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Theranostics in Nuclear Medicine Practice

Anna Yordanova [1,*], Elisabeth Eppard [1], Stefan Kürpig [1], Stefan Schönberger [2], Maria Gonzalez-Carmona [3], Georg Feldmann [4], Hojjat Ahmadzadehfar [1] and Markus Essler [1]

[1] Department of Nuclear Medicine, University Hospital Bonn, 53127 Bonn, Germany
[2] Department of Paediatric Haematology and Oncology, University Hospital Bonn, 53113 Bonn, Germany
[3] Department of Medicine 1, University Hospital Bonn, 53127 Bonn, Germany
[4] Department of Medicine 3, University Hospital Bonn, 53127 Bonn, Germany
* Correspondence: anna.yordanova@ukbonn.de;
Tel: +49 228 287 16814; Fax: +49 228 287 90 19107

Abstract:
The importance of personalized medicine is growing, since there is an urged need to avoid unnecessary and expensive treatments. In nuclear medicine, the theranostic approach is an established tool for a specific molecular targeting in means of diagnostics and therapy. The visualisation of potential targets can help to predict if a patient would benefit from a particular treatment or not. Thanks to the quick development of radiopharmaceuticals and diagnostic techniques, the use of theranostic agents is constantly rising. In this article important milestones of nuclear therapies and diagnostics in the context of theranostics are highlighted. It begins with the well-known radioiodine therapy in patients with thyroid cancer and then guides through different approaches for the treatment of advanced cancer with targeted therapies. The aim of this review is to provide a summary of background knowledge, current applications and advantages of targeted therapies and imaging in nuclear medicine practice.

Keywords: theranostics, nuclear medicine, personalized medicine

Introduction

Challenging for the modern oncology is the fact that the patients are getting older and commonly unfit for conventional chemotherapy regimens because of comorbidities or poor performance status [1]. Furthermore, the occurrence of side effects may aggravate the compliance in young and elderly patients as well [2]. To manage these problems, it is important to improve the selection of patients, to reduce the side effects and to enhance the therapeutic efficacy. Taking this into account, the combination of targeted cancer imaging and therapy is a considerable achievement for personalized medicine.
The theranostic approach in nuclear medicine couples diagnostic imaging and therapy with the same molecule, but differently radiolabelled (Figure 1). The detection of potential targets

can help to predict if a patient would benefit from a particular treatment or not. After a proper preselection of candidates, targeted nuclear therapies have proven themselves to be effective in the majority of cases with a favourable safety profile [3–6].

Nuclear imaging utilizes gamma-emitters and positron emitters ($ß^+$). Gamma-emitters such as technetium-99m or iodine-123 (^{123}I) can be located using gamma cameras (planar imaging) or SPECT (single photon emission computed tomography) [7]. Better resolution can be achieved via PET (positron emission tomography) using positron emitters, for example gallium-68 (^{68}Ga) and fluor-18 (^{18}F) [8].

Most therapeutic tracers are labelled with beta-particles ($ß^-$), which penetrate tissues and have potential cytocidal effect [3]. Beta-emitters in the routine nuclear oncology practice are lutetium-177 (^{177}Lu, tissue penetration 0.5–0.6 mm, max 2 mm, 497 keV, half-life 6.7 days) [5,9] and yttrium-90 (^{90}Y, tissue penetration: mean 2.5 mm, max 11 mm, 935 keV, half-life 64 h) [3,10–12].

The first theranostic radiopharmaceutical in the nuclear medicine history is the well-known radioiodine, used for therapy and imaging in thyroid diseases [13]. Since then the use of theranostic agents is constantly rising. Nuclear targeted therapies play an essential role especially in patients with advanced neuroendocrine tumours such as carcinoids, phaeochromocytoma and neuroblastoma [5,6,12,14–17]. Furthermore, there is a positive experience with radioligand therapies in metastatic prostate cancer [3,10,11,18] and metastatic melanoma [19].

The aim of this review is to guide through the most important milestones of nuclear theranostics in practice (Table 1), providing a summarized background knowledge and overview of current applications and advantages of targeted therapies and imaging.

