

# Molecular Imaging using PET/CT Applying $^{68}\text{Ga}$ -Labeled Tracers and Targeted Radionuclide Therapy: Theranostics on the Way to Personalized Medicine

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## ABSTRACT

Theranostics is an acronym, which exemplifies the togetherness of diagnostics and therapeutics in the individualized management of disease. The key to personalized medicine in cancer is to determine the molecular phenotypes of neoplasms, so that specific probes can be selected to target the tumor and its micro-environment. Molecular imaging and radionuclide therapy using a particular probe is based on this premise. Neuroendocrine neoplasms express somatostatin receptors, enabling the use of somatostatin analogs for molecular imaging, when labeled with the positron-emitter  $^{68}\text{Ga}$  for receptor positron emission tomography/computed tomography (PET/CT), and targeted radionuclide therapy, when labeled with beta-emitters  $^{90}\text{Y}$  and  $^{177}\text{Lu}$ .

**Keywords:** Theranostics, Molecular imaging, Targeted radionuclide therapy, PRRNT, PET/CT.

**How to cite this article:** Kulkarni HR, Baum RP. Molecular Imaging using PET/CT Applying  $^{68}\text{Ga}$ -Labeled Tracers and Targeted Radionuclide Therapy: Theranostics on the Way to Personalized Medicine. *J Postgrad Med Edu Res* 2013; 47(1):47-53.

**Source of support:** Nil

**Conflict of interest:** None declared

## INTRODUCTION

Theranostics refers to the incorporation of diagnostics and therapeutics into the individualized management of disease. Molecular imaging with positron emission tomography/computed tomography (PET/CT) using the trivalent radiometal and positron-emitter  $^{68}\text{Ga}$ , and its therapeutic counterpart for targeted radionuclide therapy (for e.g.  $^{177}\text{Lu}$ ,  $^{90}\text{Y}$ ), has paved the way to personalized medicine. The detection of molecular targets enables selection of the ideal ligand for both tumor-specific diagnosis and treatment. Molecular imaging provides useful diagnostic information concerning the metabolic or receptor status of a given tumor or its metastases for further selective targeting for therapy at the cellular/subcellular level.

Neuroendocrine neoplasms (NENs) originate from pluripotent stem cells or differentiated neuroendocrine cells and their endocrine metabolism [amine precursor uptake, and decarboxylation (APUD)] is characteristic. The overexpression of somatostatin receptors (SSTRs) provides the basis for the use of radiolabeled somatostatin (SMS) analogs. The successful application of molecular imaging

using  $^{68}\text{Ga}$  and targeted radionuclide therapy using  $^{177}\text{Lu}/^{90}\text{Y}$  labeled SMS analogs has paved the way to state of the art theranostics.<sup>1</sup>

## MOLECULAR IMAGING USING $^{68}\text{Ga}$ -LABELED PEPTIDES

The predominant overexpression in NENs of SSTR 2 forms the basis for peptide receptor imaging using  $^{68}\text{Ga}$ -labeled SMS analogs.<sup>2</sup> The peptides used are small and have better pharmacokinetic characteristics and no antigenicity as compared to antibodies.  $^{68}\text{Ga}$  is a trivalent radiometal with convenient labeling characteristics and an ideal positron emitter for PET imaging. It is derived from a  $^{68}\text{Ge}/^{68}\text{Ga}$  generator system, which has a half-life of 271 days.<sup>3</sup> A simple sodium chloride (NaCl)-based  $^{68}\text{Ga}$  eluate concentration and labeling technique (Müller's method) enables rapid and very efficient labeling of DOTA-conjugated peptides in high radiochemical purity ( $97 \pm 2\%$ ).<sup>4</sup> The SMS analog DOTATOC (DOTA-D-Phe1-Tyr3-octreotide) was developed for imaging as well as for therapy.<sup>5,6</sup> DOTA-D-Phe1-Tyr3-Thr8-octreotide (DOTATATE) has a very high affinity for SSTR 2, higher than even natural somatostatin.<sup>7</sup> DOTANOC (DOTA-1-Nal3-octreotide) has a broader spectrum and binds to SSTR 2, SSTR 3 and SSTR 5.<sup>8</sup> SSTR antagonists are currently under investigation and have been shown to have higher tumor uptake (due to more binding sites on the tumor cell surface) and to deliver higher dose to the tumors.<sup>9</sup> The first radiolabeled SMS analog to be approved for scintigraphy was  $^{111}\text{In}$ -DTPA-D-Phe1-octreotide ( $^{111}\text{In}$ -pentetate, Octreoscan) which has been in use worldwide in thousands of patients since 1999 for the scintigraphic localization of primary and metastatic NENs.<sup>10</sup>  $^{109\text{m}}\text{Tc}$ -EDDA-HYNIC-TOC (or -TATE) has also been used in a large patient population and shown to be superior to  $^{111}\text{In}$ -pentetate due to higher count rates (higher injected activity) and the use of SPECT or SPECT/CT enabling to finish the patient study within 1 day (whereas at least 2 days are necessary when using Octreoscan).<sup>11</sup>

