Current clinical application of lutetium-177 in solid tumors (Review)

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Abstract. Radionuclide-based therapy represents a novel treatment regimen for tumors. Among these therapies, lutetium-177 (^{177}Lu) has gained significant attention due to its stability and safety, as well as its ability to emit both γ and β rays, allowing for both imaging with single photon emission computed tomography and tumor treatment. As a result, ^{177}Lu can be used for both diagnosis and treatment for diseases such as prostatic and gastric cancer. Therefore, based on the available data, the present review provides a brief overview of the clinical applications of ^{177}Lu-targeted radionuclide therapy in metastatic prostate cancer, neuroendocrine tumors and other types of solid tumors, and highlights the current therapeutic effect, reduction in damage to normal tissues and future research directions, including the development of new nuclides and the application of more nuclides in different tumors. In the future, such treatments could be used in more tumors.

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1. Introduction

The number of total novel cancer cases globally is expected to reach 28.4 million by 2040, which represents a 47% increase compared with 2020 (1). The increase is expected to be higher in developing countries (64-95%) compared with developed countries (32-56%) based on demographic changes (1). On the basis of existing chemotherapy, radiotherapy, immunization, targeting and other therapies, novel diagnosis and treatment methods require investigation. Due to its advantages of integrated diagnosis and treatment, targeted radionuclide therapy has become a new strategy to further improve the prognosis of cancer.

Targeted radionuclide therapy (TRT) involves labeling radionuclides on biomolecules with a specific binding ability, which allows the biomolecule to bind to specific tumor targets, and thus the radionuclide is concentrated at the tumor site (2). The α or β particles emitted by radionuclides can then irradiate the tumor tissues specifically and ionize biological effects (low linear energy transfer), resulting in cell senescence and death within the irradiation range (3). This achieves therapeutic results with minimal effects on the surrounding normal tissues. By combining the advantages of targeted therapy and brachytherapy, TRT provides novel methods for the diagnosis and treatment of tumors. Based on current data, the present review briefly introduced the use of different ^{177}Lu drugs in treating several tumors, as well as the issues presented by the use of these drugs and future research directions.

2. Basic characteristics of radionuclide ^{177}Lu

^{177}Lu belongs to the lanthanide metal group (4) and can emit β-rays with a maximum energy of 0.49 MeV and with a half-life of 6.7 days (5). β-rays are mostly used for treatment of diseases such as prostate cancer, and the energy released by the β-particle rays of ^{177}Lu has an average range of 670 μm in soft tissue, significantly reducing the damage caused by radionuclides to nearby healthy cells. In addition, ^{177}Lu can emit two characteristic γ-rays (208 and 113 keV), which can be used as a signal source for single-photon emission computed tomography or positron emission tomography (PET) (6). These are mostly used for imaging and dosimetric analysis; for example, ^{177}Lu-prostate-specific membrane antigen (PSMA)-image and treat (I&T) PET/computed tomography (CT) is used for

pre- and post-treatment imaging in patients with metastatic prostate cancer (6,7).

3. Application of ^{177}Lu in prostate cancer

The latest global cancer data results released by the World Health Organization shows that the number of new cases of prostate cancer in 2020 was 1.41 million, ranking it second most common amongst all new tumors and the number of prostate cancer-associated mortalities in men was 380,000, making it the fifth most fatal cancer in men (1). In recent years, the prevalence of metastatic castration-resistant prostate cancer (mCRPC) has been increasing, and its prognosis is generally poor (8). The expression of PSMA in prostate cancer is higher compared with that in other tissues, including prostatic epithelial cells, the small intestine and salivary glands (9), and is 1,000 times higher compared with the lowest expression level in the kidney and small intestine (10). Therefore, precise targeted therapy with PSMA has emerged as a novel therapeutic method, resulting in a decline in prostate specific antigen (PSA) levels and an increase in overall survival (11,12).

Prostate cancer and ^{177}Lu-PSMA-I&T. 1,4,7,10-tetraazacyclododecane-1-(glutaric acid)-4,7,10-triaceticacid (DOTAGA) is a small PSMA inhibitor molecule labeled with ^{177}Lu known as ^{177}Lu-PSMA-I&T. In 2015, internal radiation therapy using ^{177}Lu-PSMA-I&T was reported to be effective and safe in two patients with metastatic prostate cancer, with no detectable side effects (13). In a study by Barna *et al* (14), ^{177}Lu-PSMA-I&T was used to treat mCRPC with a mean injection activity of 7,416±218 MBq. Follow-up imaging using Ga-PSMA PET/CT was used to determine individual tumor molecular volume. The volume of 63 individual tumors in bone, lymph nodes and liver tissues were observed to decrease by 32.3, 84.7 and 72.9% on average, respectively (14). In a trial of 49 patients with mCRPC who received at least three cycles of ^{177}Lu-PSMA-I&T (6.0 GBq), no grade III/IV adverse events were reported, indicating low nephrotoxicity or hematotoxicity, according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0) (15).

