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Radionuclide-based theranostics — a promising strategy for lung cancer

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Abstract

Purpose—This review aims to provide a comprehensive overview of the latest literature on personalized lung cancer management using different ligands and radionuclide-based tumor-targeting agents.

Background—Lung cancer is the leading cause of cancer-related deaths worldwide. Due to the heterogeneity of lung cancer, advances in precision medicine may enhance the disease management landscape. More recently, theranostics using the same molecule labeled with two different radionuclides for imaging and treatment has emerged as a promising strategy for systemic cancer management. In radionuclide-based theranostics, the target, ligand, and radionuclide should all be carefully considered to achieve an accurate diagnosis and optimal therapeutic effects for lung cancer.

Methods—We summarize the latest radiotracers and radioligand therapeutic agents used in diagnosing and treating lung cancer. In addition, we discuss the potential clinical applications

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Declarations

Conflict of interest Weibo Cai is a scientific advisor, stockholder, and grantee of Focus-X Therapeutics, Inc.; a consultant and grantee of Ac-tithera, Inc.; a consultant of Rad Source Technologies, Inc.; a scientific advisor of Portrai, Inc.; and a scientific advisor and stockholder rTR Technovation Corporation. All other authors declare no conflict of interest.

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and limitations associated with target-dependent radiotracers as well as therapeutic radionuclides. Finally, we provide our views on the perspectives for future development in this field.

Conclusions—Radionuclide-based theranostics show great potential in tailored medical care. We expect that this review can provide an understanding of the latest advances in radionuclide therapy for lung cancer and promote the application of radioligand theranostics in personalized medicine.

Keywords

Molecular imaging; Radioligand theranostics (RLT); Personalized medicine; Cancer therapy

Introduction

Lung cancer (LC) is the second most common cancer in the world and is the leading cause of cancer-related deaths. LC contributes to 11.4% of all new cancer cases and 18.0% of all cancer-related deaths [1]. Non-small cell lung cancer (NSCLC) accounts for 85% of pulmonary neoplasms with several classifications, including adenocarcinoma, squamous cell carcinomas, and large cell carcinomas [2, 3]. The remaining 15% of neoplasms are identified as either limited or extensive small cell lung cancer (SCLC) [4]. Many studies have shown that early detection, precise classification, and personalized therapy are all key to reducing mortality from LC and thus improving patient outcome [5, 6].

Nowadays, molecular imaging, especially positron emission tomography (PET)/single photon emission computed tomography (SPECT), has become an essential imaging approach for oncologic detection [7]. In this context, various probes, such as ^{18}F-FDG, ^{18}F-FLT, and ^{11}C-methionine, have been developed to visualize tumors. They are critical in diagnosing LC and valuable in clinical staging, therapeutic monitoring, and prognostic assessment of LC [8]. However, the specificity and sensitivity of most probes (e.g., ^{18}F-FDG) are limited, hardly monitoring the changes in tumor molecular biomarkers (e.g., the expressing level of immune checkpoints) or portraying the tumor microenvironment (TME) (e.g., the level of vascular abundance and immune cell infiltration) [9, 10]. Therefore, tumor cell or TME target-based PET/SPECT imaging allows for further non-invasive detection of LC-specific biomarkers and provides multi-dimensional disease information, ranging from subtypes to metastases, to guide subsequent personalized therapy of pulmonary neoplasms [11, 12].

As for the therapy, surgery is recommended for early and resectable locally advanced NSCLC. For NSCLC patients with multiple metastases who cannot undergo surgical resection, radiotherapy, chemotherapy, or systemic combination therapy are viable alternatives [13, 14]. For patients with either limited or extensive SCLC, these therapies are more routinely used, while surgery is rarely applied [15]. However, a series of severe side effects and adverse reactions may occur as a result of the therapies [16–18]. Therefore, advanced therapeutic strategies have become the focus of clinical oncology treatment. For example, immunotherapy, including immune checkpoint inhibitors, cellular immunotherapy, and cytokine therapy, can activate the immune system to suppress and prevent tumor growth in the immunosuppressive microenvironment [19]. Dozens of immunotherapeutic drugs have

been approved and have prolonged the survival of cancer patients [20, 21]. Nevertheless, drug resistance invariably occurs due to tumor mutations [22]. Personalized or precision medicine has been proposed to overcome the inherent limitations of existing therapies. Radioligand theranostics (RLT) has shown enormous potential as a newly emerged approach for managing LC [23].

Iodine-131 was first used to treat differentiated thyroid cancer back in the 1940s, given the innate ability of thyroid cancer cells to take up iodine [24]. This advancement has shaped the field of radionuclide-based cancer therapy, and significant achievements in radionuclide therapy have since been made [25]. For example, RLT agents targeting somatostatin receptor 2 ($SSTR_2$) have been successfully used in clinical practice, markedly prolonging progression-free survival (PFS) and overall survival (OS) in patients with neuroendocrine tumors (NETs) [26]. Nevertheless, suitable radioligands and targets have only been identified for a handful of cancers. In general, RLT needs specific targeting ligands (e.g., antibodies, proteins, peptides, and small molecules) to effectively deliver radionuclides to the tumor cells or TME [27]. Currently, the available radionuclides for RLT include three major types of particulate radiation: α-particles (e.g., ^{225}Ac, ^{227}Th, ^{213}Bi, and ^{211}At), β-particles (e.g., ^{177}Lu, ^{131}I, ^{188}Re, ^{186}Re, ^{90}Y, and ^{166}Ho), and auger electrons (e.g., ^{111}In and ^{125}I). Some of these radionuclides can also emit γ rays (e.g., ^{177}Lu, ^{131}I, and ^{111}In) for synchronic imaging and therapy [28, 29]. Some RLT agents have been approved for clinical use, such as ^{177}Lu-DOTATATE (Lutathera), ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) (Azedra), and ^{90}Y-ibritumomab tiuxetan (Zevalin) for the treatment of NETs, neuroblastoma, and non-Hodgkin lymphoma, respectively [30, 31]. Furthermore, there are several potential RLT agents being tested in clinical trials for treating prostate cancer, glioblastoma, breast cancer, and pancreatic ductal adenocarcinoma [32–34]. Currently, ^{177}Lu-DOTATATE, which targets $SSTR_2$, and ^{177}Lu-FAP-2286, which targets fibroblast activating protein (FAP), show great therapeutic potential in pulmonary NETs and lung squamous cell carcinoma, respectively [35, 36]. Overall, the development of novel RLT agents with good safety profile, high treatment efficacy, and wide targeting capability is ongoing. This effort may help to better manage LC patients in the future.

In the first part of this review, we summarize the available molecular/cellular targets and radiotracers for PET/SPECT imaging of LC. In the later section, we discuss the recent applications of RLT agents in LC treatment. Lastly, we provide our advice on the selection of ideal targets, radiotracers, and radiotherapeutic agents for optimal molecular diagnosis and targeted therapy of LC.

Selection of optimal targets for theranostics of LC

Radionuclide-based tumor-targeting imaging provides diagnostic applications and a deeper insight into tumor biology (including tumor immune microenvironment and vascular abundance), which could assist in staging and restaging patients and predict treatment response [37]. Therefore, the identification of LC-specific targets is vital for the diagnosis and personalized therapy of pulmonary neoplasms (Fig. 1). As such, optimal targets would greatly ensure the efficacy of LC theranostics (Table 1).

