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Targeted Radionuclide Therapy: An Evolution Toward Precision Cancer Treatment

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Abstract

Objective—This article reviews recent developments in targeted radionuclide therapy (TRT) approaches directed to malignant liver lesions, bone metastases, neuroendocrine tumors, and castrate-resistant metastatic prostate cancer and discusses challenges and opportunities in this field.

Conclusion—TRT has been employed since the first radioiodine thyroid treatment almost 75 years ago. Progress in the understanding of the complex underlying biology of cancer and advances in radiochemistry science, multimodal imaging techniques including the concept of "see and treat" within the framework of theranostics, and universal traction with the notion of precision medicine have all contributed to a resurgence of TRT.

Keywords

cancer; precision; radionuclide; therapy

Precision medicine depends on identification and use of relevant biologic targets for optimized therapeutic efficacy with the goal of improving patient outcome and diminishing toxicity compared with nontargeted approaches. The rapid pace of advances in the understanding of the complexities of cancer biology has provided unprecedented opportunities for targeted therapies, which are increasingly finding their way into more effective cancer treatment regimens. The targeted approach also allows therapies to be adapted to tackle the temporal evolution of cancer biology and refined in response to various factors including host changes in the tumor microenvironment and stresses from prior and ongoing treatments. Multitargeted approaches may allow even higher therapeutic efficacy through synergism of attacking cancer via multiple pathways and lessening the ability of tumor to adapt.

Targeted radionuclide therapy (TRT) delivers energetic particles (auger, beta, alpha) in close proximity to tumor deposits that are preferentially selected on the basis of specific biologic features [1–3]. The first application of TRT occurred nearly 75 years ago with the use of radioiodine in thyroid disorders including cancer. Since then, many other agents and conditions have employed the TRT concept, including treatments for bone pain palliation;

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radioimmunotherapy with radiolabeled anti-CD20 monoclonal anti-bodies for relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin lymphoma (e.g., ^{90}Y-inbritumomab tiuxetan, ^{131}I-tositumomab); and radiolabeled metaiodobenzylguanidine in patients with neuroblastoma, paraganglioma, and pheochromocytoma. Numerous excellent articles have been published on these topics [4–10]. More recently, TRT has had a resurgence with growing interest in exploring how various new TRT approaches fit the therapeutic algorithm of cancer. A major contributor has also been the progress with theranostics that couples diagnostic imaging with targeted therapy (the “see and treat” approach). This article briefly reviews recent developments in TRT approaches directed to malignant liver lesions, bone metastases, neuroendocrine tumors (NETs), and metastatic castration-resistant prostate cancer (CRPC) and discusses challenges and opportunities in this exciting and growing field.

Selective Internal Radioembolization of Malignant Liver Lesions

Primary and metastatic liver lesions receive preferential arterial supply from the hepatic arteries, which can be used as conduits for delivery of highly localized radiation treatment. The technique may be combined with concomitant radiosensitizing chemotherapy to shrink lesions that may then become amenable to surgical resection [11]. The toxicity to normal hepatic tissues is limited because these tissues are primarily supplied by the portal venous system. Intraarterial delivery of microsphere therapy has been shown to be safe and effective in a variety of settings [12–28]. Examples include candidates for liver transplant, unresectable hepatocellular carcinoma (HCC) even with concurrent portal vein thrombosis, unresectable or recurrent cholangiocarcinoma, and liver-dominant metastases from colorectal cancer, breast cancer, renal cell carcinoma, pancreatic cancer, melanoma, and NETs even if tumors have been heavily pretreated.

Uliel and colleagues [29] performed an excellent review of the therapy procedure including specifics of commercially available microspheres. SIR-Spheres (Sirtex Medical) are nondegradable pure β-emitter ^{90}Y-loaded resin microspheres ranging from 20 to 60 μm in diameter with specific activity of 50 Bq per microsphere. TheraSpheres (Nordion) are ^{90}Y-assimilated glass microspheres ranging from 20 to 30 μm in diameter with specific activity of 2500 Bq per microsphere. The range of microsphere diameters is similar to that of ^{99m}Tc-macroaggregated albumin (MAA), which is used for pretreatment planning.

Selective internal radiation therapy (SIRT) of malignant liver lesions is a multidisciplinary process with coordinated activities of interventional radiology and nuclear medicine services. Pretreatment planning is needed for vascular mapping followed by ^{99m}Tc-MAA hepatic perfusion delineation and pulmonary shunt calculation. As described by Uliel et al. [29], the aims of pretreatment angiography are to map the relevant regional arterial supply, identify potential vascular variants, and perform prophylactic embolization of selected vessels as needed to avoid subsequent radioembolization of nontargeted tissues with its associated radiotoxicity (Fig. 1). Procedural complications with vascular mapping are rare [30]. Hepatic perfusion imaging is performed with 99mTc-MAA (5 mCi in sterile normal saline) at the time of pretreatment vascular mapping to allow detection of particles shunted

to the lung through unrecognized collateral vessels or intratumoral neovascular arteriovenous connections.

