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REVIEW ARTICLE

Recent advances in theranostics and oncology PET: emerging radionuclides and targets

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Abstract

Theranostics, a novel integrated approach that combines cancer diagnosis and therapy by switching the radionuclide, has attracted growing attention. Various oncology PET probes other than FDG have been developed for the highly sensitive and precise detection of many types of cancer with the advancements in PET scanners, supporting the innovative development in theranostics. In therapeutic applications, radioligand therapy targeting somatostatin receptors (SSTR) and prostate-specific membrane antigen (PSMA) has already demonstrated significant clinical benefits. Terbium-161 (^{161}Tb) has emerged as a new beta and Auger electron emitter, showing greater therapeutic efficacy compared to ^{177}Lu. Alpha emitters, such as astatine (^{211}At), are currently being evaluated in investigator-initiated clinical trials, with preliminary efficacy data reported for [^{211}At]NaAt in patients with radioiodine-refractory thyroid cancer. Novel pan-tumor targeting agents, such as TROP-2, Nectin-4, LAT1, GPC-1, and EphA2, are also under development, and clinical translation of radioligand therapy is anticipated. These innovations in theranostics are expected to further broaden the scope of precision medicine in oncology.

Keywords Theranostics · Positron emission tomography · Radioligand therapy · SSTR · PSMA · Astatine · Terbium

Introduction

In recent years, theranostics—a novel approach that integrates cancer diagnosis and therapy by switching the radionuclide used to label compounds targeting specific molecules—has attracted growing attention. The term"theranostics"is a portmanteau of"therapeutics"and"diagnostics,"representing a cutting-edge technology that combines molecular imaging with targeted therapy [1].

In nuclear medicine-based theranostics (radio-theranostics), the process begins with molecular imaging to confirm the expression of specific targets. This is followed by targeted radionuclide therapy aimed at treating systemic cancer lesions [2]. Therapeutic agents labeled with alpha- or beta-emitting radionuclides selectively bind to tumor-specific targets, enabling the delivery of potent radiation directly to cancer cells while minimizing damage to surrounding healthy tissue. Among these, alpha radiation is particularly noteworthy due to its high linear energy transfer (LET) and short path length, which enable it to cause significant cytotoxicity with minimal off-target effects [3]. This makes targeted alpha therapy a promising, patient-friendly treatment strategy with substantial potential.

At the same time, cancer treatment has changed dramatically with the advent of immune checkpoint inhibitors, which are now used as standard therapy for various types of cancer [4]. Although they are often administered to patients with advanced-stage disease, they have recently been applied as neoadjuvant therapy in certain cancers as well [5]. However, sufficient therapeutic effects are not always achieved, and adverse effects can be problematic [6]. Therefore, PET imaging is expected to play an important role in predicting treatment response and monitoring side effects. Furthermore, various PET probes have been developed, and the performance of PET scanners has improved, enhancing both spatial and temporal resolution [7]. Image reconstruction techniques have also been optimized using artificial intelligence (AI), allowing for PET images with even less noise [8]. In this way, advances in oncology PET are supporting its application to radioligand therapy as part of theranostics.

This review summarizes recent trends in oncology PET and theranostics, and highlights emerging radionuclides and

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molecular targets that have attracted increasing attention in recent years.

Recent trends in oncology PET

FDG–PET and immunotherapy-related imaging

[^{18}F]FDG PET remains the standard modality for cancer staging and the diagnosis of recurrence and metastasis. The emergence of immune checkpoint inhibitors, such as anti-PD-1 antibodies (e.g., nivolumab) and anti-CTLA-4 antibodies (e.g., ipilimumab), has expanded the landscape of cancer therapy [4]. Studies have shown that [^{18}F]FDG uptake correlates with PD-1/PD-L1 expression, and PET/CT may serve as a non-invasive tool for evaluating PD-1/PD-L1 expression [9, 10]. Moreover, FDG–PET/CT has proven useful in identifying immune-related adverse events (irAEs) by visualizing abnormal uptake in the thyroid, lungs, gastrointestinal tract, muscles, and skin [11].

Recently, new immuno-PET probe, [^{18}F]AlF–NOTA–PCP2 have been developed and can effectively measure PD-L1 expression in patients with head and neck cancers, outperforming the conventional FDG PET [12]. [^{18}F]AlF–NOTA–PCP2 uptake strongly correlated with PD-L1 levels, highlighting its potential to improve patient stratification and guide personalized treatment strategies. This research was selected as the images of the year at the Society of Nuclear Medicine and Molecular Imaging (SNMMI) 2025 Annual Meeting.

Intratumoral heterogeneity and radiomics

Numerous studies have highlighted the utility of analyzing intratumoral heterogeneity for disease differentiation, gene mutation prediction, and prognosis [13, 14]. Li et al. demonstrated that FDG–PET-based heterogeneity analysis using visual assessment could distinguish solitary pulmonary tuberculosis from non-small cell lung cancer [15]. Similarly, heterogeneity parameters have been shown to predict epidermal growth factor receptor (EGFR) mutation status and treatment response in lung adenocarcinoma patients undergoing EGFR tyrosine kinase inhibitor therapy [16, 17]. However, it remains difficult to evaluate heterogeneity using simple volume of interest measurements in daily clinical practice, and future challenges will involve identifying indices that are easy to measure and incorporating them into image interpretation viewers.

