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Theranostic approaches in nuclear medicine: current status and future prospects

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Abstract

Introduction: Theranostics is an emerging field in which diagnosis and specific targeted therapy are combined to achieve a personalized treatment approach to the patient. In nuclear medicine clinical practice, theranostics is often performed utilizing the same molecule labeled with two different radionuclides, one radionuclide for imaging and another for therapy.

Areas covered: The authors review the clinical applications of different radiopharmaceuticals in the field of interest, including the well-established use of radioactive iodine in differentiated thyroid cancer, radiolabeled metaiodobenzylguanidine (MIBG) in neuroblastoma and the clinical impact of peptide radionuclide receptorial therapy (PRRT) in the management of neuroendocrine tumors. Furthermore, the more cutting-edge and recently introduced theranostic approaches will be reviewed, such as the radioligand therapy with $^{177}$Lu-prostate specific membrane antigen (PSMA) and targeted alpha therapy in castration resistant prostate cancer. Finally, the main applications of PET for the imaging of biomarkers suitable for the non-radionuclide targeted therapy will be covered.

Expert opinion: Theranostics is envisaging a revolutionary clinical approach which is deeply connected with the concept of personalized medicine and ruled by a “patient-centered” vision. In this perspective, the theranostic applications will need well-trained specialists, capable to manage not only the technological aspects of the discipline, but also to deal with the more innovative oncological therapies in a multidisciplinary setting.

Keywords: theranostics; nuclear medicine; neuroblastoma; MIBG; neuroendocrine tumors; DOTA-peptides; PSMA; microspheres;
**Article Highlights**

- Theranostics is an emerging scientific discipline combining diagnosis and targeted therapy for a personalized clinical approach.
- The diagnostic phase is aimed to identify specific biomarkers that can be predictive of response to treatment and can be applied for monitoring patients during therapy.
- In nuclear medicine, theranostic approach is usually achieved through the use of the same molecule (or two molecules as similar as possible) which are either labeled with different radionuclides or with an identical radionuclide used at a different dosage.
- For the diagnostic phase, gamma-emitter radionuclides are often used (such as $^{123}\text{I}$), although positron-emitters (such as $^{124}\text{I}$) should be preferred for the superior quality of imaging and quantitation obtained with PET technology.
- The radioactive iodine (RAI) therapy with $^{131}\text{I}$ for differentiated thyroid carcinoma represented the first example of theranostic approach. Since its introduction in nuclear medicine, many efforts have been made for achieving an accurate and personalized dosimetry.
- Metaiodobenzylguanidine (MIBG) labeled with $^{123}\text{I}$ (for diagnostic purpose) or $^{131}\text{I}$ (for therapy) has been applied for the treatment of advanced, chemorefractory high-risk neuroblastoma with promising results.
- After more than 20 years of clinical trials, the theranostic radiopharmaceutical $^{177}\text{Lu}$-DOTATATE has been approved by FDA and EMA with the trade name of Lutathera® for the treatment of progressive neuroendocrine tumors.
- Promising results have obtained for the management of castration resistant prostate cancer with the theranostic radiopharmaceuticals $^{68}\text{Ga}$-PSMA-11/$^{177}\text{Lu}$-PSMA-617.
- Molecular imaging with new PET probes (i.e. $^{89}\text{Zr}$-trastuzumab) represents a promising tool for patients’ selection and the monitoring of response to targeted non-radionuclide therapy.
1. Introduction

In ancient Roman mythology Janus Bifrons was the god of transitions and duality and, as a matter of fact, he was often depicted as having two faces looking in opposite directions, thus symbolizing the passage from past to future but also the capability of passing from a certain point of view to another one. According to this metaphoric meaning, the so-called “theranostic” discipline may be considered as the Janus Bifrons of the modern medicine, since it is the result of a successful combination of therapy and diagnostics with the aim to create a unique approach [1]. The term of “theranostics”, also referred to as “theragnostics”, was coined for the first time in the year 1998 by John Funkhouser, the CEO of PharmaNetics [2].

Although theranostics is involving a growing number of scientific disciplines, especially in the field of nanotechnology [3], this innovative medical approach is deeply connected with nuclear medicine. Radionuclide imaging, in fact, offers the unique opportunity to detect and quantify the expression of a specific tumor biomarker through the use of a certain radiopharmaceutical labeled with isotopes emitting radiations suitable for imaging and, subsequently, the same radiopharmaceutical can be labeled with a radionuclide emitting alpha or beta particles to obtain a tumoricidal effect [4]. In this scenario, the radioactive iodine ($^{131}$I) perhaps represents the oldest application of theranostics, since post thyroidectomy ablation of residual differentiated thyroid cancer (DTC) is based on the fact that thyroid follicular cells can incorporate $^{131}$I, which is both a gamma (i.e. diagnostics) and beta emitter (i.e. therapy) [5]. Thus, the same element can be used for the detection of iodine-avid residual thyroid tissue and for therapeutic purposes.

As specifically concerns the nuclear medicine contest, there are some radionuclides particularly suitable for theranostic approach, such as the already cited $^{131}$I, or luthetium-177 ($^{177}$Lu), since they are characterized by both gamma and beta emission. In other cases, different radioisotopes can be labeled to the same biomolecule, the former with diagnostic purpose and the latter for therapy. In the majority of cases, isotopes suitable for positron emission tomography (PET) imaging are
preferred in the diagnostic phase, since PET presents higher spatial resolution than conventional scintigraphy, also providing the opportunity of carrying out accurate quantitative information. As concerns the therapeutic counterpart, beta emitting radionuclides, such as yttrium-90 ($^{90}$Y) or $^{177}$Lu, are widely used, even though alpha-emitters, such as radium-223 ($^{223}$Ra) and actinium-225 ($^{225}$Ac), are emerging as useful potential tools [6].

In the panorama of personalized medicine, the theranostic approach aims to identify specific targets in patients in order to define customized pathways of therapy and also monitor the response to treatment. Targeted therapy represents a crucial role for the management of neuroendocrine tumors (NET) through the peptide receptor radionuclide therapy (PRRT) [7]. Furthermore, theranostics is providing promising results in patients affected by metastatic castration resistant prostate cancer (mCRPC) [8]. In the following, we will review the more consolidated applications of targeted imaging and therapy in nuclear medicine, also providing an overview of the more innovative applications that are moving the theranostic field forward. Table 1 summarizes the main manuscripts on the clinical application of theranostics.