PD-L1/PD-1

The overexpression of programmed death ligand 1 (PD-L1) on tumor cells promotes immune escape and restricts tumor cell killing by C $D8^+$ T cells. PD-L1 serves as a predictive biomarker, prognostic indicator, and therapeutic target for cancer immunotherapy [38, 39]. So far, five radiotracers targeting PD-L1 in NSCLC have been trialed in the clinic, including two monoclonal antibodies (mAbs), one peptide, one protein, and one single-domain antibody (sdAb) (Table 1). Since atezolizumab, durvalumab, and avelumab are approved anti-PD-L1 mAbs [40–42], zirconium-89-labeled atezolizumab and durvalumab have shown encouraging results in clinical trials as immunotherapeutics. Cancer patients who are responsive to immune checkpoint inhibitor treatment showed higher uptake of these radiopharmaceuticals [43, 44]. Other mAbs (e.g., ^{89}Zr-DFO-REGN3504, ^{89}Zr-DFO-6E11, and ^{89}Zr-C4) have generated images with strong tumor uptake and high image contrast, as demonstrated in several preclinical studies [45–47].

The optimal imaging timepoint for antibodies generally occurs several days after administration since they remain in blood circulation for a long time. Therefore, radionuclides, such as iodine-124 ($t_{1/2}$ = 4.2 days) and zirconium-89 ($t_{1/2}$ = 3.3 days), that have longer half-lives are commonly used for antibody-based imaging [48, 49]. To minimize radiation exposure to patients, imaging diagnosis using small-sized, short-circulating ligand is preferred [50]. In particular, sdAb, especially nanobodies, has small sizes and short circulation half-lives, thus demonstrating easier dissolution and faster tissue accumulation than full-length antibodies [51–53]. For instance, ^{99m}Tc-labeled NM-01, an anti-PD-L1 sdAb, could highlight tumors with a tumor-to-background ratio (TBR) of 2.3 after 2 h of patient injection [54]. Gallium-68 labeled NOTA-WL12, a peptide-based PD-L1 imaging agent, could achieve a tumor-to-lung ratio of 4.45 ± 1.89 within an hour of administration, as evidenced by PET/CT imaging, thereby improving the efficiency of evaluation [55]. Similarly, small-sized adnectins could be rapidly delivered to target tissues [56]. They could provide an optimal tumor-to-background contrast at 70–90 min post-injection and a median maximum standardized uptake values (SUV_{max}) of 6.5 for ^{18}F-BMS-986192 in immunotherapy-responsive lesions [57]. Moreover, Truillet et al. successfully optimized anti-PD-L1 IgG1 complement 4 (C4)-based radioligands that possess shorter pharmacokinetics. As-prepared fragment antigen-binding (Fab) C4 and a double-mutant IgG C4 (H310A/H435Q) could achieve a maximum TBR at 4 h and 24 h after injection, respectively. This timeframe is much shorter than C4, which achieves a maximum TBR 48 h after injection [47, 58]. Therefore, the optimization for mAbs is being improved by ensuring a high antibody affinity and lowering the ligand's molecular weight via the reduction of radiopharmaceutical's toxicity.

As an immune checkpoint molecule for cancer immunotherapies, programmed cell death protein-1 (PD-1) is mainly expressed on the surface of various immune cells [59]. The PD-1 pathway plays an important role in regulating the function of immune cells, such as T cell activation and exhaustion, formation and maintenance of memory T cells, and activation of Treg cells [60]. However, a wide range of PD-1/L1 inhibitors is recruited in multiple malignant tumors, including NSCLC. Thus, to provide a precise treatment regimen, it is critical to identify the patients who may benefit from PD-1 based immunotherapies in

advance [61]. For example, tumor uptake of ^{89}Zr-pembrolizumab is higher in patients who respond well to pembrolizumab treatment than those who do not respond to the treatment (median SUV_{peak}, 11.4 vs. 5.7) [62]. Similarly, the uptake of ^{89}Zr-nivolumab in tumors is also directly associated with treatment response (median SUV_{peak} 6.4 vs. 3.9) [57]. Hence, PD-1-PET/CT predicts response to treatment with immune checkpoint inhibitors for patients with NSCLC.

EGFR

Epidermal growth factor receptor (EGFR) has been recognized as a crucial molecular target specific for NSCLC therapy. In particular, mutated EGFR is a possible prognostic marker and a predictor of resistance in NSCLC [63]. EGFR tyrosine kinase inhibitors (TKIs) are first-line therapy for advanced NSCLC. The suitability for treatment with EGFR-TKIs depends on the EGFR mutation status in NSCLC patients [64]. Most advanced NSCLC patients would acquire resistance after treatment with the first-generation (gefitinib and erlotinib) or second-generation (afatinib and dacomitinib) TKIs, with the generation of T790M mutations as the predominant mechanism [65]. As a result, the third-generation EGFR TKIs (rociletinib and osimertinib) were developed to treat these patients with T790M mutation [66, 67]. Surprisingly, ^{18}F-gefitinib did not have satisfactory imaging results in EGFR-expressing engrafted tumor mouse models [68]. With further studies, it was shown that the high lipophilicity of the probe is a key factor affecting the imaging performance of radionuclides labeled TKIs. Increasing hydrophilicity of gefitnib can be resolved via polyethyleneglycol (PEG) modification, such as gefitinib-based ^{18}F-IRS that bind strongly to EGFR 19 exon deletion mutation [69]. Notably, dynamic PET/CT scans may provide additional information by analyzing the kinetics among different TKIs probes [70]. Dynamic ^{11}C-erlotinib-PET/CT showed that the volume of distribution was significantly higher in tumors with activated mutations as opposed to those without activated mutations (1.76 vs. 1.06) [71]. Moreover, the most promising EGFR-TKI PET candidate is N-(3-chloro-4-fluorophenyl)-7-(2-(2-(2-(2–18F-fluoroethoxy) ethoxy) ethoxy) ethoxy)-6-methoxyquinazolin-4-amine (^{18}F-MPG), which is based on the established ^{11}C-PD153035 that predict survival in NSCLC treated with EGFR-TKIs [72]. Therefore, EGFR-TKIs based treatment benefits EGFR-mutated NSCLC patients. This type of therapy also prolongs the median PFS especially when ^{18}F-MPG PET/CT indicates a SUVmax (maximum standardized uptake value) ≥ 2.23 [73].

$SSTR_2$

Bronchopulmonary NETs, including SCLC, large-cell neuroendocrine carcinoma, and atypical and typical carcinoids, account for 25% of primary lung neoplasia [74]. The somatostatin receptors (SSTRs), especially the $SSTR_2$ subtype, are overexpressed on NET cells. The somatostatin analogs, mainly octreotide and octreotide derivatives, have been developed for diagnosing and treating NETs in conjunction with various radionuclides. Since the 1990s, ^{111}In-pentetreotide (^{111}In-OctreoScan or ^{111}In-DTPA-D-Phe1-octreotide) has been used to image patients with lung carcinoids, NSCLC, and SCLC [75–77]. However, due to the limited spatial resolution and the relatively slow localization of ^{111}In-pentetreotide, (68)Gallium-DOTA-D-Phe(1)-Tyr(3)-octreotide (^{68}Ga-DOTATOC) has become a viable alternative for diagnosing, staging, and assisting in treatment decision-

making. A metaanalysis demonstrates that the clinical sensitivity (92% vs. 85.7%) and specificity (82% vs. 50%) of ^{68}Ga-DOTATOC were superior to those of ^{111}In-pentetreotide for NETs' diagnosis [78]. In addition, (68) Gallium-DOTA(0)-Tyr(3)-octreotate (^{68}Ga-DOTATATE) PET/CT imaging performs best in $SSTR_2$-positive patients (SUV > 20) [79]. Moreover, ^{68}Ga-DOTATATE outperforms ^{111}In-pentetreotide in terms of imaging sensitivity, overall accuracy, radiation dosimetry, and patient convenience [80, 81]. Hence, ^{68}Ga-DOTATATE has essentially replaced ^{111}In-pentetreotide imaging where available. Recently, ^{68}Ga-DOTA-PA1 and (^{124}I, Mn) OCT-PEG-MNPs have achieved satisfactory imaging results in preclinical studies. ^{68}Ga-DOTA-PA1 could target various subtypes of SSTRs, while (^{124}I, Mn) OCT-PEG-MNPs could target $SSTR_2$ as well as provide multimodality imaging [82, 83]. Overall, the approach to imaging patients with known NETs using ligands that target SSTRs is excellent.