Radioiodine therapy: “the gold standard” in thyroid diseases

Iodine (stable isotope iodine-127) is absorbed from the thyroid gland for producing thyroid hormones: thyroxine (T4) and triiodothyronine (T3) [20]. Thyroid hormones are vital for the pre- and neonatal development of the brain [21], growth and metabolic balance [4,22,23]. In the late 1936, Dr. Saul Hertz, director of the Thyroid clinic in Massachusetts (1931-1943), came up with the idea to administer radioactive iodine in patients with thyroid diseases. Iodine and external beam radiation were well known tools in the therapy of thyroid diseases at that time, but the combination of both was a considerably innovative approach. This idea followed a few years of preclinical studies in collaboration with the Massachusetts Institute of Technology (MIT), where the first cyclotron for medical uses had been built. The MIT-Cyclotron produced 90% iodine-130 (^{130}I, half time 12 h) and 10% iodine-131 (^{131}I, half time 8 days). Finally, on the 31th of March 1941, Dr. Hertz treated the very first patient with radioiodine (RAI, ^{130}I) [13,24,25].

The first RAI with ^{131}I in patients with thyroid cancer was performed by the group of Seidlin et al. 1946 [26]. This group studied the use of RAI in patients with metastatic carcinomas of the thyroid [26,27]. Seidlin et al. also reported one of the first cases of acute myeloid leukaemia after repeated RAI treatments [28].

^{131}I is still a gold standard in the therapy and diagnosis of differentiated thyroid cancer (TC) [29]. It is a low-cost nuclear reactor product from the neutron bombardment of tellurium-131. ^{131}I combines the characteristics of beta- (ß$^{-}$, about 90% of the radiation, mean 192 keV, mean tissue penetration 0.4 mm) and gamma emitter (about 10% of the radiation, mean 383 keV). In this way it irradiates the TC and the thyroid remnant from the inside and at the same time targeted lesions can be visualised using a gamma camera or SPECT [4,22,23].
Figure 2A shows the initial ^{131}I-planar images of a 74-year-old female with a metastatic TC (lung, bone and intracranial soft tissue metastases). The tumour marker thyroglobulin (Tg) before RAI was 572 ng/ml. After two administrations of RAI (cumulative activity 14.3 GBq), the patient was in complete remission with Tg of 0.2 ng/ml (Figure 2B).

Diagnostics and therapy with meta-iodobenzylguanidine

Meta-iodobenzylguanidine (mIBG) or Iobenguane, is a molecule similar to noradrenaline and enters neuroendocrine cells from the sympathetic nervous system either by endocytosis or by passive diffusion before being stored in the neurosecretory granules [30].
Among the used radiolabeled molecules [^{123}I]I-mIBG has a lower gamma energy than [^{131}I]I-mIBG (159 keV vs. 360 keV), which makes it more suitable for planar imaging / SPECT. Furthermore, the pure gamma emitter [^{123}I]I-mIBG consists of a shorter half time of 13 hours compared to 8 days of the combined beta and gamma emitter [^{131}I]I-mIBG leading to smaller radiation burden. Thus, higher activities of [^{123}I]I-mIBG can be injected [31]. Both [^{131}I]I-mIBG and [^{123}I]I-mIBG are used in MIBG scintigraphy for detection of neuroendocrine tumours such as neuroblastomas, phaeochromocytomas, paragangliomas, carcinoid tumours and medullary thyroid carcinomas [32]. Especially in patients with inoperable or advanced tumours with distant metastases the mIBG-imaging plays an essential role in response assessment after therapy and evaluation of potential [^{131}I]I-mIBG-therapy [33,34]. In patients with neuroblastoma and phaechromocytoma [^{123}I]I-mIBG presents high sensitivity (97% and 94%) and specifity (up to 96% and 92%), respectively [35–37]. If available, [^{124}I]I-mIBG-PET can be equally used for planning of mIBG targeted therapy [38,39].
Targeted therapy with [^{131}I]I-mIBG presents encouraging efficacy with tolerable toxicity in relapsed or refractory neuroblastoma with response rates between 20-40% being used alone or in combination with high-dose chemotherapy followed by autologous stem cell transplantation [15–17,40]. Recently, the NB2004 trial for risk adapted treatment of children with neuroblastoma closed and further analysis of the usage of mIBG therapy as first-line therapy is outstanding [15,17].

