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REVIEW ARTICLE

^{68}Gallium- and ^{90}Yttrium-/^{177}Lutetium: "theranostic twins" for diagnosis and treatment of NETs

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Abstract Abundant expression of somatostatin receptors (SSTR) is frequently identified in differentiated neuroendocrine tumors and may serve as potential target for diagnostic imaging and treatment. This article discusses the "theranostic approach" of SSTR-targeting compounds including an overview of its role for diagnosis, staging and restaging, discussing its way to being established in clinical routine, and giving an outlook about further potentially relevant developments.

Keywords Neuroendocrine tumor · Theranostic · SPECT/CT · PET/CT · PRRT · Radionuclide therapy

Introduction

Recent developments in cancer research have resulted in a wide spectrum of therapies. Due to the large heterogeneity of patients and tumors, there is an increasing demand for personalized medicine. Introduction of the theranostic approach is based on the idea of selecting patients through a diagnostic study indicating whether a patient will benefit from a therapy or not.

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The theranostic principle has been applied in the field of nuclear medicine for more than 60 years and ^{131}I and ^{89}Sr are still established in daily clinical routine. ^{131}I was first discovered in 1938 by Seaborg and Livingood at the University of California Berkeley. Already in 1946, Seidlin et al. [1] reported the therapeutic use of ^{131}I for patients with metastasized adenocarcinoma of the thyroid. Since then the combination of radiolabeled iodine for diagnostic imaging and therapy represents an established and accepted "theranostic" approach. In 1942, Pecher demonstrated that ^{89}Sr accumulates in bone tumors in animals; and later, these findings were translated to humans and ^{89}Sr was widely used in cancer patients [2, 3]. More recently, a number of new theranostic approaches have been introduced including ^{123}I-/^{131}I-labeled Metaiodobenzylguanidine (MIBG) for diagnosis and treatment of neuroblastoma [4–6]. An additional theranostic pair consisting of ^{123}I- and ^{131}I-metomidate for diagnosis and treatment of adrenocortical carcinomas (ACC) has been established at the University Hospital of Würzburg. The diagnostic scan with ^{123}I-metomidate allows for the prediction whether an ACC patient will benefit from ^{131}I-metomidate radionuclide therapy after determination of an individualized dose by dosimetry [7, 8]. First, clinical data revealed tumor control in half of the patients undergoing ^{131}I-metomidate therapy [7, 9].

In this article, we focus on the recently introduced and clinically translated "theranostic approach" of somatostatin receptor (SSTR) targeting compounds for treatment of patients with neuroendocrine tumors (NETs). We will present an overview of its role for diagnosis, staging and restaging, discussing its way to being established in clinical routine, and giving an outlook about new developments.

Theranostic twins in NET

The term "theranostics twins" includes diagnostic molecular imaging followed by a personalized treatment decision based on the predictive value of the diagnostic scan. Translated to NETs "theranostic twins" relate to the pairing of ^{111}In-/^{68}Ga-labeled diagnostic imaging and ^{90}Y-/^{177}Lu-labeled treatment compounds targeting the SSTR (Fig. 1).

The rationale of this theranostic approach bases on the fact that well-differentiated NETs usually overexpress SSTR on their tumor cell surface which may serve as diagnostic and therapeutic targets [10]. Five different membrane-bound receptors have been evaluated: SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5. Out of these potential targets usually SSTR2 is addressed for diagnosis and therapy. Using radiolabeled somatostatin analogs for functional imaging the diagnosis of NETs can be confirmed and the tumor burden (metastases) assessed. These nuclear medicine imaging procedures provide essential information about SSTR density, which is relevant for treatment decisions, and selecting patients for treatment with peptide receptor radionuclide therapy (PRRT) [11]. In general, PRRT is recommended in inoperable, metastasized cases expressing SSTR on tumor cell surface [12].