CXCR4

The CXC motif chemokine receptor 4 (CXCR4) is overexpressed in different malignancies and is often associated with tumor metastasis and poor prognosis [84]. Wester's group developed a suitable probe (^{68}Ga-CPCR4-2, also known as ^{68}Ga-Pentixafor) with high affinity to CXCR4 that displays a TBR of 16.6 in SCLC models [85]. CXCR4 PET has also been utilized in various clinical settings. ^{68}Ga-Pentixafor PET/CT not only showed higher CXCR4 density in SCLC (SUVmax = 13.2) compared to NSCLC (SUVmax = 8.8) [86] but also demonstrated high image contrast in a variety of neoplasms, particularly for hematologic malignancies, SCLC, and adrenocortical neoplasms [87]. The specific binding of ^{125}I-CPCR4-3 to tumor cell lines with different levels of CXCR4 expression is increased by 2.4 to 11-fold compared to ^{68}Ga-CPCR4-2 [88], but further validation by in vivo imaging is still required. BL01, another potent peptide antagonist of CXCR4, accumulates too much in normal lung tissue and appears to be an improper radiotracer for LC [89]. AMD3100/plerixafor is a specific inhibitor of CXCR4. ^{64}Cu-AMD3100 accumulates in CXCR4-positive tumors (%ID/g: 12.3), but with the drawback that the accumulation in the liver is too high (tumor-to-liver ratio < 1) [90, 91]. In conclusion, Pentixafor is currently the most potentially suitable ligand for CXCR4-targeted theranostics in LC.

Integrin $\alpha_v\beta_3$

As an essential component of the TME, integrin $\alpha_v\beta_3$ can promote tumor cell migration and angiogenesis [92]. Dozens of integrin $\alpha_v\beta_3$-targeting PET tracers have been tested in preclinical studies and clinical trials. Importantly, peptides containing the Arg-Gly-Asp (RGD) sequence have high affinity for $\alpha_v\beta_3$ integrin receptors. A review by Chen et al. provides an in-depth discussion of radiolabeled RGD peptides that are available in the clinics for imaging of integrin $\alpha_v\beta_3$ via PET. Some have found applications in the diagnosis, clinical staging, and treatment response monitoring of LC [93].

Although RGD peptides are excellent for evaluating tumor angiogenesis, ^{18}F-galacto-RGD, the first clinical RGD PET tracer, has lower tumor uptake and image contrast than ^{18}F-FDG (mean SUV: 2.7 ± 1.5 vs. 7.6 ± 4.9) and is less sensitive than ^{18}F-FDG for tumor staging [94]. After that, dimeric RGD peptides were developed with higher receptor affinity, higher tumor uptake, and better pharmacokinetics than their monomeric analogs [95, 96]. And

indeed, ^{18}F-alfatide I, a dimeric RGD peptide, has shown good contrast in $\alpha_v\beta_3$-positive lung tumors with a mean SUV of 2.90 ± 0.10 and a TBR of 5.87 ± 2.02. ^{18}F-alfatide I can be used to distinguish between benign and malignant lesions (the cut-off value of SUVmax is 2.65) [97, 98]. Importantly, ^{18}F-alfatide I may be useful when predicting the response in locally advanced NSCLC patients who are undergoing radiotherapy concurrently [99]. PET/CT imaging based on ^{18}F-alfatide II (or the second generation) could differentiate between tuberculosis (SUV_{max}: 2.63 ± 1.34) and lung cancer (SUV_{max}: 4.08 ± 1.51) [100], as well as offer higher sensitivity than ^{18}F-FDG-PET/CT (92% vs. 77%) in detecting bone metastases [101]. Additionally, ^{68} Ga-labeled alfatide II could detect the inter- and intra-heterogeneity of $\alpha_v\beta_3$ integrin receptors in patients with NSCLC and SCLC [102], as well as outperform ^{18}F-FDG in assessing lymph node and brain metastasis [103, 104]. Furthermore, ^{99m}Tc-3PRGD2 has demonstrated high sensitivity (88%) and specificity (94.6%) toward the diagnosis of lymph node metastasis in NSCLC [105, 106]. In terms of therapeutic response evaluation, ^{68}Ga-DOTA-E-[c(RGDfK)]2-PET/CT is a valuable tool for assessing therapy response to angiogenesis inhibitors [107]. Overall, integrin $\alpha_v\beta_3$ PET imaging is effective in evaluating tumor angiogenesis, detecting tumorigenesis and metastasis, and identifying patients who will benefit from antiangiogenesis therapy.

FAP

FAP is overexpressed in cancer-associated fibroblasts (CAFs) that are located in the tumor stroma. FAP plays a crucial role in tumor cell growth, invasion, and migration [108]. A number of quinoline-based FAP inhibitors (FAPIs), including FAPI-02, FAPI-04, FAPI-21, FAPI-34, FAPI-46, and FAPI-74, have been developed for clinical imaging applications [108, 109]. With ease of production, high contrast generation, and low radiation load, ^{18}F or ^{68}Ga-labeled FAPIs may represent a powerful radiopharmaceutical devoted to diagnostic imaging of LC. The clinical imaging results in LC patients are encouraging, especially with ^{68}Ga-FAPI-04, ^{18}F-FAPI-74, and ^{68}Ga-FAPI-74. These probes could be not only specifically taken up at very high levels at the primary tumor site, lymph nodes, and distant metastases (average S UV_{max} > 10) [110, 111] but also have a higher staging accuracy than ^{18}F-FDG (94% vs. 30%) [112]. FAPIs have the property of comparatively rapid tumor clearance and correspondingly short tumor retention time, which is not a problem for diagnosis, but becomes a drawback as an effective therapeutic radiopharmaceutical for LC [109]. To increase tumor retention, Dirk Zboralski et al. developed the FAP-2286 compound, which utilizes cyclic peptides as binding motifs [113]. The results of ^{68}Ga-FAP-2286 and ^{68}Ga-FAPI-46 accumulated in tumors are comparable in both preclinical and clinical practice [113, 114]. However, the time-integrated activity coefficient and absorbed dose of ^{177}Lu-FAP-2286 are 12 and 9 times higher than ^{177}Lu-FAPI-46 in tumors [113]. In the future, radionuclide-labeled FAP-2286 may have more therapeutic potential than FAPIs.

TIGIT

T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT), expressed on $CD4^+$, $CD8^+$, and innate lymphocytes, can be a promising immune checkpoint for immunotherapies against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and PD-L1/PD-1 [115]. TIGIT interacts with CD155 and CD122 expressed on tumor cells or antigen-presenting cells to inhibit innate and adaptive immunity by

downregulating the function of natural killer cells and T cells [116]. A novel ^{68}Ga-labeled D-peptide antagonist, or ^{68}Ga-GP12, has shown success in accessing the heterogeneity of TIGIT expression in primary tumors (SUV_{max} = 4.82) and metastatic lesions (SUV_{max} = 2.80) in NSCLC patients. This finding indicates the possibility of stratifying patients suitable for anti-TIGIT therapies via TIGIT PET imaging [117].

Selection of RLT agents for the treatment of LC

When designing an RLT agent, the targeting ligand and radionuclide should be carefully considered and appropriately selected based on the histological/genetic tumor type and patient-bound factors such as tumor size, previous treatment responses, concurrent treatments, and previous medical history. Each LC subtype has certain molecular or cellular targets that are highly expressed. For example, NSCLC patients with high EGFR expression have more than 200 distinct mutations in the structural domain of tyrosine kinase [162]. On the other hand, SSRTs-RLT is promising for SSRTs-rich pulmonary NETs in SCLC or lung carcinoid patients [163]. Therefore, a detailed work-up (e.g., imaging or tissue biopsy) is required to determine the disease histotype and stage before initiating any treatment plans (Fig. 2).