2. Iodine therapy in differentiated thyroid carcinoma

As previously mentioned, radioactive iodine therapy (RAI) has represented the oldest example of theranostic approach to cancer. Iodine is an essential element for thyroid production of hormones thyroxine (T4) and triiodothyronine (T3). Two iodine radioisotopes are routinely used in nuclear medicine practice. The former is iodine-123 ($^{123}$I), that has a half-life of 13.22 hours and emits predominant energy of 159 keV and can be applied for obtaining high quality pre- and post-therapeutic imaging. The latter is the already cited $^{131}$I which presents the characteristics of both a beta ($\beta^-$, approximately 90% of the radiation, mean: 192 keV, mean tissue penetration: 0.4 mm) and gamma (approximately 10% of the radiation, mean: 383 keV) emitter. In 1946, the radionuclide $^{131}$I was successfully applied for the treatment of thyroid carcinoma. DTC includes malignancies originating from cells delimiting thyroid follicles with 3 well studied histotypes:
follicular (FTC), papillary (PTC) and Hurtle cell carcinoma (HTC) [9]. Surgery, especially total thyroidectomy, represents the first choice of treatment: in such a case, the optimal surgical approach takes into account several factors such as histology, disease extent and the presence of lymph node involvement. It is of crucial importance preserving the neighboring anatomical structures such as nerves and blood vessels [10].

Thyroidectomy is usually followed by the whole body scintigraphy (WBS) with radioactive iodine for the detection of the residual thyroid tissue after surgery and the eventual presence of iodine-avid metatastic disease. In particular, lymph nodes are the most frequent site of colonization, especially in case of PTC [11]. As specifically concerns the role of RAI as adjuvant therapy for ablating residual tissue after surgery, according to the guidelines of the American Thyroid Association (ATA) the choice of therapeutic radioactive iodine should be limited to subjects at intermediate and high risk [12]. Figure 1 depicts a case of high risk papillary thyroid carcinoma treated with $^{131}$I.

In case of RAI, a wide range of fixed doses has been extensively used in many centers over years as empirical approach for treatment of residual thyroid tissue or distant metastases [13]. Although this approach is easy to use and quite safe according to the majority of the published reports, it is strictly dependent on physician's expertise and personal rating of the most adequate dose to be administered. There are reports suggesting that the “fixed-dose” empirical approach might lead to an underestimation of the dose delivered to malignancy or to exceed the limiting safety dose [14, 15]. On the contrary, a personalized dosimetry is aimed to maximize the radiation burden delivered to the target thus reaching a lethal effect on tumor, contextually minimizing the adverse effects due to the unwanted irradiation of the non-target organs [16]. In particular, the use of the hybrid imaging with single photon emission tomography (SPECT) and computed tomography (CT) provided a significantly contribution for the localization of iodine-avid residual tissue in the thyroid bed after surgery or to disclose lymph node metastasis, with greater accuracy as compared to whole body scintigraphy [17].
2.1 Theranostics for iodine dosimetry

From a theranostic point of view, the imaging with $^{123}$I can be used for planning a personalized dosimetry for DTC patients to be treated with $^{131}$I. More recently, the isotope iodine-124 ($^{124}$I), which is a positron-emitting radionuclide with a half-life of 4.2 days, has been introduced for the PET imaging [18]. PET/CT scan with $^{124}$I can be exploited in order to perform a voxel-based dosimetry thus calculating the dose delivered to the target lesion and to the non-target parenchyma. Which is the optimal approach for the dose calculation in DTC is still a debated issue. In a retrospective study performed by Klubo-Gwiezdzinska et al. on 87 patients affected by DTC the empirical and the dosimetry-based approaches were compared: higher efficacy for dosimetry-based method with a similar safety profile compared to empiric one was found, thus supporting the rationale for employing individually prescribed activity in high-risk DTC patients [19]. The results obtained in the aforementioned study are in contrast with those reported by Deandreis and colleagues [20], who retrospectively evaluated 352 patients with iodine-avid metastatic DTC treated with $^{131}$I according to an empiric fixed activity of 3.7 (n = 231) or by personalized activity (2.7-18.6 GBq) based on whole-body/blood clearance (WB/BC) dosimetry (n = 121) with the primary endpoint of establishing difference in overall survival (OS) between the 2 groups. The authors did not find any significant difference in OS between the 2 groups, thus concluding that WB-based dosimetry did not provide significant contribution for improving survival in comparison with fixed-dose approach. Further studies are needed to better define the incremental value of the personalized dosimetry respect to the standard fixed-doses, especially as concerns the cost-effectiveness aspect [21].

3. Metaiodobenzylguanidine in neuroblastoma

Neuroblastoma (NB) represents the most common solid tumor in children, arising from the embryonic sympathoadrenal lineage of the neural crest, almost exclusively occurring in children. Although it is a relatively rare disease with an incidence of 1 case on 8000 live births, it accounts
for about the 13% malignancy-related death in pediatric patients [22]. Neuroblastoma can arise everywhere along the sympathetic system, but the most frequent localizations are represented by the sympathetic ganglia in abdomen and by the medullary portion of the adrenal glands. According to The Children’s Oncology Group (COG), NB is stratified in low, intermediate and high-risk on the basis of several biological and clinical factors [23]. Despite many advances in therapeutic approaches, prognosis in high-risk NB remains poor.

3.1 MIBG-based theranostics for imaging

In 1979 it has been synthesized a norepinephrine analogue, namely metaiodobenzylguanidine (MIBG), capable to be incorporated into sympathetic nervous cells. MIBG was firstly labeled with the nuclide $^{131}$I and successfully applied for the scintigraphic visualization of benign and malignant neoplasia of the adrenal medulla and of ectopic pheochromocytoma [24]. In 1984, Kimming and coworkers reported a case of 2.5 years-old girl, with an abdominal mass and clinical suspicion of NB, who was administered with $^{131}$I-MIBG and submitted to planar scintigraphy. The lesion showed intense incorporation of the radiopharmaceutical and biopsy, subsequently performed through laparotomy, was positive for undifferentiated NB [25]. Since then, MIBG has been labeled with $^{123}$I, which presents optimal physical properties for the scintigraphic imaging, and has been extensively used for the diagnosis and follow-up of children affected by NB [26]. In particular, the use of hybrid SPECT/CT was found to be of utmost importance in patients’ restaging after therapy, enabling an accurate localization of the lesions and providing additional information in the 39% of cases when compared to planar scintigraphy [27].

