Advances in Radioligand Theranostics in Oncology

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Short title: Radiotheranostics in oncology

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Key Points

There is an expanding role of radiotheranostics as a safe and effective therapy option in the management of oncology patients.

There is increasing interest in developing novel radiotheranostics agents to fully exploit the huge potentials of radiotheranostics as a viable form of personalized cancer care.

Several novel cancer-expressed molecular targets are being exploited for their suitability as druggable targets in the expansion of the clinical applications of radiotheranostics.

Abstract

Theranostics with radioligands (radiotheranostics) has played a pivotal role in oncology. Radiotheranostics explores the molecular targets expressed on tumor cells to target them for imaging and therapy. In this way, radiotheranostics entails non-invasive demonstration of the in vivo expression of a molecular target of interest through imaging followed by the administration of therapeutic radioligand targeting the tumor-expressed molecular target. Therefore, radiotheranostics ensures that only patients with a high likelihood of response are treated with a particular radiotheranostic agent, ensuring the delivery of personalized care to cancer patients. Within the last decades, a couple of radiotheranostics agents, including Lutetium-177 DOTATATE (^{177}Lu-DOTATATE) and Lutetium-177 prostate-specific membrane antigen (^{177}Lu-PSMA), were shown to prolong the survival of cancer patients compared to the current standard of care leading to the regulatory approval of these agents for routine use in oncology care. This recent string of successful approvals has broadened the interest in the development of different radiotheranostic agents and their investigation for clinical translation. In this work, we present an updated appraisal of the literature, reviewing the recent advances in the use of established radiotheranostic agents such as radioiodine for differentiated thyroid carcinoma and Iodine-131-labeled meta-iodobenzylguanidine therapy of tumors of the sympathoadrenal axis as well as the recently approved ^{177}Lu-DOTATATE and ^{177}Lu-PSMA for differentiated neuroendocrine tumors and advanced prostate cancer, respectively. We also discuss the radiotheranostic agents that have been comprehensively characterized in preclinical studies and have shown some clinical evidence supporting their safety and efficacy, especially those targeting fibroblast activation protein (FAP) and chemokine receptor 4 (CXCR4) and those still being investigated in preclinical studies such as those targeting poly (ADP-ribose) polymerase (PARP) and epidermal growth factor receptor 2.

1. Introduction

There has been significant improvement in understanding the molecular mechanisms underpinning carcinogenesis. Several molecules expressed by tumor cells and in the cancer stroma have been comprehensively characterized. Ligands with high affinity for binding to these tumor-expressed molecules have also been synthesized for cancer therapy and other purposes. The field of nuclear medicine and radionuclide theranostics has exploited the advances in cancer molecular pathways to develop radioligand for oncologic diagnosis and therapy. Theranostics (or theragnostics, as it is sometimes called) is a contraction word derived from therapy and diagnostic. In nuclear medicine, theranostic (or radiotheranostics) refers to using a radioligand for functional imaging of disease while using the same radioligand or its biosimilar for the therapy of the same disease. The allure of radioligand theranostic lies in the ability to identify a druggable target in the tumor for imaging and therapy [1]. During imaging, the expression of the molecular target is determined so that only patients whose tumors express the molecular target sufficiently are treated with the therapeutic congener of the theranostic radioligand. In this manner, only patients with the highest likelihood of response are treated, and the therapy effect can be determined in post-treatment imaging [2]. Radioligand theranostic, therefore, personalizes cancer care for patients, making it a viable pillar of precision medicine [3].

The tracer principle underpinning nuclear medicine imaging and radiotheranostics is a century old [4]. The first successful application of the radiotheranostics concept was the use of radioactive iodine for the therapy of thyroid disorders in 1941 [5,6]. Radioactive iodine remains a viable option for treating benign

and malignant thyroid disorders in modern medicine [7-9]. Recently, radioligands have been developed against several molecular targets expressed by different cancers for oncologic imaging and therapy. The most recent successes are the targeting of neuroendocrine neoplasm-expressed somatostatin receptors and prostate cancer-expressed prostate-specific membrane antigen leading to the approval of these novel agents by regulatory agencies in different parts of the world. These latest developments have advanced the status of radiotheranostics as a viable therapy option in oncology and have also served as a huge drive for developing newer radiotheranostic agents for oncologic imaging and treatment. In this review, we aim to provide a general description of the radiotheranostics concept followed by a discussion of the established theranostic agents used in nuclear medicine, highlighting the recent advances in the application of these agents. Next, we will discuss the recently approved agents for cancer radiotheranostics, focusing on their approved indications and their off-label uses. We also aim to review the literature on the newer radiotheranostic agents currently at different stages of development, including those that have shown promise in limited clinical studies and those still in the developmental pipelines, that have shown potential for clinical translation.

2. The Radiotheranostics paradigm

Radiotheranostics uses ligands labeled with a radionuclide for imaging and therapy purposes. By treating only patients whose disease expresses the target of interest, radiotheranostics personalizes cancer care, prevents harm due to side effects of ineffective treatments, and saves costs by reducing futile treatment in cancer care (Figure 1). At the core of radiotheranostics is the radioligand, which, in most instances, consists of a ligand with an affinity for a molecular target expressed by the cancer cell or the components of the tumor microenvironment, a radionuclide that emits the radiation for imaging and therapy, and a chelator that links the radionuclide to the ligand (Figure 2). While in most cases, this three-part concept of a radioligand agent for radiotheranostics holds, in some cases, the radionuclide, such as in radioactive iodine for the treatment of differentiated thyroid cancer, on its own, is sufficient to act as a theranostic agent for imaging and therapy. In other instances, the radionuclide is coupled directly to the ligand without needing a chelator.

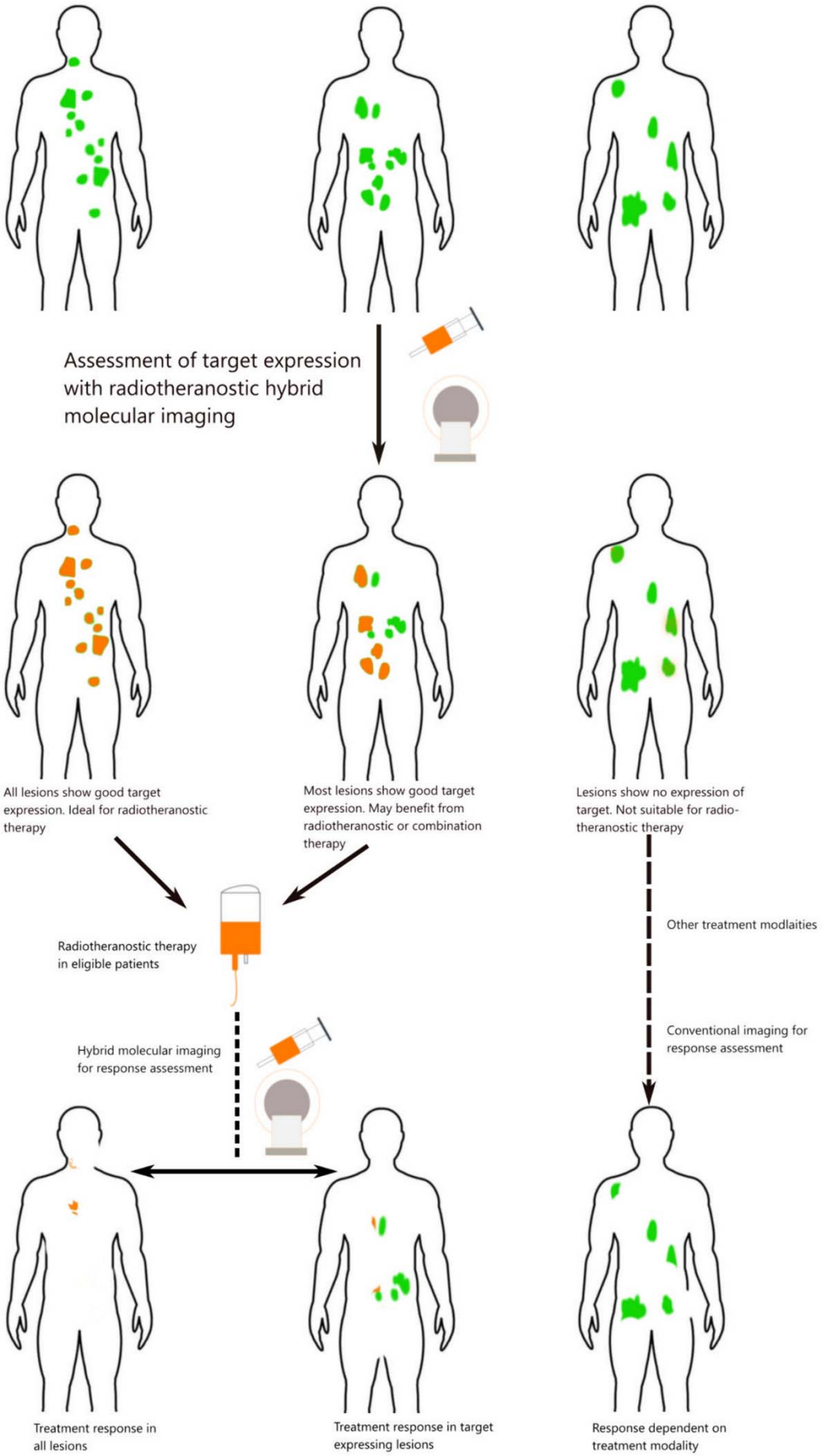

Assessment of target expression with radiotheranostic hybrid molecular imaging
All lesions show good target expression. Ideal for radiotheranostic therapy
Most lesions show good target expression. May benefit from radiotheranostic or combination therapy
Lesions show no expression of target. Not suitable for radio-theranostic therapy
Radiotheranostic therapy in eligible patients
Other treatment modlaities
Hybrid molecular imaging for response assessment
Conventional imaging for response assessment
Treatment response in all lesions
Treatment response in target expressing lesions
Response dependent on treatment modality

Fig 1 A schematic diagram depicting the radiotheranostic paradigm. In the top row, three patients with metastatic cancer are depicted. The middle row depicts the findings from radioligand imaging in which all lesions in the patients on the right demonstrate target expression making the patient a suitable candidate for targeted radioligand therapy while all lesions in the patients on the left show no target expression making them ineligible for targeted radioligand therapy. The patient depicted in the middle has heterogeneous lesions, some demonstrating targeted expression while others do not. Targeted radioligand therapy may be offered to this patient with heterogeneous lesions but in combination with other treatment modalities to take care of non-target-expressing lesions. The lower row depicts imaging findings on the post-treatment scan. Radioligand imaging for treatment response assessment is feasible in the patient on the right showing a near-complete response to treatment while morphologic imaging is indicated for response assessment in the patient on the left.