For SIR-Spheres, the amount of activity is adjusted on the basis of the calculated lung shunt fraction; < 10% shunt, no reduction; 10–15% shunt, amount is reduced by 20%; 15–20% shunt, amount is reduced by 40%; > 20% shunt, no therapy is pursued. For TheraSpheres, the upper limit of allowed activity shunted to the lungs is 16.5 mCi, calculated by multiplying the lung fraction percent by the planned therapeutic activity [29]. For either microsphere, the therapeutic activity dosage is calculated on the basis of the relevant package insert information. A recent report suggested that the prescribed radiation activity might be significantly lower for resin than for glass microspheres, which may in part result from their different specific activities [31, 32]. However, this difference in activity does not appear to lead to a significant survival difference between the two types of treatment [33]. Postprocedural planar, SPECT, or SPECT/CT imaging with the broad-spectrum bremsstrahlung radiation is done to confirm proper localization of the therapeutic activity in the intended hepatic region. However, higher resolution PET may also be performed given the internal pair production that occurs with ^{90}Y decay [34]. Pretherapy ^{99m}Tc-MAA and posttherapy ^{90}Y bremsstrahlung mean tumor-to-background ratios may show low correlation, but that should not preclude patients from receiving the radioembolization treatment with low tumor uptake on the ^{99m}Tc-MAA scan [35, 36]. A single-session, complete procedure including pretherapy angiography, vascular coil embolization as needed, ^{99m}Tc-MAA scintigraphy, and ^{90}Y SIRT appears to be feasible and can facilitate wider therapy adoption, enhance patient comfort, and reduce costs [37]. If the patient is hospitalized after radioembolization, simple methods such as a lead-lined blanket on the patient's abdomen can significantly reduce radiation exposure to hospital staff [38]. Laffont et al. [39] reported that medical staff performing ^{90}Y SIRT procedures are exposed to safe levels of radiation and that the mean finger exposure is less with glass microspheres than with resin microspheres. Riaz et al. [40] and Atassi et al. [41] provided comprehensive reviews of side effects and multimodal imaging, respectively, after radioembolization. Radiation-induced cholecystitis is a rare event occurring in about 0.8% of patients, and radioembolization of HCC activates liver regeneration, produces oxidative stress, and activates the inflammatory cytokines and the coagulation cascade [42, 43]. Procedural guidelines for SIRT have been published [44].

Sangha et al. [45] reported on the ongoing multicenter phase III randomized clinical trial SIRFLOX comparing first-line chemotherapy alone or in combination with ^{90}Y SIRT in patients with liver-dominant metastases from colorectal cancer. Preliminary results have shown that although no significant change in median overall survival and progression-free survival was found between the combined therapy arm and the chemotherapy-only arm, a significant increase in median hepatic progression-free survival favoring the combination arm was seen. Whether improved median hepatic progression-free survival will lead to improved overall survival is still unclear. A potential issue in ^{90}Y SIRT is tumor absorbed-dose inhomogeneity, which may call for more personalized approaches to administered activity in an attempt to achieve optimal clinical response [46, 47].

Assessment of response to SIRT can be challenging and may depend on treatment response criteria employed [48, 49]. Shady et al. [50] showed that the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) have poor sensitivity in this clinical setting and that the Choi criteria or metabolic criteria such as European Organization for Research and Treatment of Cancer or PET Response Evaluation Criteria in Solid Tumors applied to PET with FDG are more relevant. The same group of investigators also showed that metabolic response on FDG PET/CT can predict overall survival [51]. Another group of investigators suggested that dose volume histograms derived from PET/MRI of ^{90}Y distribution in tumor can be helpful in predicting responders and nonresponders [52].

Paprottka and colleagues [53] reported on pretherapy factors that could predict overall survival after ^{90}Y SIRT. Baseline bilirubin and cholinesterase levels, extrahepatic disease, and hepatic tumor content were independent predictors of overall survival. Moreover, a randomized phase II study of patients with HCC found that ^{90}Y SIRT significantly prolongs time to progression compared with chemoembolization (> 26 mo vs 6.8 mo; $p = 0.0012$) [54]. A recent systematic review and meta-analysis of 21 studies published about ^{90}Y SIRT for intermediate and advanced HCC reported a pooled overall survival of 58% at 1 year and 17% at 3 years after treatment. The observed pooled progression probability was 56% at 1 year and 73% at 2 years after therapy [55]. Another meta-analysis of eight studies involving 1499 patients reported significantly longer overall survival and time to progression with ^{90}Y SIRT than with transarterial chemoembolization in patients with HCC, although the latter may be preferred in patients with low hepatic reserve who are candidates for liver transplant [56]. Similar favorable pooled outcome results have been reported with systematic review and meta-analysis of data on unresectable intrahepatic cholangiocarcinoma and meta-static NETs [57, 58]. Moreover, interestingly, overall survival progressively decreases as lung shunt fraction increases from less than 5% to more than 20% [59, 60].

Hepatic radioembolization therapy is anticipated to experience robust growth as the number of indications increases and additional comparative prognostic data become available.

Bone Metastases Therapy

Bone is the target for metastases for many cancers. The biology of skeletal metastasis is a multifactorial process that involves complex interactions between intrinsic properties of tumor cells and host microenvironment factors [61]. Bone metastases are often associated with skeletal-related events (SREs), which can lead to death or significant morbidity including disability, decreased quality of life, and increased treatment cost [62]. Effective management of bone metastases remains an active area of pharmaceutical research and development [63, 64]. The primary objective of these therapies is aimed at alleviating pain and complications that are associated with bone metastases. Bone-seeking radio-isotopes, such as ^{153}Sm ethylene diamine tetramethylene phosphonate and ^{89}Sr chloride, have been used successfully for palliation of pain from bone metastases [65, 66].