As concerns the imaging of NB with $^{123}$I-MIBG, it has to be pointed out that several semiquantitative score methods were proposed for standardizing the interpretation of the images acquired before and after therapy, among them the so-called Curie-score in which patient’s body is divided into several regions for each of whom a score ranging from 0 to 3 was assigned for defining the extent of the disease [28]. In a study including a large cohort of patients (n= 280) at stage 4,
Curie score was applied for the interpretation of the $^{123}$I-MIBG images at diagnosis, after induction chemotherapy and after an autologous stem cell transplantation [29]. The authors found that the Curie score presented high prognostic value in the management of children with NB; in particular those subjects with a score > 2 after the induction therapy were characterized by a poor prognosis.

3.2 MIBG-based theranostics for therapy

MIBG represents a radiopharmaceutical with clear theranostic implications, since it can be labeled both with $^{123}$I (for diagnosis) and $^{131}$I (for therapy). In patients candidate for treatment with $^{131}$I-MIBG, the pre-therapeutic imaging with $^{125}$I-MIBG plays the crucial role of demonstrating in vivo the avidity of NB for the radioligand. Of note, the biodistribution of the 2 radiotracers is almost identical with the exception of cerebellar uptake which was noted only for $^{131}$I-MIBG and not for $^{123}$I-MIBG [30]. Although $^{131}$I-MIBG was also used for the treatment of adult pheochromocytomas and paragangliomas, $^{131}$I-MIBG as a single agent or in combination with other drugs plays a major role for the treatment of children affected by relapsed or chemorefractory NB with response rate between 20% and 40% [31, 32]. $^{131}$I-MIBG was also successfully introduced as front-line therapy for the down-sizing of NB: a group of 44 patients affected by high-risk NB was administered with at least 2 cycles of $^{131}$I-MIBG with a fixed dose of 7.4 and 3.7 GBq, respectively, and then followed by surgery, if feasible, or by neoadjuvant chemotherapy and surgery, with an overall response rate of 73% [33].

3.3 MIBG-based theranostics for dosimetry

Furthermore, the diagnostic scan can be used for calculating patients’ dosimetry according to the formalism of the Medical Internal Dosimetry (MIRD) model on the basis of the maximum tolerable dose per patient’s body weight [34]. In this context, the introduction of MIBG labeled with the positron emitter $^{124}$I ($^{124}$I-MIBG) represents a very promising approach for an accurate voxel-based dosimetry through PET/CT technology [35].
5. Peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumors

Neuroendocrine tumors (NET) are rare malignancies with an incidence of 5.86/100,000 per year and prevalence in the female sex [36,37]. NET arise from the neuroendocrine cells with a prevalent involvement of the gastrointestinal tract (62%-67%) and the lung (22%-27%). At presentation the 12-22% of the subjects exhibits metastases, the liver being the most frequent site of colonization. NET are usually classified into G1, G2 and G3 according to the mitotic index [37]. Another crucial dichotomization concerns the categorization of NET into “functioning” and “non-functioning”. “Functioning” NET produce a variety of hormones such as insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP), serotonin, somatostatin, adrenocorticotropic hormone (ACTH), which can cause a wide spectrum of symptoms [38]. Surgery is the treatment of choice but it is not always feasible due to the advanced stage of presentation.

NET are characterized by the overexpression of receptors for the endogenous peptide somatostatin, which exerts a pleitropic inhibiting effect on hormone releasing, gastrointestinal motility and cellular growth [39]. Five subtypes of somatostin receptors (SSTRs 1-5) have been identified and belong to a distinct group within the superfamily of G-protein-coupled receptors with seven transmembrane domains. NET present high density of SSTRs 2, so the synthetic long-acting analogs octreotide and lanreotide were approved and extensively applied for the treatment of NET.

5.1 Theranostics for NET imaging

Pentetreotide, a synthetic chelated analog of somatostatin labeled with the radionuclide indium-111 (\(^{111}\text{In}\)), was introduced in clinical practice for the imaging of NET, since it presents high affinity for SSTRs 2 and lower affinity to SSTRs 3 and SSTRs 5, while not significant binding was reported for the other receptor subtype [40]. Scintigraphy with \(^{111}\text{In}\)-pentetreotide has represented for many years a very useful approach for the \textit{in vivo} demonstration of SSTRs in NET. More recently, three radiopharmaceuticals, labeled with the radionuclide gallium-68 (\(^{68}\text{Ga}\)) have been developed for PET
imaging of NET: $^{68}$Ga-DOTAPhe1-Tyr3-Octreotide (DOTATOC), $^{68}$Ga-DOTA-Nal3-Octreotide DOTANOC, and $^{68}$Ga-DOTA-Tyr3-octreotate (DOTATATE) [41]. PET technology has greater sensitivity and specificity than scintigraphy with $^{111}$In-pentetreotide and allows an accurate quantitative calculation and represents a single-day procedure [42].

5.2 Theranostics for NET therapy

The demonstration of SSTRs in NET opened the door to targeted radionuclide therapy based on the administration of synthetic analogs of somatostatin labeled with beta-emitting radioisotopes, especially $^{90}$Y and $^{177}$Lu. This theranostic approach is known as peptide radionuclide receptor therapy (PRRT). Lutathera® ($^{177}$Lu-DOTATATE) has been approved in January 2018 by Food and Drug Administration (FDA) and in September 2017 in Europe by European Medicines Agency (EMA) as the first radiopharmaceutical for PRRT in progressive gastroenteropancreatic NET. It consists in the administration of $^{177}$Lu-DOTATATE, fractioned in 4 cycles of fixed activity of 7.4 GBq at the interval of 8 weeks [43]. The approval of Lutathera® was preceded by a huge number of clinical studies aimed to assess the efficacy and safety of PRRT in the last 20 years.

The first experiences in PRRT started at the beginning of 90’s using Auger’s effect by administrating high activity of the same $^{111}$In-pentetreotide, but non satisfying results were obtained [44], since Auger electrons need to be extremely close to cellular nucleus to exert effects on DNA. $^{90}$Y-DOTATOC was introduced in clinical practice in the first clinical experiences with PRRT. This radiopharmaceutical was aimed to exploit the physical properties of $^{90}$Y (Emax: 2.27 MeV, range max: 11 mm, half-life: 64 h) in order to selectively irradiate NET overexpressing SSTRs 2, also taking into account the capability of this compound to hit not only the target cells but also the neighboring malignant tissue through the so-called “cross-fire” effect [45]. $^{90}$Y-DOTATOC was administered by intravenous injection and fractioned in several cycles up to the maximum administrable dose being the kidney the dose-limiting organ with a threshold of 25-27 Gy [45]. In order to reduce nephrotoxicity, patients were coinfused before and after the administration of the
radiocompound with positively-charged amino acids. More recently, $^{177}$Lu-DOTATATE has been synthesized and applied for PRRT in order to use the properties of $^{177}$Lu (Emax: 0.49 MeV, range max: 2 mm, half-life: 6.7 days), which is both a gamma and beta emitter, thus allowing post-therapy dosimetric studies [46]. PRRT with both $^{177}$Lu-DOTATATE and $^{90}$Y-DOTATOC provided a significant rate of objective response in NET with a tolerable profile of toxicity. In a large cohort of subjects (n = 807) submitted to PRRT between 1997 and 2003, Bodei et al. found that therapy with $^{90}$Y or $^{90}$Y plus $^{177}$Lu entailed a greater nephrotoxicity than the therapy with $^{177}$Lu alone, with hypertension, haemoglobin and platelet toxicity being reported as further adverse effects [47].