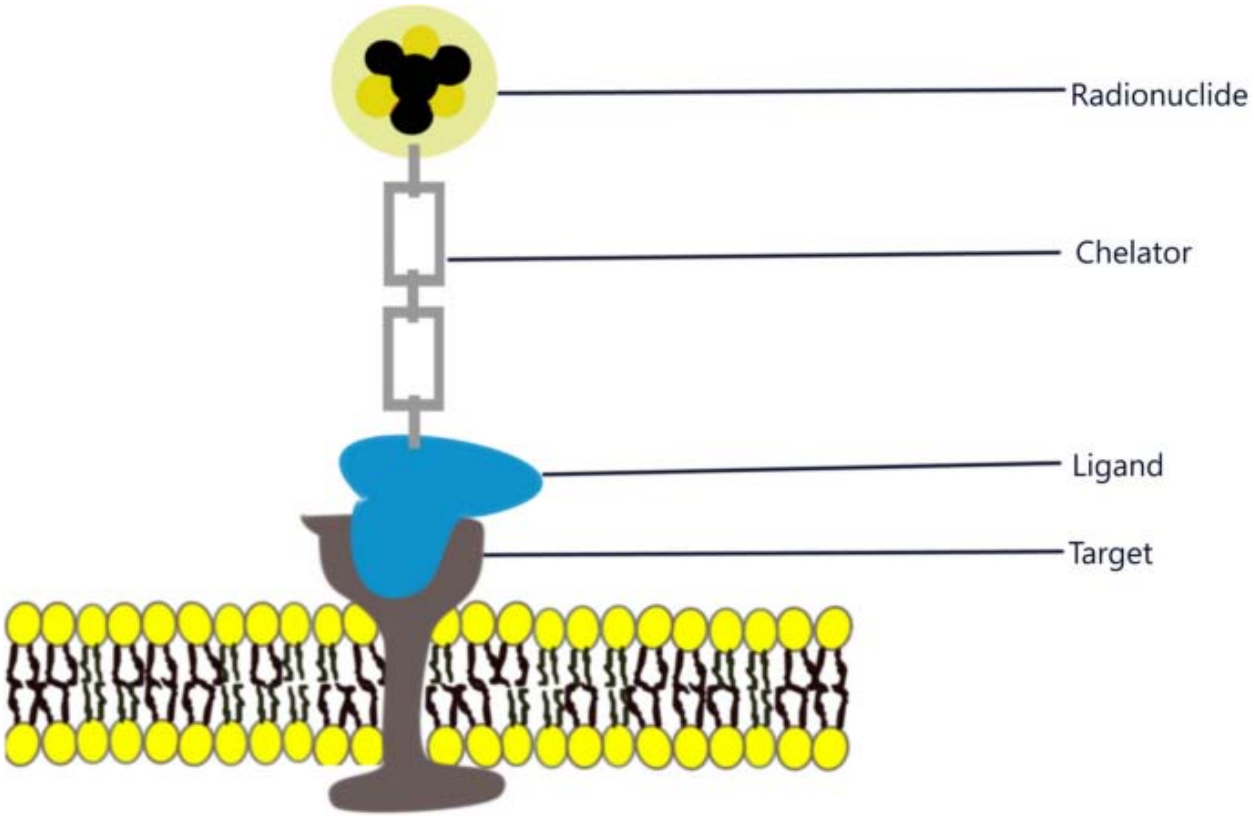


Fig 2 A schematic diagram depicting a radioligand binding to a membrane-expressed receptor.

2.1. The ligand

The ligand is the vector that conveys the diagnostic or therapeutic radionuclide to the molecular target of interest. The molecular targets exploited in radiotheranostics are those overexpressed by the cancer cell or its microenvironment with no or minimal level of expression in normal tissues. Identifying a tumor-specific target and developing a suitable ligand to target it, therefore, constitute the core of the safe application of radiotheranostics in oncology.

Ligands used for radiotheranostics are peptides, antibodies/antibody fragments/engineered antibodies, or small molecules [10-12]. Understanding the molecular target of interest is the starting point for rational ligand development [3,13]. Most ligands are synthetic congeners of the physiologic ligands for the cancer-associated molecular target. The synthetic analog of the physiologic ligand is deftly crafted to maintain a high affinity for the molecular target and in vivo stability without inducing a physiologic response. The ideal ligand for theranostics should be stable in vivo, taken up promptly by the tumor and cleared from the circulation and normal tissues, demonstrate a high affinity for a target exclusively expressed by the tumor, and be physiologically inert (not induce a pharmacologic response in vivo) [10]. The size of the ligand influences its uptake in the tumor and clearance from the background. Small molecular-sized ligands such as antibody fragments and small molecule ligands are promptly excreted by the kidneys following in vivo administration. This reduces the whole-body radiation dose and improves lesion detection rate due to a better target-to-background radioactivity ratio following radioligand administration for imaging [11]. On the contrary, large molecular-sized ligands such as whole antibodies have longer circulation time and improved tumoral uptake of radioligand but higher whole-body radiation dose [12]. In the choice of ligand, a compromise needs to be struck between small-sized ligands, which are suitable for imaging and have better radiation dose profile, versus large molecular-sized ligands, which are more ideal for radioligand therapy but have higher radiation burden to the patient [11,12].

2.2. The radionuclide

Radionuclides are the reporter molecules in the radioligands, emitting the photons used for imaging and the particle radiation responsible for tumor cell killing in radiotheranostics. Therefore, radionuclides used in theranostics can be considered diagnostic or therapeutic. The classification is based on decay mode, with radionuclides whose decay leads to the emission of photons mostly used for imaging, while those that decay by charged particle emission are primarily used for therapy. A clear delineation between diagnostic and therapeutic radionuclides is not always possible, as many of them emit a combination of photons and charged particles in their decay scheme.

2.2.1. Radionuclides for imaging

Imaging modalities for radiotheranostics are either single-photon emission tomography (SPECT) or positron emission tomography (PET). Single photon-emitting radionuclides such as technetium-99m (^{99m}Tc), Indium-111 (^{111}In), Iodine-123 (^{123}I), and Iodine-131 (^{131}I) are used for radiolabeling of ligands and have formed the core of SPECT imaging in nuclear medicine. ^{99m}Tc is readily available from the Molybdenum-99/Technetium-99m generator, making it the workhorse radionuclide for SPECT imaging in nuclear medicine. The widespread availability of installed SPECT systems in most regions of the world makes single-photon emitting radionuclides attractive for radiolabeling of theranostics ligands. The limited spatial resolution of the SPECT system compared with the PET system, especially its low sensitivity for the detection of small lesions, is an important hindrance to its widespread use. This drawback may limit the utility of SPECT imaging for accurately staging disease. However, its performance is sufficient for evaluating target expression while working up patients for radiotheranostics. SPECT imaging also plays a crucial role in confirming the uptake and retention of therapeutic radioligands in tumor lesions following treatment [14].

PET imaging plays a more prominent diagnostic role in radiotheranostics, serving as a sensitive, non-invasive tool for disease staging, target expression determination, and post-radioligand treatment response assessment. Several factors are considered in selecting a PET radiopharmaceutical for

radiolabeling of a theranostic ligand, including the availability/ease of production, physical half-life in relation to the biological half-life of the ligand, ease of radiolabeling to the ligand, range of the emitted positron, and the abundance of positron emission during decay [15]. Positron-emitting Gallium-68 (^{68}Ga) obtained from a Germanium-68/Gallium-68 (^{68}Ge/^{68}Ga) generator is, by far, the most popular radionuclide used in PET imaging for radiotheranostic purposes. The long-lived ^{68}Ge/^{68}Ga generator (physical half-life of 270 days) provides a regular supply of the radionuclide for radiolabeling of various peptides and small molecule ligands used in radiotheranostics [16]. Its short physical half-life of 68 minutes makes it ideal for radiolabeling small molecular weight ligands such as small peptides, antibody fragments, and small molecule ligands [15]. There is a limitation in the availability and ^{68}Ga activity that can be eluted from a ^{68}Ge/^{68}Ga generator. These limitations are being addressed by using cyclotron as an alternative mode of producing ^{68}Ga [17,18]. Cyclotron-produced ^{68}Ga is equivalent to Generator-produced ^{68}Ga [19]. Fluorine-18 (^{18}F), most popular for its use in producing radioflorinated fluorodeoxyglucose (^{18}F-FDG), emits positrons with lower energy and shorter range in tissue than ^{68}Ga-emitted positrons, contributing to its superior PET image resolution compared with ^{68}Ga-based radioligands. ^{18}F is, consequently, increasingly being used for radiolabeling of PET radioligands by exploring the silicon-fluoride acceptor (SiFA) chemistry [20-22].

The longer physical half-life of ^{18}F (110 minutes) allows for its centralized production and the distribution of radioflorinated radioligands to peripheral laboratories. Large molecular ligands such as whole antibodies with a slow plasma clearance must be radiolabeled with longer-lived radionuclides (than ^{18}F) matching their longer biological half-lives. A group of copper isotopes, including copper-60 (^{60}Cu), copper-62 (^{62}Cu), and copper-64 (^{64}Cu), with physical half-lives of 23.4 minutes, 9.7 minutes, and 12.7 hours, respectively, are currently being explored for radiolabeling of theranostic ligands [23]. ^{64}Cu, with its low positron energy of 650 KeV, is very promising due to its excellent image resolution and suitability for radiolabeling large molecular vectors [23,24]. Its long physical half-life makes centralized synthesis of ^{64}Cu-labeled radioligands and supply to laboratories and clinical centers feasible [24]. Other positron-emitting radionuclides with long physical half-lives and suitable for radiolabeling of large molecular vectors include Zirconium-89 (^{89}Zr, physical half-life=3.27 d) and Iodine-124 (^{124}I, physical half-life=4.2 d) [24]. The longer physical half-lives of these radionuclides allow for delayed imaging with the potential for an improved target-to-noise ratio. However, these long physical half-lives also increase the radiation dose to the patient.

2.2.2. Radionuclides for therapy

Radionuclides for therapy emit one or more of beta particles, alpha particles, or auger electrons in their decay scheme. These charged particles directly or indirectly induce DNA damage, causing cell death. There is a wide variability in the mechanisms and efficiency with which these different charged particles cause cell death. The mechanism and efficiency of DNA damage induced by the charged particles are influenced by several factors, including their range in tissue and linear energy transfer (LET), which represent the distance traveled and the amount of energy deposited in tissue per unit distance traveled, respectively (Figure 3). Therapeutic radionuclides may emit only charged particles (beta, alpha, or auger electrons) for treatment or co-emit photons (gamma or x-rays). The co-emitted photons are useful for post-treatment imaging. The post-treatment images can be used to confirm the uptake and retention of the radioligand in the tumors and for quantifying the dose delivered to tumor targets and normal tissues (dosimetry).

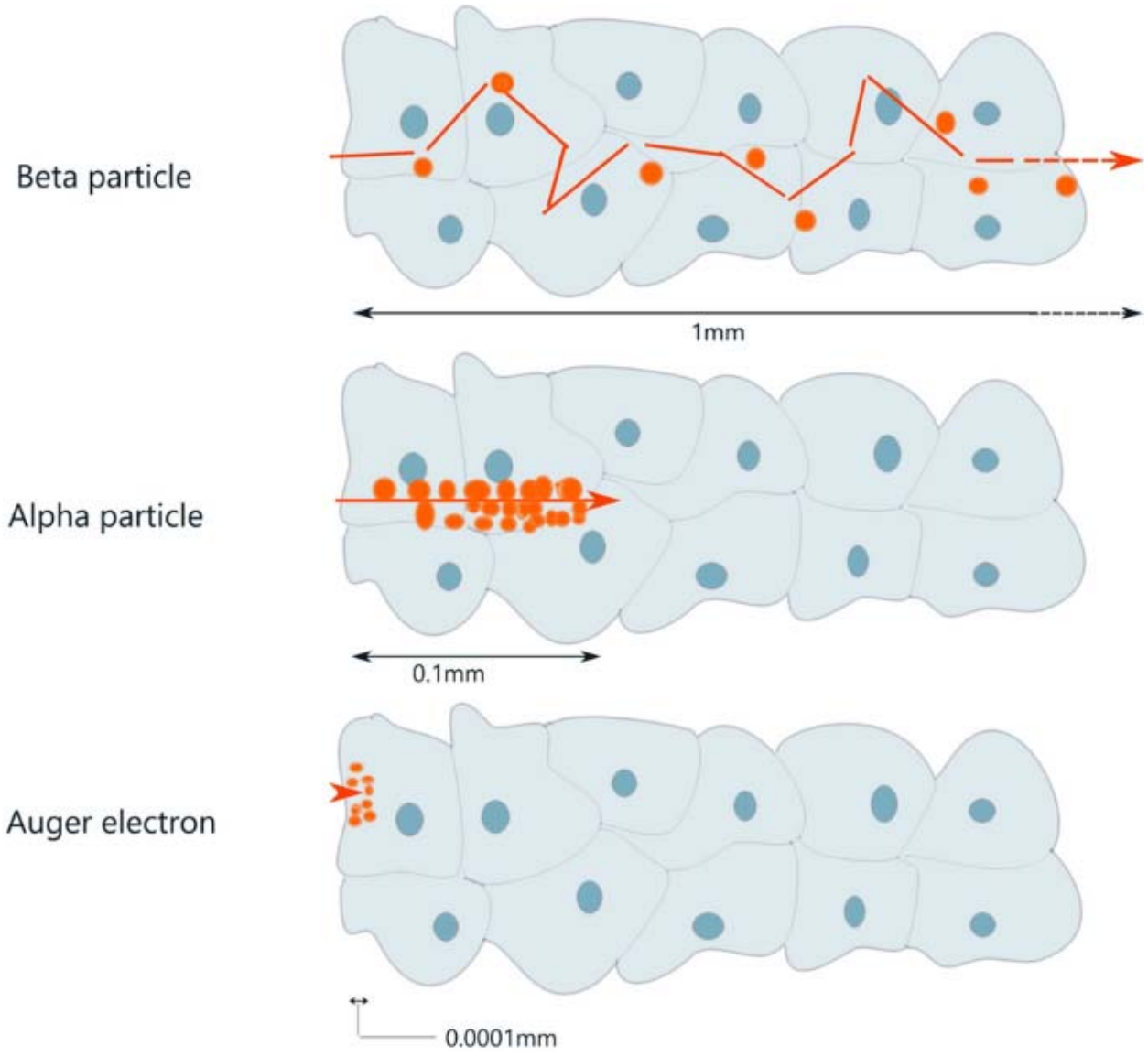


Fig 3 A Schematic diagram depicting the relative ranges of beta particle (top row), alpha particle (middle row), and Auger electron in soft tissue. Beta particles have a long-range and are suitable for treating bulky tumors. Alpha particles have a short range, limiting radiation exposure to normal tissues contiguous to the tumor. Auger electrons have a very short range in tissue and must be released close to the DNA to cause cell death.