One of the major recent strides has been the development and approval of an alpha-particle bone-seeking radionuclide for treatment of bone metastases. Alpha particles are positively charged helium nuclei (about 8000 times larger than beta particles or electrons) with a short

range of about 50–100 μm (vs several mm for beta particles) and high linear transfer energy of about 100 keV/μm (vs 0.2 keV/μm for beta particles) [67]. Alpha particles deposit very high energy in a very small distance, which often leads to irreversible double-strand DNA breaks with per-unit absorbed doses of acute biologic effects that are three to seven times greater than the damage produced by external beam or beta radiation [68, 69]. Cells are not equipped to repair double-strand DNA breaks and typically undergo apoptosis [70]. Given that the targeted cells receive high radiation doses with alpha particles, the conventional medical internal radiation dose dosimetric methods may be inappropriate, and microdosimetric methods have been developed that take into account heterogeneity and protracted exposure to internal radiation [71, 72].

The alpha therapy of choice for treatment of metastatic CRPC is ^{223}Ra dichloride (Xofigo [previously Alpharadin], Bayer HealthCare), which was approved by the U.S. Food and Drug Administration (FDA) on May 15, 2013 [73–76]. Because it is a calcium mimetic, ^{223}Ra dichloride seeks the hydroxyapatite matrix in the bone naturally. Its half-life is 11.43 days, with emitted energy distribution of 93.5% as alpha particle, less than 3.6% as beta particle, and less than 1.1% as gamma radiation [77] (Fig. 2). The Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) clinical trial was a randomized, double-blind, multinational investigation of ^{223}Ra dichloride versus placebo (saline) in men with CRPC who had symptomatic bone metastases and no visceral metastases (metastatic lymph nodes up to 3 cm in short axis were allowed) and who had adequate bone marrow reserve [78]. The study used 2:1 randomization of the treatment and placebo arms with 614 patients receiving best supportive care plus six IV injections of ^{223}Ra dichloride (each 50 kBq/kg) with each injection 4 weeks apart, and 307 patients in the placebo arm receiving best supportive care plus six IV injections of saline with each injection 4 weeks apart. The primary endpoint was overall survival defined as time from randomization to death from any cause. A number of secondary endpoints were also used, including time to first SRE.

The ALSYMPCA clinical trial found a 3.6-month survival benefit with ^{223}Ra dichloride in comparison with placebo (median, 14.9 months vs 11.3 months; hazard ratio, 0.70; 95% CI, 0.58–0.83; $p < 0.001$). The survival benefit was not affected by prior use of docetaxel chemotherapy (3.1-month survival benefit with prior docetaxel use vs 4.6-month survival benefit without prior docetaxel use). Moreover, the median time to first symptomatic SRE was significantly longer by 5.8 months with ^{223}Ra dichloride in comparison with placebo (median, 15.6 months vs 9.8 months; hazard ratio, 0.66; 95% CI, 0.52– 0.83; $p < 0.001$). The survival benefit and reduction in time to SRE has also been associated with reduced hospital stay days and improvements in quality of life [79].

Radium-223 dichloride was generally associated with low-grade myelosuppression (primarily thrombocytopenia). Jadvar et al. [80] reviewed the 1-year clinical experience with ^{223}Ra dichloride in 25 men with metastatic CRPC. About 25% of the cohort completed the entire six-dose treatment cycle. Progression of soft-tissue disease was the main reason for the cessation of therapy. Side effects were mild and manageable. A decline in the serum alkaline phosphatase level was more common than a decline in the prostate-specific antigen (PSA) level, with the latter also reflecting concurrent soft-tissue disease. A retrospective investigation of the clinical experience after 532 cycles of ^{223}Ra dichloride administration in

110 patients showed that serum alkaline phosphatase levels significantly reduced with treatment and that progression risk was associated with a decline in the serum PSA doubling time [81]. Skeletal tumor burden as assessed using ^{18}F-NaF PET/CT may be predictive of effectiveness of ^{223}Ra dichloride therapy and overall survival [82].

With regard to radiation exposure and safety, a patient of average weight receiving 3.5 MBq (95 μCi) of ^{223}Ra dichloride will emit radiation at a rate of 0.35 mSv/h (0.035 mrem/h) at 1 m immediately after administration, which entails relatively minimal radiation safety precautions. Fecal excretion is the primary method of clearance. For the sake of simplicity, however, recommendations are similar to those for radioiodine therapy [83].

Given the high efficacy and low toxicity of ^{223}Ra dichloride, the National Comprehensive Cancer Network guideline (v3.2013) incorporates ^{223}Ra dichloride treatment in the management of men with metastatic CRPC. A number of trials are now underway or planned to examine combination or sequencing of ^{223}Ra dichloride with other treatments (e.g., abiraterone acetate and enzalutamide) for metastatic CRPC as well as for other cancers such as bone-dominant metastatic breast cancer and osteosarcoma [84–86].

Peptide Receptor Radionuclide Therapy in Neuroendocrine Tumors

NETs are a heterogeneous group of tumors that stem from the neural crest with main localization in the gastroenteropancreatic tract (e.g., carcinoids, insulinoma, glucagonoma, vasoactive intestinal peptide–secreting tumors, gastrinoma, somatostatinoma). The tumors may be symptomatic through production of various peptides (e.g., diarrhea, flushing, hypoglycemia). Liver metastases are common. Although the bulk of tumor sites may be surgically resected, metastatic disease may be treated with chemotherapy, interferon, and somatostatin analog therapy [87]. FDG PET sensitivity is generally low for well-differentiated tumors, although less-differentiated and dedifferentiated tumors are more metabolically active with higher FDG accumulation [88].