Radiomics research is evolving to incorporate AI. Wei et al. developed a fusion model combining radiomics and deep learning to differentiate pancreatic ductal adenocarcinoma from autoimmune pancreatitis [18]. Machine learning models utilizing FDG–PET/CT-derived features have demonstrated high accuracy in tumor characterization, staging, and prediction of treatment response and outcomes [19]. Furthermore, deep learning has shown promise in distinguishing benign from malignant lesions and in recurrence prediction [20, 21]. Nevertheless, visual assessment remains prevalent in daily clinical practice. To standardize interpretation, the Deauville criteria and volumetric measures like metabolic tumor volume have been adopted [22, 23]. It has been reported that combining qualitative and quantitative approaches enhances diagnostic reliability in somatostatin receptor scintigraphy by measuring SUV while taking into account the range of physiological uptake in normal organs [24].

In malignant lymphoma, not only conventional parameters like SUVmax but also novel metrics such as Dmax—the maximum interlesion distance—have emerged as independent predictors of progression-free and overall survival (PFS and OS) [25]. In addition, lymph node-to-primary tumor SUV ratios have been linked to prognosis [26]. While these new indicators show promise alongside SUVmax, their clinical utility and robustness will require further validation in future studies.

Advancements in dynamic 4D and sequential PET imaging

The recent adoption of silicon photomultiplier (SiPM)-based PET systems has enabled higher sensitivity and improved spatial resolution. These technological advances have made dynamic four-dimensional (4D) PET imaging, which incorporates time as an additional dimension and evaluates the temporal changes in radiotracer distribution, a feasible method for evaluation in clinical practice in addition to conventional static spatial image assessment [27].

Dynamic 4D PET has demonstrated clinical utility across various scenarios. For example, the net influx constant in FDG–PET has been shown to distinguish lymph node metastases in lung cancer [28]. Parametric imaging using Patlak Ki, which refers to the influx rate constant estimated using the Patlak graphical analysis method, in [^{68}Ga]DOTATATE PET for patients with neuroendocrine tumors can highlight lesions with greater contrast than conventional SUV images, potentially reducing false-positive findings [29]. In prostate cancer, PSMA uptake has been observed to increase over time, and dual-timepoint imaging (0–5 min and 55–60 min post-injection) is under investigation, suggesting the potential to improve diagnostic accuracy [30, 31].

In addition, with the advent of total-body PET, it has become possible to obtain whole-body PET images of sufficient quality even with low-dose injections and without extending the acquisition time [32]. Using this technique, the feasibility of performing two types of PET imaging, such as [^{18}F]FDG and [^{68}Ga]FAPI-04, with low-dose administration

in a single day has been demonstrated [33]. However, total-body PET is very expensive and remains difficult to make widely available at this time. Therefore, it may be necessary to utilize AI to optimize imaging protocols to reduce radiation exposure for sequential PET imaging with existing PET scanners.

Emerging PET probes beyond FDG

Amino acid tracers such as [^{11}C]Methionine, [^{18}F]Fluciclovine (FACBC), and [^{18}F]Fluoroethyltyrosine (FET) are used for brain tumor imaging [34–36]. For example, [^{11}C]Methionine PET/CT enables simultaneous assessment of brain and extracranial lesions in breast cancer patients with brain metastases. Tumor-to-normal ratio (TNR), which is defined as the ratio of the radiotracer uptake in the tumor to that in the corresponding normal tissue, has been shown to be more reliable than SUVmax in differentiating recurrence from radiation necrosis [37]. The hypoxic PET probe [^{18}F]Fluoromisonidazole (FMISO) PET uptake patterns differ between IDH-mutant and IDH–wild-type gliomas, suggesting potential as a non-invasive mutation biomarker [38]. With regard to the application for radiotherapy, somatostatin receptor ligand PET using [^{68}Ga]DOTATATE has been reported to be useful for defining the radiation field for the treatment of meningiomas [39].

Fibroblast activation protein inhibitor (FAPI) PET, which targets cancer-associated fibroblasts, has demonstrated superior lesion detection and higher SUVmax in various cancers compared to FDG–PET [40] (Fig. 1). In a study that evaluated bone metastases of various cancers, SUVmax on [^{68}Ga]FAPI–PET was an independent prognostic factor for OS [41]. FAPI–PET is also being investigated for liver fibrotic diseases beyond oncology application [42, 43].

Prostate-specific membrane antigen (PSMA) PET is a highly sensitive imaging modality used across multiple stages of prostate cancer, including initial staging, detection of biochemical recurrence, and therapy planning [44, 45] (Fig. 2). Four PSMA tracers—[^{68}Ga]PSMA-11, [^{18}F]DCFPyL, [^{18}F]PSMA-1007, and [^{18}F]flotufolastat—have been approved in the U.S. or Europe. An international Phase III clinical trial (EAGLE-i trial), which assesses the diagnostic performance of [^{18}F]PSMA-1007 PET in newly diagnosed, high-risk or very-high-risk prostate cancer patients in comparison with conventional imaging, is currently underway in Japan, following prior clinical research and Phase I/IIa studies [46, 47]. In addition, new ^{99m}Tc-labeled SPECT probes are being developed to improve accessibility in regions where the availability of PET imaging is limited [48, 49]. Given the heterogeneity or absence of PSMA expression in some patients with castration-resistant prostate cancer (CRPC) [50], gastrin-releasing peptide receptor (GRPr) PET is also being investigated as a complementary imaging strategy [51].