Radiolabelled Somatostatin analogous

Neuroendocrine neoplasia (NEN) of the GEP (gastroenteropancreatic system) originates most frequently from the pancreas, jejunum, ileum, caecum, rectum, appendix and colon. The common characteristic of all GEP-NEN is the compound features of endocrine cells and nerve cells [41–43]. Good differentiated NEN overexpresses somatostatin receptors (SSTR),

especially the subtype SSTR2. Thus, SSTR is a well-established theranostic target in NEN for almost three decades [44–46].

SSTR-imaging is necessary for staging, therapy planning and follow-up. In the PET-diagnostics there are three routine somatostatin analogues (SSA)-tracers labelled with gallium-68: DOTA-TATE / DOTA-TOC and DOTA-NOC. All three tracers bind with high affinity SSTR. PET with ^{68}Ga-labelled SSTR has a high sensitivity (82-97%) and specifity (80-92%) in the detection of small primary tumours or metastases [47–49].

Peptide receptor radionuclide therapy (PRRT) is a systematic therapy in patients with advanced metastatic NEN. Required for the PRRT is a good tumour uptake in the SSTR-imaging. For therapeutic purposes the peptides DOTA-TATE and DOTA-TOC can be labelled either with ^{90}Y or ^{177}Lu. Because of the mainly renal excretion and the proximal tubular reabsorption of these tracers, the kidneys are one of the most limiting organs [50]. Due to the smaller range (2mm) and lower energy ^{177}Lu is less nephrotoxic as ^{90}Y (range max. 11 mm, pure beta emitter, higher energy). For that reason [^{177}Lu]Lu-DOTA-TATE / DOTA-TOC are in many centres the preferred agents for the therapy of NEN [5,6,51,52].

PRRT is increasingly gaining an attention. The first randomised controlled phase III study NETTER-1 (started 2012) compared the standard therapy sandostatin LAR with PRRT in patients with midgut-NEN. The study showed recently a significant clinical benefit from the therapy, achieving a prolonged progression free survival (not reached, approximately 40 months, $p < 0.001$), overall response (18%) as well as presumable longer overall survival (not reached, $p = 0.004$) [6].

Radiolabelled PSMA-ligands

Prostate cancer (PC) is the most common cancer in men in the western countries [53]. Hormone- and chemotherapy-refractory patients with metastatic PC have a poor prognosis [3,54,55]. The main cause of death in these patients is the progression to androgen-independent stage [3].

PC cells overexpress PSMA (prostate-specific membrane antigen) on the cell surface [56–59]. There are several available radiopharmaceuticals targeting PSMA: [^{68}Ga]Ga-PSMA-HBED-CC, also known as [^{68}Ga]Ga-PSMA-11 (PET), a monoclonal antibody (mAb) [^{177}Lu]Lu / [^{90}Y]Y-J591 (therapy), [^{123}I]I-MIP-1072 (planar / SPECT), [^{131}I]I-MIP-1095 (therapy), and the theranostic agent DKFZ-PSMA-617 (PSMA-617), labelled with ^{68}Ga for PET or with ^{177}Lu for therapy.

The specifity of the two commercially available PET-tracers, [^{68}Ga]Ga-PSMA-617 and [^{68}Ga]Ga-PSMA-11 is similar: 99% vs. 100%. However, [^{68}Ga]Ga-PSMA-617 has a better sensitivity: 91% vs. 76.6% [60–62].

The latest studies in patients show that the treatment with [^{177}Lu]Lu-PSMA-617 is effective and well tolerated. Nearly 70% of patients benefit from the therapy [10,18,63–68].

Figure 4A shows the pre-therapeutic [^{68}Ga]Ga-PSMA-11-images of a patient with multiple lymph node, peritoneal and bone metastases (arrows) and history of chemotherapy (first and

second line), enzalutamide and abiraterone. After three cycles of [^{177}Lu]Lu-PSMA-617 the follow-up-images showed a very good response with a substantial PSA-decline (Figure 4B).