Other relevant PET radiotracers in this clinical space include the ^{11}C- or ^{18}F-labeled amine precursors L–dihydroxyphenylalanine (e.g., ^{18}F-FDOPA) and 5-hydroxy-L-tryptophan (e.g., ^{11}C-5-HTP) and those that bind to the somatostatin receptors (SSTR, particularly subtype 2) using the chelator 1,4,7,10-tetraazacyclododecanetetraacetic acid (DOTA) including the ^{68}Ga-DOTA-peptides (^{68}Ga-DOTA-d-Phe1-Tyr3-octreotide [DOTATOC[; ^{68}Ga-DOTA-1-Nal3-octreotide [DOTANOC]; and ^{68}Ga-DOTA-DPhe1-Tyr3-octreotate [DOTATATE]) [89]. It is now well recognized that ^{68}Ga-based SSTR PET is superior to ^{111}In-based SSTR planar imaging and SPECT [90]. Procedure guidelines for PET/CT with ^{68}Ga-DOTA–conjugated peptides have been published [91]. In November 2013, the FDA designated ^{68}Ga-DOTATOC an orphan drug, and in June 2016 it approved ^{68}Ga- DOTATATE (Netspot, Advanced Accelerator Applications) for imaging NETs [92].

Along with advances in SSTR imaging, peptide receptor radionuclide therapy (PRRT) has received much attention, particularly as a theranostic companion to the new imaging agents. PRRT has been found to be an effective (with partial and complete response in up to 30% of

patients) and well-tolerated treatment of inoperable or metastatic gastroenteropancreatic NETs [93–107] (Fig. 3). The typical therapy radionuclides are ^{90}Y and ^{177}Lu, which are both beta emitters; ^{90}Y (half-life, 64.1 h) has a range in the order of 12 mm and ^{177}Lu (half-life, 6.7 d) has a range of 2 mm. Lutetium-177 also emits gamma rays that allow posttreatment imaging and dosimetry calculations. Typically, one or the other is used, but combination therapy with both isotopes has been studied [108]. The longer path length of the ^{90}Y beta particles may provide better coverage for larger metastases, and the shorter path length of ^{177} Lu may provide less off-target radiation and radiotoxicity for smaller metastatic lesions. A German multiinstitutional registry study reported on the experience with 450 patients with NET who underwent PRRT with ^{177}Lu, ^{90}Y, or both radiolabels in 54%, 17%, and 29% of cases [109]. Overall survival and progression-free survival were significantly inferior in patients who were treated solely with ^{90}Y-PRRT than in those who received any ^{177}Lu-PRRT. The responses were 5.6% complete remission, 22.4% partial remission, 47.3% stable disease, and 4% progressive disease. With regard to comparative dosimetry of ^{177}Lu-DOTATATE, ^{177}Lu-DOTANOC, and ^{177}Lu-DOTATOC, DOTANOC is associated with higher whole-body dose, whereas DOTA-TOC exhibited the lowest normal organ dose with the best tumor-to-kidney ratio [110].

Strosberg et al. [111] recently reported on the results of NETTER-1, a multicenter, randomized, controlled trial of the efficacy and safety of ^{177}Lu-DOTATATE (Lutathera, Advanced Accelerator Applications) in patients with advanced, progressive, SSTR-positive midgut NETs. This phase III trial randomly assigned 116 patients with well-differentiated, metastatic midgut NETs to receive either ^{177}Lu-DOTATATE at a dose of 7.4 GBq every 8 weeks (four IV infusions plus best supportive care including octreotide long-acting repeatable [LAR] administered intramuscularly at a dose of 30 mg) (^{177}Lu-DOTATATE group) or 113 patients to receive octreotide LAR alone that was administered intramuscularly at a dose of 60 mg every 4 weeks (control group). The primary endpoint was progression-free survival. The rate of progression-free survival at month 20 was 65.2% (95% CI, 50.0–76.8%) in the ^{177}Lu-DOTATATE group and 10.8% (95% CI, 3.5–23.0%) in the control group. Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2%, and 9%, respectively, of patients in the ^{177}Lu-DOTATATE group. None of these conditions occurred in the control group. No evidence of renal toxicity was seen. The authors concluded that treatment with ^{177}Lu-DOTATATE resulted in markedly longer progression-free survival with clinically significant myelo-suppression in less than 10% of patients. A planned final analysis will be performed for confirmation of the preliminary analysis observation of an overall survival benefit. Interestingly, chemotherapy appears to still be considered the mainstay treatment strategy and PRRT utilization is low across NET types. A study by Ezziddin and colleagues [112] showed that PRRT may be useful not only for tumors with Ki-67 tumor proliferation index of < 20% (G1 and G2) but also in patients with poorly differentiated tumors with a Ki-67 proliferation index of > 20% (G3). Given the NETTER-1 results, use of PRRT may increase [113].

The joint practice guideline of the International Atomic Energy Agency, European Association of Nuclear Medicine, and Society of Nuclear Medicine and Molecular Imaging provides an excellent resource for background historical information and practical considerations (e.g., indications, contraindications, pretherapy assessment, therapy

procedure, amino acid renal protection) for the administration of PRRT in patients with NET [114].

