VIA MEDICA

Nuclear Medicine Review 2023, 26, 77–84
DOI: 10.5603/NMR.2023.0010

ISSN 1506–9680, e-ISSN 1644–4345

Review

Diagnosis and treatment of lung cancer using nuclear medicine techniques — current state of the art

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[Received: 6 XII 2022; Accepted: 25 IV 2023]

Abstract

Lung cancer is the leading cause of cancer-related death worldwide. Planar radiography and computed tomography are the most common imaging modalities used in diagnosis, staging, and therapy response assessment. However, the role of nuclear methods in assessing the severity of the disease and the effectiveness of treatment has increased in recent years. Introducing these diagnostic modalities into standard practice in lung cancer may contribute to the personalization of treatment. In this review, we summarize the current knowledge of nuclear medicine techniques in the diagnosis and treatment of lung cancer.

KEY words: lung cancer; positron emission tomography/computed tomography; single photon emission tomography/computed tomography; nuclear medicine; theragnostic

Nucl Med Rev 2023; 26, 77–84

Introduction

Molecular imaging, owing to noninvasive measurements of tumor biology, allows the characterization of disease as well as assessment of prognosis and therapeutic response. Nuclear medicine uses radionuclides that decay in various ways for therapy and imaging procedures, where both are inseparably connected to each other. With radiopharmaceuticals, imaging techniques such as single photon emission tomography (SPECT) and positron emission tomography (PET) allow the noninvasive measurement of specific processes based on radiotracer accumulation [1]. Moreover, the change in the radionuclide labeling in many cases can change the character of the radioligand, causing cancer cell death and, therefore, participating in the treatment. These facts explain why, in addition to the standard procedures, nuclear medicine has a leading position in the imaging and therapy of lung cancer (LC), which is the most commonly diagnosed and leading cause of cancer-related death worldwide [2]. In this review, we summarize the current trends in the use of nuclear medicine techniques for the diagnosis and therapy in LC and discuss the most commonly used radiotracers for PET and SPECT combined with computed tomography (CT).

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Imaging of lung cancer

Diagnostic imaging methods in lung cancer include chest X-ray, CT, magnetic resonance imaging (MRI), endobronchial ultrasonography (EBUS), esophageal ultrasonography (EUS), and nuclear medicine imaging methods, namely, PET and SPECT routinely combined with CT [3]. MRI is less commonly used in lung imaging than CT because of a limited spatial resolution, high susceptibility differences between air spaces and pulmonary interstitium, or motion artifacts caused by respiratory and cardiac motion. Even though some new MRI techniques have recently been presented to provide better use of this modality in LC, CT remains the gold standard [4]. Radionuclides used in PET normally undergo β^+ decay [^{11}C, ^{13}N, ^{15}O, sometimes in the simultaneous presence of electron

capture (^{18}F)]. Perfect imaging radionuclide has a long half-life time and short positron range that allows good image quality to be achieved [5]. Depending on the aim of the imaging process, the chosen ligands visualize glucose metabolism, cell proliferation, somatostatin receptor expression, hypoxia, angiogenesis, or other factors. Moreover, all of them should be characterized by a high specificity and sensitivity in specific types of cancer, which will be helpful in the diagnosis and treatment of lung cancer patients.

The most commonly used radiopharmaceutical for cancer diagnosis purposes is the 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG)--radiolabelled analog of glucose, where the hydroxyl group of glucose at position 2 is substituted with the [^{18}F] radioisotope. It was shown that this radiopharmaceutical is useful in cancer staging, the detection of distant metastases, therapy planning, assessing the response to therapy, and localizing tumors with an unknown primary origin [6]. Derlin et al. [7] showed that using PET imaging in patients with non-small-cell lung cancer (NSCLC) significantly helped to avoid unnecessary thoracotomies in approximately 50% of patients compared to those who did not undergo PET imaging, and PET/CT should be used in all patients who are planned to undergo radical radiotherapy (RT), surgery or radiochemotherapy. [^{18}F]FDG PET/CT has a well-established role in assessing therapy response in various tumors, including LC, with a specificity of 92% and a sensitivity of 100% in NSCLC patients [8]. Some authors suggest that posttreatment tumor [^{18}F]FDG avidity is correlated with worse survival and the risk of local recurrence and distant metastases [9]. Recent studies have shown that performing interim [^{18}F]FDG PET during chemotherapy can predict survival and therapy response in LC patients. Vera et al. [10] noted that a higher maximum standardized uptake value (SUV_{max}) in an interim PET/CT study was associated with tumor progression and death in NSCLC patients. Despite the proven use of [^{18}F]FDG in PET/CT studies, this radiotracer has some limitations. Whereas glucose also accumulates in inflammatory cells, an [^{18}F]FDG PET/CT scan can give false-positive results, especially in lymph node staging, tuberculosis, sarcoidosis, or other pulmonary inflammation [11]. Cho et al. [12] performed early and delayed [^{18}F]FDG PET/CT scans to differentiate between tuberculosis and malignant lesions in the lung using a cut-off of 3.9 SUV_{max} in delayed imaging. Nevertheless, EBUS is still the gold standard for differentiating malignant from benign lymph nodes. Thus, the investigation of more specific tumor PET tracers that might provide additional information is necessary.