Beta particles are negatively charged electrons emitted from the nucleus of an atom and are the most used charged particles for radioligand therapy. Beta particles have a long range in tissue, about 0.5 to 12 mm (approximately 50 to 1000 cell diameters), but low LET (about 0.2KeV/μm) [25]. This extended range of beta particles in tissue indicates that the radiation damage extends beyond the tumor cell directly bound to the radioligand (the crossfire effect). The crossfire effect ensures a more homogeneous radiation dose to the tumor, especially when the tumor target is not homogenously expressed by all tumor cells. On the downside, the long range of beta particles in tissue increases the radiation dose delivered to

contiguous normal tissues. The low LET of beta particles requires a high radionuclide concentration within the tumor to achieve an effective tumor cell kill [26]. Charged particles cause cell death primarily via DNA strand breaks. Charged particles also interact with water molecules within the extracellular space, forming reactive oxygen species. DNA strand breaks may result from a direct hit by the charged particles or indirectly via reactive oxygen species (ROS)-induced DNA damage. Most of the DNA damage induced by beta particles occurs indirectly rather than by direct hits on the DNA. Since tissue oxygenation is central to the generation of ROS, hypoxic tumors are generally resistant to beta particle-emitting radioligand therapy [26,27].

Radiotheranostics began with the use of ^{131}I for the treatment of differentiated thyroid cancer. The gamma photons emitted by ^{131}I make quantitative imaging for dosimetry feasible. A few ligands, including meta-iodobenzylguanidine (MIBG) and tositumomab, have been labeled with ^{131}I for routine clinical use application as radiotheranostics agents [28,29]. Beyond these applications, ^{131}I is not commonly used as the therapy radionuclide in the newer theranostic agents due to factors including the in vivo degradation of radioiodinated ligands by deiodinase enzyme activities. Yttrium-90 (^{90}Y), with a physical half-life of 2.8 days, became popular owing to its highly energetic beta particles and long range in tissue (11 mm). Its long range in tissue makes it ideal for treating large tumors but also accounts for its higher radiation dose to normal organs [30]. ^{90}Y is a pure beta emitter and does not emit gamma photons that are usable for quantitative imaging. The bremsstrahlung radiation due to beta particle interaction in the tissue can be imaged, but the images have poor spatial resolution. Lutetium-177 (^{177}Lu) is currently the most utilized beta particle-emitting radionuclide for theranostics. The medium energy (mean E_β 134 KeV) and the short range (up to 3 mm) of its emitted beta particles ensure the deposition of its energy within the tumor while sparing normal contiguous tissues, producing similar efficacy but lower toxicities compared with ^{90}Y [30,31]. Other beta-emitting radionuclides, including Copper-67, Rhenium-188, Scandium-47, and Terbium-161, are currently being explored for their widespread application in theranostics [24,25]. Of them, Terbium-161 (^{161}Tb), which shares many of the favorable characteristics of ^{177}Lu [32], appears to have the greatest promise owing to the auger electrons it emits in addition to beta particles, making it produce a more homogeneous dose distribution within the tumor with potential for improved treatment outcome [33].

Alpha-emitting radionuclides are becoming more attractive for radiotheranostics. Alpha particles have a short range in tissue (50 – 100 µm, corresponding to about 5 – 10 cell diameters), are densely ionizing, and release approximately 400 times more energy per unit length traveled (LET > 80 KeV/µm) than beta particles [25]. The short range of alpha particles in tissue ensures energy deposition within the tumor while sparing adjacent normal tissues with the potential for reduced treatment-induced toxicity. Alpha particles cause double-stranded DNA cluster breaks regardless of cell cycle phase, which is difficult to repair compared to mostly single-stranded DNA damage induced by beta particles [34]. Unlike beta particles, most of the alpha particle-induced DNA damage result from direct hits on the DNA molecules, making targeted alpha therapy an effective radiotheranostic option for hypoxic tumors that are resistant to radioligand therapy with beta-emitting radionuclides [35,36]. These factors contribute to the superior anti-tumor effect of targeted alpha radioligand therapy compared to radioligand therapy with beta-emitting radionuclides. Most alpha-emitting radionuclides in current use decay to daughter nuclides that are radioactive and emit other alpha particles in their decay schemes. This leads to a cascade of reactions with multiple alpha particles emitted with the potential to increase energy deposition within the tumor and improve tumor killing. Alpha emission occurs with so much force that a recoil force analogous to the

recoil effect felt during the firing of a firearm [37]. This recoil energy (transmitted to the daughter nuclide) is 100-200 keV and more than a thousand times higher than the binding energy of any chemical bond [38]. The recoil effect, therefore, causes chemical bond breakage in alpha-emitting radioligands, leading to the free release of the daughter nuclides. The released daughter nuclides have chemical properties different from the parent nuclide and may be taken up by normal tissues in the body, contributing to radiation dose to these organs when the daughter nuclides are also radioactive. Of the several alpha-emitting radionuclides known, only a few have desirable characteristics favoring their exploitation for radiotheranostics, including Actinium-225, Bismuth-213, Thorium-227, Radium-223, Lead-212, and Astatin-211 [39]. Of them, Radium-223 dichloride is approved for treating skeletal metastases of prostate cancer, while Actinium-225 (^{225}Ac) has been labeled to different targeting vectors and used in several clinical studies [39]. The investigation into the radiotheranostic use of the other alpha-emitting radionuclides is expanding.

Auger electrons are ejected by energy released during the filling of vacant inner orbits that results from electron capture, internal conversion, or incident x-ray excitation of an atom. The Auger effect is associated with a cascade of atomic electron transitions, leading to the emission of 2 to more than 30 Auger electrons per decay with short range in tissue (2 to 500nm) and medium to high-energy deposition per unit distance traveled (LET of 4-26KeV/μ) [40,41]. This multitude of Auger electrons releasing high energies within a short radius in tissue causes complex DNA damage, lipid peroxidation, and protein denaturation, leading to cellular death. Auger-emitting radionuclides are most effective when their molecular vectors target the DNA directly or other molecular epitopes within the nucleus. In this way, the Auger electrons are released close to the DNA, where they cause irreparable damage, causing cellular death. Auger emitters for radiotheranostics include well-known radionuclides such as Iodine-123, Iodine-125, Indium-111, and Tin-117m. There is a growing list of other promising Auger-emitting radionuclides. Factors to consider in selecting the ideal Auger-emitting radionuclide for radiotheranostics have been recently reviewed [41].

2.3. The chelator

The chelator complexes the radionuclide (usually a radiometal) to the molecular vector (ligand) and helps build a stable radioligand. The multitudes of available chelators fall into different chemical categories, including acyclic and cyclic aminocarboxylates, pyridinecarboxylates, and aminophosphonates. In choosing from the long and expanding list of chelators, consideration must be given to labeling efficiency, in vivo stability, and metal selectivity [42]. The ideal chelator should support high radiolabeling yield at low radionuclide concentration, the radiometal-chelator complex should be resistant to hydrolysis in vivo, and the chelator should have selectivity towards the radiometal rather than other metals found in the internal milieu [42]. A linker molecule connects the radiometal-chelator complex to the vector molecule and may be modified to alter the pharmacokinetics of the radioligand. Examples of chelators commonly used in radioligands for radiotheranostics include DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DTPA (diethylenetriaminepentaacetic acid), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), and NODAGA (2-[4,7-bis{carboxymethyl}-1,4,7-triazonan-1-yl]pentanedioic acid). A detailed discussion of the characteristics of chelators is beyond the scope of this review and has been reported by others [42,43].

3. The established radiotheranostic agents

Some radiotheranostic agents have been used in routine clinical practice for decades and have been regarded as part of the therapy armamentarium in oncology. In this section, we will discuss the recent advances in theranostics applications of radioactive iodine and radioiodine-labeled MIBG. Several ongoing clinical trials are investigating strategies to broaden the clinical indications and improve the efficacy of these established agents (Table 1). Radiolabeled immunoglobulin targeting B-cell-expressed CD20 is another established radiotheranostic agent for treating relapsed or refractory low-grade follicular or transformed B-cell lymphoma with excellent and durable outcomes [44,45]. However, it is no longer commercially available for clinical use and will not be discussed.

Table 1: Some ongoing promising clinical trials investigating established radiotheranostic therapy with radioactive Iodine-131 and Iodine-131-labeled MIBG alone or in combination with other therapeutic agents

Trial number	**Radiotheranostic agent/combination or comparator**	**Target**	**setting**	**Primary outcome measures**	**Phase**
NCT03244956	Iodine-131 combined with Trametinib and Dabrafenib	NaI symporter	Metastatic radioactive iodine refractory thyroid cancer patients with RAS or BRAF mutation	Objective response rate	II
NCT04892303	Iodine-131 combined with external beam radiotherapy	NaI symporter	Metastatic well-differentiated thyroid cancer	Safety	I
NCT04560127	Iodine-131 with combined camrelizumab and apatinib	NaI symporter	Radioactive iodine refractory differentiated thyroid cancer	Progression-free survival	II
NCT03561259	Iodine-131 MIBG and Vorinostat	Norepinephrine transporter	Recurrent or progressive high-risk neuroblastoma	Overall response based on International Neuroblastoma Response Criteria	II
NCT00107289	Iodine-131 MIBG	Norepinephrine transporter	Recurrent, progressive, or refractory neuroblastoma or malignant pheochromocytoma, or paraganglioma	Response rate	II

3.1. Radioiodine theranostics of differentiated thyroid cancer

Thyroid cancer is the most common endocrine malignancy with a rising incidence. The treatment of thyroid cancer includes thyroid surgery followed by radioactive iodine therapy (RAIT). RAIT explores the sodium iodide symporter (NIS) expression by differentiated thyroid cancer (DTC) to deliver cytotoxic beta particle radiation to the cancer cells following their uptake of therapeutic ^{131}I. There is a down-regulation of the NIS expressed in thyroid cancer cells compared with normal thyroid follicular cells [46]. Elevated thyrotropin, achieved by thyroid hormone withdrawal or recombinant thyrotropin, is utilized to optimize radioiodine uptake by the thyroid cancer cells [47].