Targeted alpha therapy of NET has also been studied [115]. Chan et al. [116] reported on the safety and efficacy of ^{213}Bi-DOTATATE in a preclinical study of mice harboring NETs pretreated with L-lysine for renal protection. Lysine reduced the renal uptake of ^{213}Bi-DOTATATE by 50% without effect on the tumor uptake. A significant decline in tumor burden and improved survival were also seen with treatment. Kratochwil and colleagues [117] used intraarterial infusion of ^{213}Bi-DOTATOC in seven patients who harbored progressive NET liver metastases after treatment with ^{90}Y and ^{177}Lu-DOTATOC. Tumor binding could be seen with the 440-keV gamma emission of ^{213}Bi. All seven patients had favorable response to alpha therapy with mild hematotoxicity. With regard to potential nephrotoxicity, infusion of positively charged amino acids seems to be protective and reduce nephrotoxicity, although hyperkalemia may be an issue and needs to be monitored, especially in patients with concurrent heart disease [118]. However, overall nephrotoxicity appears to not be a major concern [119].

Response evaluation to PRRT treatment may be challenging. It has been recognized that the commonly employed structural-based RECIST criteria may be inadequate and other tumor features such as measurements of tumor volume and attenuation in CT may be needed [120]. In one study, contrast-enhanced ultrasound monitoring of perfusion changes after PRRT provided early prediction of response to treatment [121]. Accurate response assessment in this clinical setting is an area of interest and will need additional investigation.

It is readily evident that PRRT will play a major role in the treatment of patients with NETs relatively soon. Future efforts will likely focus on providing benefit to additional populations and with use of alpha particles that may provide improved therapeutic efficacy to tumors resistant to beta particle– based PR RT.

Prostate-Specific Membrane Antigen Radioligand Therapy

Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is overexpressed in metastatic prostate cancer and CRPC. PSMA undergoes constitutive internalization, has no known ligand, is not specific to the prostate gland, and is expressed in other normal (e.g., salivary glands, duodenal mucosa, proximal renal tubular cells, and neuroendocrine cells in the colonic crypts) and neoplastic (e.g., transitional cell carcinoma, renal cell carcinoma, colon carcinoma, and endothelial cells of neovasculature) tissues [122]. Nevertheless, major activity in designing and evaluating various radiolabeled agents for imaging and therapy of metastatic prostate cancer with PSMA as the biologic target has produced encouraging results [123–132] (Fig. 4). These radiolabeled agents (antibodies, antibody fragments, aptamers, and PSMA inhibitors) primarily target the extracellular moiety of the PSMA and are typically radiolabeled with ^{18}F (half-life, 110 min), ^{68}Ga (half-life, 68 min), ^{64}Cu (half-life, 12.7 h), ^{124}I (half-life, 4.2 d), and ^{89}Zr (half-life, 78.4 h) for imaging and with ^{131}I (half-life, 8 d), ^{90}Y (half-life, 64.1 h), and ^{177}Lu (half-life, 6.7 d) for therapy. The common binding domain of these agents to the extracellular moiety of the PSMA involves the glutamate-urea-lysine motif [133].

In a theranostic model, the imaging agent is used to localize and assess the extent of disease ("see"), whereas the therapeutic companion is employed to deliver therapy to identified lesions ("treat"). Although false-negatives (small lesions, neuroendocrine differentiation) and false-positives (celiac ganglia, other benign and malignant tumors) can occur with PSMA PET, the tumor-to-background uptake ratios are high, and some studies suggest that other scintigraphic evaluations such as bone scintigraphy may only rarely be needed, if at all [134]. PSMA PET may also be useful as gatekeeper not only for PSMA-based radionuclide therapy but also for other therapies such as ^{223}Ra dichloride treatment [135].

Radiolabeled PSMA-617 has shown favorable kinetics for both imaging (labeled with ^{68}Ga) and radionuclide therapy (labeled with ^{177}Lu). Yadav et al. [136] evaluated the safety and efficacy of ^{177} Lu-PSMA-617 therapy (mean administered activity, 5059 ± 1845 MBq ranging from one to four cycles) in 31 men with progressive metastatic prostate cancer [136]. Mean serum PSA levels and mean analgesic scores declined from baseline values. Only two patients experienced mild hematotoxicity, and no nephrotoxicity or hepatotoxicity was seen. Rahbar et al. [137] reported on 50 therapies with ^{177}Lu-PSMA-617 in 28 men with metastatic CRPC. Any serum PSA decline and PSA decline of 50% or more occurred in 59% and 32% of patients after one cycle and 75% and 50% of patients after two cycles, respectively. The estimated median survival was 29.4 weeks, which was significantly higher than the historical best supportive care median survival of 19.7 weeks. There were no major toxicities. The same group of authors also published the results of a retrospective study of a cohort of 145 patients with metastatic CRPC who underwent a total of 248 cycles of ^{177}Lu-PSMA-617 radionuclide therapy (one to four treatment cycles with activity range of 2–8 GBq per cycle) and were followed for a median of 16 weeks [138]. The overall biochemical response rate (PSA decline) was 45% after all therapy cycles. Grades 3 and 4 anemia, thrombocytopenia, and leukopenia occurred in 10%, 4%, and 3% of the men, respectively. In another similar study, 30 patients received one to three cycles of ^{177}Lu-PS-MA-617 radionuclide therapy [139]. A decline of more than 50% in serum PSA level was noted in 43% of patients after three cycles, and this level of decline was sustained for over 24 weeks in 27% of all treated patients. Acute hematotoxicity was mild, and xerostomia, nausea, and fatigue occurred in < 10% of patients. The salivary gland received the highest dose at 1.4 Gy/GBq, the kidney at 0.75 Gy/GBq, and the red marrow at 0.03 Gy/GBq irrespective of tumor burden or cycle. With regard to radiation dosimetry, another study reported the highest absorbed dose in the lacrimal glands at 2.82 Gy/GBq, 0.72 Gy/GBq in the salivary glands, and 0.53 Gy/GBq in the kidneys [140]. Others have reported similar results with the parotid glands receiving the highest mean radiation absorbed dose, but this result was associated with only mild reversible xerostomia in some cases [141, 142]. Despite renal clearance of the non–tumor-bound agent, the kidneys do not receive the highest absorbed dose. Nevertheless, PSMA inhibitors such as 2-(phospho-nomethyl)pentanedioic acid have been proposed for nephroprotection to diminish renal PSMA binding [143]. For the imaging counterpart, relatively high physiologic uptake of ^{68}Ga-PSMA-617 in the salivary glands and kidneys has been reported [144].