Amino acid tracers such as [^{11}C]methionine ([^{11}C]C-MET), [^{18}F]-fluoro-ethyl-tyrosine ([^{18}F]FET), and L-[3-(18)F]-α-methyltyrosine ([^{18}F]FAMT) are of interest because of their association with the amino acid transporter system and their correlation with tumor cell proliferation and the microvessel density of tumor cells. Among others, L-amino-acid-transporter (LAT-1) is the most commonly used. Since LAT-1 is mainly expressed in human malignancy because of high proliferation (in normal and benign lesions, there is no LAT-1 expression), amino acid radiotracers are helpful in the differentiation between malignant and benign lesions in LC patients [13]. Kaira et al. [14], in their study on 50 patients with NSCLC, compared 6-[^{18}F]Fluoro-l-m-tyrosine (6-[^{18}F]FMT) and [^{18}F]FDG PET and noted that [^{18}F]FMT was strongly correlated with LAT-1 expression, and a study with this radiotracer did not show any false-positive results for primary tumors and metastatic lymph nodes. The LAT-1 transporter might also be assessed in SPECT/CT using l-3-[^{123}I]iodo-α-methyl-tyrosine ([^{123}I]I-IMT). The authors showed that [^{123}I]I-IMT has a high sensitivity for the detection of primary NSCLC; however, RT may cause nonspecific uptake, which limits the use of this radiotracer in patients after irradiation [15]. Akhoundova et al. [16] assessed the pseudoprogression of brain metastases in 53 NSCLC patients, and they found that [^{18}F]FET PET correctly identified pseudoprogression in 81.8% of patients. This modality should be used as an alternative tool in distinguishing pseudoprogression from real progression [16]. Another amino acid tracer that might be useful in lung cancer patients is [^{18}F]fluoroglutamine. Accumulation of this tracer is associated with ASCT2 levels, which were increased in mice with LC compared to normal lung and cardiac tissues. Hassanein et al. [17] concluded that this radiotracer might be used as a precise diagnostic tool in LC patients.

In 2014, Wang et al. [18], in their study of 150 patients, showed that commonly used radiotracers for prostate imaging ([^{68}Ga]Ga-PSMA) may also be used in NSCLC patients. Based on their results, 54.02% of patients had PSMA-positive tumor cells, and 85.06% had PSMA(+) neovasculature endothelial cells (NECs). Moreover, PSMA-positive tumor cells were significantly more common in younger patients than in patients over 60 years old. Furthermore, PSMA(+) NECs were significantly more frequent in stages I and II than in more advanced stages of NSCLC, while no significant changes were noted in small-cell lung cancer (SCLC) patients [18]. Unfortunately, [^{68}Ga]Ga-PSMA is not routinely used in LC imaging because the value of PSMA expression needs to be clarified and requires further investigation and evaluation.