Following thyroidectomy and elevated thyrotropin level, whole-body imaging is done with radioactive ^{123}I or ^{131}I for re-staging of disease. This pre-RAIT imaging allows for the accurate staging of disease, guides the goal of treatment, and determines the activity of ^{131}I to administer for treatment [48,49]. Depending on the risk category of patients and findings on the whole-body radioiodine scan, RAIT is administered for remnant ablation of presumably benign thyroid tissue, adjuvant treatment for patients who are suspected of harboring micrometastases based on their risk category, or treatment of known metastasis [50]. The remnant ablation is a completion thyroidectomy of some sort, which improves the specificity of thyroglobulin, a glycoprotein exclusively produced by the thyroid follicular cells, as a tumor marker for long-term surveillance [51]. The goal of adjuvant RAIT is to lower the risk of disease recurrence. RAIT administered for the treatment of known DTC metastases improves progression-free, disease-specific, and overall survival [50,52,53]. Most agree upon the efficacy of RAIT in DTC for all clinical indications. The controversy relates to the category of patients that should receive the treatment. This is due to some studies reporting a lack of benefit from RAIT in patients with papillary microcarcinoma with complete tumor resection and no extrathyroidal extension, neck node metastasis, or distant metastasis [54]. While RAIT is undoubtedly beneficial in high-risk patients [55], its benefit has also been reported in patients with low-risk disease as well [56,57]. A recent phase 3 clinical trial, however, confirmed no significant difference in event rates (lymph node metastases or elevated thyroglobulin level) in patients with low-risk thyroid cancer if they received post-operative RAIT versus if they did not [58].

There is a great diversity in the genotypic alterations that drive DTC [59]. $BRAF^{V600E}$ and RAS mutations are commonly encountered in papillary and follicular thyroid carcinomas, respectively. $BRAF^{V600E}$ mutation is associated with an increased risk of recurrence and mortality in patients with papillary thyroid carcinoma [60,61]. $BRAF^{V600E}$ and TERT mutations are associated with low NIS expression and poor avidity of DTC for radioactive iodine [62]. These mutations are prevalent in patients who developed radioiodine refractory DTC (RR-DTC) [63]. RR-DTC is diagnosed when one of the following criteria is encountered, including de novo lack of radioiodine avidity in metastatic thyroid cancer, loss of radioiodine avidity in previously avid thyroid cancer lesions, avidity in some but not other thyroid cancer lesions, disease progression despite radioiodine avidity, or disease progression after treatment with a ^{131}I cumulative activity of >22.2 GBq (600mCi) [50]. RR-DTC is associated with a poor prognosis due to the limited availability of effective treatment. In recent years, drugs targeting molecular pathways overexpressed by the tumor have been investigated for their ability to restore radioiodine avidity in RR-DTC to make the patients benefit from RAIT [64,65]. In the future, the molecular aberrations present in DTC in each patient may shape the type and intensity of treatment, including the activity of radioiodine administered for RAIT. Currently, the administered activity of ^{131}I for RAIT is determined empirically or by dosimetry. The dosimetry method determines the activity of ^{131}I for RAIT according to the residence time of a small activity of ^{131}I administration followed by quantitative SPECT imaging at multiple time points. Dosimetry determines the

activity that delivers the maximum dose to the tumor while limiting normal organ radiation dose. Positron emitting ^{124}I for PET imaging is now being applied for dosimetry, taking advantage of the long physical half-life of the radionuclide (4.2 days) and the excellent spatial resolution of the PET system compared with the SPECT system [66,67].

3.2. ^{123}I/^{131}I-MIBG theranostics of tumors of the sympathoadrenal axis

Norepinephrine transporter is expressed in the pre-synaptic terminals of the sympathetic nervous system for norepinephrine reuptake. This neuronal transporter is also expressed by tumors arising from the sympathoadrenal axis and other derivatives of the embryonic neural crest cells, including pheochromocytoma, paraganglioma, and neuroblastoma. MIBG is an analog of guanethidine. Due to its structural homology with norepinephrine, it is taken up by the norepinephrine transporter into the terminal nerve ending for storage in the nerve secretory vesicles. MIBG has been radiolabeled with different radionuclides, including ^{123}I for imaging and ^{131}I for imaging and therapy of tumors arising from the sympathoadrenal axis. ^{123}I/^{131}I-MIBG SPECT imaging is a sensitive tool for localizing, staging, and re-staging of norepinephrine transporter-expressing tumors [68,69]. In line with the theranostic paradigm, the demonstration of MIBG avidity in the tumor is a prerequisite for ^{131}I-MIBG therapy.

^{131}I-MIBG therapy has been applied as a therapy option in patients with refractory neuroblastoma and pheochromocytoma/paraganglioma. In a recent meta-analysis of 26 clinical trials involving 883 patients with neuroblastoma who were treated with ^{131}I-MIBG, the proportion of patients with objective response, stable disease, and progressive disease across all studies were 39%, 31%, and 22%, respectively [70]. More favorable objective response rates (ORR) have been reported from using ^{131}I-MIBG early in the disease course, with ORR of 56 – 73% in newly diagnosed children with high-risk neuroblastoma [71,72]. In a meta-analysis of 17 studies that included 243 patients with pheochromocytoma/paraganglioma, ^{131}I-MIBG therapy induced complete, partial, and stable disease response in 3%, 27%, and 52% of patients, respectively [73].

^{131}I-MIBG, commonly used for treatment, has low specific activity, and a larger proportion of the MIBG it contains is unlabeled (labeled: unlabeled ratio of 1:2000) [74,75]. The high concentration of unlabeled MIBG may stimulate catecholamine release from the adrenergic nerve ending, contributing to catecholamine release syndrome associated with tumors of the sympathoadrenal axis [75]. The unlabeled MIBG also competitively inhibits the labeled ^{131}I-MIBI reuptake at the norepinephrine transporter [75]. High-specific-activity ^{131}I-MIBG (HSA-^{131}I-MIBG) contains almost entirely the labeled vector and is increasingly being used for treatment [76]. In the phase I dose-finding clinical trial, the maximum tolerable activity of HSA-^{131}I-MIBG was determined to be 296 MBq/kg (8 mCi/Kg) [77]. In a follow-up multicenter, open-label, single-arm investigation of HSA-^{131}I-MIBG in patients with pheochromocytoma/paraganglioma, 92% of evaluable patients achieved a partial response or stable disease, and 25% of patients had an at least 50% reduction in their baseline need for antihypertensives that lasted for at least six months [78]. Hematologic toxicities were the most common treatment-related side effects seen in 90% of patients, including 72% of patients with grade 3 or 4 toxicities or severe hematologic adverse events. Of the patients with hematologic toxicity, 25% required hematologic support in the form of packed red cell transfusion, platelet transfusion, granulocyte colony-stimulating factor, or erythropoietin therapy, while the side effects self-resolved in others [78]. The efficacy and safety of HSA-^{131}I-MIBG reported from these trials led to its FDA (Federal Drug Administration) approval in 2018 for the treatment of metastatic/inoperable pheochromocytoma/paraganglioma.

There are ongoing efforts to improve the diagnostic and therapeutic performance of radiolabeled MIBG for tumors of the sympathoadrenal axis. $^{123}I/^{131}I$ in MIBG has been substituted with ^{18}F in ^{18}F-metafluorobenzylguanidine (^{18}F-MFBG) to take advantage of the favorable spatial resolution of the PET system for improved lesion detection in patients with tumors of the sympathoadrenal axis [79]. Unlike imaging 24 hours or later post radiotracer injection with $^{123}I/^{131}I$-MIBG SPECT imaging, ^{18}F-MFBG PET acquisition commences 60 minutes after radiotracer administration. ^{18}F-MFBG PET has been shown in different studies to be a superior alternative to $^{123}I/^{131}I$ MIBG SPECT [79,80]. Similarly, ^{131}I in ^{131}I-MIBG has been substituted with the alpha-emitting Astatin-211 (^{211}At) forming ^{211}At-meta-astatobenzylguanidine (^{211}At-MABG) to explore the superior tumor-killing effect of targeted alpha therapy. Following encouraging results from the preclinical investigations of ^{211}At-MABG as a potential radiotheranostics agent for tumors of the sympathoadrenal axis, several ongoing clinical trials are investigating this agent in humans [81].

4. The newly approved radiotheranostic agents

The place of radiotheranostics as a viable therapy option in oncology was further consolidated following the approvals of radium dichloride ($^{223}RaCl_2$) for skeletal metastasis of prostate cancer, ^{177}Lu-DOTATATE targeting somatostatin receptor (SSTR) expressed by differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NET), and ^{177}Lu-PSMA-617 for prostate-specific membrane antigen (PSMA)-expressing metastatic castrat ion-resistant prostate cancer (mCRPC). $^{223}RaCl_2$ and ^{177}Lu-PSMA-617, in phase 3 clinical trials, demonstrated survival benefits for mCRPC patients compared with standard-of-care therapy options [82,83]. Radiotheranostics of prostate cancer is outside the scope of the current review, and the use of $^{223}RaCl_2$ and ^{177}Lu-PSMA-617 in prostate cancer patients will, therefore, not be discussed. PSMA, despite its name, is not specific to prostate cancer as it is expressed in other tumors, especially in tumor-associated neoangiogenesis, making it a potential radiotheranostic agent in non-prostate tumors [84]. ^{177}Lu-DOTATATE, targeting SSTR, was approved as a second-line agent in the treatment of differentiated GEP-NET. SSTR is also expressed in tumors other than GEP-NET. In this section, we will discuss the SSTR and PSMA-targeted radiotheranostics in oncology beyond prostate cancer. In Table 2, we present a summary of notable ongoing clinical trials that aimed to broaden the clinical applications of these agents.

Table 2: Some ongoing clinical trials investigated approved and experimental theranostic agents targeting neuroendocrine and sympathoadrenal tumors-expressed somatostatin receptors and PSMA expressed in non-prostate malignancies.

Trial number	**Radiotheranostic agent/combination or comparator**	**Target**	**setting**	**Primary outcome measures**	**Phase**
NCT04525638	^{177}Lu-DOTATATE combined with Nivolumab	Somatostatin receptor	Grade 3 neuroendocrine tumors or neuroendocrine carcinomas	Overall response rate	II
NCT04544098	^{177}Lu-DOTATATE as an intra-arterial or intra-hepatic infusion	Somatostatin receptor	Liver-predominant metastatic gastroenteropancreatic, bronchial or unknown primary well-differentiated neuroendocrine tumors	Feasibility of two successful intra-arterial 177Lu-DOTATATE treatment	I
NCT03478358	^{177}Lu-DOTA-EB-TATE	Somatostatin receptor	Advanced metastatic neuroendocrine tumors	Functional response on 68Ga-DOTATATE PET imaging. Safety with and without amino acid infusion	I
NCT05773274	^{177}Lu-DOTATATE versus Everolimus	Somatostatin receptor	Metastatic unresectable midgut neuroendocrine tumor progressive after 177Lu-DOTATATE therapy	Progression-free survival	II
NCT02754297	Dosimetry-guided ^{177}Lu-DOTATATE dosing	Somatostatin receptor	Progressive and/or symptomatic inoperable neuroendocrine tumors (NET)	Objective response rate	II
NCT03206060	^{177}Lu-DOTATATE	Somatostatin receptor	Inoperable pheochromocytoma/paraganglioma	Progression-free survival	II
NCT04086485	^{177}Lu-DOTATATE combined with Olaparib	Somatostatin receptor	Inoperable gastroenteropancreatic neuroendocrine tumors	Maximum tolerated dose and overall response rate	I/II
NCT05459844	^{177}Lu-Oxodotreotide	Somatostatin receptor	Inoperable, progressive, well-differentiated	Progression-free survival	III

	versus Octreotide		gastroenteropancreatic neuroendocrine tumors		
NCT05053854	^{177}Lu-DOTATATE combined with talazoparib	Somatostatin receptor	Metastatic pancreatic or midgut neuroendocrine tumor	Maximum tolerated dose	I
NCT04261855	^{177}Lu-DOTATATE combined with Avelumab	Somatostatin receptor	Metastatic Merkel cell carcinoma	Progression-free survival	Ib/II
NCT05884255	^{177}Lu-Oxodotreotide versus Octreotide LAR	Somatostatin receptor	Advanced gastroenteropancreatic neuroendocrine tumors	Progression-free survival	III
NCT04665739	^{177}Lu-DOTATATE versus Everolimus	Somatostatin receptor	Bronchial neuroendocrine tumor	Progression-free survival	II
NCT04954820	^{177}Lu-DOTATATE	Somatostatin receptor	New Progression of Intestinal Well-differentiated Neuroendocrine Tumor after prior 177Lu-DOTATATE	Objective response rate	II
NCT05477576	^{225}Ac-DOTATATE versus investigator-selected standard of care	Somatostatin receptor	Inoperable, advanced, well-differentiated gastroenteropancreatic neuroendocrine tumors that have progressed after prior 177Lu-DOTATATE	Progression-free survival	III
NCT05610826	^{177}Lu-DOTATATE versus surgical cytoreduction	Somatostatin receptor	Metastatic pancreatic neuroendocrine tumors to the Liver	Progression-free survival	II
NCT05153772	^{212}Pb-DOTAMTATE	Somatostatin receptor	Neuroendocrine tumors with or without prior 177Lu-DOTATATE treatment	Safety and objective response rate	II
NCT05359146	^{161}Tb-DOTA-LM3 versus 177Lu-DOTATOC	Somatostatin receptor	Gastroenteropancreatic neuroendocrine tumour	Safety and tolerability	0

