 Zoledronat between January 2018 and November 2018 (cumulative administered radioactivity of 34.4 GBq [930 mCi] of 177Lu). Post-therapy gamma ray scan after Lu-177 Zoledronat treatment, obtained at 22 hours (c, d), 20 hours (e, f), 23.5 hours (g, h), showed high uptake of the tumors. Partial remission of the disease was achieved after treatment (D-F).

offer significant advantages. Cu-64 is an excellent candidate for PET imaging as it decays with a half-life of 12.7 hours and emits positrons of favorably low energy (Eß+ av = 278 keV) similar to F-18 (Eß+av = 250 keV). Cu-64 has been widely used for preclinical PET imaging of various cancers.

The introduction of PET imaging with Ga-68 labeled PSMA ligands was an outstanding step forward in the diagnosis of PC. However, because of the short half-life, the application of Ga-68 PSMA is limited to clinical PET centers with radiochemistry facility and a Ga-68 generator available on site. In this regard, it would be of interest to use a PET radionuclide with a longer half-life such as Cu-64 allowing distribution of the radiolabeled PSMA ligand to PET centers that lack radiochemistry facilities and Ga-68 generators (satellite concept).

Between October 2014 and March 2015, Cu-64 labeled PSMA ligand (PSMA-617) for PET imaging in patients with PC was investigated simultaneously at two nuclear medicine centers, Austria (Vienna, Center 1) and Germany (Bad Berka, Center 2).[66] Twenty-nine patients with PC before surgery or before PRLT or with high suspicion of recurrent disease were included in this study. Safety, pharmacokinetics, dosimetry, as well as the diagnostic potential of Cu-64 PSMA-617 in PC patients were investigated.

At our center, both low radioactivity to monitor the safety and higher radioactivity to obtain optimal image quality particularly at later time points of image acquisition of Cu-64 PSMA-617 were evaluated. Among healthy organs, the salivary glands, kidneys, and liver showed the highest radiotracer uptake. There were no adverse effects or clinically detectable pharmacological effects in any of the patients after injection of the Cu-64 PSMA-617. The dose to total body per unit of activity administered average of Cu-64 PSMA-617 was equal to 0.014 mGy/MBq, whereas *T*1/2 Eff was