Ligands used for theranostics should have the following characteristics: (1) excellent specificity that allows high target affinity, (2) more reasonable pharmacokinetics for lower toxicity, and (3) longer tumor retention time to maximize tumor-killing activity. The optimization of ligands should also consider these three aspects. First, the targeting ability of the ligand to the tumor needs to be enhanced. Although rhenium-188 labeled depreotide analog P2045 has entered phase I clinical trials for RLT of advanced lung cancer, unfortunately, no significant therapeutic responses have been recorded [164]. As we have summarized in the first part of this review or Table 1, octreotide and octreotate are currently the most widely used peptides for diagnosing and treating patients with $SSTR_2$ expressing lung NETs. The in vitro affinity of ^{68}Ga-DOTATATE (octreotate) for $SSTR_2$ is approximately tenfold higher than that of ^{68}Ga-DOTATOC (octreotide) [165]. Also, both the sensitivity (96% vs. 93%) and specificity (100% vs. 85%) of ^{68}Ga-DOTATATE are higher than ^{68}Ga-DOTATOC [166]. According to Table 2, it is obvious that various octreotide- and octreotate-based beta-emitter labeled RLT agents (e.g., ^{90}Y/^{177}Lu-DOTATATE and ^{90}Y/^{177}Lu-DOTATOC) have shown good efficacy in patients with lung NET in several clinical trials [167]. Furthermore, the development of bispecific antibodies or heterodimeric peptides can also improve targeting efficiency and image quality [69, 130, 156]. Second, radiation toxicity and off-target effects could be further minimized via structure optimization of radionuclide-labeled mAbs. Radioligands could mediate a fast tumor uptake by using low molecular weight sdAbs, peptides, and small molecules targeting PD-L1, CXCR4, or EGFR rather than full-length antibodies [54, 87, 168]. And last but not least, increasing ligands retention time in tumor tissues would effectively enhance therapeutic effectiveness. FAPIs, such as ^{90}Y-FAPI-04, ^{177}Lu-FAPI-46, have a very short retention time in tumors (a significant decrease occurs 24 h after injection). However, ^{177}Lu-FAP-2286 has a durable retention time of more than 72 h in tumors [113, 169]. The latest report of ^{177}Lu-FAP-2286 for the treatment of metastatic NSCLC has encouraging clinical results with a significant reduction in lesions after 9 weeks of treatment [36].

RLT may induce potential side effects in patients, including primary nephrotoxicity and hematological toxicity [29]. Hence, the selection of suitable radionuclides is of the utmost importance for improving the therapeutic efficacy and avoiding any toxic side effects. Beta-particle emitters are commonly used for RLT [170]. For instance, the maximum energy of the main emission (*E*max) of iodine-131 is 606.3 keV, with a half-life of 8.0 d and a maximum range of 2.9 mm in soft tissue [171]. ^{131}I-labeled recombinant chimeric tumor necrosis treatment antibody (^{131}I-chTNT) has been applied to treat patients with advanced lung cancer. However, it has shown limited clinical efficacy with some degree of immunogenicity in 8.97% of patients [172–174]. On the other hand, yttrium-90 has a shorter half-life ($t_{1/2}$: 2.7 days) and higher energy (*E*max: 2280.1 keV) compared to iodine-131 [24]. Nevertheless, yttrium-90 has a longer maximum range than lutetium-177 ($t_{1/2}$: 6.7 days) in soft tissue (12 mm vs. 2 mm), allowing the glomeruli of kidneys to be exposed to radiation. Meanwhile, ^{177}Lu only affects renal tubuli, thus causing higher incidences of nephrotoxicity and anemia [171, 175]. As such, ^{177}Lu is better suited than ^{90}Y for treating patients with NETs. Furthermore, ^{177}Lu-DOTATATE has a better disease control rate, better objective response rate, longer PFS, lower hazard ratio for death, and less disease recurrence compared with ^{90}Y-DOTATOC [35]. Recently, targeted alpha-particle therapy is also of great interest due to the shorter delivery range (40–100 μm) and greater energy (5–9 MeV) of alpha particles in contrast to beta particles [175]. The alpha particles induce double-strand breaks of DNA (unable for beta particles at the same radiation dose) at multiple sites through direct energy transfer or indirect effects of ionizing radiation. Notably, alpha particles are a double-edged sword. DNA breaks are closely related to the bystander and abscopal immune effects. Thus, alpha particles generate a stronger antitumor potency and can also be toxic to surrounding normal tissues [176]. After ^{223}Ra-dichloride was approved for treating painful osseous metastases from prostate cancer [177], alpha-particle therapy is now considered an alternative to beta-particle therapy. In preclinical studies, ^{225}Ac radioimmunoconjugates showed a relatively low tumor growth rate compared to ^{177}Lu radioimmunoconjugates [178]. In clinical trials, actinium-255 labeled DOTATATE has successfully treated gastroenteropancreatic NET patients stable or refractory to ^{177}Lu-DOTATATE [179]. With the development of radiopharmaceutical therapy, alpha-particle therapy has played a major role in the management of brain, breast, and lung cancer among others [180]. For lung NETs, ^{255}Ac-DOTATATE significantly suppressed the growth of H727 and H69 tumors in mice without inducing toxicity concerns [181].

Auger electrons are also suited for RLT owing to their short emission range, low energy, and high linear energy transfer. These physical characteristics allow for strong energy deposition around the decay point [182]. Iodine-125 is one of the most extensively investigated auger emitters [183]. Treatment with iodine-125 labeled anti–EGFR mAb 425 improved median survival in patients with glioblastoma. Importantly, the combined therapy of ^{125}I-mAb 425 and temozolomide effectively extended the maximum survival benefit [184]. Unfortunately, only few ^{125}I-RLT studies have focused on LC thus far. ^{125}I has also been limited as a systemically administered RLT agent since its long physical half-life is not ideal for clinical use ($t_{1/2}$ = 60.1 days) [185]. In addition, most studies have concentrated on the dosimetry, pharmacokinetics, and biodistribution of auger electrons-labeled probes, thus prompting the need for further evaluation of their therapeutic effects [119, 186]. For instance, ^{125}I-labeled

CO1686 and HuBA-1-3D showed high specificity and activity against EGFR mutations or delta-like 1 homolog (DLK1) in LC cell lines, but the therapeutic potential of ^{125}I-CO1686 and ^{125}I-HuBA-1-3D was not assessed [187, 188]. Notably, in order to maximize efficacy and minimize toxicity, it is ideal to target auger electron-emitting isotopes to the tumor cell nuclei, even though internalization of the probe is not required for effective RLT [189–192].