NCT05918302	^{177}Lu-DOTATATE versus Everolimus	Somatostatin receptor	Neuroendocrine tumors of the lung and thymus	Progression-free survival	III
NCT05644080	^{177}Lu-PSMA	PSMA	Recurrent grade 3 and 4 gliomas	Progression-free survival, overall survival, and safety	II
NCT06059014	^{177}Lu-PSMA	PSMA	Metastatic clear-cell renal cell carcinoma	Disease control rate and safety	I/II

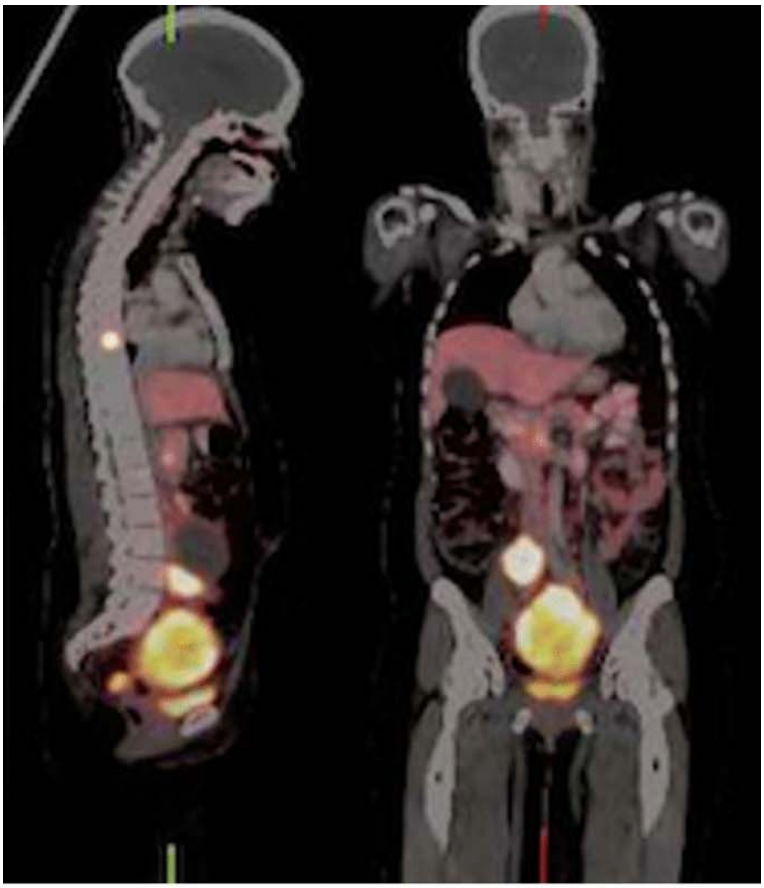
4.1. Somatostatin receptor-targeted radiotheranostics

Neuroendocrine endocrine neoplasms are a group of highly heterogeneous tumors with increasing incidence [85]. They can arise from any organ of the human body and may be well, moderately, or poorly differentiated. Most neuroendocrine neoplasms are well- to moderately differentiated and are termed neuroendocrine tumors (NETs). NETs are further classified as grade I (G1), grade II (G2), or grade 3 (G3) diseases according to their proliferating index or ki-67 index. Poorly differentiated neuroendocrine neoplasms (termed neuroendocrine carcinoma) are highly aggressive and are mostly treated with cytotoxic chemotherapy regimens. NETs are considered secretory when they secrete vasoactive amines or peptides such as serotonin, gastrin, and insulin with associated disabling symptoms leading to early clinical presentation in the disease course. Non-secretory NETs do not produce vasoactive products, which often delays clinical presentation with disease diagnosis at a very advanced stage. Radiotheranostics of NETs targets tumor membrane-expressed SSTR, the hallmark pathologic feature of NETs. Somatostatin, the natural ligand of SSTR, is produced in the central nervous system and the gastrointestinal tract for neurotransmission and regulation of cellular proliferation. Octreotide, the synthetic analog of somatostatin, is approved for its anti-proliferative effect in treating NETs.

Several modifications of the octreotide molecule have been done, and the products have been successfully radiolabeled for imaging and therapy of NETs. Exploiting the gamma photons (for SPECT imaging) and Auger electrons (for therapy) emitted by ^{111}In, ^{111}In-pentetreotide was the first successful radioligand for radiotheranostics of NETs. The therapeutic response of ^{111}In-pentetreotide was modest, with only a few patients achieving objective response to treatment [86]. Following ligand binding, the SSTR-ligand complex undergoes internalization into the cytoplasm but not the nucleus, which is required to achieve effective DNA damage by Auger electrons. Derivatives of octreotide have also been labeled with ^{68}Ga using DOTA as the chelator for PET imaging of NETs, replacing SPECT imaging of NETs with ^{111}In-pentetreotide. Octreotide derivatives radiolabeled with ^{68}Ga, and more recently to ^{64}Cu, are now the standard of care radionuclides for PET imaging of NETs due to their superior performance compared with other radionuclide techniques and conventional imaging [87,88]. For therapy, ^{90}Y has replaced ^{111}In for SSTR-targeted therapy of NETs. In a phase II study, ^{90}Y-DOTATATE therapy was effective for treating patients with progressive gastroenteropancreatic (GEP) NETs, inducing objective tumor response in 23% and disease stabilization in 77% of patients [89]. In another study, objective tumor response and disease stabilization

were found to be associated with improvement in the overall survival of NETs patients treated with ^{90}Y-DOTATATE/^{90}Y-DOTATOC [90]. The highly energetic beta particles emitted by ^{90}Y and their long range in tissue make ^{90}Y-labelled DOTA-peptide very effective for the radiotheranostics of progressive NETs, and particularly suitable for treating bulky tumors [91]. These energetic beta particles are also responsible for the side effects associated with this treatment, with up to 10% of patients treated with ^{90}Y-DOTATATE experiencing grade III/IV hematologic toxicity in one series, including 5% of patients in whom these toxicities were persistent [89].

^{177}Lu-DOTATATE explores the medium energy of the beta particles emitted by ^{177}Lu for effective tumor killing with lesser radiation dose to normal tissue due to the much lower range of the beta particles in tissue, resulting in a better safety profile of ^{177}Lu-DOTATATE radiotheranostics of SSTR-expressing NETs (Figure 4). In a prospective database study, ^{177}Lu-DOTATATE induced objective tumor response in 39% and stabilized the disease in another 43% of a mixed group of NETs patients arising from different organs [92]. In the study, progression-free survival (PFS) and overall survival were 29 months (95% CI, 26 - 33) and 63 months (95% CI, 55 – 72), respectively. Long-term toxicities were rare and included acute leukemia and myelodysplastic syndrome in 0.7% and 1.5% of the treated patients, respectively [92]. The efficacy and safety of ^{177}Lu-DOTATATE were confirmed in the NETTER-1 trial that randomized patients with progressive well-differentiated (Ki67 index ≤20%) midgut NETs in a 1:1 ratio to treatment with ^{177}Lu-DOTATATE plus 30 mg of octreotide injection every four weeks or high-dose octreotide given at 60 mg every four weeks [93]. The primary endpoint of the trial was PFS, which, at the time of initial analysis, the median PFS had not yet been reached in the ^{177}Lu-DOTATATE arm and 8.4 months (95% CI, 5.8 – 9.1) in the high-dose octreotide arm. Overall, there was a 79% lower risk of disease progression or death in the ^{177}Lu-DOTATATE arm compared with the high-dose octreotide arm. Adverse events were more common in the ^{177}Lu-DOTATATE arm, especially nausea and vomiting, which are typically induced by amino acid solution administered during treatment for renal protection in patients receiving ^{177}Lu-DOTATATE therapy [94]. Grade III/IV lymphopenia, thrombocytopenia, and neutropenia occurred in 9%, 2%, and 1% of patients who received ^{177}Lu-DOTATATE with no ^{177}Lu-DOTATATE-induced grade III/IV anemia seen [93]. These encouraging results led to the approval of ^{177}Lu-DOTATATE as a second-line agent for treating GEP NETs after the failure of first-line treatment with octreotide. In the final analysis of the NETTER-1 trial data reporting the secondary endpoint of overall survival in an intention-to-treat analysis, there was a 11.7-month difference in the median OS between study arms favoring the ^{177}Lu-DOTATATE arm. This difference in OS between study arms did not reach statistical significance because 36% of patients in the high-dose octreotide arm received ^{177}Lu-DOTATATE (cross-over) during their long-term follow-up [95].



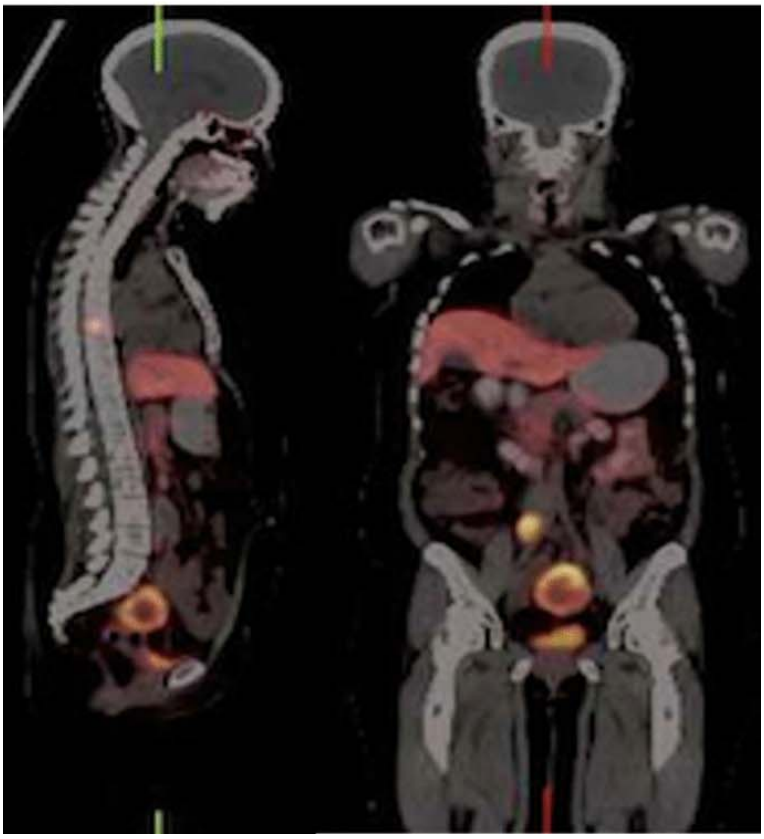


Fig 4 ^{68}Ga-DOTATATE PET/CT images of a 59-year-old female with neuroendocrine tumor of the hind gut. Baseline images (top row) show large pelvic tumor mass, mesenteric lymph node and vertebral metastases. Follow-up images after four cycles of ^{177}Lu-DOTATATE show significant reduction in tumor size with the shrunken pelvic mass showing necrotic center, consistent with good response to treatment.