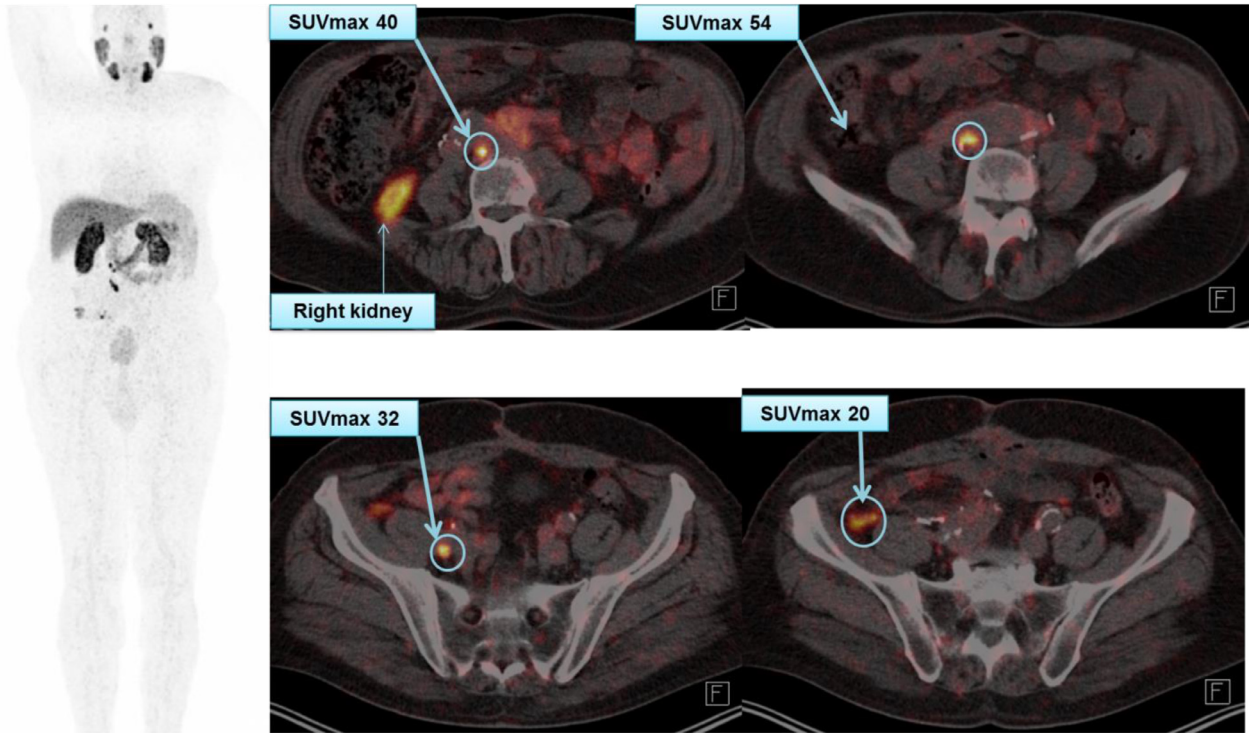

Figure 4 Cu-64 PSMA PET/CT in a patient restaged with progressive disease. Cu-64 PSMA PET/CT demonstrates multiple abdominopelvic lymph node metastases. MIP image and axial PET/CT fusion images were shown with arrows indicate positive findings with SUVmax of 54.

7.8 hours (*T*1/2 Biol = 20.2 hours). In 23 of 29 patients, at least one focus of pathologic tracer uptake suspicious for primary disease in the prostate lobe or recurrent disease was detected (Fig. 4). Lesions suspicious for PC were detected with excellent contrast as early as 1 hour p.i. with high detection rates even at low PSA levels. It demonstrated the high potential of Cu-64 PSMA ligand PET/CT imaging in patients with recurrent disease and in the primary staging of selected patients with progressive local disease. The acquired PET images showed an excellent resolution of the detected lesions with very high lesion to-background contrast. Furthermore, the long half-life of Cu-64 allows distribution of the tracer to clinical PET centers that lack radiochemistry facilities for the preparation of Ga-68 PSMA ligand (satellite concept).

Scandium 44 (Sc-44)—Cyclotron-Produced Sc-44 DOTATOC

Scandium, a trivalent rare earth metal, is of particular interest in terms of radiotheranostics.[53,67] Among the different radioisotopes of scandium, scandium-44 (Sc-44) is a PET radionuclide ($T_{1/2}$ = 3.97 hours, Eβ$^+$ = 632 keV), which can be made available, using a cyclotron production route, in substantial quantities as a highly pure product.[68] As a trivalent metal, with similarities to lanthanides and rare earth elements, the chemical properties of Sc-44 enable stable coordination with a DOTA chelator, allowing the use of commonly used targeting ligands.[69] These characteristics give Sc-44 a unique potential for clinical PET application.