Another prospective single-arm trial included 40 patients diagnosed with mCRPC who received 86 cycles of ^{177}Lu-PSMA-I&T at a dose of 3.70-14.43 GBq per cycle from December 2019 to September 2021, with a median follow-up of 8 months (16). The findings revealed that six patients (15%) developed mild reversible dry mouth, and 28 patients (70%) developed grade 1-4 bone marrow dysfunction (anemia, thrombocytopenia and leukopenia) during follow-up (toxicities were assessed following the CTCAE v5.0). Serum PSA is the most significant marker for evaluating therapeutic biochemical response. PSA levels were obtained every 4 weeks before and after treatment. A reduction of ≥30% from baseline is considered a partial response, a >25% increase in PSA above baseline is defined as disease progression, and PSA levels with changes between <-30% and <+25% are considered disease stabilization. PSA levels were assessed after treatment and accompanied by partial remission in 25 patients (62.5%), stable disease in five patients (12.5%) and progression in ten patients (25%). Trials have shown that ^{177}Lu-PSMA-I&T can achieve significant PSA reduction and tumor remission in patients with mCRPC (16,17).

To evaluate the predictive effect after treatment, a trial involving 301 patients demonstrated that the extent of bone metastases and their changes were potential markers for predicting treatment outcomes in patients with mCRPC (18). A previous single-arm phase I study of ^{177}Lu-PSMA-I&T neoadjuvant therapy in high-risk prostate cancer before radical prostatectomy included 14 patients with high-critical-limited-stage prostate cancer, defined as PSA >20 ng/ml, biopsy Gleason score ≥8, or clinical T stage ≥3a, who tested positive for PSMA between December 2019 and December 2021 (19). Furthermore, two or three doses of ^{177}Lu-PSMA-I&T (7.4 GBq) were administered at 2-week intervals, and surgery (including lymph node dissection) was performed 4 weeks after the final dose. The main adverse reactions of this treatment were the incidence of perioperative complications and organ functional toxicity, including bleeding, infection, pneumonia and pulmonary embolism. After two doses, the PSA level was reduced by 17%, and after three doses it was reduced by 34%. No severe intraoperative complications were observed in 13 patients (one patient did not undergo surgery due to heart problems), while four (30%) patients developed postoperative complications (including pneumonia, pulmonary embolism, urinary leakage and urinary tract infection) (19).

Preliminary studies have demonstrated that neoadjuvant therapy with ^{177}Lu-PSMA-I&T followed by surgery is safe; however, further data should be obtained from long-term follow-up (19). These findings suggest that patients treated with ^{177}Lu-PSMA-I&T show decreased PSA levels and fewer serious adverse events, contributing to tumor remission (16-18).

Prostate cancer and ^{177}Lu-PSMA-617. ^{177}Lu-PSMA-617 is a small molecule inhibitor labeled with ^{177}Lu using 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) as a chelating agent (20,21). In March, 2022, the U.S. Food and Drug Administration (FDA) approved the administration of ^{177}Lu-PSMA-617 for the treatment of adult patients with mCRPC, making it the first targeted radioligand therapy to be approved by the FDA (22).

In a meta-analysis, Kim and Kim (23) included 10 studies involving 455 patients with mCRPC. The analysis showed that ^{177}Lu-PSMA-617 therapy resulted in a combined PSA reduction rate of 68.00% [95% confidence interval (CI), 63.55-72.22%] and with PSA levels reduced by >50% in 34.45% of patients (95% CI, 30.14-38.97%). In phase II, single-arm, single-center trials by Violet *et al* (24) and Hofman *et al* (25), ^{177}Lu-PSMA-617 radionuclide therapy had a high response rate, low toxicity and decreased pain in patients with metastatic castration-tolerant prostate cancer who progressed following conventional therapy (including taxane-based chemotherapy and second-generation antiandrogen therapy). The FDA authorized ^{177}Lu-PSMA-617 as a prostate cancer treatment in March 2022 based on a phase III experiment conducted by Sartor *et al* (26).

An international, open-label, Phase III clinical trial involving 84 centers (52 centers in North America and 32 in Europe) was conducted (26). Patients were randomly assigned in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 (injection of 7.4 GBq once every 6 weeks, lasting 4-6 cycles) plus standard

protocol-approved treatment (^{177}Lu-PSMA-617 group) or standard treatment only (e.g., abiraterone and enzalutamide) (control group). Among the 831 patients with metastatic castration-tolerant prostate cancer treated with at least one androgen receptor pathway inhibitor and one or two taxane receptor inhibitors, 581 were included in the analysis set. ^{177}Lu-PSMA-617 + standard therapy significantly extended imaging-based progression-free survival (PFS) time compared with standard therapy (median, 8.7 vs. 3.4 months; hazard ratio for progression or death, 0.40; 99.2% CI, 0.29-0.57; P<0.001) and OS (median, 15.3 vs. 11.3 months; hazard ratio for death, 0.62; 95% CI, 0.52-0.74; P<0.001). The most frequent adverse reactions in the ^{177}Lu-PSMA-617 group were fatigue, dry mouth and nausea; however, these events were usually grade 1 or 2 (Response Evaluation Criteria in Solid Tumors, version 1.1) (27) and had little impact on the quality of life.