The advantage of PET/CT is its ability to quantify the disease at a molecular level. Therefore, SSTR PET/CT using  $^{68}\text{Ga}$  clearly has an edge over SPECT/CT using gamma-emitting radionuclides. Hofmann et al demonstrated this for the first time with  $^{68}\text{Ga}$ -DOTATOC as compared to

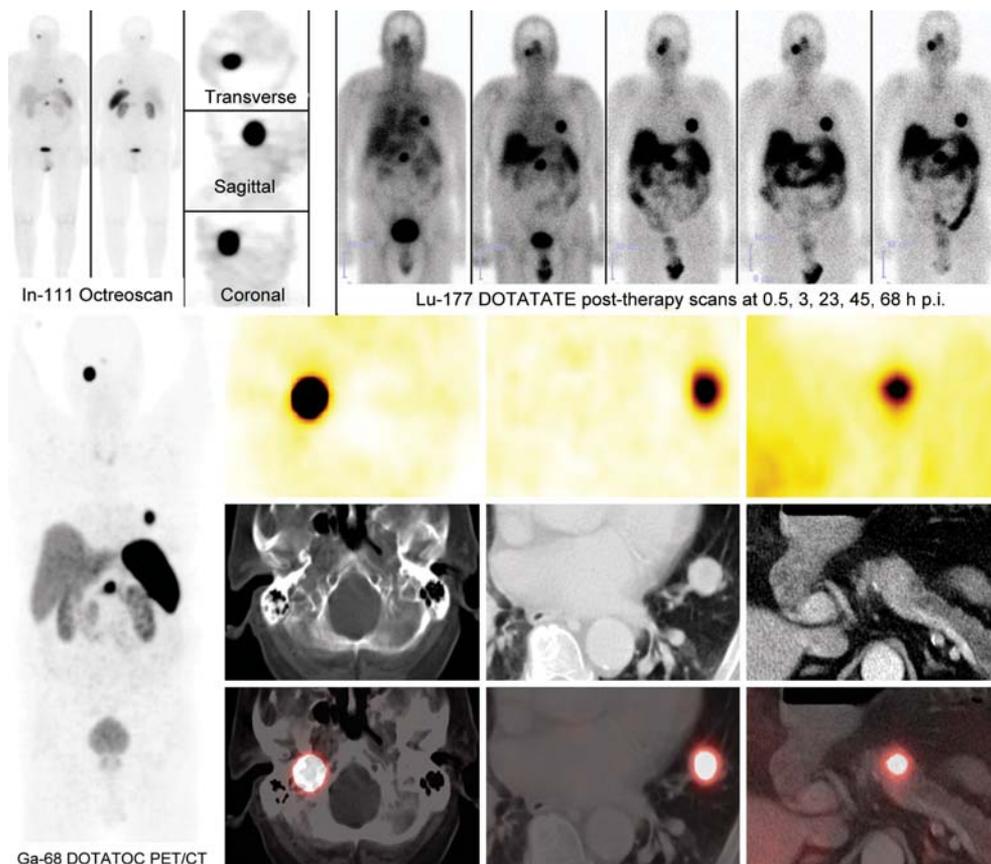
$^{111}\text{In}$ -octreotide SPECT (CT taken as reference) in detecting upper abdominal metastases.<sup>12</sup> In a more recent study by Gabriel et al,  $^{68}\text{Ga}$ -DOTATOC PET was proven to be superior to  $^{111}\text{In}$ -DOTATOC and  $^{99\text{m}}\text{Tc}$ -EDDA-HYNIC-TOC in the detection of NEN metastases in the lung, bones, liver and brain.<sup>13</sup> In our own experience with more than 7,000 SSTR PET/CT studies (currently over 20 per week) performed at the Zentralklinik Bad Berka,  $^{68}\text{Ga}$ -SSTR PET is able to detect many lesions which are not routinely detected by CT, magnetic resonance imaging (MRI), skeletal scintigraphy or ultrasonography. Our group (Kaemmerer et al 2011) demonstrated for the first time, a close correlation between  $\text{SUV}_{\text{max}}$  and immunohistochemical scores for the quantification of SSTR (particularly subtype 2A) in NEN tissue.<sup>14</sup> Thus the real power of molecular imaging using  $^{68}\text{Ga}$  SSTR PET/CT, is in quantifying the SSTR density on tumor cells before planning of targeted radionuclide therapy, highlighting the principle of theranostics (Fig. 1).