[70] Moreover, in combination with the therapeutic match, Sc-47 ($T_{1/2}$ = 3.35 days, Eß− = 162 keV, Er = 159 keV, I = 68%), one of the truly theranostic radionuclide pairs could be clinically established, following the theranostic strategy with Sc-44/Sc-47 pairs.[67]

Cyclotron production of Sc-44 would be regarded as a more feasible option for routine application of 44Sc-based radiopharmaceuticals compared with the Ti-44/Sc-44 generator-based production,[53,71] which provides only small activities in larger volumes. In a proof-of-concept study, we demonstrated, for the first time, the application of cyclotron produced Sc-44 in a clinical setting by using it with DOTATOC in patients with NENs.[72] The production of Sc-44 was carried out through the Ca-44(p,n)Sc-44 nuclear reaction at Paul Scherrer Institute (PSI), Switzerland. The production of Sc-44 at the research cyclotron at PSI allowed separation of sufficient quantities of activity to be shipped over a distance of about 600 km from PSI (Switzerland) to Bad Berka (Germany), where radiolabeling was performed, yielding radiochemically pure ^{44}Sc-DOTATOC. The transport left PSI 1 hour later to arrive in Bad Berka a further 8 hours later, which corresponded to a total decay of two and a half *T*1/2 of ^{44}Sc. This implies that, Sc-44 doses for several patients, when produced centrally at a medical cyclotron, could be delivered to distant PET imaging centers over several hundred kilometers. The quality control of the Sc-44-labeled product revealed a radiochemical purity of >99% based on TLC and HPLC methods. Two patients participated in this proof-of-concept study. The preparation of the patients included blood sampling for laboratory analysis, the morning before PET imaging, as part of the routine restaging procedure. The patients received an