^{177}Lu-PSMA-I&T vs. ^{177}Lu-PSMA-617. The distinction between the two PSMA-targeting medications, ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T, lies in the chelating agents they use. A study with 110 patients with mCRPC from two locations (University Hospital Würzburg and University Hospital Bonn), including 55 who received ^{177}Lu-PSMA-I&T and 55 who received ^{177}Lu-PSMA-617, revealed no significant differences in the harmful effects of the two at a dose of roughly 6.0 GBq per 8 weeks. Survival with ^{177}Lu-PSMA-I&T and ^{177}Lu-PSMA-617 was comparable with a median OS time of 12.0 vs. 13.0 months, respectively, with no serious grade III/IV toxicity (28). In another study that assessed the safety, biological distribution and dosiology in 138 patients, 51 individuals were administered ^{177}Lu-PSMA-I&T at 6.1±1.0 GBq and 87 patients received ^{177}Lu-PSMA 617 at 6.5±1.1 GBq (one injection). The mean dose of ^{177}Lu-PSMA-617 was higher compared with ^{177}Lu-PSMA-I&T (0.04 vs. 0.03 Gy/GBq), and the systemic half-life of ^{177}Lu-PSMA-I&T (35 h) was shorter compared with that of ^{177}lu-PSMA-617 (42 h). Of all the healthy organs, the lacrimal glands had the highest mean absorbed tumor dose of ^{177}Lu-PSMA-I&T and ^{177}Lu-PSMA-617 (5.8 vs. 5.9 Gy/GBq), but patients tolerated the therapy without any acute side effects (29). A study that further evaluated the difference in efficacy between ^{177}Lu-PSMA-617 plus standard therapy (hormone therapy, bisphosphonates and radiotherapy) and ^{177}Lu-PSMA-617 alone showed that combined therapy extended the duration of pain exacerbation compared with ^{177}Lu-PSMA-617 alone (30). It is hoped that future studies can include the combined use of nuclides with other drugs (such as targeted drugs and chemotherapy drugs), and it is hoped that new progress and breakthroughs can be made in the treatment of mCRPC through combination therapy.

Prostate cancer and ^{177}Lu-J591. J591 is a deimmunizing monoclonal antibody that binds to PSMA and has internalized properties (internalization of a putative ligand) (31,32). Participants received 75 mg/m docetaxel once every 21 days for 2 cycles, with two progressive increments of 'Lu-1591' at cycle 3 (1.48 GBq/m^2, up to 2.96 GBq/m^2). Docetaxel was administered in cycle 3 (half of the Lu-J591 dose 2 to 3 days before docetaxel and the other half of the dose 2 weeks after docetaxel), with the fourth cycle of docetaxel given 6-9 weeks after the third cycle. No dose-limiting toxicity was observed at any of the tested dose levels. Grade 4 neutropenia without fever was found in eight patients (53.5%). Subsequently, two patients (13.3%) developed thrombocytopenia, and no grade ≥3 non-hematological toxicity was observed. A PSA decrease of >50% after treatment with ^{177}Lu-J591 was seen in 11 patients (73.3%). The results suggest that a single ^{177}Lu-J591 fractionated course in combination with docetaxel is a viable option for patients with mCRPC (33). A review of the various phase I and II trials of ^{177}Lu-J591 in metastatic prostate cancer showed improved OS, and in almost all cases, myelosuppression is tolerable and reversible (31). While ^{177}Lu-J591 may be considered a potential treatment option, the effectiveness of its combination with docetaxel still requires additional research and clinical trials to establish its efficacy and safety.

Prostate cancer and [^{177}Lu] Ludotadipep. Ludotadipep is a new PSMA inhibitor tagged with ^{177}Lu, which contains a 4-iodophenyl butanoic group that can bind to albumin and prolong circulation time and boost absorption in tumors. A prospective study from Korea evaluated the efficacy of ^{177}Lu Ludotadipep in patients with ^{18}F-PSMA-PET/CT-positive mCRPC. From November 2020 to March 2022, a total of 30 patients were enrolled for single dose of ^{177}Lu Ludotadipep radiopharmaceutical therapy (34). Patients were divided into five groups (n=6) and given an increasing dose of 1.9, 2.8, 3.7, 4.6 and 5.6 GBq for each group. In this study, 29 patients who received ^{177}Lu Ludotadipep (one patient found to deviate from the inclusion criteria after enrollment), 36 treatment-emergent adverse events (58.6%) and four adverse drug reactions (10.3%) were observed. Overall 16 (66.7%) of the 24 participants with complete 12-week follow-up data showed a reduction in PSA levels, and nine (37.5%) of those subjects showed a PSA decline of ≥50%. At the 12th week after receiving a single dosage of ^{177}Lu Ludotadipep, five of the 24 patients (20.8%) displayed disease progression (a ≥25% increase in PSA levels from the baseline), suggesting that ^{177}Lu Ludotadipep may be a promising new treatment for mCRPC (34).