Melanin-targeting in patients with metastatic melanoma

Promising approach in patients with metastatic melanoma is the specific targeting of melanin. The new developed theranostic agents: [^{123}I]I- / [^{131}I]I-BA52 and [^{18}F]F- / [^{131}I]F-ICF15002 may play a considerable role in the future.
BA52 is a melanin-binding benzamide. Labelled with I^{123}, it shows a specific binding of the metastases in the planar imaging / SPECT and can help selecting patients, who would probably benefit from the therapy. In a pilot study [^{131}I]I-BA52 proved to be effective in 3/5 patients, who were treated with more than 4.3 GBq [19].
ICF15002 is an arylcarboxamide derivative and as a small molecule can passively enter the cell and bind to melanin. The PET-tracer is radiolabelled with ^{18}F and [^{131}I]I-ICF15002 is designed for the therapy. However, both tracers are still in the preclinical phase of their studies [69].

Conclusion

In nuclear medicine, theranostics combines diagnostic imaging and therapy with the same but differently radiolabelled molecule. The visualisation of potential targets can help to predict if a patient would benefit from a particular treatment or not. In properly preselected patients targeted nuclear therapies have proven themselves to be effective with a favourable safety profile. To conclude, the combination of targeted cancer imaging and therapy is a considerable contribution to personalized medicine and may play an increasingly important role in the future.

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Theranostic molecule		Iodine	mIBG	SSA	PSMA-ligands	Benzamide/ Arylcarboxamide
Target		thyroid-cancer-cells	neurosecretory granules	SSTR, especially the subtype SSTR2	PSMA	melanin
Imaging agent	**Planar imaging/ SPECT**	^{131}I and ^{123}I	[^{131}I]I-mIBG, [^{123}I]I-mIBG	SSA labelled with indium-111	[^{123}I]I-MIP-1072	[^{123}I]I-BA52
	PET	^{124}I	[^{124}I]I-mIBG	[^{68}Ga]Ga-DOTA-TATE [^{68}Ga]Ga-DOTA-TOC [^{68}Ga]Ga-DOTA-NOC	[^{68}Ga]Ga-PSMA-11 [^{68}Ga]Ga-PSMA-617	[^{18}F]F-ICF15002
Therapeutic agent		^{131}I	[^{131}I]I-mIBG	[^{177}Lu]Lu-DOTA-TATE [^{177}Lu]Lu-DOTA-TOC [^{90}Y]Y-DOTA-TOC [^{90}Y]Y-DOTA-TATE	[^{177}Lu]Lu-J591 [^{90}Y]Y-J591 [^{131}I]I-MIP-1095 [^{177}Lu]Lu-PSMA-617	[^{131}I]I-BA52 [^{131}I]I-ICF15002
Indication		thyroid cancer	neuroblastomas, phaeochromocytomas, paragangliomas, carcinoid tumours and medullary thyroid carcinomas	NEN, especially GEP-NEN	metastatic prostate cancer	metastatic melanoma

Table 1: Overview of theranostic agents

Legend: mIBG: meta-iodobenzylguanidine; SSA: somatostatin analogous; SSTR: somatostatin receptors; NEN: neuroendocrine neoplasia; GEP: gastroenteropancreatic system

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Figure 1: Theranostic principle in the nuclear medicine: combining diagnostic imaging and therapy with the same molecule, but differently radiolabelled. In case of RAI, the radioisotope (^{131}I or ^{123}I) can be directly mediated by the sodium-iodide symporter in the thyroid cells. In other cases it can be more complex. The image shows a simplified model of a radiopharmaceutical, consisting of a binding molecule, which binds the target, and a linking molecule, which binds the radioisotope. Examples of such theranostic molecules are DOTA-TOC / DOTA-TATE and PSMA-617.