In a bicentric study,  $^{68}\text{Ga}$  DOTANOC PET/CT localized the primary tumor in 59% of cases with cancer of unknown provenience (CUP-NET), significantly higher than the

detection rate (39%) reported in the literature for  $^{111}\text{In}$ -Octreoscan.<sup>15</sup>

PET/CT is also useful in the early and accurate detection of response to therapy and to assess the prognosis of a patient. In a study involving 47 patients, the  $\text{SUV}_{\text{max}}$  of  $^{68}\text{Ga}$ -DOTANOC was significantly higher in patients with well-differentiated pancreatic NENs, indicating a higher SSTR 2 expression.<sup>16</sup>  $\text{SUV}_{\text{max}}$ , therefore, has a prognostic value and correlates with the clinicopathologic features of well-differentiated NENs.  $^{18}\text{F}$ -FDG PET has a role in comprehensive tumor assessment in intermediate and high-grade tumors: intense metabolic activity of the tumors/metastases indicates a poor prognosis due to the presence of aggressive tumor clones.<sup>17</sup>

Many new  $^{68}\text{Ga}$ -labeled tracers including both peptides and nonpeptidic tracers are becoming available, thereby demonstrating the potential of  $^{68}\text{Ga}$  to become the  $^{99\text{m}}\text{Tc}$  for PET.<sup>18</sup> The biphosphonate-based agent BPAMD—4-[[bis-(phosphonomethyl)) carbamoyl]methyl}-7, 10-bis (carboxymethyl)-1, 4, 7, 10-tetraazacyclododec-1-yl acetic acid labeled with  $^{68}\text{Ga}$  is one such option for the



**Fig. 1:** A 74-year-old patient with three concurrent primary neuroendocrine neoplasms—a glomus tumor, a primary lung NET and a separate primary NEN in the pancreas.  $^{111}\text{In}$ -octreotide scintigraphy (upper left) performed externally, showed focal uptake at the three sites, SPECT of the skull was reported to be suspicious for a brain metastasis.  $^{68}\text{Ga}$ -DOTATOC PET/CT (below, maximum intensity projection image on the extreme left) demonstrated a very intense somatostatin-receptor positive lesion ( $\text{SUV}_{\text{max}}$  148) in projection to the right carotid body (left), suggestive of a glomus tumor. The carcinoid tumor in the left lung and the pancreas NEN can be seen on the transverse PET/CT slices (successively toward the right). The patient underwent PRRNT with 7.9 GBq  $^{177}\text{Lu}$ -DOTATATE. The  $^{177}\text{Lu}$ -DOTATATE post-therapy planar scans at multiple time intervals (upper right) also showed intense uptake in the three tumors

personalized theranostics of skeletal lesions.<sup>19</sup> PET/CT with  $^{68}\text{Ga}$ -BPAMD provides high-resolution and quantitative evaluation of osteoblastic bone metastases.