Functional NETs produce highly debilitating clinical symptoms, which are effectively controlled by ^{177}Lu-DOTATATE therapy [96]. The improvement in symptoms due to NETs resulting from ^{177}Lu-DOTATATE therapy is associated with improvement in the quality-of-life of patients. In the analysis of the health-related quality-of-life data from the NETTER-1 cohort, the time to deterioration in the quality-of-life defined as ≥10% decline in each quality-of-life domain assessed with standardized quality-of-life questionnaire was significantly longer in the ^{177}Lu-DOTATATE arm compared with the high-dose octreotide arm [97]. These results confirm that, in addition to its safety and ability to prolong survival, ^{177}Lu-DOTATATE radioligand therapy improves the quality of life of NETs patients. In this time of shrinking health budgets, the cost of any healthcare intervention must be commensurate to the benefits due to it. Several groups have reported ^{177}Lu-DOTATATE to be more cost-effective than high-dose octreotide [98].

^{177}Lu-DOTATATE is approved as a second-line agent for progressive well-differentiated (Ki67 index ≤20%) GEP NET. Well-differentiated high-grade (Ki67>20%) NET express SSTR sufficiently to make off-label treatment with ^{177}Lu-DOTATATE feasible. Several studies have reported the safety and efficacy of SSTR-targeted radiotheranostics with ^{177}Lu-DOTATATE alone or in combination with other anti-cancer agents, such as chemotherapies in well-differentiated high-grade NETs [99]. The NETTER-2 trial is a phase III randomized trial investigating the safety and efficacy of ^{177}Lu-DOTATATE plus standard dose of long-acting octreotide versus high-dose long-acting octreotide in patients with metastatic/inoperable high-grade (Ki67 index of ≥10 to ≤ 55%) GEP NETs (NCT03972488). Preliminary results published by the study sponsor in the media suggest that the primary endpoint of favorable PFS was reached. When published in the medical literature, these results will validate using ^{177}Lu-DOTATATE in well-differentiated high-grade GEP NET.

Tumors of the sympathoadrenal axis, especially pheochromocytomas/paragangliomas, express SSTR sufficiently and have been treated off-label with ^{177}Lu-DOTATATE. A recent meta-analysis of 10 studies reported a pooled disease control rate of 0.83 (95% CI, 0.74 – 0.87) among patients with pheochromocytoma/paragangliomas treated with ^{177}Lu-DOTATATE [100]. Despite not yet being approved for this indication, this high disease control rate (combination of the rates of complete response, partial response, and stable disease) demonstrates the efficacy of ^{177}Lu-DOTATATE in advanced pheochromocytoma/paragangliomas. ^{177}Lu-DOTATATE has many merits over ^{131}I-MIBG (the approved radiotheranostic agent) for treating pheochromocytomas/paragangliomas. Several drugs interfere with the tumor uptake of ^{131}I-MIBG, necessitating their discontinuation prior to ^{131}I-MIBG therapy. Free radioiodine is present in the ^{131}I-MIBG solution and is taken by the thyroid gland. Pharmacologic intervention for thyroid blockade is necessary to prevent radiation-induced thyroid damage. ^{131}I-MIBG therapy requires in-hospital admission and management by a medical team skilled at radiation protection. These and some other factors associated with ^{131}I-MIBG therapy but not ^{177}Lu-DOTATATE radioligand therapy make the latter a more attractive option in deciding the radiotheranostic agent in the management decision of pheochromocytomas/paraganglioma [101]. The efficacy of ^{177}Lu-DOTATATE radioligand therapy has been reported for other SSTR-expressing tumors, such as bronchial carcinoids, meningiomas, and medullary thyroid carcinomas [102-104]. Meningiomas are benign intracranial tumors associated with

high morbidity and mortality. The mainstay therapy approach for meningiomas is surgery with or without adjuvant radiotherapy. In a group of patients with progressive, treatment-refractory meningioma who were ineligible for re-operation, ^{177}Lu-DOTATATE halted disease progression in 40% of patients with an overall median PFS and OS of 7.8 months (95%CI, 5.3 – 10.3) and 13.6 months (95%CI, 10.3 – 17.0), respectively [105]. While ^{177}Lu-DOTATATE radiotheranostics is not approved for non-GEP NETs, it represents a viable therapy option that can be considered, especially in patients with limited treatment options provided sufficient SSTR is confirmed on imaging and adequate bone marrow and renal function is established [94]. Prospective trials are needed to confirm the safety of their use and the survival advantage it confers in these non-GEP NETs.

Despite its overall efficacy, some patients do not respond to ^{177}Lu-DOTATATE. Other patients who respond initially, experience disease progression over time. For example, 12% of the NETTER-1 cohort received retreatment with ^{177}Lu-DOTATATE, ^{177}Lu-DOTATOC, or ^{90}Y-DOTATOC during long-term follow-up [97]. Therefore, efforts have been geared toward improving the efficacy of SSTR-targeted radioligand therapy. Such efforts include a combination approach to therapy (for example, combining ^{177}Lu-DOTATATE with chemotherapy), ligand modification to enhance their circulation time, and the replacement of SSTR agonist with an antagonist as the targeting vector [106]. The combination of ^{177}Lu-DOTATATE therapy with chemotherapy is desirable for aggressive NETs due to the potential for improved treatment outcomes compared to either therapy alone [107]. This combination is, however, also associated with a high risk of treatment-induced adverse effects, especially hematologic toxicities. The SSTR-targeting vector in DOTATATE is a small peptide with rapid renal clearance from plasma. A radioligand with a higher molecular weight has a longer plasma circulating half-life, increased overall tumor uptake, and consequently increased radiation dose to the tumor. One strategy to increase the molecular weight of radioligands for radiotheranostics is by introducing albumin-binding motifs into the radioligand [108]. In ^{177}Lu-DOTA-EB-TATE, Evans Blue (EB) is introduced as an albumin-binding motif to increase the bioavailability of the radioligand for improved tumor uptake. Several clinical studies have reported the safety and efficacy of ^{177}Lu-DOTA-EB-TATE in NETs patients [109,110]. A head-to-head comparison of ^{177}Lu-DOTA-EB-TATE versus ^{177}Lu-DOTATATE, in a clinical trial setting, is necessary to determine their comparative safety and efficacy in NETs patients. JR11 is an SSTR antagonist that has been complexed to ^{177}Lu using DOTA as the chelator for radiotheranostics of SSTR-expressing NETs. Unlike agonist-based SSTR-targeting radionuclides, ^{177}Lu-DOTA-JR11 does not undergo internalization after receptor binding yet shows up to five times higher tumor accumulation than internalizing ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC [111,112]. ^{177}Lu-DOTA-JR11 also demonstrates higher retention in normal tissues as shown in a recent phase I/II study, which reported a disease control rate of 94.7%, but 42.5% of patients experienced grade $\geq$3 treatment-related toxicities, especially bone marrow toxicity [113].

Evidence is emerging supporting the favorable potential of targeted alpha therapy of SSTR-expressing tumors using ^{225}Ac-DOTATATE. In a study that investigated the efficacy of ^{225}Ac-DOTATATE in 32 patients with progressive metastatic NETs with a prior history of treatment with ^{177}Lu-DOTATATE, morphologic response was achieved in 24/32 patients during an 8-month follow-up period, including partial remission in 15 and stable disease in 9 patients [114]. Long-term toxicities of ^{225}Ac-DOTATOC were reported in another study that followed up patients with different SSTR-expressing tumors who were treated with 1 to 5 cycles of ^{225}Ac-DOTATOC after failing approved lines of treatments for their disease. The leading acute toxicities in these patients were dose-dependent thrombocytopenia and leucopenia, while chronic kidney disease emerged as the most common long-term adverse event [115]. The rate of glomerular filtration

rate (GFR) loss in the study cohort was reported to be comparable to the rate of GFR loss in NETs patients treated with SSTR-targeting beta-emitting radioligands [115].

4.2. PSMA-targeted radiotheranostics beyond prostate cancer

The expression of PSMA in non-prostate malignancies is the basis for the off-label application of PSMA-targeted radiotheranostics in non-prostate tumors, including salivary gland and thyroid gland tumors [116]. The large number of tumors that overexpress PSMA in the tumor cells or tumor-associated neovasculature demonstrate the broad applicability of PSMA theranostics in oncology. Despite these wide potential applications, much of the evidence relates to PSMA PET imaging of non-prostate cancer, with limited literature reporting PSMA-targeted therapy of non-prostate malignancies. In this section, we will discuss PSMA radiotheranostics of salivary gland tumors and radioiodine refractory thyroid cancer as the archetypal non-prostate cancer malignancies where the utility of PSMA-targeted radiotheranostics has been explored. For these tumors and other non-prostate cancer malignancies not discussed here, PSMA-targeted radiotheranostics is not approved for their routine treatment but offered on compassionate grounds in patients with these tumors with PSMA overexpression after exhausting or are ineligible for approved treatments.

4.2.1. PSMA-targeted radiotheranostics of salivary tumors

Salivary gland tumors are rare types of head and neck tumors. The first-line therapy approach for localized salivary gland tumors is surgery with or without adjuvant radiotherapy. Malignant salivary gland tumors often recur after initial first-line treatment. Treatment for progressive recurrent disease includes repeat surgery, radiotherapy, or a combination of both for localized disease. Systemic therapy is offered to patients with metastatic disease. The choice of systemic therapy for metastatic salivary gland cancers (SGC) is influenced by the pattern of molecular target expression in the disease, including human epidermal growth factor 2 (HER2), androgen receptors, and others. The choice of systemic therapy, therefore, includes chemotherapy, HER2 targeting with Trastuzumab, anti-androgen therapy, immunotherapy, and other targeted therapies. These agents, alone or in combination, show good anti-cancer activity initially, but SGC progression eventually occurs [117]. Immunohistochemical analysis has confirmed PSMA expression in normal salivary gland tissue and tumor cells of SGC [118]. PSMA PET imaging has emerged as a valuable tool for re-staging SGC and confirming PSMA expression in tumor lesions [119,120]. For SGC sufficiently expressing PSMA, PSMA-targeted radiotheranostics with ^{177}Lu-PSMA is, therefore, a reasonable therapy option for consideration in patients with metastatic progressive SGC. Recently published case studies and small series have reported the effectiveness of ^{177}Lu-PSMA in treating advanced SGC, especially adenoid cystic carcinoma [121-123]. Most treated patients achieved pain relief, while objective tumor response was recorded in a small fraction of patients treated with ^{177}Lu-PSMA for different SGC. Further work is necessary to explore the potential clinical utility of PSMA-targeted radiotheranostics in SGC, especially since not all patients tolerate the treatment or demonstrate objective response [120,123].

4.2.2. PSMA-targeted radiotheranostics of radioiodine refractory thyroid cancer

There are very limited therapy options available to patients with radioiodine refractory differentiated thyroid carcinoma (RR-DTC). In a retrospective study of five patients, the utility of PSMA-targeted imaging and therapy of RR-DTC radiotheranostics was reported [124]. PSMA expression in RR-DTC and eligibility for PSMA-targeted radiotheranostic was confirmed in 3 of 5 patients. Of the two patients who received

two cycles of ^{177}Lu-PSMA, one achieved partial response to treatment while the disease progressed in the other despite the treatment. In the data presented, there is wide variability in the PSMA avidity within and between patients, emphasizing the role of PSMA imaging in patient selection [124]. The mixed pattern of response shown may also be related to the heterogeneity of PSMA expression demonstrated in the lesions on PET imaging.