^{111}In-labeled twins

^{111}In-DTPA-octreotide, binding to SSTR2, was the first and most widely used radiopharmaceutical for detecting and staging NETs [13]. Planar images should be performed and, if available, single photon emission computed tomography (SPECT) after 4 and 24 h [14]. With an overall sensitivity of 80 % ^{111}In-DTPA-octreotide scintigraphy (including SPECT) seems to be an effective method to detect tumor burden [15]. However, reduced detection rate has been reported in small and deep-seated lesions, even when using hybrid SPECT/CT scanners [16]. Historically verified, ^{111}In can not only be used for diagnosis and staging of NETs, but also for treatment: treating 40 patients by using the Auger electron emitting radionuclide ^{111}In, partial remission (PR) was reported in one patient, minor remission in six patients and stable disease (SD) in 14 patients [17]. In another study, only two of 27 patients (8 %) showed imaging-based morphological PR [18]. Due to the short particle range and the resulting limited tissue penetration, tumor regression only rarely occurred [19].

Thus, in the previous decade, the use of ^{111}In was abandoned and replaced by the following new theranostic twins.

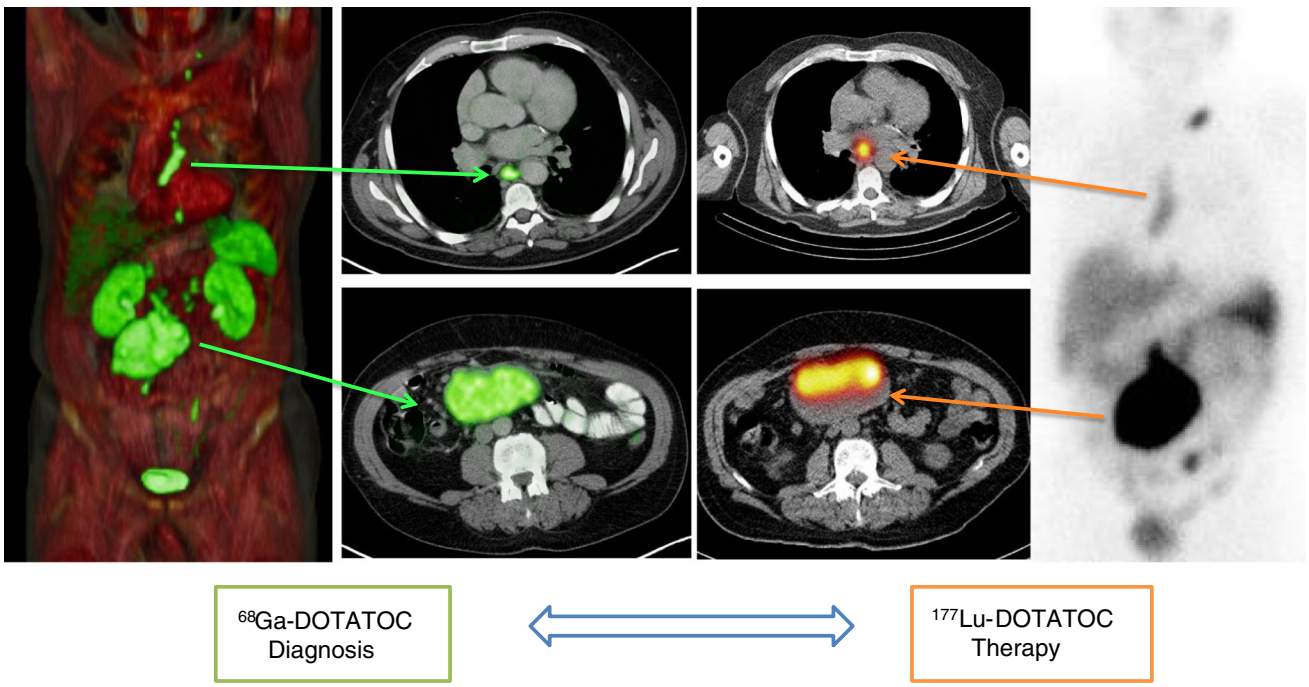

Fig. 1 69-year-old male suffering from Ileum NET (primary tumor) with paraaortal thoracic lymph node metastases. *Left* pretherapeutic ^{68}Ga-DOTATOC PET/CT (*anterior view*, *trans-axial view*) showing primary tumor (ileum) and paraaortal mediastinal lymph node metastases. *Right* posttherapeutic fused SPECT/CT after administering 7.4 GBq ^{177}Lu-DOTATATE showing prominent uptake in the primary tumor and paraaortal thoracic lymph node metastases