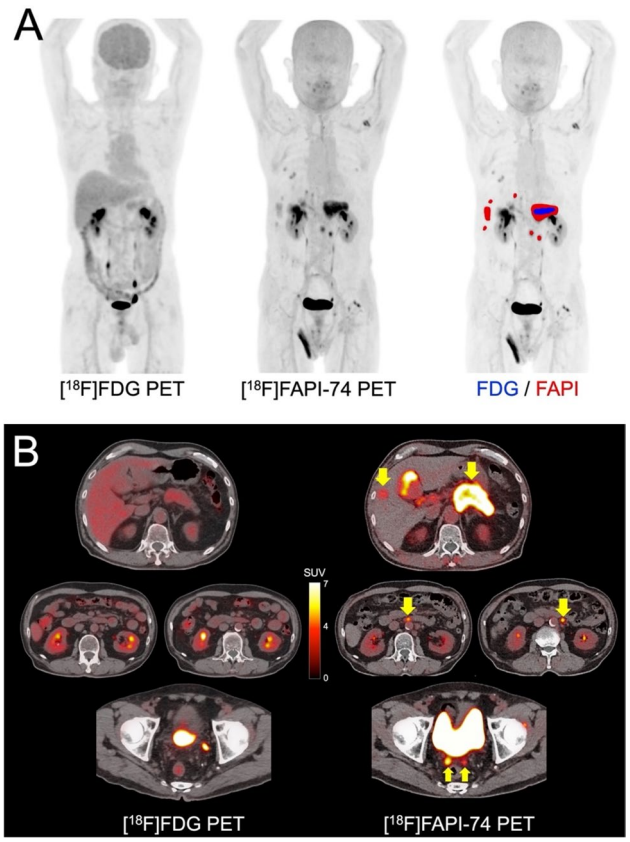

Fig. 1 68-year-old male patient with multiple lymph node and peritoneal metastases of pancreatic cancer. **A** Comparison of the maximum intensity projection (MIP) images: the image on the right shows fusion with positive lesions on [^{18}F]FAPI-74 PET (red-colored area) and [^{18}F]FDG PET (blue-colored area), **B** PET/CT fusion images on [^{18}F]FAPI-74 PET and [^{18}F]FDG PET (arrows indicated metastatic lesions). [^{18}F]FAPI-74 PET detected more metastatic lesions compared with [^{18}F]FDG PET (SUVmax of the primary lesion is 9.4 and 3.2, respectively). (Cited from reference no. 40 in accordance with the open access policy.)

In breast cancer, 16α-[^{18}F]fluoro-17β-estradiol (FES)–PET has demonstrated higher radiotracer uptake and greater lesion detection rates compared to FDG–PET in estrogen receptor (ER)–positive breast cancer [52]. Furthermore, FES PET not only allows for whole-body assessment of ER expression but also serves as a valuable predictive biomarker for assessing the likelihood of response to endocrine therapy response [53]. FES–PET can help guide treatment decisions, monitor therapeutic efficacy, and potentially detect resistance early, thereby contributing to more personalized management strategies for patients with ER–positive breast cancer.

As described above, many promising PET probes targeting various molecules other than FDG have been developed for the highly sensitive and precise detection

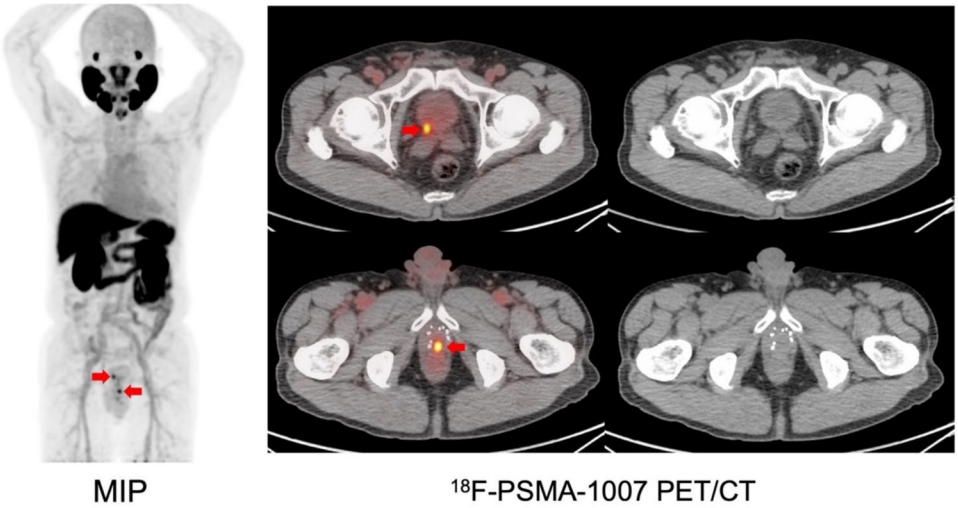

Fig. 2 [^{18}F]PSMA-1007 PET in patient with biochemical recurrence after ^{125}I-seed implantation (PSA at PET: 3.32 ng/mL) (MIP: maximum intensity projection). Focal uptakes are observed on PSMA–PET (red arrows) and biopsy on the caudal lesion revealed a recurrence. Radiation therapy (cyber-knife) is performed targeting the two lesions and PSA value shows a decrease. (Cited from reference no. 46 in accordance with the open access policy.)