Newer radiolabeled peptides targeting the gastrin and cholecystinin receptors have shown promising preclinical results in medullary thyroid cancer.<sup>20</sup> Exendin-3 and exendin-4, targeting the glucagon-like peptide-1 (GLP-1) receptors in insulinomas have been radiolabeled with  $^{68}\text{Ga}$  for receptor PET/CT imaging.<sup>21,22</sup>  $^{68}\text{Ga}$ -labeled arginine-glycine-aspartic acid (RGD) PET/CT (first in human use at our center) may be useful for noninvasive tumor detection and monitoring of expression of alpha v beta 3  $\{\alpha(v)\beta(3)\}$  integrins which are involved in angiogenesis as well as for monitoring the therapeutic response to antiangiogenic agents used for immunotherapy of tumors.<sup>23</sup>  $^{68}\text{Ga}$ -PET imaging of the chemokine receptor CXCR4, which is expressed by many tumors, holds great promise for the future.<sup>24</sup>

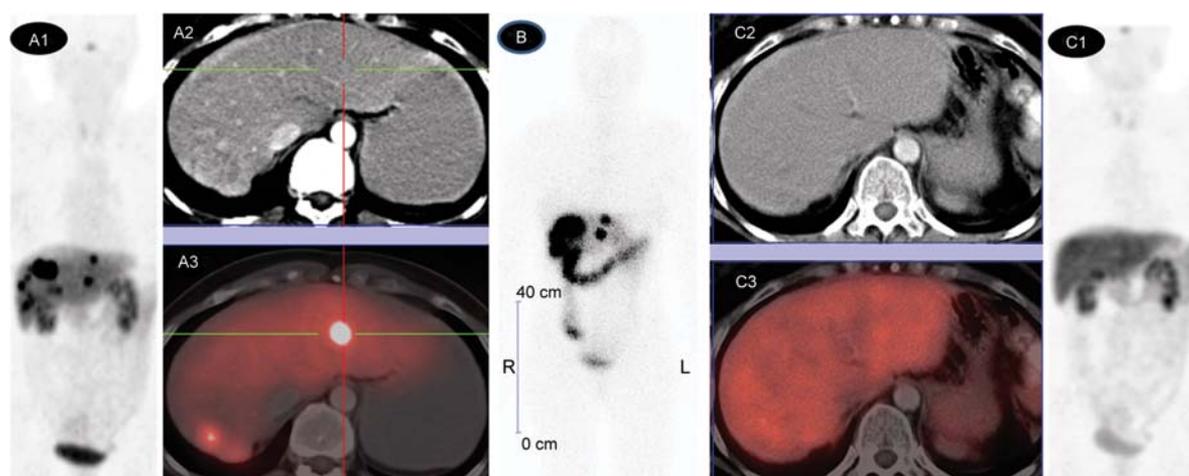
Our group was the first to use the  $^{68}\text{Ga}$ -labeled gastrin releasing peptide receptor (GRP-R) selective bombesin analog AMBA  $\text{CH}_2\text{CO-G-4-aminobenzoyl-Q-W-A-V-G-H-L-M-NH}_2$  and the GRP-R antagonist demobesin in humans for imaging of metastatic breast, lung and prostate cancers.<sup>25</sup> Other  $^{68}\text{Ga}$ -labeled tracers which have been applied by our group for the first time in humans are  $^{68}\text{Ga}$ -labeled macroaggregates (MAA) for lung perfusion PET/CT,  $^{68}\text{Ga}$ -DOTA-alpha-MSH (melanocyte stimulating hormone) for metastatic ocular melanoma, and the  $^{68}\text{Ga}$ -labeled affibody molecule targeting human epidermal growth factor receptor 2 (HER2) as well as a  $^{68}\text{Ga}$ -labeled growth hormone releasing hormone (GHRH) antagonist.<sup>26-28</sup>  $^{68}\text{Ga}$  is therefore a very practical, affordable and a highly promising radionuclide for clinical use in PET/CT imaging.