4. Application of ^{177}Lu in neuroendocrine tumors (NETs)

NETs are rare, heterogeneous tumors that originate from cells of the diffuse endocrine system (35). Approximately two-thirds of NETs occur in the gastrointestinal and pancreatic systems, including the stomach, small intestine, colon, appendix, rectum and pancreas. The most common NET subtype is the gastrointestinal pancreatic NET (GEP-NET) (36). An analysis of United States cancer data showed that the incidence of gastrointestinal neuroendocrine tumors has continuously increased each decade from 1977 to 2016 (37). Currently, surgery is the primary therapeutic method for GEP-NETs because most GEP-NETs are inert. In addition, severe cases are treated with radiochemotherapy, molecularly targeted medicine.

Most pancreatic and GEP-NETs express somatostatin receptor (SSTR)2 and 5, these receptors can be chelated to a β-emitting radioisotope ^{177}Lu for therapy. The new approach for treating advanced NETs is peptide receptor radionuclide therapy (38).

Somatostatin is a peptide with a potent and broad antisecretory action. SSTRs which belong to the G protein-coupled receptor family, are widely distributed in various tissues of

the body and are classified into five subtypes (SSTR1-5) (39). SSTR2 is associated with gastrointestinal neuroendocrine system (40).

NETs and ^{177}Lu-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid-D-phenylalanine 1-tyrosine 3-threonine 8-octreotide (^{177}Lu-DOTA-TATE) also known as DOTA-octreotate. ^{177}Lu-DOTA-TATE is a labeled precursor of DOTA-modified octreotide. Octreotide is a somatostatin analogue that is used to control NET progression (41). A ^{177}Lu-labeled SSTR agonist has been used to treat somatostatin receptor positive GEP-NETs (42). The FDA approved the first radiopharmaceutical for the treatment of GET on January 26, 2018.

An open, randomized, phase III clinical trial (NETTER-1) enrolled 231 patients with locally advanced or metastatic, well-differentiated, somatostatin receptor-positive midgut neuroendocrine tumors. Patients were randomly assigned (1:1) to receive intravenous ^{177}Lu-DOTA-TATE 7.4 GBq + intramuscular long-acting octreotide (30 mg every 8 weeks) (experimental group) or high-dose long-acting octreotide (60 mg every 4 weeks) (control group). According to the NETTER-1 trial, which was reported on July 24, 2016, the estimated rate of PFS at 20 months was 65.2% (95% CI, 50.0-76.8%) in the experimental group and 10.8% (95% CI, 3.5-23.0%) in the control group. The response rate (complete plus partial) in the experimental group was 18%, whereas it was only 3% in the control group (P<0.001). Preliminary findings show that using ^{177}Lu-DOTA-TATE markedly increases the PFS (43). In a 2021 follow-up analysis the median OS for the experimental group was 48.0 months (95% CI, 37.4-55.2 months), while the control group OS was 36.3 months (95% CI, 25.9-51.7 months). The OS of the experimental group did not improve significantly compared with that of the control group, and there was no statistically significant difference in OS. However, in absolute terms, there was a difference of 11.7 months in the median OS between ^{177}Lu-DOTA-TATE and octreotide alone groups. In the experimental group, 111 patients (3%) experienced serious adverse events related to treatment that were grade 3 or worse. During the 100 months of follow-up, 2% of patients developed myelodysplastic syndrome, yet no other experimental group patients experienced renal impairment that was grade 3 or worse. Although the OS was not statistically significant, the results showed that the 11.7 monthly difference in the median OS between ^{177}Lu-DOTA-TATE treatment and high-dose long-acting octreotide treatment alone may be considered clinically relevant (44).

A study compared PFS and OS in ^{177}Lu-DOTA-TATE and patients with advanced and unresectable gastrointestinal neuroendocrine tumors treated with everolimus and sunitinib (45). In comparison to everolimus, sunitinib and best supportive care, the results of the primary analysis demonstrated that ^{177}Lu-DOTA-TATE may be a more effective therapy choice. In a study evaluating the efficacy and safety of ^{177}Lu-DOTA-TATE in 30 patients with NET and extensive bone metastases, radiological evaluation at the end of treatment showed partial response in five patients, stable disease in 20 patients, and progressive radiological disease in three patients. Clinical progress was observed in another two patients (46).

NETs and ^{177}Lu-DOTA-JR11 (^{177}Lu-OPS201). ^{177}Lu-OPS201 is a novel somatostatin antagonist with high affinity for SSTR2 (47). *In situ* testing in a SSTR2-positive neuroendocrine model in mice reveals that ^{177}Lu-OPS201 causes a greater decrease in living tumor tissue, a significant delay in tumor growth and increased toxicity compared with ^{177}Lu-DOTATOC (an SSTR agonist that primarily targets SSTR2). Likewise, the use of the ^{177}Lu-OPS201 has been shown to increase tumor uptake of agonist ^{177}Lu-DOTA-TATE *in vitro* (47); however, it has not been validated at clinical trial stage. According to a recent *in vitro* study, ^{177}Lu-OPS201 has a high affinity, and ^{177}Lu-OPS201 has at least four times more receptor-binding sites compared with ^{177}Lu-DOTA-TATE. In conclusion, ^{177}Lu-OPS201 has demonstrated faster binding, slower dissociation and a longer cell retention period compared with ^{177}Lu-DOTA-TATE (48).