of cancer, and these probes are expected to be useful not only for diagnostic imaging but also for theranostics. Furthermore, FDG PET also plays a complementary role depending on tumor differentiation status and will not be completely replaced by emerging PET probes. Combined evaluation using dual [^{68}Ga]DOTATATE and FDG PET/CT has been reported to be useful as a prognostic biomarker in metastatic gastroenteropancreatic neuroendocrine neoplasms [54].

Recent trends in targeted radioligand therapy

[^{177}Lu]DOTATATE (Lutathera)

[^{177}Lu]DOTATATE is a targeted radiopharmaceutical used for the treatment of somatostatin receptor (SSTR)–positive gastroenteropancreatic neuroendocrine tumors (GEP–NETs). The NETTER-1 trial demonstrated significantly prolonged PFS in midgut NETs, leading to FDA and PMDA approval [55]. The NETTER-2 trial showed that combining [^{177}Lu]DOTATATE with octreotide long-acting release (LAR) significantly improved PFS in previously untreated advanced GEP–NETs [56]. In April 2024, FDA approval was extended to include pediatric patients aged 12 years and older.

In terms of predicting treatment efficacy, a retrospective analysis of 40 patients with NETs treated with [^{177}Lu]DOTATATE demonstrated that visual and quantitative analyses of baseline SSTR–PET may be useful indicators for predicting treatment outcomes. A low mean whole-body SUV and presence of SSTR–PET-negative lesions on baseline SSTR–PET may predict shortened PFS [57].

PSMA-targeted radioligand therapy

PSMA expression was observed on PSMA–PET in 95% of patients with metastatic castration-resistant prostate cancer (mCRPC) [58], indicating a promising target for radionuclide therapy. In the TheraP trial, [^{177}Lu]PSMA-617 showed higher PSA response rates and fewer grade 3 or 4 adverse events compared to chemotherapy with cabazitaxel (66% vs. 44% PSA responses; grade 3–4 adverse events: 33% vs. 53%) [59]. In the VISION trial, [^{177}Lu]PSMA-617 (Pluvicto) was shown to improve OS in patients receiving best supportive care after taxane chemotherapy for mCRPC (15.3 months vs. 11.3 months, HR 0.62), and was approved by the FDA in 2022 [60]. Furthermore, in the PSMAfore study, in patients with mCRPC who had not received taxane chemotherapy, [^{177}Lu]PSMA-617 prolonged radiographic PFS compared to a change in androgen receptor pathway inhibitor (ARPI), with a favorable safety profile (11.6 months vs. 5.6 months, HR 0.49). FDA approval for its use prior to chemotherapy was granted in April 2025 [61]. Recently, [^{177}Lu]PSMA-617 in combination with hormone therapy provided a statistically significant and clinically meaningful benefit in radiographic PFS in patients with PSMA–positive metastatic hormone-sensitive prostate cancer (mHSPC), compared to hormone therapy alone, based on interim results from the Phase 3 PSMAddition trial (NCT04720157). Thus, the indication for PSMA-targeted radioligand therapy (RLT) is being shifted earlier in the treatment sequence, expanding the number of eligible patients.

The validity of criteria for companion diagnostics using PSMA–PET in real-world clinical practice for PSMA-targeted RLT is also under evaluation. While the VISION trial used PSMA–PET/CT-based inclusion criteria, the TheraP trial employed dual-tracer imaging, including FDG–PET/CT. Retrospective application of the VISION

trial's inclusion criteria shows benefits in OS and PFS following PSMA–RLT, but the TheraP criteria may be too stringent for patients with advanced prostate cancer. Therefore, more relaxed eligibility criteria, such as those used in the VISION trial, may facilitate broader access to PSMA-targeted therapy [62].

[^{131}I]MIBG and radioiodine therapy

Metaiodobenzylguanidine (MIBG) is a norepinephrine analog that is used as both a diagnostic and therapeutic radiopharmaceutical, particularly in the management of pheochromocytoma, paraganglioma, and neuroblastoma [63]. Structurally similar to norepinephrine, MIBG is selectively taken up by adrenergic nerve terminals and tumor cells through the norepinephrine transporter. [^{131}I]MIBG has been approved in Japan since 2022 for the treatment of pheochromocytoma and paraganglioma, with expanded coverage for MIBG–positive neuroblastoma beginning in April 2025. In pediatric patients with high-risk neuroblastoma, myeloablative therapy with [^{131}I]MIBG in combination with high-dose chemotherapy and bone marrow transplantation has shown high efficacy, with 67% achieving complete remission [64].