Currently, only a proportion of $SSTR_2$-targeted RLT agents developed for lung NETs are in clinical trials. Treatment with ^{177}Lu-DOTATATE could result in an objective response rate of 39% for all bronchial and gastroenteropancreatic NET patients, with PFS and OS of 29 and 63 months, respectively [167]. Compared with chemotherapy or targeted therapy, $SSTR_2$-targeted RLT agents had longer median PFS in the unmatched (2.5 years vs. 0.7 years) and matched (2.2 years vs. 0.6 years) populations [193]. Compared with everolimus-treated advanced pancreatic NETs, ^{177}Lu-DOTATATE therapy had a better objective response rate (47% vs. 12%), disease control rate (81% vs. 73%) as well as longer PFS (25.7 months vs. 14.7 months), and also had a better safety profile [194]. In addition, the efficacy of combination of ^{177}Lu-DOTATATE is superior to monotherapy. For example, ^{177}Lu-DOTATATE plus somatostatin analogs correlated with the highest probability (99.6%) of the longest PFS [195]. The combination of ^{177}Lu-DOTATATE with carboplatin/etoposide chemotherapy prolonged survival vs. ^{177}Lu-DOTATATE or chemotherapy alone [136]. ^{177}Lu-DOTATATE and capecitabine therapy lengthen median OS and PFS in advanced metastatic NETs [196], and ^{177}Lu-DOTATATE plus nivolumab showed signs of antitumor activity in patients with relapsed/refractory extensive-stage SCLC [197]. RLT agents for other targets or other types of LC are still under development, with no definitive results on their therapeutic efficacy. Herein, we propose two recommendations to promote the use of RLT drugs in LC management. On the one hand, it is necessary to advance different types of RLT agents into preclinical and clinical studies. More specifically, the main focus should be the therapeutic evaluation of tumors using alpha particles- and auger electrons-emitting radionuclides labeled ligands. On the other hand, to combat the challenges of single-drug therapies and drug resistance, personalized treatments that combine chemotherapy, radiosensitizers, small molecule kinase inhibitors, and other therapeutic agents will yield better patient outcome.

Conclusion and future perspectives

A critical concern in the management of LC is the difficulty of determining the patient characteristics that would benefit from certain treatments. At present, tissue biopsy, which is an invasive procedure, is the gold standard for cancer confirmation. However, due to intra-tumor phenotypic heterogeneity, biopsy often leads to erroneous tumor status classifications. As a result, repeat biopsies are necessary to give more accurate diagnoses, but this approach puts a significant burden on patients [214]. In contrast, PET and SPECT are non-invasive in nature and can be used to determine the expression level of specific molecules or mutation status of oncogenes in tumor cells, while monitoring the immune response in the TME [57, 215]. Thus, nuclear medicine could be an ideal therapeutic strategy to prospectively identify the patient populations that may benefit from a drug prior to its administration and subsequently personalize the treatment by employing suited radioligands.

The application of radioligands offers several invaluable advantages for targeted theranostics of LC. First, RLT agents can identify molecular targets in vivo without the need for biopsy and provide personalized therapeutic solutions for each individual. As we have summarized in Table 1, PET or SPECT imaging allows for the non-invasive detection of tumor mutation status as well as specific biomarkers in tumors and TME. Second, RLT can overcome the challenges of low vascular abundance and heterogeneous receptor expression on tumor cells. By changing the size and modifying the water solubility of ligands, the capability of RLT agents may be improved in terms of their affinity and specificity. Moreover, combined therapies, as opposed to single drug-targeted treatments, can improve further therapeutic efficacy and reduce toxic side effects [216]. Numerous combined-therapeutic strategies have been evaluated, including the combination of drugs that modulate immune checkpoints, improve tumor perfusion, upregulate target receptors, induce tumor cell DNA damage, and inhibit DNA damage repair [217]. Lastly, RLT can be used to estimate a patient's prognosis and inform treatment decisions by tracking tumor response and progress via real-time longitudinal monitoring. For example, immuno-PET has been used to assess and predict therapeutic efficacy by examining the immune activation status of primary tumors and systemic lymphoid organs before and after treatment [218].

In spite of the considerable merits of RLT in oncological treatment, its limitation is still noticeable, namely, the problem of non-negligible toxicity. However, there are three aspects that we can take into account to improve the current procedures to alleviate the toxicity of RLT agents. The first step is to take some options to reduce the drug's toxic effects depending on the patient's health status. For example, the patient may be infused with nephroprotective amino acids [219]. Secondly, as discussed in the previous section, we should choose the optimal ligand and radionuclide to minimize toxicity. Finally, RLT combined with chemotherapy or immunotherapy can reduce toxicity by reducing the dosage of TRT drugs and achieve better therapeutic results.

In summary, RLT could provide tailored and personalized medical care for each individual patient. The application of RLT for targeted theranostics of LC is in its infancy, but this topic is gaining considerable interest and more research progress will be made in the coming years. Besides, the safety of radionuclide application in tumor diagnosis and treatment has been clinically proven for many years, and an increasing number of mAbs, peptides, and small molecules are increasingly entering clinical trials. Once suitable targets can be identified and safer and more effective ligands developed for LC treatment, we anticipate that RLT will provide great clinical benefits as either an adjuvant or first-line treatment for patients with early, advanced, relapsed, or treatment-resistant LC in the future.

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Data availability

Not applicable.

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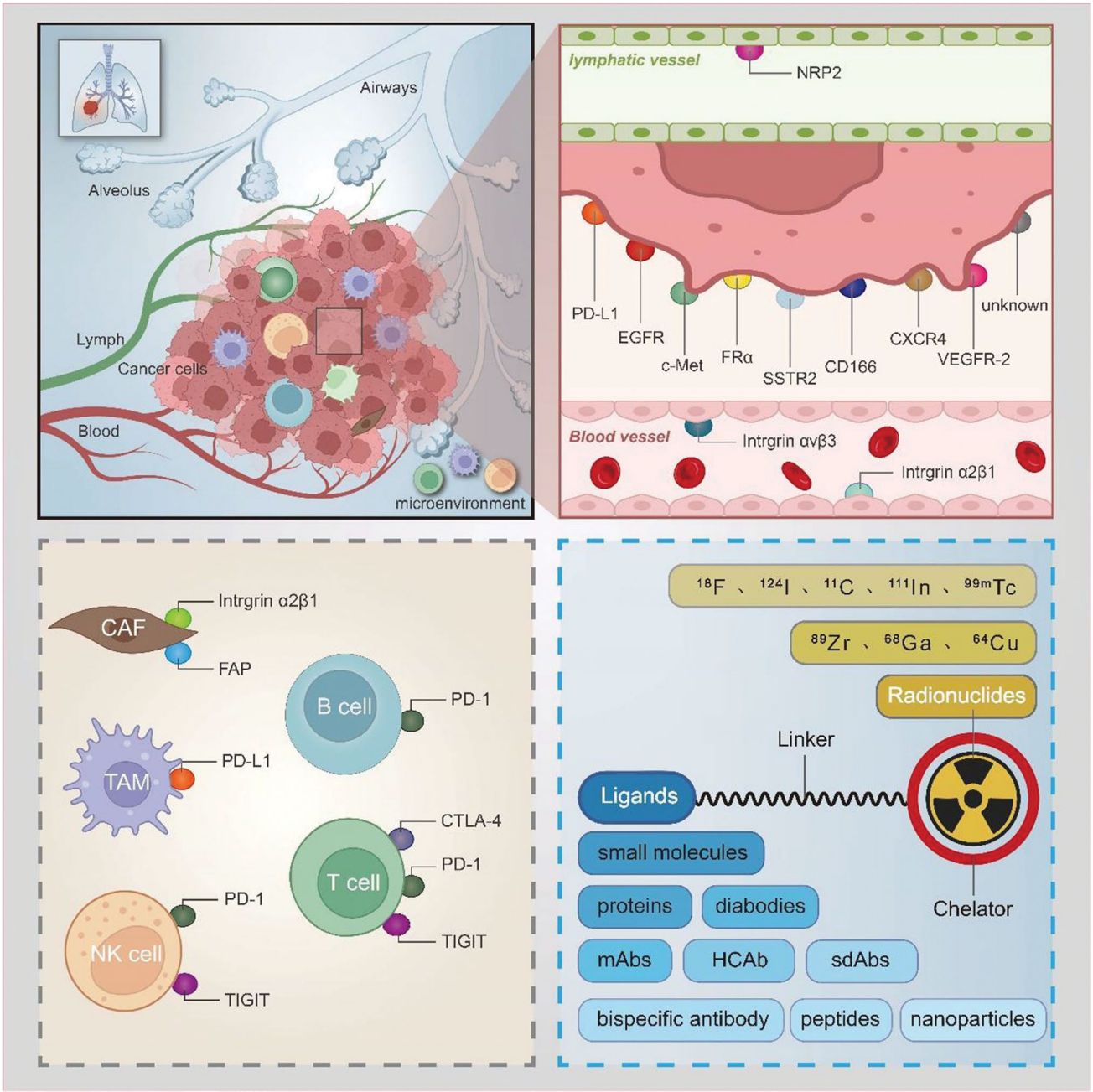

Fig. 1.