## TARGETED RADIONUCLIDE THERAPY

Radionuclide therapy can be specifically directed against molecular targets, utilizing the same probes as for molecular imaging, but labeled with a therapeutic (e.g. beta, alpha, auger emitters) radionuclide. The molecular basis of peptide receptor radionuclide therapy (PRRNT) is the receptor-mediated internalization and intracellular retention of the radiolabeled SMS analog. Upregulation of SSTR 2 in the peritumoral vessels is another target, accounting for antiangiogenic response after radionuclide therapy.<sup>29</sup>

$^{90}\text{Y}$ - and/or  $^{177}\text{Lu}$ -labeled DOTATATE or DOTATOC are the most frequently used peptides for PRRNT.  $^{90}\text{Y}$  produces a 'cross-fire effect' due to the relatively high energy (935 keV) and tissue penetration range (up to 12 mm) of the emitted beta particles, and is therefore preferable for larger tumors.  $^{177}\text{Lu}$  on the other hand, emits intermediate-energy beta particles (133 keV), having a relatively short tissue penetration range (up to 2 mm), which makes it preferable for smaller tumors. Due to additional two gamma peaks at 113 and 208 keV,  $^{177}\text{Lu}$  is also suitable for imaging with a gamma camera for post-therapeutic dosimetry.

Several studies have shown promising results with PRRNT of well-differentiated NENs (Fig. 2). Objective response rates (complete and partial) were observed in 30% of the patients treated with  $^{177}\text{Lu}$ -DOTATATE with very few adverse effects, and a significant benefit in median overall survival (median survival from start of treatment was 46 months).<sup>30</sup> In a study of a large cohort of patients treated with  $^{90}\text{Y}$ -DOTATOC, though response was associated with longer survival, there was also a risk of significant nephro-



**Fig. 2:** A 44-year-old female patient with metastatic pancreatic NEN, initially diagnosed 10 years back, status post-distal spleno-pancreatectomy was treated with two cycles of DUO-PRRNT using 7.5 GBq of  $^{177}\text{Lu}$ -DOTATATE (first cycle) and 3 months later administering  $^{90}\text{Y}$ -DOTATATE for the second cycle. A complete remission was observed 2 years after the second cycle, possibly due to an additional delayed antiangiogenic effect. (A1, A2, A3: Pre-PRRNT SSTR PET/CT; B:  $^{177}\text{Lu}$ -DOTATOC whole-body post-therapy scan 68 hours after the first PRRNT demonstrates intense uptake in the hepatic metastases; C1, C2, C3: SSTR PET/CT 2 years after the second PRRNT cycle; A1, C1: Maximum intensity projection images; A3, C3: transverse fused PET/CT images showing complete molecular response to PRRNT in the hepatic metastases; A2, C2: Corresponding CT images)

toxicity.<sup>31</sup> Neoadjuvant PRRNT can be administered in inoperable NENs so that the tumor is rendered operable by inducing radiation-induced necrosis with the possibility of complete cure after surgery.<sup>32</sup>

The aim of PRRNT is to deliver the highest possible dose to the tumor and at the same time prevent damage to normal organs. The different metabolism or receptor density in organs and tumor lesions accounts for interpatient differences in dose delivery. Therefore, individualized patient dosimetry is mandatory. The mean absorbed doses to normal organs and tumors are estimated using the MIRD scheme (OLINDA/EXM).<sup>33</sup> Pretherapeutic dosimetry for further personalizing PRRNT with SSTR PET/CT is possible using longer lived positron emitters, e.g. <sup>44</sup>Sc, <sup>86</sup>Y or <sup>64</sup>Cu. The first human study using the longer-lived, generator-derived, trivalent metallic positron emitter <sup>44</sup>Sc (scandium-44) coupled to DOTATOC was performed in Bad Berka in 2009. <sup>44</sup>Sc has a half-life of 3.9 hours and is derived from a titanium-44/scandium-44 generator, which has a half-life of approximately 60 years.<sup>34,35</sup>