5. Clinical application of ^{177}Lu in other diseases

Fibroblast activating protein (FAP) overexpression in cancer and ^{177}Lu-FAP-2286. FAP is expressed in a number of malignancies. ^{177}Lu-FAP-2286 is a FAP-binding cyclic peptide consisting of seven amino acids, of which two cysteine residues pass through an aromatic partial ring that is linked to the DOTA chelating agent (49). FAP-2287 (a murine surrogate for FAP-2286) is well targeted for ^{177}Lu targeted radionuclide therapy, rapidly accumulates in tissues and persists in tumors for a long time (50).

A trial has been performed that involved 11 patients with advanced pancreatic, breast, rectal and ovarian cancers receiving ^{177}Lu-FAP-2286. The results showed that the dosage of administration of ^{177}Lu-FAP-2286 (5.8±2.0 GBq; range, 2.4-9.9 GBq) was well tolerated, and no adverse or clinically detectable pharmacological effects were found or reported in any patient. The systemic effective dose was 0.07±0.02 Gy/GBq (range, 0.04-0.1 Gy/GBq). The mean absorbed doses in kidney and red bone marrow were 1.0±0.6 Gy/GBq (range, 0.4-2.0 Gy/GBq) and 0.05±0.02 Gy/GBq (range, 0.03-0.09 Gy/GBq), respectively. No grade 4 adverse events were observed; however, grade 3 adverse reactions occurred in three patients, including one pancytopenia, one leukopenia and one pain response. ^{177}Lu-FAP-2286 is widely used in adenocarcinoma and is well tolerated with few side effects (51). These results indicate that ^{177}Lu-FAP-2286 has encouraging clinical data and deserves further exploration.

Meningioma and ^{177}Lu-DOTA-TATE. At present, there is no evidence-based systemic treatment for patients with progressive meningioma who are unable to receive surgery or external radiotherapy. External radiation therapy was given to 15 patients with meningioma, all of whom had received radiotherapy and 14 of whom had surgery and then received ^{177}Lu-DOTA-TATE (7.5-29.6 GBq). ^{177}Lu-DOTA-TATE was administered with a maximum activity of 7.4 GBq per cycle with a maximum of 4 cycles. In this cohort, the interval between the cycles was a median of 9 weeks (range, 6-14 weeks). Subsequently, six patients (40%) were stable following treatment. The median PFS of the whole cohort was 7.8 months, with a 6-month PFS rate of 60%. The median OS was 13.6 months, with a 12-month OS rate of 60%. Prior to therapy, their average monthly tumor

growth rate (TGR) was 4.6% for the surface and 14.8% for the volume. The surface and volume were scanned and determined by magnetic resonance imaging. The TGR decreased to 3.1% in surface (P=0.016) and 5.0% in volume (P=0.013) per month after treatment. The results suggest that ^{177}Lu-DOTA-TATE can control tumor growth (52).

Metastatic salivary gland cancer and ^{177}Lu-PSMA-617. PSMA is expressed on tumor cells or in the tumor neovasculature in salivary gland carcinoma, particularly in certain subtypes such as salivary gland and salivary duct carcinomas (53,54). There have been cases of salivary gland malignancies that show significant uptake in ^{68}Ga-PSMA-11 PET-CT (55-57). Therefore, in view of the encouraging results of patients treated for CRPC, the potential use of ^{177}Lu-PSMA-617 to treat metastatic salivary gland cancer has been assessed.

In a retrospective study by Klein Nulent *et al* (58), six patients were treated with ^{177}Lu-PSMA-617. This cohort included four adenoid cystic carcinomas, one adenocarcinoma (not otherwise specified) and one acinic cell carcinoma. A total of four patients reported instant reduction of tumor-related symptoms; the most common improvement was a reduction in pain, followed by a reduction in fatigue. Two individuals demonstrated a radiological response, indicating either stable disease or a partial remission. All treatment-related clinical and hematological adverse events were graded using the CTCAE standard version 5.0. This study demonstrated that palliative ^{177}Lu-PSMA-617 for salivary gland cancer is safe and generally well tolerated.

A 56-year-old man with progressive metastatic salivary cancer who received treatment every 6 weeks and was first evaluated after four courses (cumulative activity of 24.3 GBq ^{177}Lu-PSSMA-617) showed stable disease on imaging according to Positron Emission tomography Response Criteria In Solid Tumor (PERCIST) criteria (59).

Metastatic thyroid cancer and ^{177}Lu-DOTA-TATE/^{177}Lu-PSMA-617I. A number of studies have shown that PSMA is expressed in thyroid cancer, and significant uptake can be observed with 68Ga-PSMA-11 PET-CT (60-63). Therefore, ^{177}Lu-PSMA-617 has been used to treat metastatic thyroid cancer. Assadi and Ahmadzadehfar (64) treated a patient with progressing thyroid cancer and neck and lung metastases with ^{177}Lu-PSMA. The patient previously received 25.9 GBq ^{131}Iodine and sorafenib for 6 months, and radioligand therapy targeting the somatostatin receptor using ^{177}Lu-DOTA-TATE. As the patient exhibited persistent disease progression and severe breathing difficulties, the patient was then treated with 7.4 GBq ^{177}Lu-PSMA-617. With whole-body SPE-CT imaging, there was a higher level of whole-body imaging with ^{177}Lu-PSMA-617 compared with receiving ^{177}Lu-DOTA-TATE, suggesting that treatment with ^{177}Lu-PSMA-617 is potentially more effective compared with ^{177}Lu-DOTA-TATE for the treatment of this patient. However, the patient died unexpectedly of cardiac arrest two weeks after treatment.