Radioiodine (^{131}I) is a standard treatment for differentiated thyroid cancer (DTC), used for the ablation of residual thyroid tissue after total thyroidectomy and for the treatment of distant metastatic disease, especially in patients with iodine-avid lesions [65]. Recently, a retrospective cohort analysis of patients from the SEER database showed that ^{131}I therapy was associated with a survival benefit in DTC patients with distant metastasis [66]. In addition, adjuvant radioiodine therapy has been shown to be beneficial for achieving biochemical remission and prolonging disease-free survival in patients undergoing reoperation for cervical lymph node recurrence in papillary thyroid cancer. Patients who received ^{131}I demonstrated significantly better biochemical remission rates than those who did not. It has been shown that adjuvant radioiodine therapy after reoperation for patients with recurrent or residual thyroid cancer may contribute to biochemical remission and extend disease-free survival to some extent [67].

A retrospective study examining the relationship between changes in serum thyroglobulin levels before and after radioiodine therapy and recurrence-free survival in patients with DTC showed that these changes were associated with radiographic PFS. Patients with decreased post-therapy thyroglobulin levels had a favorable prognosis, even if thyroglobulin remained detectable after ^{131}I therapy [68].

Thus, while ^{131}I therapy has been performed for many years, high-level evidence regarding its prognostic efficacy had been limited, but such evidence is now gradually accumulating. Although the optimal timing of postoperative ^{131}I in DTC patients remains unclear due to a lack of definitive evidence [69], deferring initial radioiodine therapy beyond 180 days following total thyroidectomy may be associated with inferior survival outcomes in patients with differentiated thyroid cancer [70].

Dosimetry and practical considerations

Dosimetry and post-therapeutic imaging are also important for monitoring and predicting treatment efficacy and side effects in RLT. In the future, it may be possible to achieve personalized medicine by determining the injection dose that maximizes therapeutic efficacy while minimizing major side effects through dosimetric calculation. Accurate dosimetry typically requires time-lapse imaging at multiple timepoints, but there is a recent trend toward simplified assessment using single-timepoint imaging [71]. However, since planar imaging alone tends to overestimate the absorbed dose, it has been reported that combining at least one SPECT acquisition is preferable [72].

In addition, in countries with strict radiation safety regulations, such as Japan and Germany, therapy using ^{131}I or ^{177}Lu requires hospitalization in an isolated radionuclide therapy room or a specially equipped treatment room, and securing such rooms is often a logistical challenge. To be discharged, patients must meet specific release criteria on radiation dose, and a practical prediction formula has been developed to estimate the dose rate reduction around patients after administration with [^{177}Lu]DOTATATE. It has been reported that a predictive formula incorporating maximum tumor diameter and creatinine clearance shows a strong correlation with dose rate reduction and can serve as a useful tool for post-treatment patient management [73].

Future outlook for theranostics

Next-generation beta-emitter

Currently, lutetium-177 (^{177}Lu; half-life: 6.7 days) is the primary beta-emitting radioisotope used in the development of RLT agents, but terbium-161 (^{161}Tb; half-life: 6.9 days), which has a similar half-life and beta radiation energy, is gaining increasing attention [74]. ^{161}Tb emits not only beta particles but also Auger electrons and internal conversion electrons. Auger electrons deposit their energy within a few nanometers, causing dense ionization near DNA and the effective induction of DNA double-strand breaks when the radionuclide is internalized close to the cell nucleus [75]. As a result, [^{161}Tb]PSMA-617 has shown greater therapeutic efficacy than [^{177}Lu]PSMA-617 in both in vitro studies and tumor-bearing animal models [76].

In addition, in a preclinical study comparing an SSTR-targeting agonist (with internalization) and an antagonist

(LM3; without internalization), labeling with ^{161}Tb demonstrated superior therapeutic effects compared to ^{177}Lu, suggesting that Auger electrons emitted by ^{161}Tb may exert cytotoxic effects on the cell membrane [77]. Clinical use of ^{161}Tb-labeled agents targeting PSMA and SSTR2 antagonists has already been reported [78, 79], with several clinical trials currently in progress. Their future outcomes are eagerly awaited.

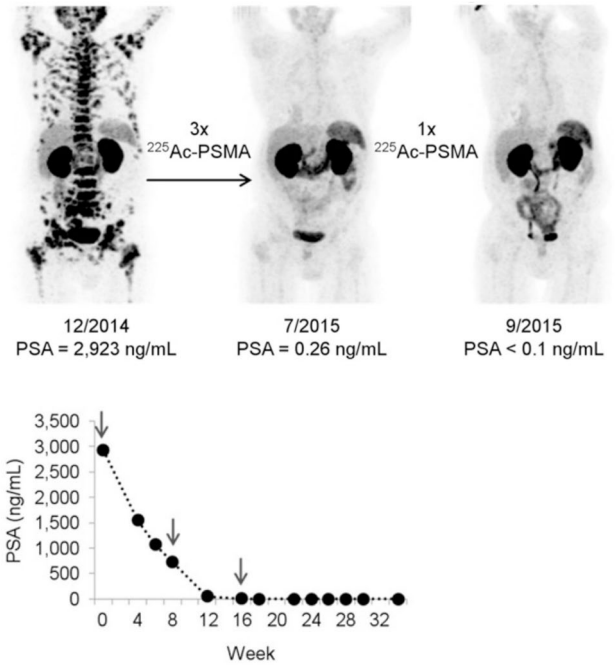

Fig. 3 [^{68}Ga]PSMA-11 PET/CT scans in a metastatic castration-resistant prostate cancer patient with diffuse bone metastases after administration of [^{225}Ac]PSMA-617. Complete remission was achieved after four cycles of treatment. (Cited from reference no. 79 in accordance with the open access policy.)