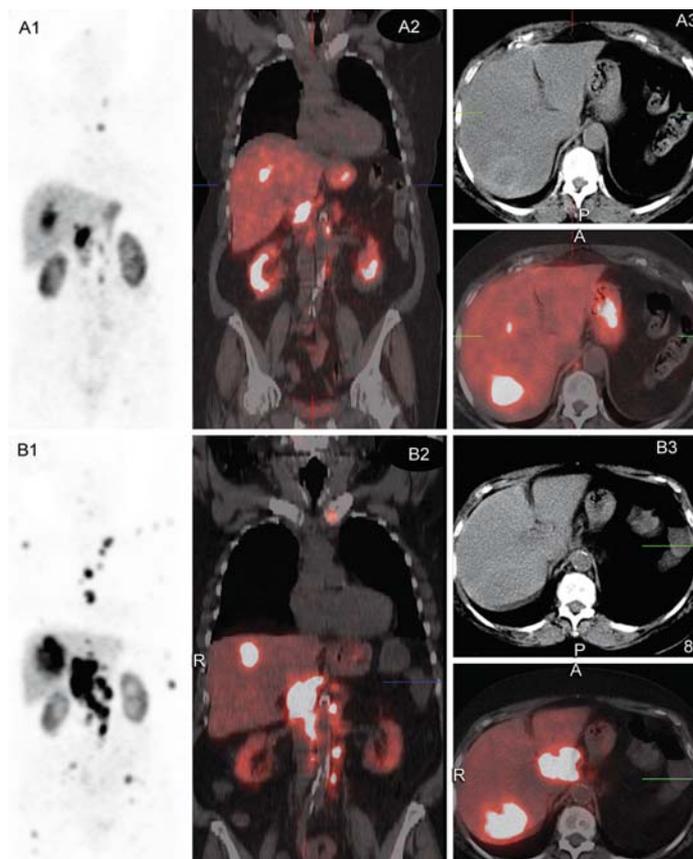
Kidneys are the dose limiting organs for PRRNT since radiolabeled peptides (due to their small sizes) are filtered

through the glomerular capillaries in the kidneys and subsequently reabsorbed by and retained in the proximal tubular cells.<sup>36</sup> Long range of the <sup>90</sup>Y beta particles increases the potential for kidney toxicity. The proximal tubular reabsorption of these radiolabeled peptides can be competitively inhibited by positively charged molecules, such as L-lysine and/or L-arginine. Plasma expanders like Gelofusine also help in preventing uptake in the tubules.

Acute reversible hematological toxicity is quite frequent, especially after <sup>90</sup>Y-labeled peptide therapy. The possibility of mild and progressive bone marrow toxicity exists after repeated cycles and the potential risk of development of myelodysplastic syndrome (MDS) or overt leukemia in patients receiving high bone marrow doses, especially in patients previously treated with alkylating chemotoxic agents must be considered.<sup>37</sup>

### THE BAD BERKA EXPERIENCE

The Bad Berka Theranostics and Neuroendocrine Tumor Center was certified as ENETS Centre of Excellence in March 2011. At our center, a dedicated multidisciplinary