Other radiolabels being explored for PSMA-617 include auger electrons (^{125}I), alpha particles (e.g., ^{211}At, ^{213}Bi, ^{225}Ac), and cyclotron-produced ^{44}Sc (half-life, 4.04 h) [145–148]. Kratochwil and coworkers [149] reported very early results in two patients with

metastatic CRPC who underwent first-in-human treatment with ^{225}Ac-PSMA-617 at a dose of 100 kBq/kg administered bimonthly. Both patients had marked decline in serum PSA levels without hematotoxicity. PSMA imaging and therapy (I&T) agents, which can be radiolabeled with ^{68}Ga for imaging and with ^{177}Lu for therapy, are also being used [150]. From an imaging point of view, the PSMA I&T has been shown to have high detection rates of recurrent prostate cancer comparable with ^{68}Ga-PS-MA [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N′-diacetic acid (equivalent to ^{68}Ga-PSMA-11) [151]. With regard to radiation dosimetry for ^{177}Lu-PSMA I&T agents, the mean absorbed organ doses have been reported as 0.72 ± 0.21 Gy/GBq for the kidneys; 0.12 ± 0.06 Gy/GBq for the liver; and 0.55 ± 0.14 Gy/ GBq for the parotid, 0.64 ± 0.40 Gy/GBq for the submandibular, and 3.8 ± 1.4 Gy/GBq for the lacrimal glands [152]. Therefore, as with ^{177}Lu-PSMA-617, ^{177}Lu-PSMA I&T agents are associated with the highest doses to the lacrimal and salivary glands.

Interestingly, higher PSMA expression has been seen in tumor cells exposed to anti-hormonal treatment [153, 154]. This finding, at least theoretically, provides a possible opportunity to synergize antiandrogen therapy with PSMA-based radionuclide therapy. In summary, the current and steadily growing evidence strongly indicates that PSMA-based theranostics will play a major role in the management of prostate cancer.

Future Prospects

TRT research and clinical use are advancing rapidly. New targets in cancer cells such as gastrin-releasing peptide receptor, integrins, melanocyte-stimulating hormone receptor, melanocortin-1 receptor, glucagonlike peptide-1 receptor, chemokine receptor, folate receptor, and others may provide additional opportunities for more cancer types to move the field forward even further [155–163]. Similarly, incorporation of other high-energy alpha particles (e.g., ^{213}Bi, ^{211}At, ^{225}Ac) is under investigation [164]. Other novel combined treatment methods such as radiovirotherapy (use of oncolytic viruses to deliver radionuclide therapy into infected cancer cells) are also exciting recent developments [165].

Aside from scientific advancements, key issues need to be worked out for TRT to thrive as a legitimate and active component of cancer therapy [166, 167]. Regulatory and reimbursement agencies must coordinate their requirements so that safety, efficacy, and payment follow seamlessly without major delays for the introduction of the therapy into the clinical setting. Reimbursement must be sufficient to ensure that the therapy is not underutilized solely on the basis of financial loss. Access and availability of therapeutic agents must be assured across all geographic areas and clinical practice models. Comparative and cost-effectiveness investigations will need to follow. The medical curricula must also include education on TRT so that the next generation of physicians and ancillary medical personnel are all familiar with this emerging therapy modality.

Conclusion

TRT began with thyroid radioiodine therapy but has expanded to include many other radionuclides and cancers. The current momentum and stimulating results pave the way for

TRT to grow its footprint in the care of patients with cancer and likely other diseases in the era of precision medicine.

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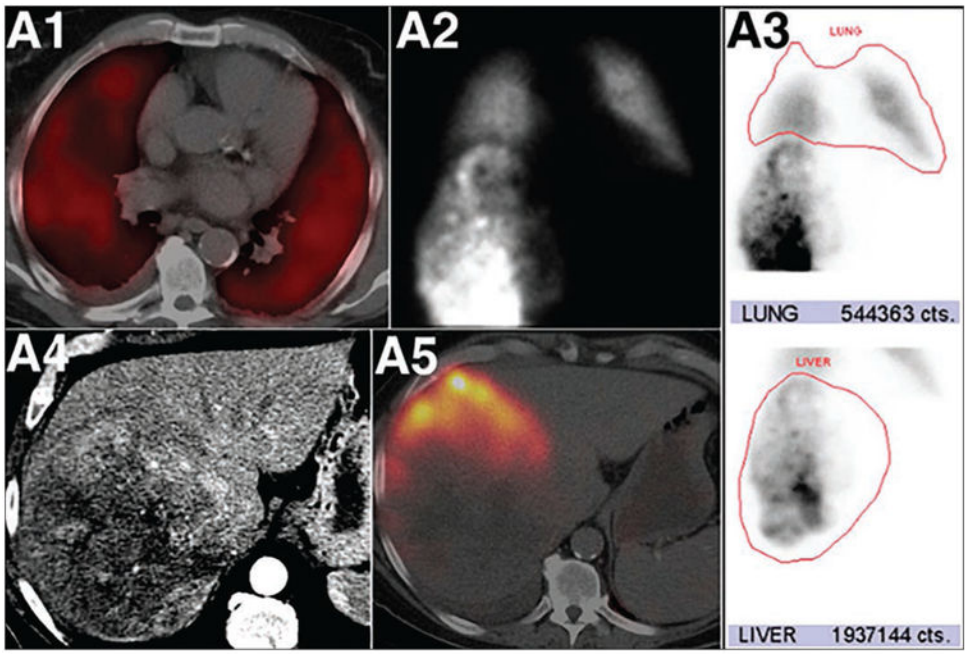