The cornerstone in PRRT studies has been represented by the phase 3 clinical trial NETTER-1 (https://clinicaltrials.gov/ct2/show/NCT01578239), whose results have been recently published [48]. In the cited research 229 patients affected by well-differentiated, metastatic midgut NET were randomly assigned to be treated with $^{177}$Lu-DOTATATE plus best supportive care consisting in octreotide long-acting repeatable (LAR) or to be administered with LAR alone at a dose of 60 mg every 4 weeks. The results of the trial showed that the estimated rate of progression-free survival at month 20 was 65.2% in the $^{177}$Lu-DOTATE group and 10.8% in the control group. Furthermore, the response rate was much higher in the former group (i.e. 18%) as compared to the group receiving only octreotide (i.e. 3%). Of note, grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia were registered in 1%, 2%, and 9%, respectively, of the subjects treated with $^{177}$Lu-DOTATATE. A further improvement in NET management will be achieved by combining imaging through PET/CT with $^{68}$Ga-DOTA-peptides and the data obtained from molecular NET transcriptomic analysis, namely NETest, in the perspective of a more and more personalized approach to therapy. In a recent paper published by Malczewska and colleagues, a concordance between NETest with imaging was evaluated: NETest was 92% concordant with anatomical imaging (CT/MRI), 94% with $^{68}$Ga-DOTA-peptides PET/CT and 96% with dual modality (CT/MRI and PET/CT) [49]. Figures 2 and 3 show clinical cases of NET patients treated with PRRT.
6. Castration Resistant Prostate Cancer

Prostate cancer (PC) represents one of the most common malignancies in men and a leading cause of death due to cancer in males [50]. The first line treatment of PC is represented by surgery, when feasible, or by ablative radiotherapy. Since PC is a hormone-dependent malignancy, androgen deprivation therapy (ADT) is widely used for treating patients with advanced disease and also for those subjects with localized disease but at high-risk of relapse. In case of PC progression in spite of ADT the disease is defined as castration resistant prostate cancer (CRPC) [51], which represents an aggressive status and a therapeutic challenge for physicians. The management of PC has been deeply changed by the introduction in screening of the prostate specific antigen (PSA), which is an androgen-regulated serine protease produced by both prostate epithelial cells and prostate cancer. The routine use of PSA test in clinical practice led to an increased detection of patients at an early stage and a significant improvement in survival [52].

6.1 PSMA-targeted imaging

The first attempts for the targeted imaging of PC were represented by the introduction of the radiolabeled monoclonal antibody (MoAb) \(^{111}\)In-capromab pendetide, also known as ProstaScint® (Cytogen Corporation, Princeton, NJ), capable of efficiently binding to an intracellular epitope (N-terminus) of the prostate-specific membrane antigen (PSMA) molecule [53]. \(^{111}\)In-capromab resulted useful in several clinical settings, particularly in those subjects with suspicion of disease relapse after prostatectomy or radiotherapy. In a large cohort of 183 men who had undergone surgery and with increasing values of PSA, immunoscintigraphy was able to disclose recurrence in the 60% of cases [54]. It has to be highlighted that conventional scintigraphic imaging (planars and SPECT) presents limited spatial resolution, but this drawback can be partially overcome by using hybrid SPECT/CT system [55]. In this regard, Kimura et al. demonstrated the usefulness of SPECT/CT for the detection of seminal vesicle invasion in recurrent prostate cancer after primary in situ therapy: in 59 subjects who biochemically failed primary in situ treatment, SPECT/CT with
111In-capromab, as compared to the results of biopsy, presented a sensitivity, specificity, positive predictive value, and negative predictive value of 37.5%, 88.2%, 33.3%, and 90.0% respectively [56].

The promising results obtained using 111In-capromab in diagnostics triggered the research for its therapeutic counterpart: in a phase I study, Deb and colleagues used the 90Y-CYT-356, a MoAb directed against the same epitope recognized by capromab, for the radioimmunotherapy (RIT) of 12 patients affected by metastatic CRPC [57]. Of note, none of the enrolled subjects obtained a complete or partial response. The main limitation of 111In-capromab was represented by its capability of binding only to an intracellular portion of PSMA. Furthermore, the use of MoAbs in imaging and therapy arise issue due to their immunogenicity [58].

A turning point in PC theranostics was achieved by the development of 68Ga-labeled PSMA HBED-CC, namely PSMA-11, which belongs to the category of PSMA-inhibitors and is able of binding to the extracellular portion of PSMA with satisfying characteristic of clearance and biodistribution [59]. Although several PSMA-inhibitors have been introduced in clinical practice, the aforementioned 68Ga-PSMA-11 is currently the most diffuse radiopharmaceutical for PET imaging. In a retrospective analysis on 1007 patients submitted to PET/CT with 68Ga-PSMA-11, this imaging approach was able to detect at least one lesion with characteristics suggestive of recurrent PC in the 79.5% of the examined subjects [60]. In a recently published paper, the clinical impact of PET/CT with 68Ga-PSMA was evaluated in a cohort of 431 patients with prostate cancer from 4 Australian centers [61]. In such cases, the results of PET/CT was capable to change the planned management in the 51% of patients, with greater impact in the group of subjects presenting biochemical failure after definitive surgery or radiation treatment (62% change) than in those undergoing primary staging (21% change).

6.2 PSMA targeted therapy
As concerns the therapeutic aspects, it has to be pointed out that CRPC is an aggressive disease, with limited treatment options including chemotherapy, hormonal treatment with enzalutamide/abiraterone or the most recently introduced cellular therapy (sipuleucel-T). In case of patients with symptomatic bone metastases, the alpha-emitter radiopharmaceutical $^{223}$Radium-dichloride (Xofigo®) has been recently introduced in the clinical practice after the promising results obtained from the registrative clinical trial ALSYMPCA [62, 63]. However, $^{223}$Radium-dichloride is not adequate for treating CRPC patients with visceral metastases, since its action is limited only to the skeletal lesions.