5. On the horizon – promising radiotheranostic agents with potential for widespread clinical applications

Following the success recorded with the recent clinical introduction of ^{68}Ga-DOTATATE and ^{177}Lu-DOTATATE for radiotheranostics of well-differentiated GEP-NETs and ^{68}Ga-PSMA and ^{177}Lu-PSMA for radiotheranostics of prostate cancer, there have been tremendous interests in developing other theranostic pairs for oncologic applications. Several novel targets have been explored, and radiolabeled ligands targeting them have been developed. At the forefront of these novel agents in the developmental pipeline are radiolabeled ligands targeting fibroblast activation protein and the chemokine receptor CXCR4. These radiotheranostic agents have been comprehensively characterized in preclinical studies, and available clinical evidence supports their further exploration for their potential application in routine clinical practice (Table 3).

5.1. FAP-targeted radiotheranostics

The cancer mass comprises the tumor cells and the tumor microenvironment (TME). TME has several constituents, including the stroma and infiltrating immune cells. Cancer-associated fibroblasts (CAF) are the most abundant cellular components of the TME and play critical roles in tumor formation and progression, including cellular proliferation, infiltration, angiogenesis, extracellular matrix remodeling, metabolic reprogramming, inflammation and immune evasion, and resistance to anti-cancer treatment [125]. Fibroblast activation protein (FAP) is a type II glycoprotein integral to the membrane of CAF and is involved in extracellular matrix remodeling and fibrogenesis via its serine protease activity [126]. FAP is expressed in the majority of epithelial tumors but has a low level of expression in normal tissues [127]. This makes it a suitable target for cancer imaging and therapy.

Table 3: Some ongoing early-phase clinical trials investigating novel radiotheranostic agents targeting tumor-associated molecules and receptors.

Trial number	Radiotheranostic agent/combination or comparator	Target	setting	Primary outcome measures	Phase
NCT04849247	^{177}Lu-FAPI	FAP	FAP-expressing cancers	Safety	I
NCT05410821	^{177}Lu-DOTA-EB-FAPI	FAP	Metastatic radioactive iodine refractory thyroid cancer	Safety, tolerability, and maximum tolerated dose	I
NCT05963386	^{177}Lu-DOTA-EB-FAPI	FAP	FAP-expressing cancers	Safety and tolerability	I
NCT06081322	^{177}Lu-EB-FAPI	FAP	Advanced cholangiocarcinoma and pancreatic tumors	Safety, tolerability, and objective response rate	I
NCT06132737	^{90}Y-Pentixather	CXCR4	Recurrent or refractory primary or isolated secondary central nervous system lymphoma.	Safety and tolerability	I/II
NCT03872778	^{177}Lu-NeoB	GRPR	Advanced or metastatic solid tumors, including breast cancer, lung cancer, prostate cancer, gastrointestinal stromal tumors, and glioblastoma, for whom no standard therapy is available	Safety, tolerability, dosimetry, and disease control rate	I/IIa
NCT05870579	^{177}Lu-NeoB combined with Ribociclib and Fulvestrant	GRPR	ER+, HER2-, GRPR+ advanced or metastatic breast cancer that relapsed during or within 12 months of prior (neo)adjuvant endocrine therapy.	Dose-limiting toxicity	I
NCT02088645	^{177}Lu-PP-F11N	CCK2R	Metastatic medullary thyroid carcinoma	Maximum tolerated dose	I
NCT04674722	^{188}Re-NM-02	HER2	HER2+ metastatic breast cancer	Safety and tolerability	I

Following the recognition of the suitability of FAP as a theranostic target, several inhibitors of FAP have been developed and conjugated to radionuclides for imaging of various cancers. The earliest FAP inhibitors (FAPi), including FAPi-01, FAPi-02, FAPi-04, and FAPi-46, were small molecular ligands with fast uptake by the tumor cells and prompt renal clearance, making them suitable for imaging with excellent target-to-background radioactivity ratio [128,129]. These favorable biodistribution characteristics and the overexpression of FAP in several solid tumors have contributed to the excellent diagnostic performance of FAP-targeted PET imaging reported in the literature, outperforming FDG PET for some indications due to the detection of lesions missed on FDG PET, leading to a change in management decision [130-132]. FAP-targeted PET imaging has also been used as a surrogate marker for the in vivo characterization of tumor biology, including tumor hypoxia, showcasing the interrelatedness of different tumor biology that drives aggressive behavior [133]. The earlier developed FAPi radioligands have good tumor uptake and background clearance but show rapid washout from the tumor [134,135]. The characteristics of an ideal radioligand for radionuclide therapy include good uptake and prolonged intra-tumoral retention for improved radiation dose to the tumor. Radiotheranostics with these FAPi molecules, including FAPi-04 and FAPi-46, with rapid washout from the tumor produced a modest clinical response [136]. To address this limitation of rapid washout of the radioligand from the tumor, new generations of FAPi have been developed to improve tumor retention for optimal cytotoxic dose delivery. Strategies explored in improving intra-tumoral retention of radiolabeled FAPi for cancer theranostics include ligand conjugation to albumin binders, ligand dimerization, and small molecular ligands substitution with larger peptides [137].

FAPi-2286 has a cyclic FAP binding motif with the cyclic structure of the peptide conferring higher binding affinity, target selectivity, and improved plasma stability. In a preclinical investigation, FAPi-2286 showed significantly higher tumor retention than FAPi-46 [138]. Intra-tumoral radioligand retention was demonstrated up to 10 days after treatment with 2.4 GBq of ^{177}Lu-FAPi-2286 in a patient with widespread metastatic breast cancer [139]. ^{177}Lu-DOTAGA.(SA.FAPi)$_2$ is another FAPi radioligand consisting of dimerized FAPi molecule with squaramide (SA) as the linker, DOTAGA as the bifunctional chelator and ^{177}Lu as the therapy radionuclide [140]. In a group of 15 RR-DTC patients who received a total of 45 cycles of ^{177}Lu-DOTAGA.(SA.FAPi)$_2$, all patients showed biochemical evidence of response to treatment (decline in thyroglobulin level) [141]. Among the seven patients who were imaged with ^{68}Ga-DOTA.SA.FAPi PET/CT for imaging-based response assessment, four showed partial response while the other 3 showed stable disease. Further modifications to FAP-targeting ligands for improved tumor retention and radiation dose delivery have been investigated in several preclinical studies and are awaiting clinical translation [136]. So far, the available evidence shows that FAP-targeted PET imaging will contribute to advancing clinical imaging of many tumors due to its superior diagnostic performance than the currently utilized imaging techniques in routine clinical practice. As for FAP-targeted radionuclide therapy, emerging evidence supports further investigation for its improvement and advancement into routine clinical practice.

5.2. CXCR4-targeted radiotheranostics

Chemokine receptor 4 (CXCR4) is a transmembrane G-protein coupled receptor that exerts its biological effect by binding stromal-derived factor 1 (SDF-1, also known as CXC12), its natural ligand. It is ubiquitously expressed in embryonic and adult tissues as well as in diseased states, including tumor cells [142]. It is well-known for its role in modulating the trafficking of hematopoietic cells from the bone marrow to the peripheral circulation and as a co-receptor of the human immunodeficiency virus. Plerixafor, a synthetic antagonist of CXCR4, is approved for mobilizing hematopoietic stem cells from the bone marrow for

harvesting for transplantation in patients with hematologic malignancies [143]. In cancer cells, CXCR4 and its ligand, CXCL12, promote aggressive tumor biology, including proliferation, invasiveness, angiogenesis, and metastasis. Patients whose cancer expresses CXCR4, therefore, have significantly shorter OS and PFS than patients with CXCR4-negative tumors [144].

Due to its critical roles in cancer evolution and its overexpression in several hematologic and solid tumors, ligands targeting CXCR4 were developed and labeled with radionuclides for radiotheranostics. Pentixafor labeled to ^{68}Ga (^{68}Ga-Pentixafor) was the first diagnostic CXCR4-targeting agent successfully used in the clinics for oncologic and inflammation/infection imaging [145,146]. Recently, the level of CXCR4 expression was characterized using ^{68}Ga-Pentixafor PET/CT in 690 patients with different solid and hematologic malignancies, validating the role of this imaging technique for selecting patients for CXCR4-targeted radioligand therapy [145]. Typically, in radiotheranostics, a vector complexed to a diagnostic radionuclide is used for imaging, while the same vector complexed to a therapeutic radionuclide is used for treatment. With CXCR4-targeted radiotheranostics, ^{68}Ga-Pentixafor is used for imaging, but complexing of therapeutic radionuclide to pentixafor reduced its affinity for the target by about ten folds, making it unsuitable as a therapy vector [147]. Instead, PentixaTher, with a higher affinity for the CXCR4 target, is complexed to ^{177}Lu or ^{90}Y for therapy of CXCR4-expressing tumors [148]. Most of the current experience with CXCR4-targeted radioligand therapy is in its application in hematologic malignancies due to the over-expression of CXCR4 in these tumors. Good anti-tumor activity of ^{177}Lu- or ^{90}Y-PentixaTher has been reported from small studies that included patients with multiple myeloma who have failed multiple lines of treatment [149,150]. Similar demonstrable anti-tumor activity has been reported in patients with other tumor types treated with ^{177}Lu- or ^{90}Y-PentixaTher, including diffuse large B-cell lymphoma and relapsed T-cell lymphoma [151,152]. A remarkable response to ^{90}Y-PentixaTher was recently reported in eight patients with desmoplastic small round cell tumor, a rare malignant mesenchymal tumor with limited available effective treatment [153]. This represents one of the rare applications of CXCR4-targeted radiotheranostic in non-hematologic malignancy.

Hematopoietic cells over-express CXCR4 resulting in high accumulation and retention of radiolabeled PentixaTher in the bone marrow with a resultant high radiation dose to the red marrow. This is a double-edged sword as high marrow accumulation of the therapeutic radioligand helps eradicate tumors within the marrow but also results in radiation dose to the red marrow, causing hematologic toxicities. Indeed, hematologic toxicity is the commonest and most severe adverse effect of CXCR4-targeted radiotheranostics [154]. Treatment with CXCR4-directed radiotheranostics is, therefore, administered at a myeloablative dose, which is soon followed by hematopoietic stem cell transplantation. The shorter half-life of ^{90}Y makes it a better radionuclide than ^{177}Lu for CXCR4-targeted radiotheranostics, allowing for the earlier institution of hematopoietic stem cell transplantation soon after therapy and before sepsis, a common cause of mortality in the treated patients, sets in. Because stem cell transplantation is not well-validated for non-hematologic malignancies, CXCR4-targeted theranostics currently plays a limited role in these conditions. There are ongoing efforts to develop novel CXCR4 ligands, attempting to build on the current ligand's success while improving its weakness [155-157].

6. In the pipeline – radiotheranostic agents with the potential for clinical translation

There are several targets overexpressed by specific tumors or groups of cancers sharing similar biological attributes. Radiotheranostic agents for imaging and therapy can be developed to target these motifs overexpressed by the cancer cells or components of the tumor microenvironment. This, therefore, presents limitless opportunities for possible radiotheranostic agents that can be designed to target cancer cells for oncologic treatment. Consequently, several radioligands exploiting different molecular targets expressed by cancer cells and cells of the tumor microenvironment have been investigated to varying extents in preclinical studies. Some of these novel agents have been investigated in limited published clinical studies and a few ongoing clinical trials (Table 3). In this section, we will briefly highlight a few of the most promising radioligands, which we believe have the greatest promise for clinical translation.