Fig. 1.

Marked pulmonary ^{99m}Tc-macroaggregated albumin (MAA) shunting in patient with hepatocellular carcinoma. Fused SPECT/CT axial image (A1) of chest shows diffuse ^{99m}Tc-MAA pulmonary activity in relation to shunted MAA particles. Anterior planar static image (A2) of chest and upper abdomen after ^{99m}Tc-MAA administration into right hepatic artery shows heterogeneous ^{99m}Tc-MAA distribution activity in liver and diffuse pulmonary activity. ROIs around lung and liver (*red outlines*, A3) lead to calculation of high lung shunt fraction of 21.9%. Axial contrast-enhanced CT (A4) shows large heterogeneous right liver mass. Fused SPECT/CT image of liver (A5) does not show significant localization of ^{99m}Tc-MAA in right liver mass. High lung shunt fraction precluded this patient from radioembolization therapy. This research was originally published in *JNM*. Uliel L, Royal HD, Darcy MD, et al. From the angio suite to the gamma-camera: vascular mapping and ^{99m}Tc-MAA hepatic perfusion imaging before liver radioembolization—a comprehensive pictorial review. *J Nucl Med* 2012; 53:1736–1747. © by the Society of Nuclear Medicine and Molecular Imaging, Inc.

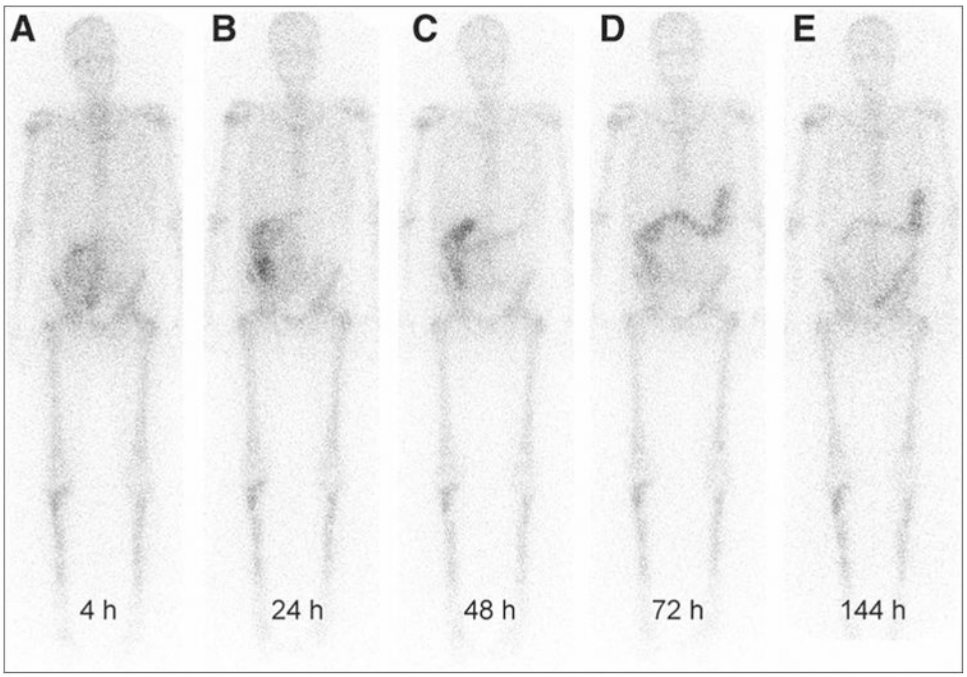

Fig. 2.

Temporal biodistribution of ^{223}Ra dichloride as imaged by low yield gamma emission of radioisotope. Activity is localized primarily in bone and to some extent in colon. This research was originally published in *JNM*. Chittenden SJ, Hindorf C, Parker CC, et al. A phase 1, open-label study of the biodistribution, pharmacokinetics, and dosimetry of ^{223}Ra dichloride in patients with hormone-refractory prostate cancer and skeletal metastases. *J Nucl Med* 2015; 56:1304–1309. © by the Society of Nuclear Medicine and Molecular Imaging, Inc.