In this scenario, the introduction of the theranostic radiopharmaceutical $^{177}$Lu-PSMA-617 has provided a potentially useful new tool for the management of CRPC subjects through the so called radioligand therapy (RLT). In a German multicentric study including 145 patients with metastatic CRPC treated with RLT between February 2014 and July 2015 through 1-4 therapy cycles and an activity range of 2-8 GBq per cycle [64], the authors reported an overall biochemical response rate of 45% after all the scheduled cycles, with a tolerable toxicity profile. Of note, in a paper published by Ferdinandus et al., the grade of $^{68}$Ga-PSMA uptake measured as SUVmax was found not to be a significant predictor of response in patients with CRPC submitted to RLT, most probably due to the fact that more aggressive lesions, thus characterized by a more severe prognosis, express higher PSMA levels [65]. In a retrospective study by Rahbar et al., the response to RLT was evaluated in 71 patients who had received 3 cycles of $^{177}$Lu-PSMA-617 every 8 weeks. In such cases, a PSA decline ≥50% and some PSA decline was registered in 56% and 66% of the patients, with a relevant number of subjects showing delayed response, even if they did not respond to the first cycle of the therapy [66]. In a recently published prospective, single-arm study performed by Yadav and coworkers, the efficacy and safety of RLT with $^{177}$Lu-PSMA-617 was assessed in 90 subjects with metastases from CRPC in progression after chemotherapy or 2nd line hormone treatment [66]. All the subjects underwent PET/CT with $^{68}$Ga-PSMA to be enrolled for RLT. At 2- to 3-month interval after the 1st therapy and at the end of the assessment, a significant decline in PSA was registered in
32.2% and 45.5%, respectively, while the disease control rates according to the radiographic and PET response criteria were 77% and 71%.

The aforementioned researches suggest a possible role for RLT in managing patients with CRPC, but further studies with larger series are needed. In this context, the ongoing phase 3 clinical trial VISION (https://clinicaltrials.gov/ct2/show/NCT03511664) will be helpful to this aim: the primary objective of this study is to compare progression free survival (PFS) and OS in subjects with progressive PSMA-positive CRPC who will receive $^{177}$Lu-PSMA-617 in addition to best supportive/standard of care versus those subjects who are treated with best supportive/best standard of care alone.

7. Radioembolization of Hepatic Tumors

Selective internal radiation therapy (SIRT) also known as transarterial radioembolization (TARE) consists in a loco-regional approach to primary and secondary hepatic tumors. The rationale of this therapy is based on the unique vascularization of liver that receives blood from both the hepatic artery and the portal vein. It has been demonstrated that hepatic malignancies are mainly vascularized by the hepatic artery and its branches, while non-neoplastic parenchyma is primarily supplied by the portal system [67]. In SIRT/TARE, the beta-emitter radionuclide $^{90}$Y, embedded in resin or glass microspheres, is injected directly into the blood flow through a catheter placed in the hepatic artery. As a matter of fact, two distinct devices are currently available for $^{90}$Y-radioembolization, the former based on glass microspheres (TheraSphere, Biocompatibles UK Ltd., Farnham, United Kingdom) and the latter consisting in resin microspheres (SIR-Spheres; Sirtex Medical Ltd, Australia) [68]. It is worth mentioning that, although the 2 kinds of microspheres (i.e. glass and resin ones) present different physico-mechanical and activity properties, they were found to have similar efficacy in clinical trials [69].
Before enrolling patients for TARE, it is recommended that an initial angiography is performed to evaluate the anatomy of the mesenteric system and the hepatic arterial bed. Once the injection site has been identified, the $^{90}$Y- procedure is simulated through a scintigraphy with $^{99m}$Tc-macroaggregated albumin ($^{99m}$Tc-MAAs), in which an activity (i.e. 150–200 MBq) of $^{99m}$Tc-MAAs is intra-arterially injected into the arterial branch selected for the treatment. Although $^{99m}$Tc-MAAs have similar but not identical physical-chemical properties as compared to resin or glass microspheres, several published reports indicate that $^{99m}$Tc-MAAs may be considered an acceptable surrogate marker of $^{90}$Y-microspheres and are routinely used to simulate their distribution to the liver, lungs and gastrointestinal tract [70]. The use of $^{99m}$Tc-MAAs as predictive biomarker in TARE was supported by several evidences. In particular, Garin and colleagues calculated, using a quantitative analysis of the SPECT/CT exam, the tumor dosimetry and non-tumor dosimetry in 36 patients affected by HCC, sixteen of whom characterized by portal vein tumor thrombosis (PVTT), submitted to TARE with glass microspheres [71]. Of note, the authors found that the dose delivered to the tumor was the only parameter associated with response on multivariate analysis, with the uptake of $^{99m}$Tc-MAAs along PVTT being a strong predictor of response. However, in order to achieve a personalized approach to TARE several factors have to be taken into account, paying particular attention to tumor biology, aggressiveness and immunological environment [72, 73]. Figure 4 depicts an example of theranostic approach to TARE/SIRT in a HCC patient treated with resin-microspheres.

More recently, poly (l-lactic acid) microspheres loaded with holmium-166 ($^{166}$Ho-PLLA-MS) have been developed [74]. $^{166}$Ho presents favorable characteristics for theranostics with emission of both beta-particles (1.77 MeV) and gamma rays (80.57 keV) and has a half-life of 26.8 h [75]. While the beta-emission can be exploited for therapeutic purposes, the photon emission can be used for scintigraphic imaging and dosimetric analysis. Furthermore, $^{166}$Ho presents paramagnetic characteristic so that $^{166}$Ho-PLLA-MS can be successfully imaged with magnetic resonance (MRI), also for dosimetric purposes [76]. In the phase 1 HEPAR trial
15 subjects with liver metastases were treated with intra-arterial $^{166}$Ho-radioembolization at whole-liver doses of 20 Gy (n=6), 40 Gy (n=3), 60 Gy (n=3), and 80 Gy (n=3). In subjects receiving 80 Gy, dose-limiting toxicity occurred in 2 patients: grade 4 thrombocytopenia, grade 3 leucopenia, and grade 3 hypoalbuminaemia in one patient, and grade 3 abdominal pain in another patient [77]. Thus, the maximum tolerated dose was established at 60 Gy for the whole liver. On this path, the ongoing phase 2 HEPAR PLUS trial (https://clinicaltrials.gov/ct2/show/NCT02067988) might be useful to better assess the clinical usefulness of $^{166}$Ho-PLLA-MS in clinical practice. The study is aimed to assess tumor response, complete and partial response according to RECIST 1.1, and toxicity in 30–48 patients with >3 measurable liver metastases according to RECIST 1.1. The included subjects will receive additional $^{166}$Ho-RE within 20 weeks after the 4th and last cycle of PRRT with 7.4 GBq of $^{177}$Lu-DOTATATE.