intravenous bolus injection of 78 MBq and 96 MBq Sc-44 DOTATOC, respectively. Eight sets of PET/CT scans were acquired with each patient at multiple he time points after Sc-44 DOTATOC injection. Sc-44 DOTATOC PET/CT demonstrated excellent uptake of the radiopeptide in lesions of both patients.[72] PET/CT acquisitions, performed at different time points after injection of Sc-44 DOTATOC, allowed detection of even very small lesions on delayed scans. The best image quality was achieved at 4 hours after administration of Sc-44 DOTATOC. No clinical adverse effects were observed or reported by either patient during, immediately after, or at follow-up checks of the patients after administration of Sc-44 DOTATOC. Given the promising decay properties and resolution capability using PET, Sc-44 has the potential to be used as an alternative to the short-lived Ga-68 for PET imaging of NENs. Sc-44 may be advantageous with regard to the half-life, as it opens the possibility of a centralized production of Sc-44 labeled peptides and their shipment to hospitals with PET centers that do not have a radiopharmacy on site. Sc-44 also promotes applications for imaging processes of ligands having slower pharmacokinetics profiles, and attractive for theranostic application with Lu-177, Y-90, or Sc-47 as therapeutic counterparts.

Actinium-225 (Ac-225)

TANDEM Alpha-Beta PRLT (a Combination of Lu-177 PSMA and Ac-225 PSMA)

Actinium-225 (Ac-225) is a relatively long-lived alpha emitter with a half-life of 9.9 days.[73] The predominant decay path of Ac-225 yields net four alpha particles with energies ranging from 5.8 to 8.4 MeV and associated tissue ranges of 47-85 μm.[74] The distinct advantages of alpha emitters for cancer therapy include the short range of alpha radiation in human tissue that allows the selective killing of targeted cancer cells while sparing surrounding healthy tissue, and the high energy of alpha radiation of several MeV and its associated high linear energy transfer leads to highly effective cell killing via DNA double strand and DNA cluster breaks, which are largely independent of cell cycle and oxygenation status.[74,75] Consequently, Ac-225 for targeted alpha therapy (TAT) can kill cells, which otherwise exhibit resistance to treatment with beta irradiation and therefore offer a therapeutic option for patients resistant to conventional treatment or even beta-irradiation treatments.[11,76,77]

In PC patients, under therapy with Lu-177 PSMA, despite the high doses delivered to tumors, approximately a fourth to a third of the patients are refractory to treatment, presenting with primary progression under PRLT. Hematological toxicity tends to be frequent after Lu-177 PSMA in patients having disseminated bone and bone marrow involvement. The application of alpha-emitters with a short range and high linear energy transfer is a very promising option to overcome this limitation. Recent reports of the remarkable therapeutic efficacy of ^{225}Ac-labeled PSMA have underlined the clinical potential of targeted alpha therapy in heavily pretreated metastatic mCRPC patients.[76,78] Severe xerostomia was the dose-limiting toxicity for Ac-225 PSMA activities. Therefore, further modifications of the treatment regimen regarding the adverse events were necessary to yield maximal response.