In an additional study, two patients received ^{177}Lu-PSMA-617 therapy for thyroid carcinoma. One patient showed disease progression on imaging 1 month later, the other patient showed partial, temporary response of lung and

Table I. Recruiting clinical trials of ^{177}Lu targeted radionuclide therapy for tumors expressing SSTR and PSMA (except neuroendocrine tumor and prostate cancer) in the past 5 years.

NCT	Starting date	Phase	Target	Vector	Isotope	Application	Administration Route	Primary outcome
NCT04529044	2022-09-01	II	SSTR	Dotatate	Lu-177	Recurrent breast cancer	I.V	ORR
NCT05198479	2023-01	II	SSTR	DOTA0-Tyr3-Octreotate	Lu-177	Metastatic NPC	I.V	PFS
NCT04903899	2021-05-19	II	SSTR	DOTATATE	Lu-177	Neuroblastoma	I.V	Assess the response of treatment.
NCT05644080	2023-03-28	N/A	PSMA	PSMA I&T	Lu-177/Ga-68	Glioma	I.V	AEs/efficacy
NCT05918302	2023-07	III	SSTR	Edotreotide	Lu-177	Neuroendocrine tumors	I.V	PFS
NCT05109728	2022-05-10	I	SSTR	DOTA-TATE	Lu-177	Glioblastoma	I.V	DLTs
NCT03971461	2019-05-15	II	SSTR	Lutathera	Lu-177	Meningioma	I.V	PFS
NCT05214820	2022-01-17	II	PSMA	^{68}Ga-PSMA	Ga-68	Endoradiotherapy	I.V	Tumor uptake

SSTR2, somatostatin receptor subtype 2; PSMA, prostate-specific membrane antigen; NPC, metastatic nasopharyngeal cancer; ORR, overall response rate; PFS, progression free survival; DLTs, number of participants with dose limiting toxicities; AEs, adverse events; NCT, national clinical trial; I.V, intravenous; PFS, progression-free survival; N/A, not applicable; I&T, image and treat.

Table II. New targets of clinical trials of ^{177}Lu targeted radionuclide therapy for solid tumors in the past 5 years.

NCT	Starting date	Phase	Target	Vector	Isotope	Application	Administration route	Primary outcome
NCT05623891	2022-12	I	ED-B	B5-IgG4	Lu-177	Solid Tumors	I.V	Tissue distribution/ Dosimetry/AEs
NCT05815394	2023-03-03	I	NY108	DOTA	Lu-177	Prostate cancer	I.V	Tissue distribution/AEs
NCT04786847	2022-01-30	I	PSMA	TLX591	Lu-177	MPC	I.V	AEs
NCT05723640	2023-05-10	I	FAP	LNC1004	Lu-177	Solid tumor	I.V	DLTs/safety/MDT
NCT05410821	2022-06-15	I	FAP	DOTA-EB-FAPI	Lu-177	Thyroid cancer	I.V	Safety/tolerability/MDT
NCT05603559	2023-01-01	I	PSMA	P17-087/088	Lu-177	mCRPC	I.V	Dosimetry/AEs
NCT05013086	2021-10-01	I	Integrin αvβ3	AB-3PRGD2	Lu-177	NSCLC	I.V	Standardized uptake value
NCT05130255	2022-11-17	I	GD2	DOTA	Lu-177	Solid tumors	I.V	DLTs
NCT04997317	2021-04-21	I	SSTR2	satoreotide	Lu-177	Meningiomas	I.V	Therapeutic index/safety
NCT03872778	2019-07-24	I/II	GRPR	NeoB	Lu-177	Solid tumor	I.V	DLTs/MDT
NCT04665947	2020-12-18	I	ABM-5G	DOTA	Lu-177	Pancreatic cancer	I.V	DLTs/RP2D
NCT05706129	2023-03-14	I/II	DPI-4452	DOTA	Lu-177/Ga-68	Solid tumors	I.V	TEAEs/DLTs/ORR
NCT05868174	2023-05-23	I	CAIX	Peposertib	Lu-177	Solid tumors	I.V	DLTs/safety
NCT05432193	2022-07-13	I	FAP	PNT6555	Lu-177	Solid tumors	I.V	AEs
NCT04711135	2022-08-31	II	SSTR	Lutetium	Lu-177	GEP-NETs	I.V	Absorbed radiation doses/AEs
NCT04647526	2021-02-25	III	PSMA	PNT2002	Lu-177	mCRPC	I.V	rPFS
NCT04469127	2023-01-30	I/II	αvβ3	DOTA	Lu-177	Breast cancer	I.V	Safety and tolerability
NCT05533242	2023-06	I	6A10	DOTA	Lu-177	Glioblastoma	I.V	MDT/safety
NCT05178693	2022-04-25	I	SSTR	ASTX727	Lu-177	NETs	I.V	To determine whether pre-treatment with ASTX727 results in re-expression of SSTR2

PSMA, prostate-specific membrane antigen; FAP, fibroblast activation protein; SSTR2, somatostatin receptor subtype 2; GRPR, gastrin-releasing peptide receptor; CAIX, carbonic anhydrase IX; MPC, metastatic prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; NSCLC, non-small cell lung cancer; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; I.V, intravenous; AEs, adverse events; DLTs, number of participants with dose limiting toxicities; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; TEAEs, treatment emergent adverse events; ORR, overall response rate; rPFS, radiographic progression-free survival; NCT, national clinical trial.