8. **PET imaging for personalized non-radionuclide targeted therapy**

Beyond the theranostic applications based on the clinical use of radionuclide pairs (diagnostic/therapeutic), theranostics also consist in the detection of specific biomarkers (i.e. receptors, transporters), that can be successfully exploited for targeted therapy. As specifically concerns breast cancer (BC), in the past years many advances have been made for the identification of several molecular targets linked to specific tumor biology and behaviour, such as human epidermal growth factor 2 (HER-2), hormone receptors, gastrin releasing peptide receptor (GRPR), folate receptor (FR) etc [78]. In particular, 16alpha-[(18)F]fluoroestradiol-17beta ($^{18}$F-FES) has been applied for the PET detection of estradiol receptor (ER) in patients affected by advanced BC. In a study performed by Dehdashti et al., a cohort of 51 post-menopausal women with advanced estrogen-receptor positive BC was submitted to PET/CT scan with $^{18}$F-FES before treatment with estradiol, among the enrolled subjects, seventeen responded and 31 did not respond to hormone therapy [79].
Of note, responders showed higher SUV values in tumors than non-responders, thus suggesting that PET with $^{18}$F-FES may present a predictive value on the response to hormone therapy.

Another molecular target of utmost importance for the management of BC is represented by HER-2. The HER family includes transmembrane proteins that activate intracellular signaling pathways in response to extracellular signals. The amplification of the HER2 gene has been found correlated with more aggressive tumors, characterized by high rate of proliferation and poor prognosis [80]. In patients submitted to anti-HER-2 therapy, the detection of HER-2 expression is of crucial importance to select those subjects who are more likely to benefit from the aforementioned treatments. In particular, trastuzumab (Herceptin; Genentech, South San Francisco, CA) represented the first humanized MoAb approved by FDA for the treatment of HER-2 positive BC. Trastuzumab, binding to the extracellular domain of HER-2, proved able to suppress tumor growth and proliferation through different mechanisms. Beyond trastuzumab, other drugs targeting HER-2 have been subsequently introduced such as pertuzumab (Perjeta; Genentech, South San Francisco, CA) and trastuzumab emtansine (T-DM1), in which trastuzumab is linked with DM-1, a potent inhibitor of microtubule polymerization [81].

However, it has been highlighted that many patients, initially responding to anti HER-2 therapy, became resistant during treatment mainly due to the loss of HER-2 expression. To identify the loss of HER-2 in patients undergoing targeted therapy, repeated biopsies are necessary. In this scenario, the imaging of HER-2 status before and during targeted therapy would be of utmost importance not only for patients’ selection but also for the early identification of acquired resistance, in order to promptly switch non-responders to more effective treatment and also avoiding the need for repeated biopsies. To this aim, trastuzumab has been labeled with the radionuclide Zirconium-89 ($^{89}$Zr) that is characterized by good spatial resolution and has a half-life of 3.27 days [82]. The long physical half-life of $^{89}$Zr makes this isotope particularly suitable to match antibodies biological half-life. The conjugation of $^{89}$Zr with the MoAb is achieved through a specific chelator, namely desferrioxamine-
B (DFO) [83]. In this regard, it is worth mentioning the ZEPHIR trial, a multicenter study that enrolled patients from Belgium and the Netherlands [84]. The authors included 56 women, affected by metastatic BC positive for HER-2 at immunoist ochemistry or in situ hybridization, who underwent PET/CT scan with $^{89}$Zr-trastuzumab before being submitted to T-DM1. Of note, PET with $^{89}$Zr-trastuzumab identified HER2-positive lesions in 39 patients, twenty-eight of whom showed response to the T-DM1 treatment. Further studies with larger cohorts are needed to validate the use of PET with $^{89}$Zr-trastuzumab as theranostic imaging agent in metastatic BC.

Epidermal Growth Factor Receptor (EGFR) is another biomarker of utmost importance for targeted therapy. EGFR aberrant activation or expression has been documented in many epithelial malignancies such as colorectal and lung cancer. In this context, molecular imaging with SPECT or PET probes plays a critical role for the \textit{in vivo} identification of EGFR expression in metastases. However, radiolabeled MoAbs such as $^{64}$Cu-DOTA-cetuximab and $^{111}$In-DOTA-cetuximab present several limitations [85]. In this specific field, an innovative approach based on the aptamer technology holds the promise to provide a useful tool for the \textit{in vivo} imaging of EGFR status [86].

9. Conclusions

Theranostics in nuclear medicine is aimed to combine diagnostic and therapy though the utilization of the same molecule (or molecules as similar as possible) which are either labeled with different radionuclides or with an identical radionuclide used at different dosage. This therapeutic approach is deeply connected with the concept of personalized medicine [87] and is focused not so much on the disease, but rather on the patient considered according to the Latin word “\textit{persona}” which, in turn, derives from the Greek word “πρόσωπον” (prosopon). Worthy of note, in the Greek ancient theater, the term “πρόσωπον” was also used to mean the “mask” that the actor was used to wear on his face to interpret a certain character and symbolize a specific emotional status to the audience. In this “patient-centered” vision, theranostics is aimed to disclose the “πρόσωπον” of the disease, thus providing precious information about the presence and biodistribution of specific targets in order to
achieve a customized treatment on patient's specific characteristics (i.e. receptor or transporter expression/ genomic profiling/ immunological setting etc...). Further studies are needed to better understand how much this innovative approach will be able to improve patients’ quality of life, also as concerns the cost/effectiveness issues.

10. Expert Opinion

In the early days of the “theranostic era”, priority lies in combining technological and cultural improvements. In particular, a continuing technological updating of SPECT/CT and PET/CT devices is of utmost importance for achieving a sensitive detection of imaging biomarkers and providing accurate quantitative data, as well as for personalized dosimetric purposes. In this context, the new digital PET/CT device is expected to move the field forward. In a recently published retrospective study, a group of 88 patients with PC who underwent digital PET/CT (dPET/CT) with $^{68}$Ga-PSMA-11 were matched for clinical parameter with another cohort of 88 subjects examined with the same radiopharmaceutical but through analogic PET/CT (aPET/CT) [88]. The authors found out that dPET/CT was able to detect a significantly higher number of lesions as compared with aPET/CT, especially in subjects with low PSA value.