We performed the first clinical and dosimetry study of tandem alpha-beta PRLT, concurrently administering both Lu-177 PSMA-617 and Ac-225 PSMA-617 in PC patients with widespread metastases, having progressed after multiple previous therapies including Lu-177 PSMA. Tandem alpha-beta PRLT using 3-5 MBq of Ac-225 PSMA-617 concurrently applying 6-7.5 GBq Lu-177 PSMA-617 was performed in 4 patients. Two patients received 8 and 10 MBq Ac-225 PSMA-617, respectively. For preliminary safety evaluation, renal dose estimations were made for Ac-225 PSMA-617 in two patients using OLINDA. Mean absorbed renal dose with Ac-225 PSMA were 0.5 SvRBE5/MBq and 1.7 SvRBE5/MBq, respectively; with Lu-177 PSMA were 0.6 and 1.52 mSV/MBq, respectively. The assumptions in the estimation regarding Ac-225 included instant decay of instable daughter nuclides, relative biological effectiveness of 5 and biodistribution similar to Lu-177 PSMA-617. Excellent response with nearly complete remission was observed on Ga-68 PSMA PET/CT in two patients after tandem PRLT (Fig. 5). PSA reduced by more than 99% from 153 to 0.9 ng/mL and from 186 to 0.1 ng/mL, respectively. No xerostomia was reported by any patient. There was no fall in hemoglobin or blood counts despite disseminated bone marrow metastases. No organ toxicity was noted. Tandem alpha-beta PRLT administering Ac-225 PSMA-617 and Lu-177 PSMA-617 in combination enables dose estimations, and appears to be feasible, safe, and effective in end-stage metastatic PC refractory to Lu-177 PSMA. The lower administered activity of Ac-225 PSMA could possibly minimize the risk of dose-limiting toxicity like xerostomia. There might be a potential synergistic effect employing together two radionuclides with different emission characteristics.

Intra-arterial Ac-225 DOTATOC Targeted Alpha-PRRT

The alpha emitters Ac-225 and Bi-213 labeled somatostatin analogue have already demonstrated promising therapeutic effects in animal studies.[79,80] It seemed reasonable that peptide targeted alpha therapy delivered directly to metastases via intra-arterial administration might offer effective therapy to NEN patients who have acquired resistance to other therapies. Kratochwil et al performed targeted alpha therapy with an intra-arterial infusion of Bi-213 DOTATOC in 7 patients with advanced NET who had undergone previous PRRT cycles with beta emitters and presented with relapsed/refractory disease, showing considerable antitumor effects, and even overcame resistance against beta radiation.[76,78,81]

Ac-225 DOTATOC alpha-radiation peptide therapy was investigated in our center in 10 patients with metastatic NENs progressing after Y-90/Lu-177 DOTATOC therapy. The very first intra-arterial targeted alpha peptide radionuclide therapy using Ac-225 DOTATOC (IA-ART) was performed in a patient with advanced, progressive NENs