Potential biomarkers in pulmonary tumors for PET or SPECT imaging and representative ligands and radionuclides for RLT. Abbreviations: PD-1/PD-L1, programmed cell death protein-1/ligand-1; EGFR, epidermal growth factor receptor; TIGIT, T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FAP, fibroblast activation protein; FRα, folate receptor alpha; CD166, activated leukocyte cell adhesion molecule; SSTR2, somatostatin receptor 2; NRP-2, neuropilin receptor type-2; CXCR4, CXC chemokine receptor 4; VEGFR-2, vascular endothelial growth factor receptor-2; c-Met, the receptor of hepatocyte growth

factor; TAM, tumor-associated macrophages; mAbs, monoclonal antibodies; sdAbs, single-domain antibodies; HCAb, heavy chain-only antibody

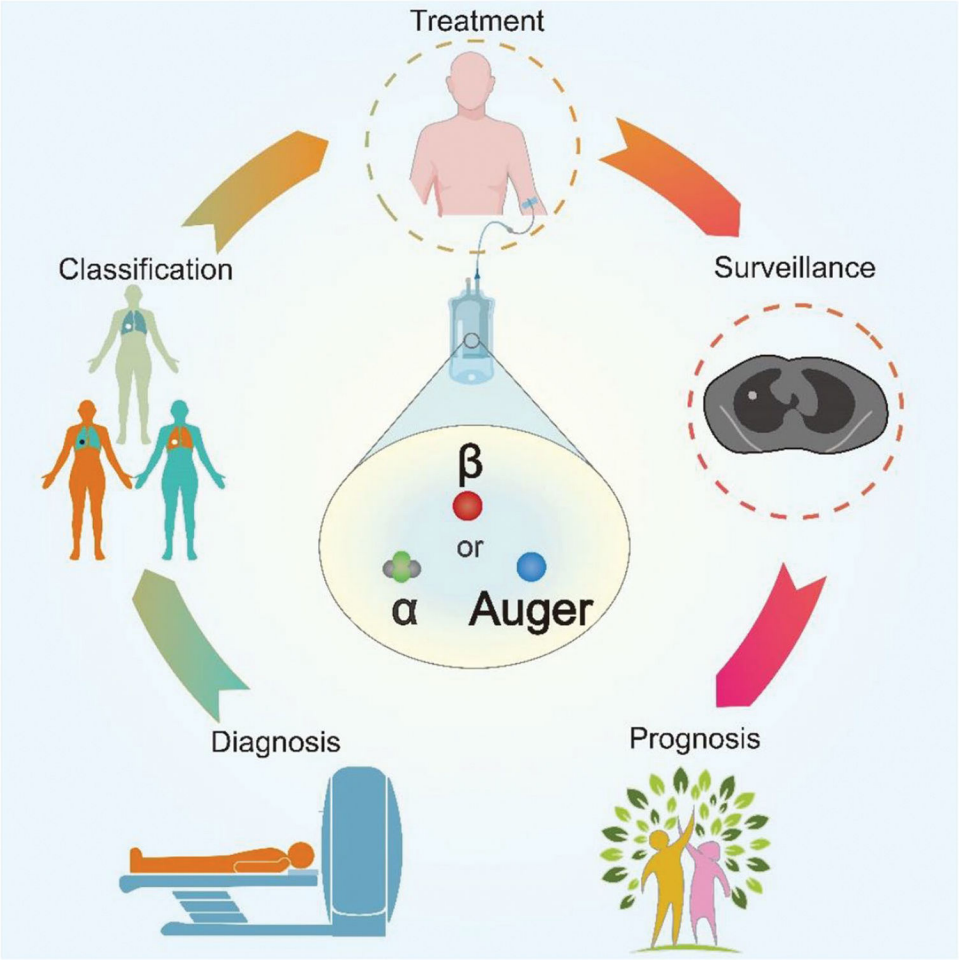

Fig. 2.
Theranostic procedures for RLT

Table 1

Overview of targets and properties of tracers for PET/SPECT imaging of lung cancer

Targets	Location	Tracers	Properties	Classification (cell lines)	Tumor uptake	Study type	Ref
PD-L1	T	^{89}Zr-atezolizumab	mAbs	NSCLC	Median SUV_{max}: 9.7	C	[43]
		^{89}Zr-durvalumab	mAbs	NSCLC	Median SUV_{max}: 4.9	C	[44]
		^{68}Ga-NOTA-WL12	Peptides	NSCLC	SUVmax: 4.9 TBR: 4.9	C	[55]
		^{18}F-BMS-986192	Proteins	NSCLC	Median SUV_{max}: 6.5	C	[57]
		^{99m}Tc-NM-01	sdAbs	NSCLC	TBR: 2.3	C	[54]
		^{89}Zr-DFO-REGN3504	mAbs	NSCLC (NCI-H441, HCC827)	%ID/g: 52.3 (NCI-H441) %ID/g: 38.7 (HCC827)	P	[45]
		^{89}Zr-DFO-6E11	mAbs	NSCLC (HCC827)	%ID/g: 5.1 TBR: 12.8	P	[46]
		^{89}Zr-C4	mAbs	NSCLC (PDX, A549)	%ID/g: 5.0	P	[47]
		^{64}Cu-NOTA-rhPD1	Proteins	NSCLC (HCC827)	%ID/g: 9.0 TBR: 14.5	P	[50]
		^{124}I-SIB-SHR-1316	mAbs	NSCLC (PDX)	SUV: ~0.5 TBR: 5.3	P	[48]
		^{64}Cu-NOTA-Nb6	HCAb	NSCLC (A549)	TBR: 2.1	P	[118]
		^{89}Zr-avelumab	mAbs	NSCLC (HCC827)	In vitro	P	[49]
CCK-2R	T	^{111}In-IP-001	Small molecules	NSCLC (A549)	%IA/g: 2.4 TBR: 15.7	P	[119]
EGFR	T	^{11}C-erlotinib	Small molecules	NSCLC	V_T: 1.8 (Mutant) V_T: 1.1 (Wild-type)	C	[71]
		^{18}F-IRS	Small molecules	NSCLC	SUV_{max}: 2.4 (Mutant)	C	[69]
		^{11}C-PD153035	Small molecules	NSCLC	SUVmax ≥ 2.9	C	[72]
		^{18}F-MPG	Small molecules	NSCLC	SUVmax ≥ 2.2 (Mutant) SUVmax < 2.2 (Wild-type)	C	[73]
		^{18}F-afatinib	Small molecules	NSCLC	TBR ≥ 6.0 (Mutant) TBR < 6 (Wild-type)	C	[120]
		^{89}Zr-cetuximab	mAbs	NSCLC	SUVmax: 1.18—4.74	C	[121]
		^{18}F-FEA-erlotinib	Small molecules	NSCLC (HCC827)	%ID/g: 0.7 TBR: 1.4	P	[122]
		^{18}F-icotinib	Small molecules	NSCLC (A549)	%ID/g: 0.9	P	[123]
		^{111}In-DOTA-cetuximab ^{64}Cu-DOTA-cetuximab	mAbs	NSCLC (HCC827)	%ID/g: 26.9 (^{111}In-DOTA-cetuximab) SUVmean: 4.4 (^{64}Cu-DOTA-cetuximab)	P	[124]
c-Met	T	^{89}Zr-DFO-H2	Diabodies	NSCLC (HCC827, HCC827-GR6)	%ID/g: 1.1 (HCC827) %ID/g: 1.8 (HCC827-GR6)	P	[125]
		^{99m}Tc-HYNIC-Cmbp	Peptides	NSCLC (H1993)	%ID/g: 4.7	P	[126]