Table III. Ongoing clinical trials of ^{177}Lu targeted radionuclide therapy combined with other solid tumor treatments in the past 5 years.

NCT	Starting date	Phase	Target	Combination treatment	Application	Primary outcome
NCT05340374	2022-07-14	I/II	PSMA	Cabazitaxel + ^{177}Lu-PSMA-617	mCRPC	DLTs/MTD/RP2D
NCT04525638	2020-06-29	II	SSTR	Nivolumab + ^{177}Lu-DOTATATE	NENS	ORR
NCT05766371	2023-06-30	II	PSMA	Pembrolizumab + ^{177}Lu-PSMA-617	CRPC	rPFS
NCT03874884	2019-07-09	I	PSMA	Olaparib + ^{177}Lu-PSMA-617	mCRPC	DLTs/MTD/RP2D
NCT05150236	2022-04-29	II	PSMA	Ipilimumab + Nivolumab + ^{177}Lu-PSMA-617	mCRPC	PSA-PFS
NCT04886986	2021-06-30	I/II	PSMA	^{225}AC-J591+ ^{177}Lu-PSMA-I&T	mCRPC	DLTs/MTD
NCT05613894	2023-06-26	Ib	PSMA	Cabozantinib + ^{177}Lu-PSMA-617	mCRPC	DLTs
NCT05239533	2022-02-16	II	Anti-carbonic anhydrase IX monoclonal antibody	Nivolumab + ^{177}Lu-girentuximab	Kidney cancer	MTD/ORR
NCT05868174	2023-05-23	I	CAIX	Peposertib + ^{177}Lu-TLX250	Solid tumors	DLT/safety
NCT04720157	2021-06-09	III	PSMA	SoC + ^{177}Lu-PSMA-617	mHSPC	rPFS
NCT05663710	2023-06-30	II	SSTR	Cabozantinib + Nivolumab	RCC	Incidence of PFS
NCT04261855	2020-10-08	I/II	SSTR	Avelumab + ^{177}Lu-DOTATATE	MCC	PFS
NCT05383079	2022-09-13	I/II	PSMA	^{223}Ra + ^{177}Lu-PSMA-I&T	mCRPC	DLTs/MTD/RP2D
NCT05724108	2023-03-15	II	SSTR	Triapine + ^{177}Lu-DOTATATE	NENS	ORR
NCT05249114	2022-12-28	I	SSTR	Cabozantinib + ^{177}-Lu-DOTATATE	NENS	MTD PFS
NCT05687123	2023-04-28	I	SSTR	Sunitinib Malate + ^{177}Lu-DOTATATE	Pancreatic NENS	AEs
NCT04750954	2021-06-04	I	SSTR	Peposertib + ^{177}Lu-DOTATATE	Pancreatic NENS	RP2D
NCT05682443	2023-07-01	II	PSMA	ONC-392 + ^{177}Lu-PSMA-617	mCRPC	rPFS
NCT05247905	2022-03-16	II	SSTR	Capecitabine + Temozolomide	Pancreatic NENS	PFS
NCT04086485	2022-10-03	I/II	SSTR	Olaparib + ^{177}Lu-DOTATATE	GEP-NET	MTD/ORR
NCT04614766	2022-09-30	I/II	SSTR	Lutathera + Azedra	SPORE-3	MTD/ORR

PSMA, prostate-specific membrane antigen; CAIX, carbonic anhydrase IX; SSTR, somatostatin receptor subtype; SoC, standard of care; mCRPC, metastatic castration resistant prostate cancer; OPC, oligometastatic prostate cancer; NENS, neuroendocrine neoplasms; CRPC, castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; RCC, renal cell carcinoma; MCC, Merkel cell carcinoma; GEP-NET, gastroenteropancreatico neuroendocrine tumor; SPORE-3, mid-gut neuroendocrine tumors; DLTs, number of participants with dose limiting toxicities; MTD, maximum tolerated dose; RP2D, recommended Phase 2 dose; PSA PFS, prostate-specific antigen progression free survival at 1 year; bPFS, biochemical progression free survival; ORR, overall response rate; rPFS, radiographic progression-free survival; AEs, adverse events.

liver metastases (65). Side effects were not mentioned in either of these two case reports of thyroid carcinoma.