It has to be kept in mind that theranostics is a revolutionary approach and represents a unique opportunity for nuclear medicine. In this context, a paradigm shift is needed in which nuclear medicine has to place itself in the crossroads between therapy and imaging. To date, the educational training in nuclear medicine is mainly focused on the diagnostic and technological counterpart, with particular emphasis on hybrid PET/CT and SPECT/CT imaging. The nuclear medicine community has to make an effort to improve its clinical culture and multidisciplinary participation in the perspective of being not a passive audience, but rather an active promoter of the ongoing “theranostic revolution” [89].

9.1 Five-year view
Radiopharmacy is a field that is expected to rapidly evolve in the next few years. In this respect, the radionuclide copper-64 (\(^{64}\text{Cu}\)) is gaining more and more attention in the scientific community. Copper is an essential element in many metabolic processes involving cell differentiation, metabolism and growth. Furthermore, human copper transporter 1 (CTR1), a transmembrane protein responsible for copper intracellular incorporation, was found to be overexpressed in many malignancies. \(^{64}\text{Cu}\) is a cyclotron-produced radionuclide with an intermediate half-life (12.7 h) that decays by both positronic and beta-particles emission, making it suitable for theranostic applications. The radiopharmaceutical \(^{64}\text{CuCl}_2\), a substrate for CTR1, is under investigation with promising results as a potential theranostic agent in several pre-clinical and clinical trials regarding tumors such as melanoma or prostate cancer [90,91].

It has to be pointed out that the implementation of alpha-emitters in theranostics is another field which is rapidly moving towards. Actually, as concerns the targeted alpha therapy (TAT) the only radiopharmaceutical approved for clinical use is represented by the already cited \(^{223}\text{Ra-dichloride [62]. Although they are characterized by a shorter range of penetration in comparison with beta-particles, alpha-emitters present several interesting characteristics such as their capability of producing double-strand breaks of DNA, severe chromosomal damage such as shattered chromosomes at mitosis and complex chromosomal rearrangements, destruction of tumoral cells independently of oxygenation, and the potential to overcome resistance against beta-emitters [92]. TAT with \(^{213}\text{Bi-DOTATOC is providing preliminary encouraging results for the treatment of NET resistant to }^{177}\text{Lu-DOTATATE [93]. Furthermore, RLT with }^{225}\text{Ac-PSMA-617 is under evaluation for the management of subjects with CRPC as an alternative approach to }^{177}\text{Lu-PSMA-617 [94]. However, well-designed multicenter studies with larger cohorts are needed to further assess the clinical impact of TAT in the theranostic field, especially as concerns the incidence of toxicity and adverse events [95].}
Lastly, theranostic developments will trigger research for new biomarkers and probes. In this regard, the already mentioned EGFR represents a very interesting target for innovative theranostic approaches. In such a field, the new technology of aptamers has been introduced. Aptamers are single-stranded DNA/RNA oligonucleotides that can be obtained from the systematic evolution of ligands by exponential enrichment (SELEX) technology [96]. Aptamers are reported to be highly specific for the target and characterized by low immunogenicity. As specifically regards EGFR, it has been recently developed a $^{18}$F-labeled RNA aptamer which showed highly selective targeting ability in mouse tumor models expressing different levels of EGFR. Although this approach needs to be validated by further studies, it is reasonable to hypothesize that it will represent an expanding field of research for theranostics in the future [97].

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Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.
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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers

1. Ahmadzadehfar H, Essler M. It is time to move forward into the era of Theranostics. EJNMMI Res. 2018;8:9.


- Interesting study demonstrating the clinical usefulness of hybrid SPECT/CT for the accurate detection of iodine-avid sites after radioiodine therapy.


- Retrospective study with a large cohort demonstrating the substantial equivalence between whole body dosimetry and fixed doses as concerns patients’ survival after radioiodine therapy.


• Retrospective study highlighting the usefulness of hybrid imaging in clinical practice.


• Very interesting study introducing a score for standardizing MIBG scan interpretation after therapy.


• Very useful and complete review on the biological basis and clinical application of MIBG.


• Interesting report on the potential usefulness of the PET tracer 124I-MIBG for personalized dosimetry.


- Retrospective study concerning the usefulness of 68Ga-DOTANOC PET for the assessment of response in NET liver metastases treated with 90Y-microspheres.


- Complete review on the clinical studies performed with 177Lu-DOTATATE and 90Y-DOTATOC.


- Clinical study with a large cohort assessing the clinical usefulness and the toxicity of 177Lu-DOTATATE.

Very interesting clinical study assessing the tolerability of PRRT performed with different radiopharmaceuticals.


This cornerstone study demonstrated that patients affected by progressive NET who were treated with PRRT had a significantly longer progression free-survival than those receiving the best standard of care.


- Clinical retrospective study with a large cohort of patients demonstrating the clinical usefulness of PET/CT with 68Ga-PSMA in the clinical setting of recurrent prostate cancer.


- Multicentric clinical study demonstrated that radioligand therapy is capable to obtain response in the 45% of the enrolled subjects.


Legend to Figures

**Figure 1.** (A) $^{131}$I whole body of a 40 years old woman submitted to radioiodine therapy for a differentiated thyroid carcinoma, which had been previously treated with thyroidectomy (histology was positive for papillary carcinoma, pT2pN1b): the images clearly show residual tissue in the cervical anterior region (black arrow). Thyroglobulin level was 20 ng/mL. (B) $^{131}$I whole body acquired 8 months after radioiodine therapy (3700 MBq) aimed to ablate residual thyroid tissue: no sites of pathological uptake are evident, but only physiological iodine retention in nasal mucosa and intestine. Thyroglobulin level was 0.2 ng/mL.

**Figure 2.** (A) pre-treatment whole body with $^{111}$In-pentetreotide in a 62 years old woman with advanced gastrointestinal NET: high uptake of the radiopharmaceutical is well evident in the hepatic metastases (black arrow). (B) whole body with $^{111}$In-pentetreotide acquired 1 month after the completion of 4 cycles of PRRT with Lutathera®, demonstrates regression of some treated lesions.

**Figure 3.** (A) pre-treatment contrast enhanced CT in a patient affected by well differentiated NET located in the pancreatic tail (white arrow). (B) pre-treatment SPECT with $^{111}$In-pentreotide shows a focal area of highly increased tracer uptake corresponding to the pancreatic lesion (triangulation). (C) SPECT with $^{111}$In-pentetretide acquired 1 month after the completion of 4 cycles of PRRT with Lutathera®, demonstrates an impressive regression of the pancreatic tumor (triangulation).