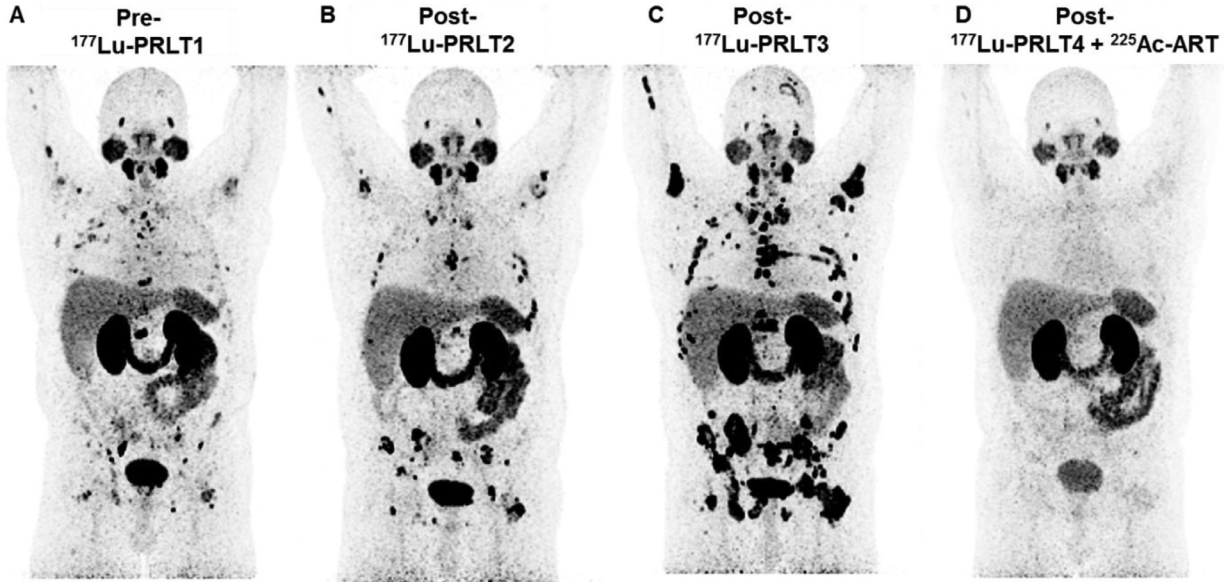

Figure 5 A 57-year-old patient (first diagnosis in 2012) with progressive mCRPC, and with extensive bone and lymph nodes metastasis, had undergone repeated ADT, chemotherapy, and external beam radiotherapy, who received three cycles of Lu-177 PSMA PRLT (cumulative administrated radioactivity 21.8 GBq) between April 2017 and October 2017, and then prognosed (A-C). In February 2018, the patient received TANDEM alpha-beta PSMA radioligand therapy (Lu-177 PSMA + Ac-225 PSMA), and achieved excellent response with complete remission (D). The treatment was very well tolerated and had no significant side effect.

resistant to conventional therapy and progression after DUO-PRRT (Fig. 6). Ac-225 DOTATOC PRRT was very well tolerated and effective. As previously reported for Bi-213 DOTATOC by Kratochwil et al, targeted Alpha-PRRT may present a valuable additional treatment option in advanced NENs resistant to PRRT with beta emitters—and becoming a clinical reality with the availability of Ac-225.

Terbium (Tb-152/Tb-161)

Terbium (Tb), a lanthanide, is unique in that it presents four medically interesting radionuclides, for SPECT (Tb-155) and PET (Tb-152) imaging and for α-therapy (Tb-149) and β-/Auger-e- therapy (Tb-161).[82] Although the use of the positron-emitting nuclide Ga-68 is considered a success in diagnostic applications, this radionuclide is not suitable for pretherapeutic dosimetry estimations due to its short half-life of only 68 minutes. The use of Tb-152 may be a solution to address this issue. It decays with a half-life of 17.5 hours by the emission of positrons ($E\beta+ = 1140$ keV, $I\beta+ = 20.3\%$) without the emission of $\alpha-$ or $\beta-$-particles, but by the co-emission of several γ-rays. It would be an exact diagnostic match to Tb-161 and Tb-149, as well as to other therapeutic radiolanthanides, like Lu-177. The current availability of Tb-152 is scarce. The nuclide can be produced, however, by proton-induced spallation and on-line mass separation, followed by chemical separation.[83]

To first investigate Tb-152 in a clinical proof-of-concept PET/CT study, Tb-152 was produced through 1.4 GeV proton-induced spallation in a tantalum target at the ISOLDE facility (CERN, Geneva, Switzerland), and was separated from the collection matrix and impurities at PSI. Phantom studies were performed with a clinical PET/CT scanner at Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois or CHUV), Switzerland, and at ZBB, Germany, in order to determine the image quality and investigate the possibility of Tb-152 based PET quantification. As part of the first-in-human study, the Tb-152 solution was processed further to ensure high-quality radiolabeling. DOTATOC was labeled with Tb-152 at ZBB's radiopharmacy, and used for a first-in-human clinical PET/CT study.[84,85] The radiochemical purity of the final product, performed at ZBB, was >97%, thereby allowing its application without any further purification. Due to the small application volume (<3 mL), it was not necessary to determine and adjust the osmolarity of the final product. The specific activity of the sterile-filtered and applied product (145 MBq) was 1.37 MBq $nmol^{-1}$, calculated for 150 μg DOTATOC. Tb-152 DOTATOC was administered to a patient with metastatic well-differentiated functional NEN of the ileum, presenting for restaging 8 years after the sixth cycle of PRRT. As part of the routine restaging procedure, blood samples from the patient were sent to the institutional laboratory for analysis. The patient received a bolus intravenous injection of 145 MBq of Tb-152 DOTATOC. Four sets of whole-body PET/CT scans of the patient were acquired over two consecutive days. The time points of image acquisition were 25 minutes, 2 hours, 17 hours, and 24 hours after injection of the radiopharmaceutical, respectively. The physiological distribution of Tb-152 DOTATOC was similar, but not identical, to the distribution of Ga-68 DOTATOC. The PET/CT images acquired using Tb-152 DOTATOC in this study were adequate for diagnostic purposes; allowing the visualization of even small metastases (Fig. 7).[84]