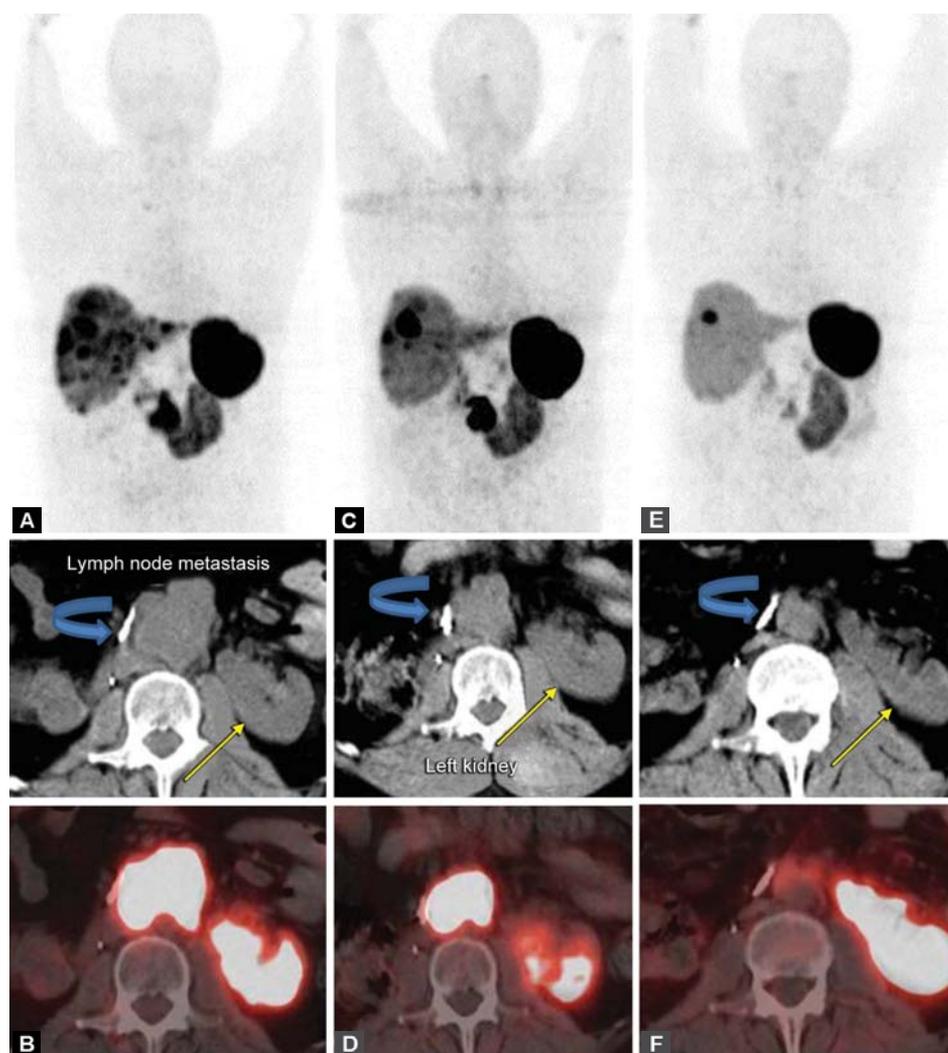


**Fig. 3:** A 77-year-old female patient with a well-differentiated, functioning (glucagonoma) neuroendocrine neoplasm of the pancreas (status post left pancreatectomy and splenectomy) developed progressive hepatic, peritoneal and lymph node metastases. The patient underwent five cycles of peptide receptor radionuclide therapy with a total administered activity of 30.3 GBq Lu-177. The follow-up Ga-68 DOTATOC PET/CT (6 months after the fifth cycle) showed stable disease (A1, A2 and A3). However, after 1 year, there was a significant progression of disease with new lesions and increase in the SUVmax (extremely intense somatostatin receptor expression—B1, B2 and B3). The renal function was normal. Hence, there was an indication for repeat PRRNT (A1, B1:Maximum intensity projection images; A2, B2: Coronal fused PET/CT images; A3, B3: Transverse fused PET/CT and the corresponding CT images) which resulted again in a very good therapy response

team of experienced specialists is responsible for the management of NEN patients (over 1,200 patient visits per year). We have been treating progressive well-differentiated NENs with PRRNT using  $^{177}\text{Lu}$  and/or  $^{90}\text{Y}$  since more than a decade, having treated around 1,100 patients (over 4,000 treatment sessions). Patient selection for PRRNT is based on the Bad Berka score, which takes several parameters into account, importantly the SUVs on SSTR PET (for referrals: Krenning's score on somatostatin receptor scintigraphy) for determining somatostatin receptor density, renal function and many other factors (Fig. 3).<sup>38</sup> Management of every patient is individualized, administering low or intermediate radioactivity by frequent therapy cycles (up to 9), i.e. applying the 'long-term low-dose' and not the 'short-term high-dose' concept (Figs 4A to F). Patients are well-hydrated and receive an amino acid infusion containing lysine and arginine over 4 hours beginning 30 minutes