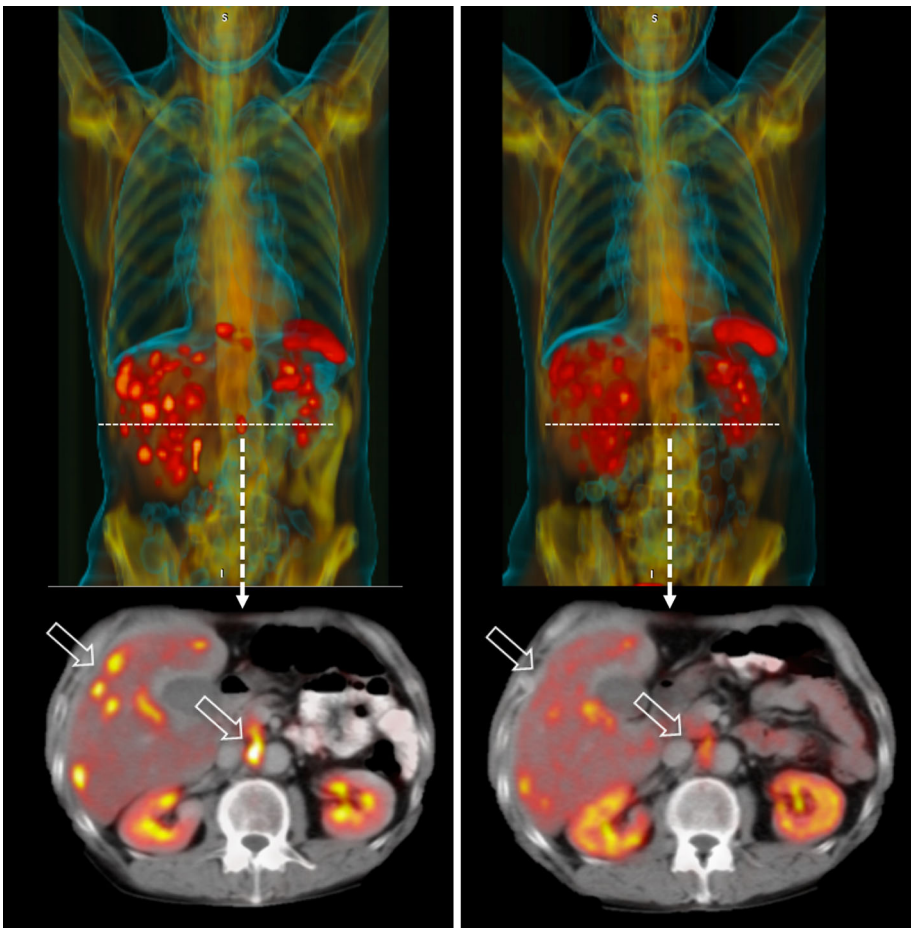

Fig. 2 56-year-old male suffering from unresectable pancreatic NET (primary tumor) with liver metastases and retroperitoneal lymph node metastases. *Left* pre-therapeutic ^{68}Ga-DOTATOC PET/CT (*anterior view*, *trans-axial view*) showing liver metastases and retroperitoneal lymph node metastases. *Right* post-therapeutic ^{68}Ga-DOTATOC PET/CT (*anterior view*, *trans-axial view*) after administering 22.3 GBq ^{177}Lu-DOTATOC over the course of 3 treatment cycles showing reduced uptake in the metabolically regressive liver and retroperitoneal lymph node metastases (staging 10 weeks after last treatment cycle)