Targeted alpha therapy

Since alpha particles emit high energy over a short range, they are expected to be very effective in treating refractory patients who are resistant to conventional beta-ray therapy (Fig. 3) [80]. Among alpha-emitting radionuclides, radium-223 (Ra) is used for treating bone metastases in mCRPC, accumulating in osteoblastic lesions with increased bone turnover due to its calcium-mimetic properties. Although ^{223}Ra was shown to extend OS in the ALSYMPCA trial [81], its therapeutic effect—such as PSA reduction—was limited, because it does not directly target tumor cells. However, the PEACE-3 study demonstrated that combination therapy with enzalutamide and ^{223}Ra significantly prolonged OS (42.3 months vs. 35.0 months, HR 0.69) [82]. Fracture risk had been a concern with this combination, but it was confirmed that the use of bone-protecting agents did not increase the incidence of fractures [83]. Nevertheless, since ^{223}Ra cannot be easily used as a radiolabeled compound, further development has been limited.

Currently, clinical trials are underway for targeted alpha therapy using three alpha-emitting radionuclides: actinium-225 (^{225}Ac), lead-212 (^{212}Pb), and astatine-211 (^{211}At) (Table 1) [84]. Targeted alpha therapy with [^{225}Ac]DOTATATE has shown promising results, improving overall survival even in patients who are refractory to prior [^{177}Lu]DOTATATE therapy, with minimal toxicities in GEP–NETs [85]. In mCRPC patients, [^{225}Ac]PSMA RLT has demonstrated that approximately 60% of patients achieve a PSA decline of more than 50%, and 70–80% of patients experience some PSA decline after therapy [86, 87].

In the case of astatine, Japan has taken a leading role, having completed an investigator-initiated clinical trial using sodium astatide ([^{211}At]NaAt) (Alpha-T1 study: NCT05275946), and currently conducting trials with [^{211}At]PSMA-5 (Alpha-PS1 study: NCT06441994) and [^{211}At]

Table 1 Comparison of recent therapeutic radionuclides with alpha or beta emission

	^{177}Lu	^{225}Ac	^{212}Pb	^{211}At
Radiation	β	α	α/(β)	α
Half-life	7 days	10 days	10.6 h	7.2 h
Therapeutic effect	+	+ +	+ +	+ +
Exposure to surroundings	High	Low	Low–moderate	Low
Isolation	Required	Not required	Not required?	Not required
Outpatient treatment	×*	○	○?	○
Domestic production	×	×	×	○
Cyclotron manufacturing	×	Possible	×	○
Imaging	○	×	○	○
Approval status	FDA approved	No	No	No

+: moderate therapeutic effect; + +: strong therapeutic effect,?: data or consensus currently limited or under investigation,○: generally feasible; ×: not generally feasible, *: depending on regulatory authority regulations in each country)

MABG (jRCT2021220012) (Fig. 4) [88, 89]. In the clinical trial using [^{211}At]NaAt, tolerability and evidence of efficacy were confirmed in patients with radioiodine-refractory thyroid cancer [90]. While the supply of alpha-emitting radionuclides has historically been a limiting factor, industrial production is now underway, and a manufacturing and distribution infrastructure is being established, raising expectations for large-scale availability in the near future [84].

Emerging molecular targets

Development is also underway for new targets in RLT. Carbonic anhydrase IX (CA IX) is a cancer-associated enzyme activated by hypoxia on cell membranes in various tumors, supporting pH regulation as well as cancer cell invasion and metastasis [91]. It catalyzes the reversible conversion of carbon dioxide to bicarbonate and protons, and interacts with various molecules that transport ions and metabolites across cell membranes [91]. CA IX is highly expressed in clear cell renal cell carcinoma, and earlier development efforts primarily focused on antibodies, such as [^{89}Zr]-DFO–girentuximab [92]. The recent emergence of small molecules and peptides has enabled the initiation of clinical research and trials using [^{68}Ga]DPI-4452 PET, [^{64}Cu]PD-32766 PET, and [^{177}Lu]DPI-4452 (NCT05706129) [93]. In [^{68}Ga]-DPI-4452 PET, some metastatic lesions showed SUVmax exceeding 100, suggesting promising uptake characteristics; however, the correlation with the therapeutic efficacy of [^{177}Lu]DPI-4452 remains to be conclusively demonstrated.