Macroaggregated albumin (MAA) is routinely used in the ventilation/perfusion (V/Q) protocol of lung imaging when pulmonary embolism is suspected. Traditionally, diethylenetriamine pentaacetic acid labeled with ^{99m}Tc ([^{99m}Tc]Tc-DTPA) in aerosol form is given via an inhalation mask to the patient to obtain a ventilation image, and [^{99m}Tc]Tc-MAA is administered intravenously to acquire a perfusion image [19]. Patients referred to surgery because of lung cancer should undergo [^{99m}Tc]Tc-MAA lung scintigraphy to assess postoperative pulmonary function. Chirindel et al. [20] compared 2D scintigraphy and 3D-quantitated lung perfusion SPECT/CT in preoperative LC patients. They concluded that 3D quantification is significantly different and more accurate than 2D methods and changed surgical management in 14% of patients. Genseke et al. [21] performed a preoperative quantification of pulmonary function with [^{99m}Tc]Tc-MAA SPECT/low-dose CT. Their study showed that the quantification of lobar perfusion is significantly different than planar scintigraphy and might provide information for the therapy of these patients. Hirano et al. [22] used [^{99m}Tc]Tc-DMSA in the evaluation of primary LC in SPECT on a group of 31 patients. They noticed that this tracer shows a sensitivity of approximately 90% in primary tumors and that the uptake was higher in squamous-cell carcinoma than in adenocarcinoma. However, this tracer should not be used in the evaluation of the extension of mediastinal tumors and lymph node metastases because of high blood-poll activity. Since PET offers higher spatial resolution and temporal resolution, higher sensitivity for detecting radioactive decay, and quantitative capability, a trial of substituting [^{99m}Tc] with [^{68}Ga] using the same carrier molecules as conventional V/Q imaging was performed. Le Roux et al. [23] showed that [^{68}Ga]Ga-carbon nanoparticles synthesized the same way as for the production of Technegas and MAA and labeled with the same radionuclide can

be used for PET ventilation and perfusion imaging, respectively. The authors show that establishing an accurate V/Q functional map is crucial in clinical situations such as the preoperative assessment of LC patients (including those who are referred for lung volume reduction surgery) and in RT planning. Le Pennec [24] showed "substantial" (mean kappa coefficient of 0.79) interobserver agreement in the interpretation of [^{68}Ga] V/Q PET/CT scans for the diagnosis of suspected acute pulmonary embolism in a group of 24 cancer patients. The mean kappa coefficient was 0.39 lower for CT pulmonary angiography interpretation. Although the attention is attracted by the inhomogeneity of the group patients in this study (PECAN study), where the primary malignancies were of different origins, including the lung, head and neck, breast, etc., it does not have any substantial meaning for the purpose of this study. Moreover, on the basis of published articles, one can see the advantages of PET/CT over SPECT/CT in V/Q imaging.

The presence of hypoxia is usually associated with a worse prognosis and resistance to RT and chemotherapy. Several nitroimidazole compounds labeled with [^{18}F] are able to detect and visualize hypoxia using PET: [^{18}F]-fluoromisonidazole ([^{18}F]FMISO), [^{18}F]-fluoroazomycin arabinoside ([^{18}F]FAZA) and [^{18}F]-fluoroerythronitroimidazole ([^{18}F]FETNIM). Moreover, some authors also suggested diacetyl-bis(N4-methylthiosemicarbazone) labeled with [^{60}Cu] ([^{60}Cu]Cu-ATSM) due to the high membrane permeability and low redox potential of the compound for hypoxia imaging [13]. [^{60}Cu]Cu-ATSM and [^{18}F]FDG were evaluated as additional tools in monitoring therapeutic response in NSCLC patients. A lower tumor-to-muscle ratio in [^{60}Cu]Cu-ATSM was associated with a positive therapeutic response; however, the differences in SUV_{max} values between responders and nonresponders were nonsignificant. Sachpekidis et al. [25] compared [^{18}F]FDG and [^{18}F]FMISO in unresectable NSCLC patients planned to undergo RT. They concluded that the majority of the [^{18}F]FDG-avid tumors showed an absence of hypoxia, indicating that they are potentially sensitive to RT. A 2-nitroimidazole nucleoside analog [^{18}F]-flortanidazole ([^{18}F]F-HX4) PET was used by Zeger et al. [26] in NSCLC patients (n = 15), where the authors noted that this tracer shows uptake in the majority of NSCLC lesions. In addition, it has been shown that [^{18}F]HX4 PET has the potential to be a better hypoxia imaging biomarker than [^{18}F]FMISO because of its possibility of use with a shorter injection-acquisition time, but it still needs validation in a group of patients.