6.1. GRPR-targeted radiotheranostics

Gastrin-releasing peptide receptors (GRPR) are G-coupled receptors that modulate various physiologic functions, including gastrointestinal hormone secretion, gastric and pancreatic exocrine hormone secretion, and smooth muscle contraction. Gastrin-releasing peptide (GRP), the natural ligand of GRPR, is structurally similar to bombesin, a linear tetradecapeptide first extracted from the skin of the European frog, *Bombina bombina*. GRPR is overexpressed in many human solid tumors, including cancers of the prostate, breast, pancreas, lung, and brain [158]. The radiotheranostic prospects of GRPR have attracted much interest for over a decade [159]. The first group of ligands developed to target GRPR were agonists of the receptors, which were abandoned due to their ability to activate the GRPR in vivo and cause gastrointestinal side effects. This led to the development of antagonists of the GRPR as vectors for radiotheranostics of GRPR-expressing tumors. NeoBOMB1 and RM2 are antagonists of GRPR with good in vivo stability. These ligands have been labeled with ^{68}Ga, and their utility for prostate cancer imaging has been reported extensively in the literature [160]. Their utility in non-prostate malignant has also been reported, albeit to a lesser extent [161]. In a cohort of breast cancer patients, ^{68}Ga-RM2 uptake was demonstrated in primary breast cancer and its metastasis, while normal breast tissue showed moderate and variable radiotracer uptake [162]. There was a positive association between ^{68}Ga-RM2 PET positivity and estrogen receptor and progesterone receptor positivity [162]. The therapeutic potential of GRPR targeting has been investigated with ^{177}Lu-NeoB in preclinical models of breast cancer and gastrointestinal stromal tumor (GIST) [163,164]. Both studies reported good retention of the radioligand by the tumor with off-target uptake in the normal pancreas, liver, and kidneys. No evidence of pancreatic damage was seen, but some renal changes suggestive of radiation damage were reported. Sequel to these encouraging results from preclinical studies, ^{177}Lu-NeoB is being investigated in a first-in-human phase I/IIa clinical trial to determine its safety, tolerability, whole-body distribution, radiation dosimetry, and anti-tumor activity in patients with different advanced solid tumors expressing GRPR, including breast cancer, prostate cancer, lung cancer, glioblastoma, and GIST (NCT03872778).

6.2. CCK_2R-targeted radiotheranostics

The cholecystokinin receptors (CCKR) are another G-coupled receptor in the gastrointestinal tract, where they modulate several physiologic functions, including gall bladder contraction, gastric acid secretion, and intestinal motility. The natural ligands for these receptors are gastrin and cholecystokinin. The cholecystokinin 2 receptor (CCK_2R) has attracted a lot of interest as a suitable radiotheranostic target due to its overexpression in tumors such as medullary thyroid carcinoma (MTC), ovarian stroma tumors, and small cell lung cancer [165]. Interestingly, it is also overexpressed in gastrointestinal tract tumors not

expressing SSTRs, such as insulinomas, carcinoids, and GIST. Several radiolabeled gastrin analogs have been developed for CCK_2R-targeted radiotheranostics of tumors, especially MTC [166,167]. The radiotheranostic agents have witnessed several iterations of modifications over the last two decades to address challenges associated with the earlier agents, such as receptor stimulation by the earlier CCK_2R agonists producing side effects, especially with high peptide concentration during therapy, increased renal accumulation causing renal toxicity, and in vivo instability [166,167]. MGS5 chelated to radiotheranostic metals (^{68}Ga, ^{111}In, and ^{177}Lu) with DOTA is a novel minigastrin analog that has shown promise as a CCK2R-trageting radiotheranostic agent due to its affinity for the membrane-bound target, low uptake in normal tissues, and good in vivo stability [168]. The clinical performance of ^{68}Ga-DOTA-MGS5 was recently reported in six MTC patients, where 87 lesions with excellent target-to-background activity were seen on PET/CT imaging [169]. This encouraging preliminary data justifies further clinical investigation that will pave the way for investigating the therapeutic benefit of CCK2R-targeted radiotheranostics.

6.3. HER2-targeted radiotheranostics

Human epidermal growth factor receptor 2 (HER2) is a membrane receptor kinase whose dimerization with other receptors in the HER receptor family results in autophosphorylation of tyrosine residues within the cytoplasmic domain of the heterodimer and initiates downstream signal pathways leading to cellular proliferation [170]. HER2 is overexpressed in several tumors, including cancers of the breast, ovary, endometrium, gastrointestinal tract, lung, and bladder. HER2 is well-recognized as a druggable molecular target for monoclonal antibodies (trastuzumab and pertuzumab), which are approved for the therapy of HER-2 expressing tumors, particularly breast cancer. These monoclonal antibodies are effective therapy, but resistance against them may develop over time. Radioimmunotherapy, a monoclonal antibody chelated to a therapeutic radionuclide, is a strategy with the potential to improve the treatment outcome of HER2-expressing tumors, especially considering that monoclonal antibodies acting on HER2 increases the radiosensitivity of the tumor cells [171]. Radioimmunotherapy agents targeting tumors expressing HER2 have been developed and explored [172-174]. Whole antibodies have a long residence time in circulation and increase whole-body radiation dose. Antibody fragments and pre-targeting immunotherapy approach are strategies recently explored to improve tumor dose delivery while reducing normal tissue dose [172,173]. These preclinical investigations show that combination therapy in radioimmunotherapy leads to better treatment outcomes than treatment with either cold monoclonal antibody or radiolabeled antibody fragment alone [172]. The finding holds great promise and warrants further evaluation for clinical translation.

6.4. PARP-targeted radiotheranostics

DNA damage abounds in cancer cells. Poly (ADP-ribose) polymerases (PARP) are recruited to the site of DNA damage as single-strand DNA repair enzymes. PARP inhibitors (PARPi) bind to the NAD+ binding pocket of PARP enzymes, inhibiting the repair process, and inducing further DNA damage. Because PARPi inhibitors are trapped in the DNA, they can serve as vectors to convey Auger electrons- emitting radionuclides that cause lethal irreparable DNA damage and, consequently, tumor cell death. Modified PARPi have been labeled with radionuclides for imaging and therapy of PARP-expressing tumors [175,176]. ^{123}I is the most characterized Auger electron emitter for PARP-targeted radiotheranostics. ^{123}I-PARPi has been shown in several preclinical models of human tumors to be safe and induce effective anti-tumor characteristics with prolongation of survival of the treated animals [177-179]. These encouraging results led to the recent report of the first-in-human application of ^{123}I-PARPi SPECT/CT imaging, which showed

good radiotracer tumor uptake in a patient with small cell neuroendocrine tumor that had failed multiple lines of therapy [180]. This clinical report demonstrates the feasibility of ^{123}I-PARPi imaging as a non-invasive tool to assess PARP expression in tumors and pave the way for investigating the therapeutic potential of Auger electron-based radionuclide therapy of PARP-expressing tumors.

7. Conclusion and future perspectives

Over the last few decades, radiotheranostics has contributed significantly to managing oncology patients. The recent confirmation of the life-prolonging effect of ^{177}Lu-DOTATATE and ^{177}Lu-PSMA compared with standard of care in phase 3 clinical trials leading to their approval for the treatment of GEP-NET and advanced prostate cancer, respectively, has further brought to light the tremendous potential radiotheranostic holds in oncology (Table 4). Consequently, there has been significant interest in the number of novel radiotheranostic agents in the developmental pipeline and those being investigated in different phases of clinical trials in preparation for routine clinical deployment (Tables 1-3). There has also been a great deal of industry interest in funding these developmental efforts, portending a promising future for radiotheranostics and its clinical application.

The current success and the promising future of radiotheranostics have resulted from the safety and efficacy of the different theranostic agents, showing good anti-tumor activity, prolonging patients' survival, and improving quality of life. Despite this overall successful treatment outcome, not every patient treated demonstrated an objective response to treatment while some with initial response to treatment eventually develop disease progression. Also, despite the general safety of most radiotheranostic agents (treatment-related adverse events usually reversible and of lesser grade in severity), some patients develop impairment in organ function on long-term follow-up, especially renal failure and hematologic malignancies. These indicate the need for continued refinement of the agents to improve their safety and efficacy, which would be required to establish radiotheranostics as a pivotal therapy option that can be deployed early in the disease course of different oncologic conditions. The goal of refining radiotheranostics should be the improvement of the therapeutic index (increase tumor killing while reducing adverse effects of treatment) of radiotheranostics agents. There are several ways to achieve this, including dosimetry optimization, improving the specificity of the radioligands for tumor-specific targets while reducing uptake and residence in normal tissues, improving radiosensitivity of the tumors, and designing combinatorial approaches for rationale use of radiotheranostics with other groups of anticancer drugs (such as cytotoxic chemotherapy, immunotherapy, external beam radiotherapy, PARPi, among others).

Dosimetry ensures that cytotoxic radiation dose is delivered to the tumor within a reasonable safety margin for normal tissues. A very conservative radiation dose approach has been used in radiotheranostics, with many agents given at an administered activity of 200 mCi (7.4 GBq) for four cycles. Evidence supporting the safety of higher administered activities and treatment cycles abound. Combined with further research on radiation biology to advance our understanding of the biology of tumors and normal tissues when exposed to radiation, the practice of dosimetry needs to be further simplified and standardized to aid its widespread application in routine clinical practice.

Table 4: Summary indications and clinical efficacy data for approved and promising radiotheranostic agents used in non-prostate malignancies.

Agent	Indication	Efficacy data	Approval status
Iodine-131	Ablation of remnant thyroid tissue post total thyroidectomy in low-risk DTC	No impact on survival or recurrence. Improves the clinical value of serum thyroglobulin use as a tumor marker during surveillance.[50]	Approved
	Adjuvant therapy or treatment of known metastatic disease in high-risk DTC	Improved overall and disease-free survival.[52]	
	Adjuvant therapy in intermediate-risk DTC	Improved disease-free survival only in patients >45 years with primary tumor >4 cm, microscopic extrathyroidal invasion, and/or lymph node metastases.[53]	
HSA-^{131}I-MIBG	Metastatic or unresectable pheochromocytoma and paraganglioma	Induces at least a 50% reduction in anti-hypertensive use for at least 6 months in 25% of patients.[78]	Approved
		Induces objective tumor response in 92% of patients with evaluable lesions who received at least 1 treatment cycle, including 23% with partial response and 65% with stable disease.[78]	
^{177}Lu-DOTATATE	Metastatic or inoperable grade I and II GEP-NETs	Reduces the risk of disease progression or death by 79%.[93]	Approved

^{177}Lu-DOTA-JR11	Unresectable grade I/II GEP-NETs, typical or atypical lung carcinoid or paraganglioma/pheochromocytoma	Median PFS of 28.1 months and a median duration of response of 17.9 months. 21.1% and 73.7% of patients achieved partial response and stable disease, respectively.[113]	Not approved
^{225}Ac-DOTATATE	Advanced, progressive metastatic GEP-NETs after prior ^{177}Lu-DOTATATE	Induces disease control in 75% of patients (partial response in 46.9% and stable disease in 28.1%).[114]	Not approved
^{177}Lu-DOTAGA.(SA.FAPi)$_2$	FAP-expressing radioiodine-refractory DTC that progressed on TKIs	Induces molecular response in 46.7% of patients (partial response in 26.7% and stable disease in 20.0%).[141]	Not approved
^{177}Lu-Pentixather	Relapsed or refractory multiple myeloma	Demonstrates anti-tumor effect in 83% of evaluable patients, with median PFS of 54 days and median OS of 223 days.[150]	Not approved

DTC: Differentiated Thyroid Cancer; GEP-NETs: Gastroenteropancreatic Neuroendocrine Tumors; FAP: Fibroast Activation Protein; PFS: Progression-Free Survival; OS: Overall Survival

Molecular targets explored for radiotheranostics are non-specific and are also expressed by normal tissues, which explains some of the off-target effects of radiotheranostics. One potential strategy to optimize the delivery of the therapy agent, specifically to the tumor-expressed targets, is using nanotechnology. This may be particularly helpful in mitigating the toxicity from alpha-emitting daughter nuclides released into circulation during alpha-targeted radiotheranostics, where alpha emission results in bond breakage liberating the daughter radionuclides that accumulate in normal tissues.

The safety and efficacy of novel drugs must be demonstrated in well-designed clinical trials before approval for use in routine clinical practice. The global nuclear medicine community has understood this, translating into the burgeoning number of clinical trials of different phases investigating different radiotheranostic agents for various indications. This is a welcome development that should be supported, with the next step being the facilitation of the transfer of clinical trial expertise across the field.

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