Advanced renal cell cancer and ^{177}Lu-cG250. Previous studies have shown that carbonic anhydrase IX is almost universally expressed (>90%) in metastatic clear cell renal cell carcinoma (ccRCC), and its expression in healthy tissues has been extensively evaluated, but is limited to gastrointestinal mucosa and gastrointestinal associated structures, with much lower expression levels compared with those in ccRCC (66,67). Thus, ^{177}Lu-girentuximab (cG250) was used to treat ccRCC. Diagnostic Indium111-cG250 imaging confirmed cG250 accumulation in 23 patients with progressive ccRCC metastases (68). In this phase I study, patients received a high-activity dose of ^{177}Lu-cG250. At 3 months after the initial treatment, 74% of patients had stable illness (evaluated by PERCIST), and one patient had a partial response that persisted for 9 months. Mean growth of target tumor lesions was reduced from 40.4% in the 3 months before treatment to 5.5% 3 months after the first treatment cycle. There were no significant non-hematological adverse effects noted (68).

Additionally, in a phase II study, 14 patients with ccRCC were treated with ^{177}Lu-cG250, of which eight patients had stable disease and one had partial regression. The treatment was generally well tolerated (69).

Metastatic bone tumors and ^{177}Lu-EDTMP. A study by Elboga *et al* (70) found that ^{177}Lu-ethylenediamine tetramethyle nephosphonic acid (EDTMP) effectively relieved pain caused by bone metastases in patients with breast or prostate cancer. Of the 75 patients treated with ^{177}Lu-EDTMP, 59 responded positively, while 16 did not. The pain score was analyzed, and patients who responded had markedly lower pain scores after each radiopharmaceutical treatment. A meta-analysis involving 172 patients revealed that ^{177}Lu-EDTMP had a significant effect on relieving bone pain, suggesting that this agent could be a good choice when other pain-relieving radiopharmaceuticals are not available (71).

Currently, it is proposed that a ^{177}Lu-EDTMP rapid kit be developed based on its success in palliative treatment, which, if successfully implemented, could greatly reduce pain in terminal cancer patients (72).

6. Present problems and future research directions

At present, the main problem with ^{177}Lu TRT is the limited variety of drugs used in clinical practice, and the need for further improvement in clinical efficacy. ^{177}Lu TRT is a promising treatment method for solid tumors, but currently only ^{177}Lu-DOTA-TATE and ^{177}Lu-PSMA-617 have been approved treatment for NETs and prostate cancer, respectively. Moreover, the response rate of ^{177}Lu TRT for mCRPC was from 32.3 to 68%, and ^{177}Lu-DOTA-TATE for neuroendocrine tumors was only 18%.

Future research on ^{177}Lu TRT should focus on expanding the application of ^{177}Lu-DOTA-TATE and ^{177}Lu-PSMA-617 to other diseases that express PSMA or SSTR. There are currently ongoing clinical trials assessing the activity of ^{177}Lu-DOTA-TATE and ^{177}Lu-PSMA-617 on SSTR and PSMA-expressing tumors as listed in Table I. This includes breast cancer, metastatic nasopharyngeal carcinoma, neuroblastoma, glioblastoma and glioma, NETs of the lung and thymus for SSTR-expressing tumors and upper metastatic gastric cancer for PSMA-expressing tumors.

Likewise, future research should focus on the development of more ^{177}Lu TRT targets in solid tumors. In the past 5 years, the ongoing clinical trials of new targets for ^{177}Lu TRT have included fibronectin ED-B, NY108, TLX591, LNC1004, 3PRGD2 and GD2 (Table II).

Lastly, the use of ^{177}Lu TRT in combination with other treatments should be explored. For example, in a preclinical model (murine model), ^{177}Lu-FAP-2287 enhanced anti-PD-1-mediated tumor growth inhibition by modulating the tumor microenvironment and increasing the recruitment of tumor-infiltrating $CD8^+$ T cells (50). Another study showed that concurrent rather than sequential blockade of the PD-1/PD-L1 axis combined with ^{177}Lu TRT improves OS and long-term tumor control (73). The study of the metabolism principle of nuclide in the body can further clarify the treatment method in the future to improve the survival period. A Phase I study of the ^{177}Lu-DOTA^0-Tyr^3-Octreotate combination with nivolumab was well tolerated and showed signs of antitumor activity for patients with neuroendocrine tumors of the lung (74). In the past 5 years, the number of ongoing clinical trials of ^{177}Lu TRT combined with other treatments for solid tumors has increased. A list of the current trials is shown in Table III. The results of these clinical trials will likely improve the current options for ^{177}Lu TRT treatments.

7. Conclusions

^{177}Lu TRT have been successfully applied in patients with NETs or metastatic prostate cancer, resulting in prolonged PFS, OS and improved quality of life with tolerable toxicities. However, ^{177}Lu TRT are rarely used to treat other solid tumors and clinical efficacies need to be improved. The use of ^{177}Lu-DOTA-TATE and ^{177}Lu-PSMA-617 should be expanded to various diseases, and more new targets for ^{177}Lu TRT should be researched and developed. Lastly, ^{177}Lu TRT in combination with other treatments provide further treatment options for solid tumors.

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Authors' contributions

TN and MF drafted the manuscript. BL, FG and BT participated in the data review and collection for the study. XD

conceived the study and reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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