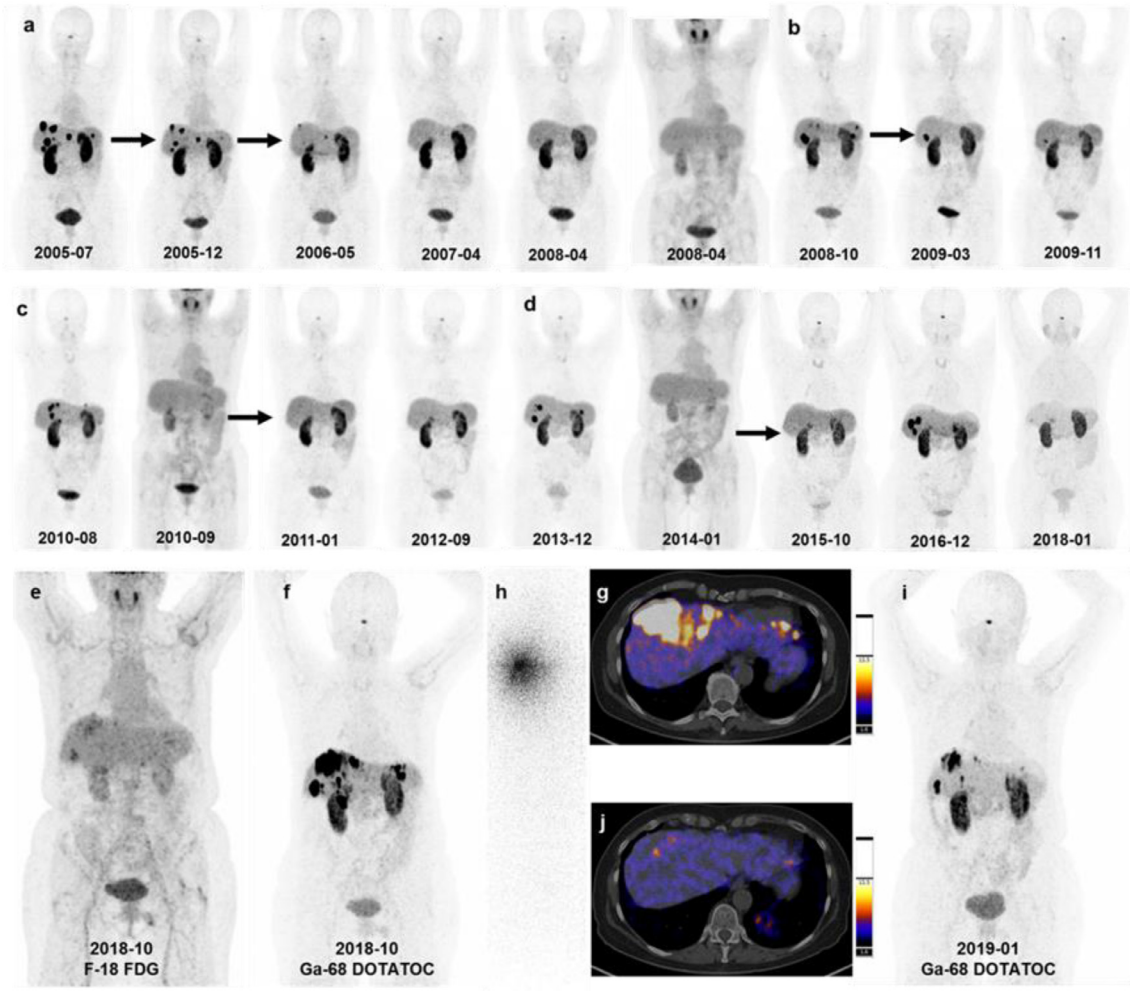

Figure 6 A 50-year-old woman was diagnosed in 1999 with a pancreatic neuroendocrine neoplasm with hepatic metastases. Ga-68 DOTATOC PET/CT showed intense somatostatin receptor expression in the primary tumor and multiple hepatic metastases. Pancreatectomy, splenectomy, lymph node dissection, and partial liver resection were performed. The patient was then treated between 2002 and 2014 with eight cycles of peptide receptor radionuclide therapy, using both Y-90 and Lu-177 (DUO-PRRT); the cumulative administered radioactivity was 44.5 GBq (a-d). In 2017, relaparotomy, radiofrequency thermoablation, and transarterial chemoembolization were performed with mixed response. Severe progression with multiple hepatic metastases occurred in October 2018 (f, g), when increased glycolysis (FDG uptake) was also demonstrated in some of the hepatic lesions (e). The patient was then treated by intra-arterial α-radiation therapy using 8.4 MBq Ac-225 DOTATOC (h). The treatment was well tolerated, no adverse effects were noted during IA-ART and in follow-up. Three months later, a very good response (partial remission) was demonstrated by Ga-68 DOTATOC PET/CT (i, j) and MRI (not shown). No hematological toxicity, nephrotoxicity, or any liver dysfunction was observed.

The isotope Tb-161 (half-life = 6.89 days) exhibits similar decay properties as Lu-177, but the additional emission of Auger electrons allows for combined β/Auger electron therapy. Preclinical therapy studies performed at PSI demonstrated the superiority of Tb-161 over Lu-177, which was attributed to the co-emission of Auger electrons.[86] Additional side effects to the kidneys were not observed.[87] Theoretical calculations of the absorbed radiation dose in spheres of different diameters revealed that Tb-161 can effectively irradiate isolated tumor cells and micrometastases, due to its decay spectrum combining β− particles of medium energy and Auger electrons.[88] These promising characteristics warrant clinical investigation using Tb-161, when steady supply in sufficient quantities can be guaranteed. A first-in-human study to analyze the pharmacokinetics and dosimetry of Tb-161 DOTATOC compared to Lu-177 DOTATOC has been performed recently and further investigations are planned for the near future. Tb-161 is thus a promising alternative for Lu-177 in the context of PRRT and, together with the other radioisotopes (eg, Tb-152, β+ for PET), fulfills the concept of theranostics.

Conclusions

Personalized, targeted molecular radiotherapy of malignant tumors, tailored to the individual patient in a PRECISION