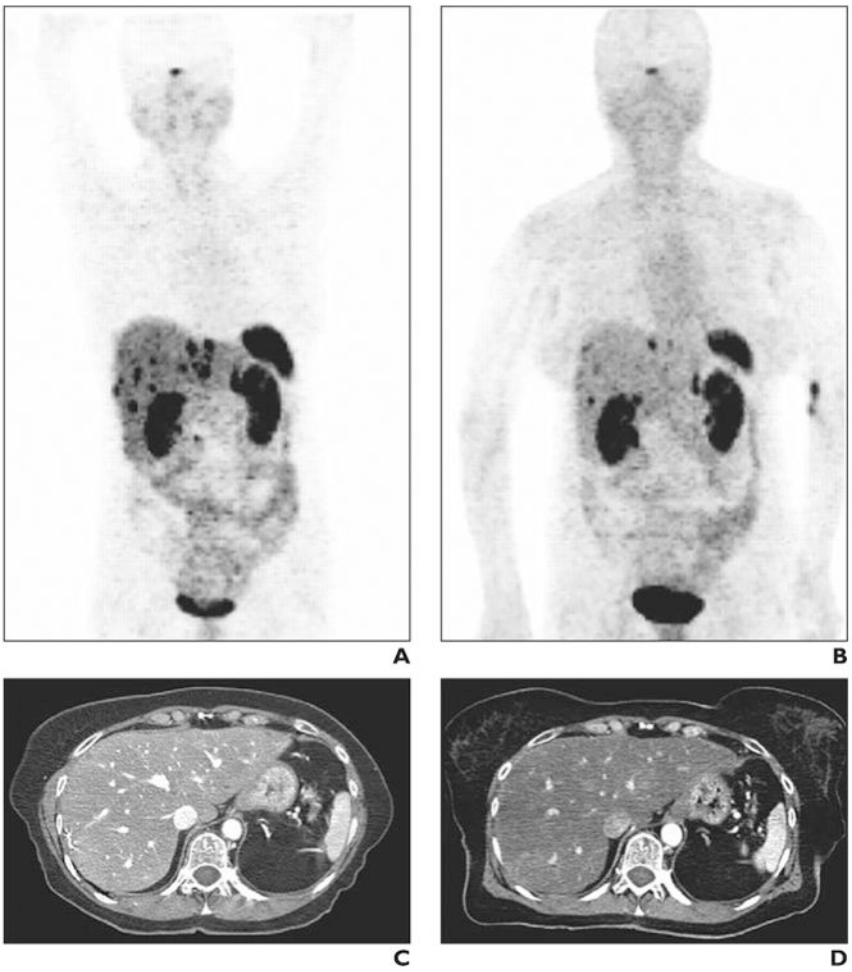

Fig. 3.

Favorable treatment response to ^{177}Lu-DOTA-dPhe1,Tyr3-octreotate (DOTATATE) therapy in patient with hepatic metastases from resected pancreatic head primary neuroendocrine tumor. This research was originally published in *JNM*. Gabriel M, Oberauer A, Dobrozemsky G, et al. ^{68}Ga-DOTA-Tyr3- octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy. *J Nucl Med* 2009; 50:1427–1434. © by the Society of Nuclear Medicine and Molecular Imaging, Inc. A and B, Gallium-68 DOTATATE PET scans before (**A**) and after (**B**) four cycles of ^{177}Lu-DOTATATE show decline in number of intensity of hepatic lesions. **C** and **D**, Contrast-enhanced CT scans before (**C**) and after (**D**) treatment show no significant interval change in morphology of hepatic lesions.

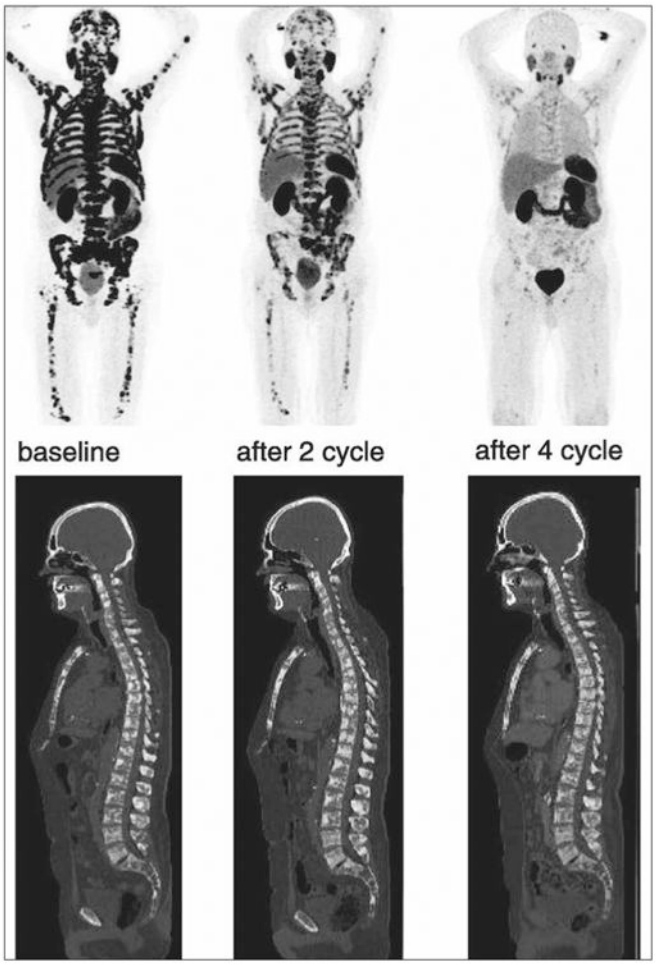

Fig. 4.

Excellent response to ^{177}Lu prostate-specific membrane antigen (PSMA)-617 therapy in man with extensive metastatic castration-resistant prostate cancer. Gallium-68 PSMA PET/CT was performed at baseline before first, after second, and after fourth cycles of therapy show disappearance of all lesions after fourth therapy cycle. CT did not show major morphologic changes in bone metastases. (Used with permission from [132])