^{68}Ga and ^{90}Y/^{177}Lu labeled twins

Recently, PET tracers have replaced ^{111}In-DTPA-octreotide for diagnostic imaging of NETs. Three ^{68}Ga labeled somatostatin analogs are currently routinely used in clinical practice: ^{68}Ga-DOTA-D-Phe-Tyr3-octreotide (DOTATOC), ^{68}Ga-DOTA-1-Nal(3)-octreotide (DOTANOC) and ^{68}Ga-DOTA-D-Phe-Tyr3-octreotate (DOTATATE). All these compounds bind with a high affinity to SSTR2 on the tumor cell surface [16]. Compared with ^{111}In-DTPA-octreotide, ^{68}Ga-DOTATATE PET/CT was found to be the superior functional imaging modality especially in small lesions with a low density of SSTRs because of its higher resolution [20]. Initial results were confirmed by Haug et al. in a larger patient cohort. Offering better imaging properties, ^{68}Ga-SSTR PET/CT was able to depict NETs with an accuracy of 87 % [21] (Fig. 2). In 2010, conventional imaging's such as CT or endoscopic ultrasound were compared to PET/CT in 90 patients. SSTR PET/CT led to a modification of staging in 29 % and management of therapy in 76 % of patients [22]. Additionally, PET is more patient friendly since it can be done as a single imaging session performed within 30–60 min after injection [16] as opposed to multiple day imaging required for ^{111}In- DTPA-octreotide scintigraphy.

Currently, the most commonly used isotopes for treatment intended radiolabeling of somatostatin analogs are the ß-emitting isotopes ^{90}Y with DOTATOC or ß- and y-emitting ^{177}Lu with DOTATATE. Otte et al. [23] reported treatment in a palliative setting of 29 patients with advanced SSTR-positive tumors by administering at least 3.7 GBq of ^{90}Y-DOTATOC in 127 single treatment cycles. Only three patients suffered from progressive disease. Waldherr et al. [24] injected 7.4 GBq ^{90}Y-DOTATOC (4 treatment cycles, time interval of 6 weeks) resulting in 5 % complete responses (CR) and 18 % PR. The most common reported side effect was renal impairment with a decline in creatinine clearance of 7.3 % per year [25].

However, ^{177}Lu-DOTATATE seems to be better tolerated than ^{90}Y [25]. Thus, it is also routinely used as the "theranostic twin" to ^{68}Ga. 310 NET patients treated with 27.8–29.6 GBq (4 treatment cycles, time interval of 6–10 weeks) showed a survival benefit of 40–72 months from diagnosis in comparison to historical controls [26]. Quality of life improved significantly after ^{177}Lu-DOTATATE [27] and even in patients undergoing repeat salvage

PRRT a median PFS of 13 months was reported [28]. At least two treatment cycles should be performed because PFS seems to be determined by the injected dose [29]. The most important delayed side effects significant renal impairment and myelosuppression occur in approximately 1 % of patients [30, 31]. Amino acid (AA) solutions are recommended directly prior and during PRRT to reduce renal absorbed dose and subsequent damage to the renal parenchyma. Treating physicians should be aware of potentially life-threatening acute hyperkalemia which can occur as an acute side effect, of administering AA [14, 32].

Because of deeper tissue penetration the high energy ^{90}Y beta emitter is recommended for larger lesions, whereas the lower energy ^{177}Lu should be administered for smaller lesions. A combination of ^{90}Y-/^{177}Lu-DOTATATE demonstrates better therapy response in comparison to single-injection of ^{90}Y-DOTATATE by providing a significantly longer median OS [33].

The term "theranostics" emphasizes the inseparability of diagnosis and therapy. However, individual treatment planning determining prognosis should be part of this concept. ^{68}Ga-DOTATATE PET/CT can also predict progression-free-survival (PFS) in patients undergoing PRRT: Evaluating the early prediction of clinical outcome 3 months after the initial treatment cycle, the tumor-to-spleen SUV ratio was able to independently predict the time-to-progression in patients undergoing SSTR PET/CT [34].

In summary, the diagnosis and therapy monitoring of NETs can be assessed by using functional imaging with different somatostatin analogs. ^{111}In-labeled twins were used in the last decade showing a good overall sensitivity and treatment effects. However, in small and deep-seated lesions, ^{68}Ga-labeled radiopharmaceuticals for PET are superior, even superior to stand alone contrast-enhanced multislice CT [35]. For its twin, ^{177}Lu or ^{90}Y DOTATATE/DOTATOC, good results for overall survival, improvement of quality of life but also less side effects were demonstrated [26, 27].