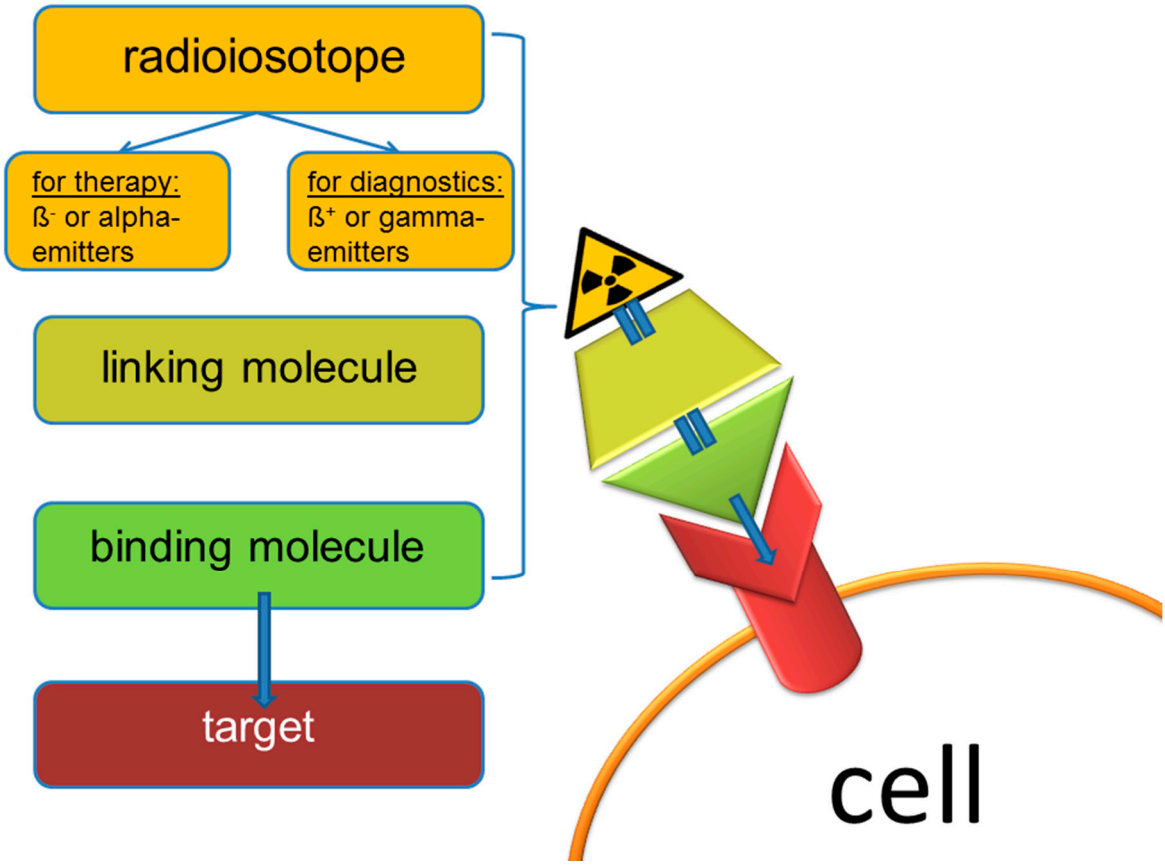

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Figure 2:

2A: Initial ^{131}I-planar images of a 74-year-old female with a metastatic TC (lung, bone and intracranial soft tissue metastases, marked with arrows). The tumour marker thyroglobulin (Tg) before RAI was 572 ng/ml.

2B: After two administrations of RAI (cumulative activity 14.3 GBq), the patient was in complete remission with Tg of 0.2 ng/ml. The planar images show only a physiologic uptake of the radiotracer in the gastrointestinal tract and pharyngeal mucosa (marked with an asterisk).