[^{18}F]-Fluoro-3'-deoxy-3'-L:-fluorothymidine ([^{18}F]FLT) is a thymidine analog introduced for cell proliferation imaging that is strongly correlated with nuclear protein Ki-67 expression [27]. Recently, Alwadani et al. [28] noted that this tracer had better specificity but lower sensitivity than [^{18}F]FDG in the diagnosis and staging of LC patients. Moreover, it was correlated with time to progression and progression-free survival (PFS) but was less correlated with tumor size and overall survival (OS). According to the authors, this ligand may not be a good choice for imaging patients with SCLCs due to its limited uptake, but in other cases, [^{18}F]FLT provides predictive values for therapy. In 2014, Trigonis et al. [29] showed that RT significantly decreased [^{18}F]FLT uptake in NSCLC patients and that this radiotracer has the potential to report an early radiation response. They also showed that [^{18}F]FLT decreases significantly after 5–11 fractions of RT. Furthermore, Allen et al. [30] noted a significant decrease in [^{18}F]FLT uptake in NSCLC and pleural mesothelioma patients after finishing chemotherapy with better diagnostic accuracy than [^{18}F]FDG, which is compatible with the findings of the previously mentioned work [28].

Cancer-associated fibroblasts play a pivotal role in tumor aggressiveness, progression, and recurrence [31]. Fibroblast activation protein (FAP) is overexpressed in several different histopathological tumor types. FAP inhibitors labeled with ^{68}Ga have been shown to accumulate in 28 different types of cancers [32]. Kratochwil et al. [32], in their study on 28 different types of cancers, showed that sarcoma, breast cancer, esophageal carcinoma, cholangiocarcinoma, and LC had the highest SUV_{max} values (above 12) for [^{68}Ga]Ga-FAPI PET/CT and that this tracer may become a potential candidate for noninvasive tumor characterization [32].

Angiogenesis participates in tumor growth and metastasis; thus, there is an emergent need to find a method allowing the noninvasive imaging of this process. [^{18}F]alfatide is a novel molecular probe that allows the evaluation of angiogenesis and is used for treatment planning and therapeutic response assessment in several types of cancers, including LC [13]. Zhou et al. [33] used this tracer in detecting metastatic lymph nodes in NSCLC patients with 100% sensitivity, 94.9% specificity, and 95.4% accuracy, and the SUV_{max}, $SUV_{mean,}$ and SUV ratios were significantly higher in metastatic lymph nodes than in metastases-free lymph nodes. Wei et al. [34] showed that SUV uptake in lymph nodes using [^{18}F]alfatide may be linked with survival in stage II–IV LC. Another radiotracer used in assessing tumor angiogenesis in PET/CT is the tripeptide of Arg-Gly-Asp (RGD) labeled with [^{68}Ga]. Kang et al. [35] compared $\alpha_v\beta_3$ between NSCLC and SCLC patients using [^{68}Ga]Ga-RGD_2 PET/CT. They found that the uptake of [^{68}Ga]Ga-RGD_2 was significantly lower in SCLC patients than in NSCLC patients. Oxboel et al. [36] showed a correlation between [^{64}Cu]Cu-NODAGA-RGD tumor uptake and integrin $\alpha_v\beta_3$ expression in neuroendocrine tumors (NETs) in mice. They also suggest that this tracer may potentially be used in humans for imaging angiogenesis in PET/CT.

Neuroendocrine tumors are distinct from other lung malignancies. For NETs, in addition to standard imaging methods, including CT or MRI, nuclear medicine techniques have started to play an important role in staging and assessing therapy response. In this case, [^{18}F]FDG might give false-negative results. Therefore, the development of more specific radiotracers, such as somatostatin analogs labeled with [^{68}Ga], provides better diagnostic accuracy [37]. Recently, 3 main [^{68}Ga]Ga-DOTA (1,4,7,10-tetraaza-cyclododecane-tetraacetic acid) peptides have been used in routine PET/CT studies and show different affinities for somatostatin receptors (SSTRs). [^{68}Ga]Ga-DOTA-TATE shows the highest binding to SSTR2 and [^{68}Ga]Ga-DOTA-TOC to SSTR5, while [^{68}Ga]Ga-DOTA--NOC shows good affinity to SSTR3 and SSTR5 [38]. Kayani et al. [39], in a small group of patients (n = 18), compared [^{68}Ga]Ga--DOTA-TATE and [^{18}F]FDG PET/CT examinations in pulmonary NETs. High [^{68}Ga]Ga-DOTA-TATE uptake was noted in all patients with typical carcinoids, while in 4 patients, [^{18}F]FDG was low or negative. Conversely, when compared with tumor histology, high--grade tumors showed high [^{18}F]FDG uptake, while 3 of 5 showed only mild accumulation of [^{68}Ga]Ga-DOTA-TATE. No false-positive uptake was shown using [^{68}Ga]Ga-DOTA-TATE, while 3 false-positives were noted using [^{18}F]FDG. The authors concluded that patients with low-grade tumors (typical carcinoids) may benefit more from [^{68}Ga]Ga-DOTA-TATE, whereas patients with high-grade or atypical tumors will benefit more from the standard [^{18}F]FDG [39].