Trophoblast cell surface antigen 2 (TROP-2) is a transmembrane glycoprotein highly expressed in various solid tumors and is involved in cell adhesion and signal transduction [94]. It promotes tumor formation and metastasis and is overexpressed in many cancers, including pancreatic, breast, colorectal, bladder, and non-small cell lung cancers, while showing minimal expression in normal tissues [95]. An anti-TROP-2 antibody–drug conjugate (ADC) has already been approved for triple-negative

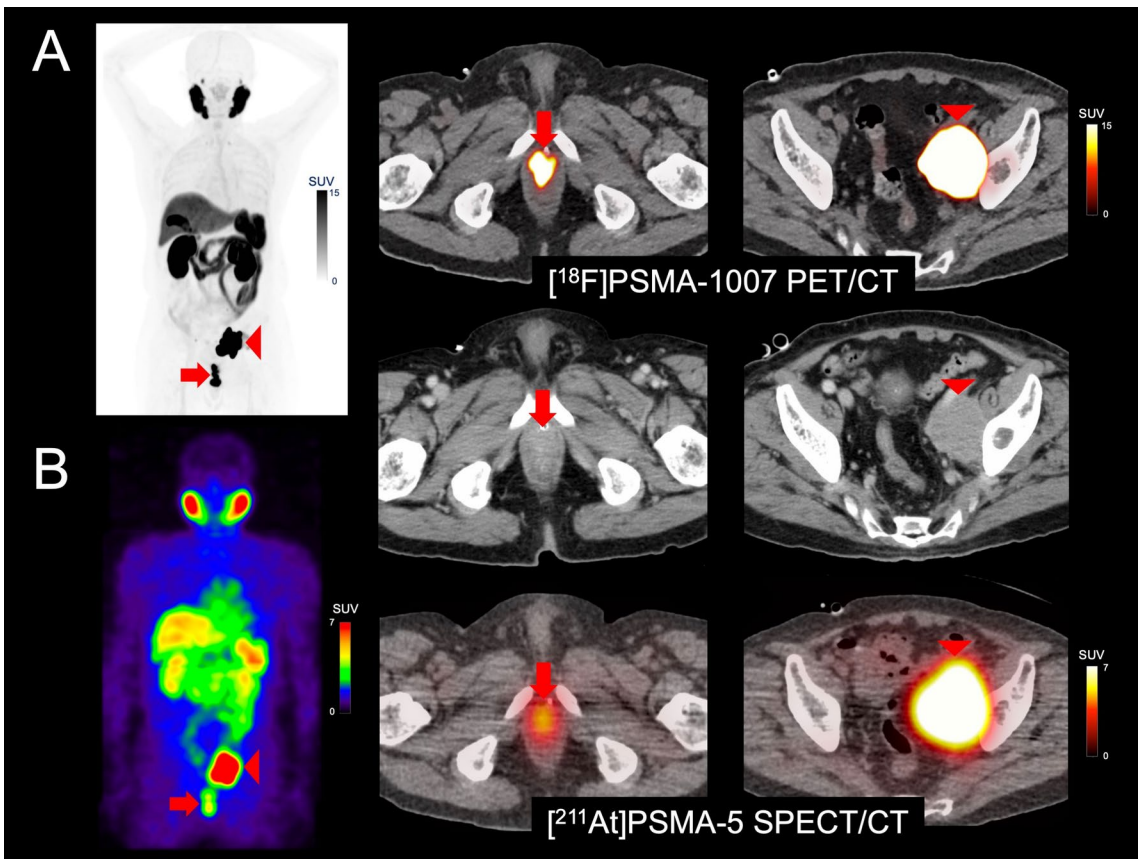

Fig. 4 [^{211}At]PSMA-5 was administered to a man in his 70 s with metastatic castration-resistant prostate cancer refractory to standard treatment, including androgen receptor signaling inhibitors, docetaxel, and cabazitaxel. Pre-treatment [^{18}F]PSMA-1007 PET/CT (**A**) and [^{211}At]PSMA-5 SPECT/CT (**B**) images showed similar distribution patterns, with high uptake in recurrent/metastatic lesions (left: maximum intensity projection, right: fusion and contrast-enhanced CT images). Both images revealed high accumulation in the soft tissue mass within the prostate area (SUVmax = 60.7 on [^{18}F]PSMA-1007 PET and 4.9 on [^{211}At]PSMA-5 SPECT) (arrows) and in the enlarged left external iliac lymph node metastasis (SUVmax = 143.7 and 17.6, respectively) (arrow heads). (Cited from reference no. 85 in accordance with the open access policy.)

breast cancer. In addition, [^{68}Ga]MY6349 PET, developed by Chen et al., has demonstrated high uptake in various cancer types, including breast cancer (Fig. 5) [96]. It has also been shown that [^{68}Ga]MY6349 PET/CT can detect early therapeutic response to ADC treatment in triple-negative breast cancer [96]. ^{89}Zr/^{177}Lu-labeled TROP-2 antibodies have also been developed and evaluated in preclinical studies [97]. Clinical translation using small molecules or peptides for TROP-2-targeted RLT is anticipated in the near future.

Nectin-4 is a transmembrane protein and a member of the cell adhesion molecule family that interacts with other Nectin family members (especially Nectin-1), thereby enhancing intercellular adhesion [98]. In the tumor microenvironment, it promotes cell proliferation, migration, and invasion, and is highly expressed in various epithelial tumors, including bladder, lung, breast, and head and neck cancers. Conversely, in normal tissues, it is expressed only at low levels in select skin, lung, and placental tissues. A Nectin-4-targeted ADC (enfortumab vedotin) has already been approved for