Targets	Location	Tracers	Properties	Classification (cell lines)	Tumor uptake	Study type	Ref
		^{18}F-FPC	Small molecules	NSCLC (H1993)	%ID/g: 2.5 TBR: 2.4	P	[127]
		^{89}Zr-Onartuzumab	mAbs	NSCLC (HCC827, HCC827ErlRes)	%ID/g: 30.2 (HCC827) %ID/g: 38.1 (HCC827ErlRes)	P	[128]
		^{89}Zr-PRS-110	Proteins	NSCLC (H441)	%ID/g: 5.9	P	[129]
c-Met & EGFR	T	^{89}Zr-DFO-amivantamab	Bispecificantibody	NSCLC (HCC827)	In vitro	P	[130]
FRα	T	^{18}F-AzaFol	Small molecules	NSCLC	%IA/g: 0.5	C	[131]
NTR	T	^{18}F-NT	Small molecules	NSCLC (H1299)	%ID/g: 1.9 TBR: 7.8	P	[132]
CD166/ ALCAM	T	^{89}Zr-CX-2009	Probody	H292	%ID/g: 21.8	P	[133]
$SSTR_2$	T	^{99m}Tc-depreotide	Peptides	Lung carcinoids NSCLC	TBR: 2.6	C	[134]
		^{68}Ga-DOTATOC (octreotide)	Peptides	NSCLC	Mean SUV: 2.0	C	[135]
		^{68}Ga-DOTATATE (octreotate)	Peptides	SCLC (NCI-H69)	SUV_{max}: > 20 (positive) TBR: 12.6	CP	[79] [136]
		^{68}Ga-DOTA-PA1	Peptides	NSCLC (A549)	%ID/g: 5.2	P	[82]
		(^{124}I, Mn) OCT-PEG-MNPs	Nanoparticles	SCLC (NCI-H69)	%ID/g: 8.0	P	[83]
UT receptor	T	^{111}In-DOTA-Huii	Peptides	NSCLC (A549)	%ID/g: 0.8 TBR: 2.8	P/CR	[137]
CD 146	T	^{64}Cu-NOTA-YY146	mAbs	NSCLC (H460)	%ID/g: 7.4	P	[138]
CEA	T	^{99m}Tc-anti-CEA nanobody	Nanobody	NSCLC (H460)	%ID/g: ~3.0	P	[139]
CXCR4	T	^{68}Ga-Pentixafor (^{68}Ga-CPCR4-2)	Peptides	NSCLC SCLC	Average SUV_{max}: ~8.5 Average SUV_{max}: ~12.0	C	[87]
		^{64}Cu-AMD3100	Small molecules	LC (3LL: CXCR4-transfected)	%ID/g: 12.3	P	[90]
		^{89}Zr-MDX-1338	mAbs	NSCLC (H1155)	%ID/g: 36.2 TBR: 41.0	P	[140]
VEGFR-2	T	^{64}Cu-NOTA-RamAb	mAbs	NSCLC (HCC4006)	%ID/g: 9.4±0.5	P	[141]
CD30	T	^{89}Zr-Df-BV	mAbs	NSCLC (H460)	%ID/g: 9.9	P	[142]
CD38	T	^{89}Zr-Df-daratumumab	mAbs	NSCLC (A549)	%ID/g: 8.1	P	[143]
CD133	T	^{89}Zr-DFO-αCD133	mAbs	SCLC (NCI-H82)	%ID/g: 50.8	P	[144]
Lewis Y	T	^{111}In-hu3S193	mAbs	SCLC	-	C	[145] [146]
Unknown	T	^{99m}Tc-(tricine)-HYNIC-(Ser)3-J18	Peptides	NSCLC (A549)	%ID/g: 1.1 TBR: 5.6	P	[147]
Integrin $\alpha_v\beta_6$	T	^{18}F-$\alpha_v\beta_6$-BP	Peptides	NSCLC	SUV_{max}: 1.0–13.5 TBR: 17.3–67.5	C	[148]
		^{68}Ga-SFITGv6	Peptides	NSCLC	Mean SUV_{max}: 3.3	C	[149]

Targets	Location	Tracers	Properties	Classification (cell lines)	Tumor uptake	Study type	Ref
		^{68}Ga-DOTA-R01-MG	Peptides	NSCLC (H1975)	%ID/g: 2.5 TBR: 5.2	P	[150]
		^{68}Ga-TRAP(SDM17)$_3$	Peptides	NSCLC (H2009)	%ID/g: 2.1 TBR: ~22.0	P	[151]
		^{68}Ga-avebehexin	Peptides	NSCLC (H2009)	%ID/g: 0.6 TBR: 10.8	P	[152]
Integrin $\alpha_v\beta_3$	T/TME	^{18}F-galacto-RGD	Peptides	NSCLC	Mean SUV: 2.7	C	[94]
		^{18}F-AlF-NOTA-PRGD2 (^{18}F-Alfatide I)	Peptides	NSCLC (CMT-167)	Mean SUV: 2.9 TBR: 5.9	C	[97]
		^{68}Ga-NOTA-PEG4-E[c(RGDfK)]2 (^{68}Ga-Alfatide II)	Peptides	NSCLC	SUV$_{max}$: 3.7 SUV$_{max}$: 3.9SUV$_{max}$: 3.8	C	[103] [104] [102]
		^{99m}Tc-3PRGD2	Peptides	NSCLC	TBR: 5.8 TBR: 2.8	C	[106] [105]
		^{68}Ga-DOTA-E-(cRGDfK)2	Peptides	NSCLC	Median SUV$_{max}$: 4.3	C	[107]
		^{68}Ga-NODAGA-THERA-NOST	Peptides	Lung carcinoids	SUV$_{max}$: 4.8 TBR: 1.5	C	[153]
		^{99m}Tc-RGD-4CK	Peptides	NSCLC	%ID/g: 4.1 TBR: 3.8	P	[154]
Integrin $\alpha_2\beta_1$	T/TME	^{68}Ga-DOTA-A2B1	Peptides	NSCLC (A549)	%ID/g: 2.5 TBR: 1.5	P	[155]
SSTR$_2$ & Integrin $\alpha_v\beta_3$	T/TME	^{68}Ga-NOTA-3P-TATE-RGD	Peptides	NSCLC SCLC Lung carcinoids	Mean SUV$_{max}$: 4.1 Mean TBR: 5.2 TBR: 4.5 (NSCLC) 6.1 (SCLC) 36.1 (Lung carcinoids)	C	[156]
NRP-2	T/TME	^{131}I-anti-NRP-2	mAbs	NSCLC (A549)	%ID/g: 4.6 TBR: 3.8	P	[157]
CTLA-4	T/TME	^{64}Cu-DOTA-ipilimumab	mAbs	NSCLC (A549)	%ID/g: 9.8	P	[158]
FAP	TME	^{18}F-FAPI-74 ^{68}Ga-FAPI-74	Small molecules	NSCLC	Average SUV$_{max}$: 12.7 Average SUV$_{max}$: 11.4	C	[110]
		^{68}Ga-FAPI-04	Small molecules	LC	Average SUV$_{max}$:> 12	C	[111]
		^{68}Ga-FAP-2286	Peptides	NSCLC	SUV$_{max}$: 7.3	C	[36]
PD-1	TME	^{89}Zr-nivolumab	mAbs	NSCLC	Median SUV$_{max}$: 6.4	C	[57]
		^{89}Zr-pembrolizumab	mAbs	NSCLC	Mean SUV$_{max}$: 6.5	C	[159]
TIGIT	TME	^{68}Ga-GP12	Peptides	NSCLC	SUV$_{max}$: 4.8	C	[117]
TAM	TME	^{64}Cu-Macrin	Nanoparticles	NSCLC (KP1.9)	%ID/g:~6 SUV: 1.3	P	[160]
Hypoxic tumor	TME	^{68}Ga-HP-DO3A-NI	Small molecules	NSCLC (A549)	%ID/g: 0.9 TBR: 5.0	C	[161]