Moreover, [^{68}Ga]Ga-MAA was used to diagnose pulmonary embolism and assess pulmonary function. [^{68}Ga]Ga-ventilation/perfusion PET/CT scanning was performed in LC patients before surgery. Additionally, [^{68}Ga]Ga-V/Q respiratory-gated (4-D) PET/CT was helpful in RT planning for NSCLC patients and reduced the dose to the functional lung using 3D conformal RT [38, 39]. NETs may be imaged using different radiotracers in SPECT or SPECT/CT methods, such as metaiodobenzylguanidine labeled with iodine-121 ([^{121}I]I-MIBG) or [^{111}In]In-DTPA). [^{111}In]In-DTPA shows a high affinity for SSTR2 and is used in staging and assessing the extent of disease in SCLC and lung NETs. Moreover, in some cases, performing an [^{111}In]In-DTPA measurement is helpful for stratifying patients who can be treated with somatostatin analogs and chemotherapy [40]. The development of a new generation of CT scanners has allowed solitary pulmonary nodules (SPNs) to be diagnosed in approximately 50% of smokers aged above 50 years [41]. However, the differentiation of malignant from benign SPNs is still challenging. Peptide analogs of somatostatin (depreotide) labeled with a metastable radioisotope of technetium ([^{99m}Tc]) have been widely used in assessing SPNs and showed affinity to SSTR2, SSTR3, and SSTR5. Blum et al. [42], in their multicentre trial on a group of 114 patients, concluded that [^{99m}Tc]Tc-depreotide showed 96.6% sensitivity and 73.1% specificity in the detection of SPNs. Another radiotracer used in SPNs was ^{99m}Tc-ethylenediamine diacetic acid/hydrazine nicotinamide (HYNIC)-TATE ([^{99m}Tc]Tc-HYNIC-TATE), which diagnosed SPNs with a sensitivity of 100% and a specificity of 79% [43].

Zolmitriptan, which is a selective serotonin receptor agonist labeled with ^{99m}Tc, is used for imaging perfusion in the lung. Some authors have shown that ^{99m}Tc-zolmitriptan is a better lung imaging tracer than currently available tracers because it is not a blood product and shows high uptake in the lung along with low uptake in other organs (except the kidneys and urinary bladder). The highest activity in the lung is seen 30 min and 1 h post-injection of the radiotracer and then decreases [44].

Ehlerding et al. [45] showed that in a mouse with NSCLC, [^{64}Cu]Cu-DOTA-ipilimumab is able to accumulate cytotoxic T-lymphocyte-associated protein (CTLA-4)-expressing tumors *in vivo* and has the potential to be a highly specific imaging tracer in personalized medicine [45]. England et al. [46] synthesized ^{89}Zr--Df-nivolumab to show the biodistribution of PD-1 (programmed death type 1 receptors) expression in tumor cells in LC. They concluded that this tracer showed high binding affinity to T-cells expressing PD-1 both *in vivo* and *in vitro* and may help in the design and development of new immune checkpoint inhibitors. Moreover, its use as a noninvasive immunotherapy biomarker may support the diagnosis, monitoring, and stratification of patients [46–48]. In 2021, Takagi et al. [49] reported that the delta-like 1 homolog (DLK-1), expressed in several tumors, could become a promising prognostic factor for tumor metastasis and recurrence after NSLC resection. DLK1 may become a new therapeutic target in RIT, but it needs to be confirmed in further studies.