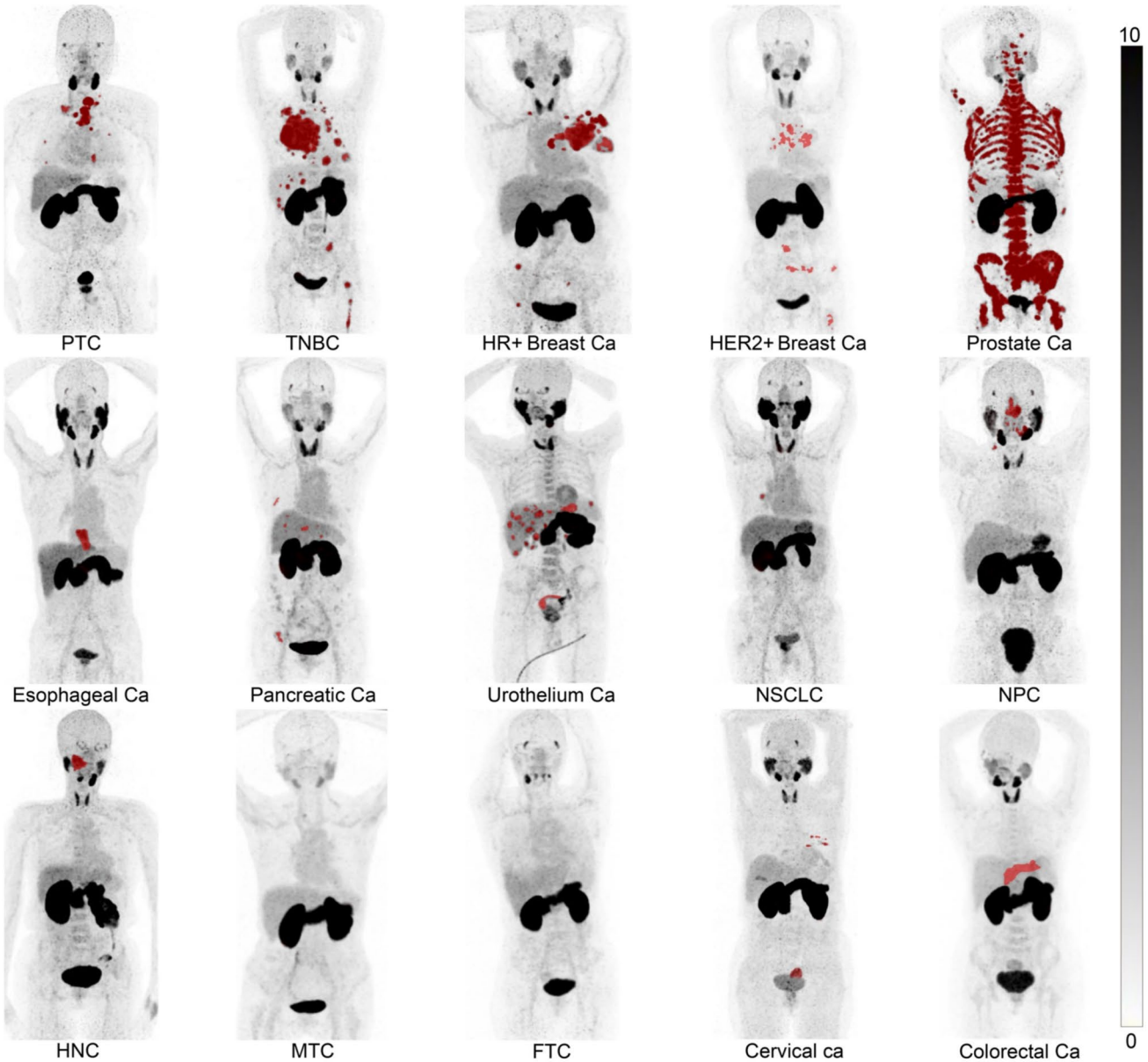

Fig. 5 [^{68}Ga]MY6349 PET/CT imaging targeting TROP-2 in patients with 15 different histologically confirmed tumor entities. Ca, cancer; FTC, follicular thyroid carcinoma; HER2, human epidermal growth factor receptor 2; HNC, head and neck cancer; HR, hormone receptor; MTC, medullary thyroid cancer; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; PTC, papillary thyroid carcinoma; TNBC, triple-negative breast cancer. (Cited from reference no. 92 in accordance with the open access policy.)

unresectable urothelial carcinoma that has progressed after chemotherapy [99]. [^{68}Ga]N188 PET targeting Nectin-4 has shown high accumulation in lesions, correlating with Nectin-4 expression levels as confirmed by immunohistochemistry in patients with advanced urothelial carcinoma [100]. [^{68}Ga]N188 PET imaging has also been reported in a small cohort of patients with various types of cancer, suggesting its potential for theranostics application [101].

Furthermore, PET imaging and therapeutic agents targeting pan-tumor molecules such as LAT1, GPC-1, and EphA2 have already been developed and are currently undergoing optimization for clinical translation [102–104]. PET probes that demonstrate high tumor accumulation and detection sensitivity—such as those used in PSMA theranostics—also hold great promise as therapeutic agents. These highly promising theranostic radioligands are expected to be incorporated into future clinical practice.

Summary

This review highlights recent advancements in oncology PET imaging and theranostics, with a focus on emerging radionuclides and molecular targets. As the field of theranostics continues to evolve, these innovations are expected to further broaden the scope of precision cancer diagnosis and treatment.

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Declarations

Conflict of interest All authors declare that they have no conflicts of interest related to this manuscript.

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