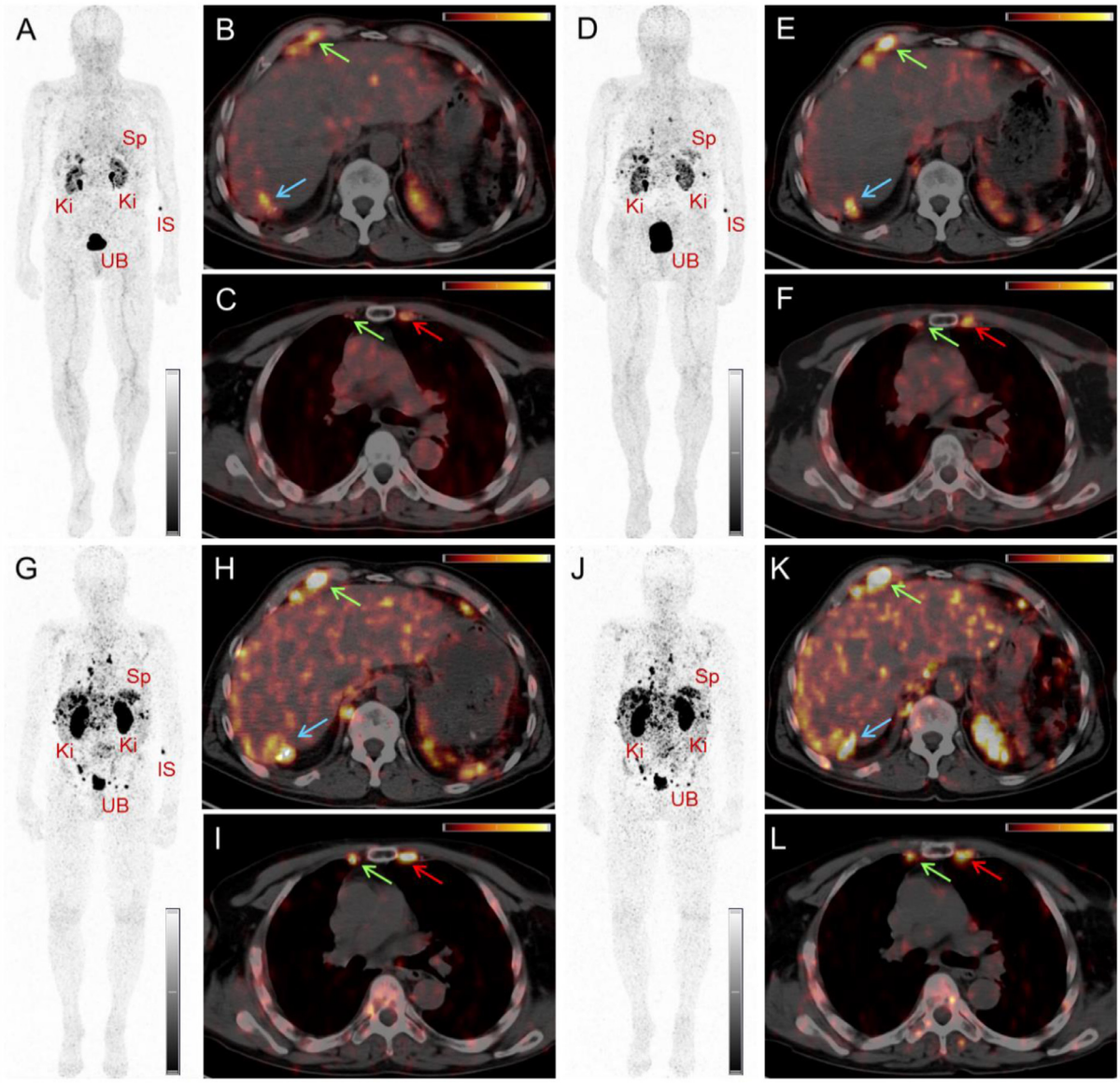

Figure 7 PET/CT images of a patient with neuroendocrine neoplasm of the terminal ileum obtained at 25 minutes (A-C), 2 hours (D-F), 17 hours (G-I), and 24 hours (J-L) after injection of Tb-152 DOTATOC, respectively. (A, D, G, J) Maximal intensity projection (MIP) images show the kidneys (Ki), the urinary bladder (UB), the spleen (Sp), and the injection site (IS); (B, C, E, F, H, I, K, L) transverse sections of PET/CT fusion images demonstrate radiopeptide uptake in lymph nodes metastases in the right costophrenic region and right internal mammary chain (green arrows), as well as in segment 7 of the liver (blue arrows) and in a skeletal metastasis in the left third rib adjacent to the sternocostal junction (red arrows). UB, urinary bladder; SI, site of injection; Ki, kidneys; Sp, spleen. (Image reproduced from Baum et al.[84])

ONCOLOGY setting is moving from innovation to implementation in a real-world setting ("from the shadows to storm the market")[89] and will be in the mainstream of future applications for the treatment of cancer. New strategies are offered including the development of new indication of theranostics, the validation of new targets, optimized pharmacokinetics, theranostic radionuclide pairs, and improvements in dosimetry, with the goal of improving clinical outcomes for individual patients and minimizing unnecessary side effects for those less likely to have a response to a particular treatment. More efforts to further optimize the potential of radiopharmaceuticals and a deeper understanding of all relevant steps relevant including genetics mechanisms for the beneficial of the patient at an individual level are needed. Dramatic shortening of acquisition time needed for molecular imaging ("from 30 minutes to 30 seconds") by using novel hardware devices (like the Explorer, total-body PET/CT) are already gaining momentum.[90]

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