The detection of C-X-C chemokine receptor 4 (CXCR4) is associated with worse prognosis, tumor aggressiveness, tumor metastasis, and a higher probability of recurrence and has been reported in 23 different tumors. The percentage of CXCR4-positive cells ranges from 12% in breast cancer to > 90% in NSCLC, mesothelioma, prostate cancer, gastric cancer, and renal carcinoma. The noninvasive CXCR4 receptor in PET/CT studies significantly contributes to the clinical management of patients. Several CXCR4 PET tracers that vary in terms of metabolism, appropriate contrast, radiochemical purity, preparation, and affinity have been studied [50]. [^{64}Cu]Cu-AMD3465 might potentially allow the visualization of renal and hepatic tumors expressing high CXCR4 levels; however, the kidneys and liver receive high radiation doses [51]. [^{68}Ga]Ga-CPCR4.2, compared to [^{64}Cu]Cu-AMD3465, shows limited uptake in the kidneys, the liver, and in nontargeted tissues, thus allowing better visualization of certain tumors (including lymph nodes), including non-small cell lung adenocarcinoma [52, 53].

Therapy for lung cancer

The treatment of patients with lung cancer involves different strategies that include surgery, RT, chemotherapy, immunotherapy, molecular targeted therapy, laser therapy, photodynamic therapy, cryosurgery, electrocautery, and best supportive care only. Moreover, the use of chemoprevention, radiosensitizers, and new combinations of treatments (including drug conjugates) are currently in clinical trials. Most recently, targeted therapies and radioimmunotherapies have started to play an important role in this process, focusing on the use of radionuclide-based therapy. Radiopharmaceutical therapy depends on the tumor's intrinsic radiation properties and the dose absorbed by the tumor. The therapeutic target is achieved by phenotypic molecular imaging and radiopharmaceutical dose optimization [54].

This type of treatment is based on radioactive substance administered to the bloodstream of the patient. Although both chemotherapy and radionuclide therapy are systemic treatments, radionuclide therapy specifically targets tumor cells, damaging their DNA while reducing potential side effects by avoiding healthy tissue. Since alpha, Auger, and beta emitters (e.g., ^{177}Lu, ^{68}Ga, ^{225}Ac, ^{64}Cu, ^{67}Cu, ^{64}Ni, and ^{64}Zn) have different features, such as energy, path length, and LET, they serve different purposes. Therefore, beta emitters are more likely to be used for targeting solid tumors, and alpha and Auger emitters are more likely to be used for targeting micrometastatic disease [55]. Moreover, for both targeted therapy and radioimmunotherapy, it is necessary to bind the emitter to a molecular carrier that strongly holds it and delivers it directly to the tumor and metastasis. Two approaches have been introduced into clinics, namely, direct conjugation of radioisotopes compatible with an appropriate imaging modality (e.g., PET) tagged to monoclonal antibodies (mAbs) and pre-targeting of the tumor, where the radionuclide is administered independently from the antibody vehicle [56]. In the second case, there are two possible strategies, namely, the administration of radioactive biotin for selective localization on antibody-streptavidin conjugates or the use of radioactive metal chelators and specific antibodies capable of binding to a tumor-associated antigen and to a metal chelator simultaneously.

Dho et al. [57] in 2018 presented the results of therapy using Lutetium-177 [^{177}Lu]-labeled chimeric mAbs against glycosylphosphatidylinositol-anchored protein-CD55 (decay-accelerating factor) for both SPECT imaging and targeted RT of micrometastases and small tumors. The ^{177}Lu-anti-CD55 antibody was created by CD55-specific single-chain variable fragment (scFv) selection from naïve chicken scFv phage-display library, then converted to IgG and labeled with ^{177}Lu-radionuclide. The biodistribution and

treatment capabilities of the generated structure were tested *in vivo* in male BALB/c nude mice with pleural metastatic lung cancer (H460 cell line), showing reduced growth and improved median survival. It has also been shown both *in vitro* and *in vivo* that using ^{177}Lu-anti-CD55 can enhance the antitumor activity of cisplatin. An indicative synergistic effect was observed in the H460 and H368 cell lines, reducing cell viability by 44.2% and 47.9%, respectively [57].