Theranostic approach in clinical routine

Nowadays, the most commonly used "theranostic twins" for treatment of NETs are ^{68}Ga and ^{90}Y-/^{177}Lu-DOTATATE/DOTATOC showing higher response rates and improvement of life quality [14].

Labeling of the twins

Preparation of radiopharmaceuticals should be performed according to the current regulations on radiation protection and guidelines on Good Radiopharmacy Practice ensuring strict hygiene requirements [36].

^{68}Ga PET is usually used for pre-therapeutic proof of target expression, for staging and follow-up of patients. The half-life of the ^{68}Ga isotope is favorable with 68 min. The use of a ^{68}Ge/^{68}Ga-generator ensures a continuous cyclotron-independent supply with ^{68}Ga [37]. The only stable chemical form of Ga at physiological conditions is Ga^{3+} which still needs a bifunctional chelating agent (BCA) to bind to a target vector such as peptides or proteins [38]. Since the labeling process can be performed just prior to the PET/CT examination it is possible to inject an optimal amount of radioactivity.

^{177}Lu is produced by a nuclear reactor in two different ways: via "direct pathway" (irradiation of ^{176}Lu) or via "indirect pathway" (irradiation of ^{176}Yb producing ^{177}Yb decaying to ^{177}Lu). A specific activity of 37–74 MBq ^{177}Lu per microgram is generally recommended [14]. The method of synthesis is widely described in literature [39–41].

Therapeutic procedure

Like any other nuclear medicine therapy, PRRT has to be performed according to the local legal and ethical requirements and a recommendation of a multidisciplinary tumor board is desirable. The ward of the nuclear medicine department must provide trained staff including physicians, radiochemists and medical physicist experts. General radiation safety arrangements are mandatory. However, official regulations with special focus on radionuclides used for PRRT do not exist; in summary, these requirements differentiate from one country to another [14].

Toward intercontinental patient care

In Japan and other non-European countries, PRRT using effective SSTR-targeting compounds like ^{177}Lu-DOTATOC are currently not available. To implement the entire "theranostic" concept, the use of the "theranostic twins" but also individual tailored treatment planning prior to PRRT is indispensable. To overcome this shortcoming, the Würzburg department of nuclear medicine among others provides special medical services for patients which do not have access to PRRT in their home countries including patient preparation at their home institution (e.g. renal scintigraphy, ^{111}In-DTPA-octreotide scintigraphy). Additionally, management of transfer to Germany is provided. If required also in-house renal scintigraphy, measurement of blood values (with special focus on renal/hematological parameters) but also the more sensitive ^{68}Ga-DOTATOC PET/CT scan proving receptor expression on tumor cell surface can be provided. To avoid environmental radiation exposure after PRRT as well as to guarantee a better post-therapy monitoring, the patients are constrained to stay

hospitalized for a total of 3–5 days. After being discharged, patients are encouraged to avoid contact to small children and pregnant persons for the next 5–7 days; special paperwork to allow for a return flight will be provided.

Dose estimation as part of "theranostic" concept to minimize toxicity

The term "theranostic twins" does not only refer to the use of peptides labeled with diagnostic or therapeutic radionuclides, but also emphasizes the personalized patient preparation prior to and after PRRT. The kidneys are the dose-limiting organ in PRRT and therefore kidney function has to be assessed prior to therapy by laboratory tests, 24 h urine collection and/or renal scintigraphy [14]. Van Binnebeek et al. reported in a case presentation as well as in a prospective phase II trial on the role of individualized dosimetry-based activity reduction of ^{90}Y-DOTATOC to prevent severe and rapid kidney function deterioration by maximizing the delivered tumor dose and minimizing the biological effective dose (BED) to potential risk organs (kidney, bone marrow). The authors used ^{111}In-pentetreotide for dose estimation and reported a maximal tolerable kidney dose of 37 Gy BED as the threshold to avoid severe loss of kidney function in ^{90}Y-DOTATOC [42, 43].