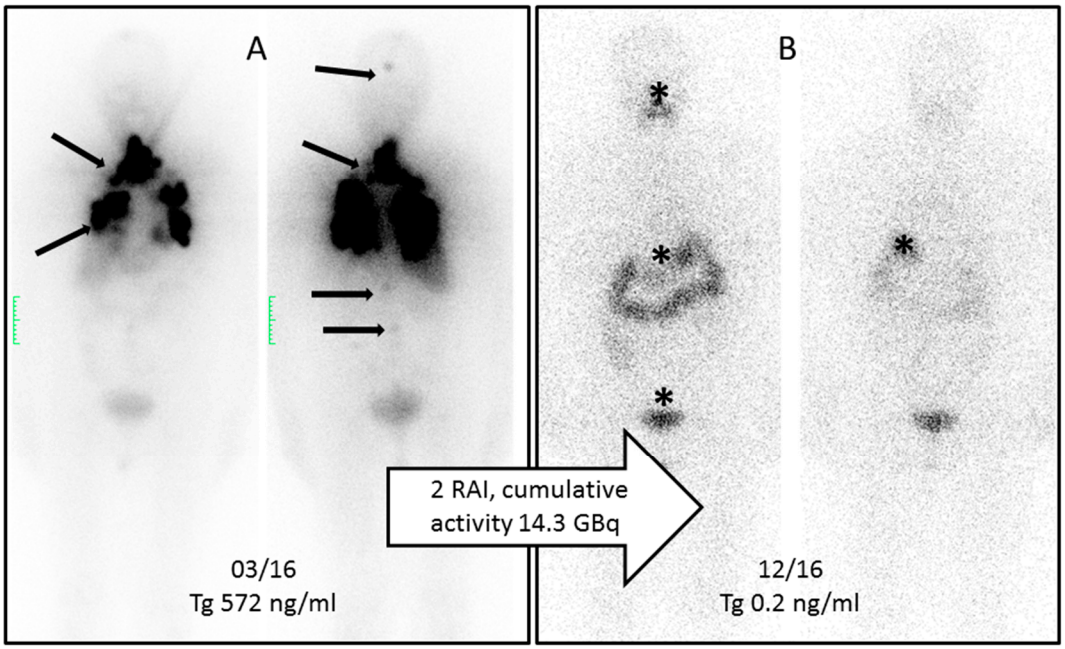

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Figure 3:

3A: Maximum intensity projection (MIP) PET image ([^{68}Ga]Ga-DOTA-TOC) of a male patient with neuroendocrine tumour (unknown origin) 23 months after the baseline PRRT (three cycles, cumulative activity 19.6 GBq). The patient had a recurrence of disease with multiple metastases in the bone, lung, liver and lymph nodes (marked with arrows).

3B: After another course of PRRT (three cycles, cumulative 43.4 GBq) the PET-images showed a partial response.

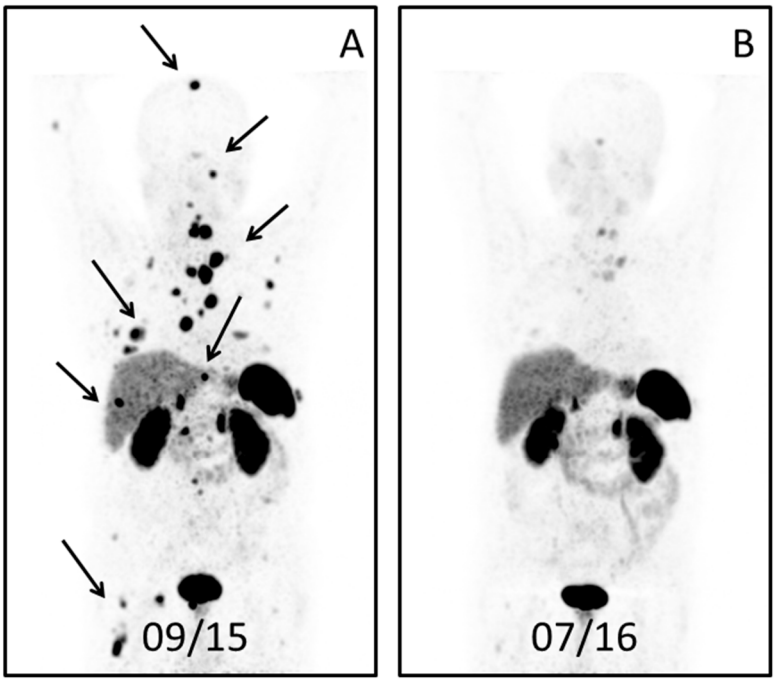

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Figure 4:

4A: Pre-therapeutic [^{68}Ga]Ga-PSMA-11-images of a patient with multiple lymph node, peritoneal and bone metastases (arrows) and history of chemotherapy (first and second line), enzalutamide and abiraterone.

4B: After three cycles of [^{177}Lu]Lu-PSMA-617 the follow-up-images showed a very good response with a substantial PSA-decline.