**Figure 4.** Theranostic approach in TARE/SIRT in a 72 years old woman affected by HCC. (A) CT axial slice demonstrates a large area of enhancement corresponding to the hepatic tumor located in the IV segment. (B) Angiogram shows an area of contrast enhancement corresponding to the tumor (black arrow). (C) Pre-treatment SPECT/CT acquired after the selective administration of $^{99m}$Tc-MAAs depicts tracer deposition within the hepatic lesion. (D) PET/CT acquired on $^{90}$Y-positronic photopeak after administration of SIR-spheres® demonstrates satisfying tumor targeting, although some differences between the pre-therapeutic distribution of the $^{99m}$Tc-MAAs and the post-treatment location of the $^{90}$Y-microspheres are visible. Pre-treatment level of alphafetoprotein (AFP) was 115 ng/mL, AFP level 4 weeks after TARE/SIRT results 5 ng/mL.
### Table 1. Summary of the main manuscripts on the applications of theranostics in clinical practice

<table>
<thead>
<tr>
<th>References</th>
<th>Year of publication</th>
<th>Type of study</th>
<th>Theranostic Radiopharmaceuticals</th>
<th>Patients</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al.</td>
<td>2018</td>
<td>Retrospective study</td>
<td>$^{131}$I-MIBG</td>
<td>170</td>
<td>Hybrid SPECT/CT is capable to significantly improve the imaging of high risk neuroblastoma, also impacting on clinical management.</td>
</tr>
<tr>
<td>Zilioli et al.</td>
<td>2017</td>
<td>Prospective study</td>
<td>$^{131}$I-MIBG</td>
<td>365</td>
<td>Hybrid SPECT/CT resulted superior to whole body planar scan for the detection of iodine-avid sites after radiiodine therapy.</td>
</tr>
<tr>
<td>Deandreis et al.</td>
<td>2017</td>
<td>Retrospective, multicenter study</td>
<td>$^{131}$I-MIBG</td>
<td>352</td>
<td>Whole body dosimetry provided no significant advantage in overall survival as compared to fixed doses in radiiodine therapy.</td>
</tr>
<tr>
<td>Afshar-Oromieh et al.</td>
<td>2017</td>
<td>Retrospective study</td>
<td>$^{68}$Ga-PSMA-11</td>
<td>1007</td>
<td>PET with $^{68}$Ga-PSMA detects with high accuracy recurrent prostate cancer</td>
</tr>
<tr>
<td>Rahbar et al.</td>
<td>2017</td>
<td>Multicenter clinical study</td>
<td>$^{177}$Lu-PSMA-617</td>
<td>145</td>
<td>In patients with castration resistant prostate cancer, RLT was found to provide response in 45% of the enrolled patients.</td>
</tr>
<tr>
<td>Strosberg et al.</td>
<td>2017</td>
<td>Prospective, randomized, controlled trial</td>
<td>$^{177}$Lu-DOTATATE</td>
<td>229</td>
<td>Patients affected by progressive NET who were treated with $^{177}$Lu-DOTATATE had a significantly longer progression free-survival than those receiving the best standard of care.</td>
</tr>
<tr>
<td>Filippi et al.</td>
<td>2016</td>
<td>Retrospective, single center</td>
<td>$^{68}$Ga-DOTANOC</td>
<td>15</td>
<td>The study demonstrated the high accuracy of $^{68}$Ga-PSMA in prostate cancer detection and the association between detection rate and PSA levels</td>
</tr>
<tr>
<td>Gebhart et al.</td>
<td>2016</td>
<td>Prospective, multicenter</td>
<td>$^{89}$Zr-trastuzumab</td>
<td>56</td>
<td>The authors evaluated the feasibility of a personalized dosimetry for $^{131}$I-MIBG based on a 4-time point PET/CT imaging.</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>2015</td>
<td>Feasibility study</td>
<td>$^{124}$I-MIBG/$^{131}$I-MIBG</td>
<td>1</td>
<td>The authors demonstrated that PRRT with $^{177}$Lu-DOTATATE is tolerated better than that with $^{89}$Zr-DOTATOC or with the cocktail $^{177}$Lu$^{90}$Y.</td>
</tr>
<tr>
<td>Boidei et al.</td>
<td>2015</td>
<td>Retrospective, single center</td>
<td>$^{90}$Y-DOTATOC/$^{177}$Lu-DOTATATE</td>
<td>807</td>
<td>The study demonstrated the high accuracy of $^{177}$Lu-DOTATATE in prostate cancer detection and the association between detection rate and PSA levels</td>
</tr>
<tr>
<td>Afshar-Oromieh et al.</td>
<td>2014</td>
<td>Retrospective analysis</td>
<td>$^{68}$Ga-PSMA-11</td>
<td>319</td>
<td>Radioembolization with $^{188}$Ho-microspheres were found effective and safe for treating hepatic tumors.</td>
</tr>
<tr>
<td>Smits et al.</td>
<td>2012</td>
<td>Phase I clinical study</td>
<td>$^{188}$Ho-microspheres</td>
<td>15</td>
<td>Large clinical study assessing the clinical impact of $^{177}$Lu-DOTATATE in patients with NET.</td>
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<tr>
<td>Kwekkeboom et al.</td>
<td>2005</td>
<td>Clinical study</td>
<td>$^{111}$In-pentetreotide/$^{177}$Lu-DOTATATE/$^{131}$I-MIBG</td>
<td>131</td>
<td>$^{131}$I-MIBG therapy in neuroblastoma provided response in 39% of patients but hematological toxicity was registered.</td>
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<td>Howard et al.</td>
<td>2005</td>
<td>Clinical study</td>
<td>$^{131}$I-MIBG</td>
<td>28</td>
<td>The paper discusses the pros and cons of the 2 major approaches to dosimetry in radioactive iodine therapy for differentiated thyroid carcinoma.</td>
</tr>
<tr>
<td>Van Nostrand et al.</td>
<td>2002</td>
<td>Review</td>
<td>$^{131}$I-MIBG</td>
<td>N.A.</td>
<td>The authors elaborated a score for standardizing the comparison of MIBG scan in high risk neuroblastoma treated with chemotherapy.</td>
</tr>
<tr>
<td>Ady et al.</td>
<td>1995</td>
<td>Prospective, single study</td>
<td>$^{125}$I-MIBG</td>
<td>27</td>
<td>PET: positron emission tomography; SPECT: single photon emission tomography; MIBG: metaiodobenzylguanidine; PRRT: peptide radionuclide receptorial therapy; PSMA: prostate specific membrane antigen;</td>
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