Helisch et al. [44] demonstrated that both ^{86}Y-DOTATOC (chemically identical to ^{90}Y) and ^{111}In-pentetreotide are feasible to pre-therapeutically calculate the cumulative organ and tumor doses identifying patients with high radiation burden to the kidneys. Concerning post-therapeutic dosimetric approaches, the following data has to be collected up to 3 days after PRRT: urine, blood, whole-body-scans, planar images but also SPECT alone/fused-SPECT/CT [14]. Software tools like OLINDA/EXM using this equation provide internal dose information and especially dose calculations [45]. However, a general recommendation for performing pre-/post-therapeutic dosimetry is not given. Due to its y-emission, post-therapeutic scintigraphy of ^{177}Lu-DOTATATE allows staging/imaging and dosimetry by using the same radiolabeled tracer. Thus, during the first treatment cylce of ^{177}Lu-DOTATATE, a post-therapeutic dosimetry might be useful [14, 46].

Outlook

In general, PRRT is recommended for inoperable, metastasized NETs expressing SSTR2 on the tumor cell surface [12].

Radiosensitizing, SST receptor expression increase and neoadjuvant treatment strategies

The synergism of radiolabeled compounds with chemotherapy may lead to higher efficacies. Claringbold et al. [47] reported that the addition of the radiosensitizing chemotherapeutic drug capecitabine resulted in tumor control in 94 % of patients without severe toxicity. The same research group administered ^{177}Lu-octreotate in combination with capecitabine and temzolomid in advanced low-grade NETs demonstrating 2-year survival rate of 90 % [48].

Furthermore, receptor expression on tumour cells could be increased by addressing different molecular targets prior to PRRT. This might guarantee a higher saturation of SST receptors expressed on the tumor cell surface which could lead to higher BED. A Swedish research group reported a higher uptake of ^{177}Lu-DOTA-Tyr^3-octreotate in external-beam irradiated small cell lung cancer cells which might be caused by an up-regulation of SSTR2 [49]. These findings may constitute a promising treatment option in the future.

On a final note, the use of PRRT in a neoadjuvant setting to downstage/downsize inoperable patients could be beneficial but has not been studied sufficiently to date.

Locoregional procedures in case of discontinuing PRRT

Radioembolization with ^{90}Y microspheres has been described as a safe and effective treatment option in unresectable cancers of the liver [50]. Due to their hypervascularity liver-dominant NET metastases are well-suited for locoregional therapeutic procedures such as radioembolization (selective internal radiation therapy, SIRT) but also transarterial chemoembolization (TACE) combining the cytotoxic effect of intra-arterial chemotherapy with an embolizing ischemic approach [51]. Injection of ^{90}Yttrium-microspheres into liver metastases as salvage therapy after PRRT resulted in a median OS of 29 months [52]. TACE and transarterial embolization (TAE) demonstrated the same PFS of 36 months in patients suffering from advanced NET. However, less side effects are described for TAE [53].

"High dose" approach in PRRT

Ongoing studies are trying to determine the role of dosimetry for minimizing kidney and bone marrow damage by potentially offering the possibility of increasing the administered activities. Currently, up to a maximum of 7.4 GBq per treatment cycle is regarded as safe [54]. Using the absorbed dose to "risk organs" as the limiting factor, treatment with ^{177}Lu-DOTATATE could be individualized

to avoid under-/overtreatment, minimize side effects and to be able to administer the maximum activity per treatment cycle. Forrer et al. [55] reported high inter-patient variability of bone marrow absorbed doses. Thus, individual dosimetry and a personalized "high dose" approach appear feasible. Results of standard PRRT (by using 7.4 GBq ^{177}Lu-DOTATOC) according to practical guidance [14] could be compared to a tailored "high dose" treatment by injecting the maximum tolerable dose per cycle. Pre-therapeutic dosimetry assesses the individual kinetic behavior in every patient which might be helpful in maximizing the cumulative dose but also optimizing the BED.

Conclusion

In summary, PRRT is an effective and safe treatment option for patients suffering from advanced NET. The "theranostic twins" ^{177}Lu- and ^{68}Ga-DOTATATE are routinely used in clinical practice with well-established response rates. Ongoing prospective multicenter trials such as NETTER-1 will hopefully confirm these results in larger patient populations awarding PRRT a higher clinical acceptance [56]. The importance of dose estimation as part of the "theranostic" concept and also pre-therapeutic up-regulation of SSTR expression should be kept in mind as potential innovations of PRRT [42, 43, 49].

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