PD-1/PD-L1 programmed cell death protein-1/ligand-1, *EGFR* epidermal growth factor receptor, *TIGIT* T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain, *CCK-2R* cholecystokinin-2 receptor, *CTLA-4* cytotoxic T-lymphocyte-associated protein 4, *FAP* fibroblast activation protein, *FRα* folate receptor alpha, *NTR* neurotensin receptor, *CD166/ALCAM* activated leukocyte cell adhesion molecule, *SSTR2* somatostatin receptor 2, *NRP-2* neuropilin receptor type-2, *CXCR4* CXC chemokine receptor 4, *VEGFR-2* vascular endothelial growth factor receptor-2, *MET* the receptor of hepatocyte growth factor, *TAM* tumor-associated macrophages, *TME* tumor microenvironment, *mAbs* monoclonal antibodies, *sdAbs* single-domain antibodies, *HCAb* heavy chain-only antibody, *PDX* patient-derived xenograft, *TBR* tumor background ratio, *T* tumor, *P* preclinical, *C* clinical, *CR* case reports, *%IA/g* percent of injected activity per gram of tissue, *%ID/g* percent of injected dose per gram of tissue

Table 2

Characteristics and pro/cons of RLT agents studied for lung cancer therapy

Isotope	$T_{1/2}$ (d)	Agent	Target	Properties	Pros	Cons	Studies		
^{225}Ac α, β, γ	9.9	^{225}Ac-DOTATATE	$SSTR_2$	Peptides	Tumor growth suppression Relatively greater efficacy and lower toxicity	Nephrotoxicity Chronic progressive nephropathy	Lungcarcinoids (H727, H69	P	[181]
		^{225}Ac-SC16.56/ N149	DLL3	mAbs	Tumor growth suppression Extended life expectancy	Lower drug–antibody ratio	SCLC (PDX)	P	[178]
^{227Th} α, β	18.7	^{227}Th-anetumab	MSLN	mAbs	Significant survival benefit In vivo effective in a disseminated model of lung cancer	Suppression of white blood cells	NSCLC (NCI-H226)	P	[198]
^{131}I β, γ	8.0	^{131}I-chTNT	Necrotic tumors	mAbs	Tumor necrosis targeted therapy	Bone marrow suppression Hematological toxicities	NSCLC	C	[172] [173]
		^{131}I-cNGEGQQc	$\alpha_3\beta_1$ Integrin	Peptides	Tumor growth suppression	Limited dose administration (High kidney uptake)	NSCLC (H1975, L78)	P	[199]
		^{131}I-RGD-BSA-PCL	$\alpha_v\beta_3$ integrin	Nanoparticles	Extended life expectancy Longer residence times in tumor	Intratumoral injection	NSCLC (NCI-H460)	P	[200]
		^{131}I-TQGMNP	Glucuronidase enzyme	Nanoparticles	Multimodality imaging: SPECT and MRI Tumor growth suppression	Hematologic toxicity	NSCLC (A549)	P	[201]
		^{131}I-prohy	Necrotic tumors	Small molecules	Tumor necrosis targeted radiotherapy Tumor growth suppression Extended life expectancy	Unclear the exact mechanism for the necrosis affinity of protohypericin Therapeutic effect needs to be further verified	NSCLC (A549)	P	[202]
^{177}Lu β, γ	6.7	^{177}Lu-DOTATATE	$SSTR_2$	Peptides	Extended life expectancy Better disease control rate, objective response rate, progression-free survival, lower hazard ratio for death and disease recurrence compared with ^{90}Y-DOTATOC	Nephrotoxicity Anemia Thrombocytopenia Hematologic toxicity Myelodysplastic syndrome Leukemia	Lungcarcinoids	C	[35] [167]
		^{177}Lu-FAP-2286	FAP	Peptides	Significant decrease in lesion size and SUV_{max} Longer tumor retention	Headache Abdominal pain Anemia Hematologic toxicity	NSCLC	C	[36] [203]
		^{177}Lu-DOTA-HA100-N	CD44 and CD13	Hyaluronan modified by peptide	Targeting malignant cancers with abundant blood vessels	Low tumor accumulation Easily degradable	NSCLC (NCI-H292)	P	[204]
		^{177}Lu-SC16.56 ^{177}Lu-N149	DLL3	mAbs	Higher drug–antibody ratio	Relatively lower efficacy compared to ^{225}Ac-labeled agents	SCLC (PDX)	P	[178]

Isotope	$T_{1/2}$ (d)	Agent	Target	Properties	Pros	Cons	Studies		
		^{177}Lu-DOTA-RS7	EGP-1	mAbs	Tumor growth suppression	Body weight loss Hematologic toxicity	NSCLC (Calu-3)	P	[205]
		^{177}Lu-EB-RGD	Integrin $\alpha_v\beta_3$	Peptides	Tumor growth suppression Longer half-life and higher retention in the blood pool High tumor accumulation Longer tumor residence time	Body weight loss	NSCLC (PDX)	P	[206]
		^{177}Lu-DOTA-E(cRGDfK)2	Integrin $\alpha_v\beta_3$	Peptides	Tumor growth suppression High tumor accumulation Rapid excretion by urinary route	Potential nephrotoxicity and hematological toxicity	NSCLC (A549)	P	[207]
^{90}Y β	2.7	^{90}Y-DOTATOC	$SSTR_2$	Peptides	Extended life expectancy	Nephrotoxicity Anemia Leukopenia Thrombocytopenia	Lung carcinoids	C	[136] [35]
		^{90}Y-FF-21101	Placental (P)-cadherin	mAbs	Complete response achieved in patients with high P-cadherin expression	Low expression of P-cadherin in Lung carcinoids Lymphopenia Leukopenia Thrombocytopenia	Lung carcinoids	C	[208]
		^{90}Y-MAb-6	CDH3/P-cadherin	mAbs	Tumor growth suppression and regression	Body weight loss	NSCLC (H1373)	P	[209]
^{90}Y β ^{177}Lu β, γ	2.7 6.7	^{90}Y/^{177}Lu-DOTATATE	$SSTR_2$	Peptides	Therapy with tandem radioisotopes provides longer overall survival than with a single radioisotope	Hematological toxicity Nephrotoxicity	Lung carcinoids	C	[210]
^{188}Re β, γ	0.7	^{188}Re-P2045	$SSTR_2$	Peptides	Short plasma half-life Well tolerated	Lymphopenia No responses	NSCLC	C	[164]
		^{188}Re-cetuximab	EGFR	mAbs	Tumor growth suppression Extended life expectancy	Body weight loss	NSCLC (NCI-H292)	P	[211]
		^{188}Re-bevacizumab	VEGF	mAbs	Tumor growth suppression	No significant tumor regression	NSCLC (A549)	P	[212]
^{166}Ho β, γ	1.1	^{166}Ho-IG-cisplatin	Selective delivery to tumors using an external magnet	Nanoparticles	Combination of radiotherapy with chemotherapy Enhanced permeability and retention effect Targeted delivery in the presence of a magnetic field	Lack of active targeting	NSCLC (A549)	P	[213]

*SSTR*2 somatostatin receptor 2, *DLL3* delta like 3 protein, *MSLN* mesothelin, *EGP-1* epithelial glycoprotein-1