before PRRNT. Patients who are treated with Y-90 receive in addition Gelofusine over 3 hours. Applying these nephron-protective measures, end-stage renal insufficiency was observed in only 1 out of the 1,100 patients (less than 0.1%) treated at our center (>4,000 treatment sessions). Before each new treatment cycle, a complete restaging is performed both by morphologic (CT/MRI) and molecular imaging studies (particularly  $^{68}\text{Ga}$ -SSTR PET/CT, and in selected cases  $^{18}\text{F}$ -FDG or  $^{18}\text{F}$ -fluoride PET/CT additionally), blood chemistry and tumor markers (CgA, serotonin, specific hormones). Renal function is serially determined by  $^{99\text{m}}\text{Tc}$ -MAG3 scan/TER and by  $^{99\text{m}}\text{Tc}$ -DTPA (GFR) measurements. All data are entered into a structured database containing 270 items per patient.

The systematic use of both  $^{90}\text{Y}$  and  $^{177}\text{Lu}$  labeled with SMS analogs in sequence (DUO-PRRNT) and concurrently (TANDEM-PRRNT) was also pioneered by our group. This



**Figs 4A to F:** A 60-year-old patient with NEN of the right kidney with extensive bilateral liver metastases (size 3.7 cm in S7) and retroperitoneal lymph node (size up to 6.5 cm) and bone metastases presented in a poor general condition, lymphedema and deranged renal function with a TER of 35% (A, B:  $^{68}\text{Ga}$ -SSTR PET/CT before PRRNT). After two cycles of PRRNT, using 7 and 7.5 GBq of  $^{177}\text{Lu}$ -labeled DOTA-SMS analogs respectively, there was a successive significant response according to molecular imaging criteria as well as a significant reduction in size of the lymph node metastases and an improvement in renal function, probably due to resolution of the lymphatic obstruction (C, D: SSTR PET/CT after first PRRNT cycle; E, F: SSTR PET/CT 4 months after second PRRNT cycle)

accounts for the variable sizes of tumors and inhomogeneous distribution of SSTRs.  $^{177}\text{Lu}$ -DOTATATE is predominantly used for smaller metastases or in patients with impaired renal or hematological function. Intra-arterial use of  $^{90}\text{Y}$ -labeled DOTATATE and DOTATOC, as a highly targeted therapy for hepatic metastases and large primary tumors was also inaugurated by our center. Recently, we performed for the first time a superselective intra-arterial PRRNT for treatment of a large meningioma with  $^{90}\text{Y}$ -DOTATOC with evidence of partial response after the first cycle. An analysis of 416 GEP-NEN patients treated at the BBNETC showed a median overall survival from the time of first diagnosis of 210 months and a median survival after the first PRRNT of 59 months.

The theranostic potential of the bisphosphonate BPAMD has been explored using  $^{177}\text{Lu}$ -BPAMD for the treatment of widespread, progressive and painful skeletal metastases refractory to conventional treatment.<sup>39</sup> Dosimetric studies showed that due to the very long half-life of the radiopharmaceutical in the metastases (>80 hours), high mean absorbed doses to the tumors, ranging from 2.4 to 209 mGy/MBq (the wide range was due to different sizes of the lesions) were observed. An excellent pain palliation could be achieved, corresponding with a significant reduction in osteoblastic activity of the bone metastases as seen on the follow-up  $^{18}\text{F}$  sodium fluoride PET/CT. Only mild-to-moderate changes in blood cell counts were observed. Overall, the treatment was well-tolerated by all patients without any significant adverse effects.

$^{177}\text{Lu}$ -demobesin therapy was administered in 2009 for the first time at our center and so was a novel GRP-R antagonist labeled with  $^{177}\text{Lu}$  in a patient with metastatic prostate cancer. This is indeed an exciting future prospect for the theranostics of GRP-R positive tumors with  $^{68}\text{Ga}/^{177}\text{Lu}$ -labeled tracers.<sup>40</sup>

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