In 2016, Azad et al. [58] presented the coupling of mAbs, commonly used for cancer therapy and imaging with CXC chemokine receptor 4 (CXCR4), which interacts with the endogenous ligand CXCL12 of the G-protein coupled receptor to mediate normal biological functions, including stem cell homeostasis. The group used both [^{89}Zr]Zr-CXCR4-mAb and its native unmodified analog for the detection of CXC expression and therapy, respectively. The therapeutic response of CXCR4-mAb was demonstrated in immunodeficient mice harboring H1155 (high expression of CXCR4) and A549 NSCLC and in SUM149 (high expression of CXCR4) and MDA-MB-231 TNBC (triple negative breast cancer) tumor xenografts. In contrast to A549 and MDA-MB-231, the treatment (10 mg/kg) showed a significant reduction in tumor growth, weight, and proliferation levels in H1155 xenografts compared to controls (vehicle and control mAb). The most important result showed that the uptake of [^{89}Zr]Zr-CXCR4-mAb and the therapeutic efficacy of CXCR4-mAb are correlated with the levels of CXCR4. Therefore, the combination of [^{89}Zr]Zr-CXCR4-mAb-PET with non-radiolabelled mAb therapy may provide an excellent treatment for patients with CXCR4 expression.

An interesting approach was presented by Pirooznia et al. [59]. The group conjugated cyclic RGD peptide-E(cRGDfK)$_2$ to DOTA and labeled it with ^{177}Lu ([^{177}Lu]Lu-DOTA-E(cRGDfK)$_2$). This was already the next step of the project where the first stage was focused on using the same peptide labeled with ^{68}Ga for the early diagnosis, staging, and posttreatment imaging of NSCLC [60]. *In vitro* characteristics (stability and specific binding) and cellular uptake were evaluated in the A549 (as integrin αvβ3 positive) and NIH-3 T3 (as negative control) cell lines. More than 95% of the structures remained intact and stable in human serum albumin (HAS) up to 144 h postincubation, which makes them suitable for *in vivo* procedures. The binding of the radiopeptide to NIH-3T3 was low in comparison with that to A549. *In vivo,* potential (distribution and peptide receptor radionuclide therapy) was performed in mice with NSCLC tumors. Biodistribution showed that in normal mice, radiopeptides were taken up by the kidneys and then the bladder due to secretion via the urinary system. In lung tumor-bearing mice, high tumor uptake and no retention in other organs over time postinjection were observed. Additionally, the therapeutic efficiency was clearly visible by significantly delayed tumor progression compared with the control (normal saline) group. Taking all the information together, one can see the potential of the presented peptide as a theragnostic compound for radionuclide therapy and imaging of LC [60].

Another approach, which has become very popular recently, is the conjugation of radioisotopes to liposomes [61] with additional modifications.

Ming et al. [62] investigated the biological effect and therapeutic effectiveness of ^{131}I-labelled arginine-glycine-aspartate-bovine serum albumin-polycaprolactone ([^{131}I]I-RGD-BSA-PCL) *in vitro* and *in vivo*. The authors prepared liposomes modified by polyethylene glycol (PEG) and covalently linked the RGD peptide on their surface. Furthermore, the RGD-BSA-PCL and BSA-PCL structures were radiolabelled using iodine-131 ([^{131}I]). The *in vitro* study was conducted in the NCI-H460 LC cell line and focused on targeting $\alpha_v\beta_3$ integrin binding and the cellular uptake of cells using confocal microscopy. Liposomes efficiently bind to cancer cells. The maximum uptake level was observed after 6 h of incubation with [^{131}I]I-RGD-BSA-PCL and 4 h of incubation with [^{131}I]I-BSA-PCL, where the iodide uptake of ^{131}I-RGD-BSA-PCL was higher than that of [^{131}I]I-BSA-PCL. Furthermore, significant apoptosis of NCI-H460 cells was caused by using both structures. NCI-H460 tumor xenografts were induced in BALB/c nude mice for *in vivo* studies. The uptake in normal organs (heart, liver, spleen, kidneys, brain, stomach, intestine, and bone) was similar for both [^{131}I]I-BSA-PCL and [^{131}I]I-RGD-BSA-PCL. The mean tumor uptake at 24 and 72 hours was much higher for [^{131}I]I-RGD-BSA-PCL. The treatment using an intratumoral injection of [^{131}I]I-RGD-BSA-PCL significantly prolonged the survival of mice with tumor inhibition and growth delay and no treatment toxicity signs (weight loss).

Chang et al. [63] published a comprehensive review summarizing the multidisciplinary achievements of researchers in nanotargeted [^{188}Re]-liposomes, including *in vitro* and *in vivo* studies and clinical investigations. This review clearly shows that liposomes radiolabelled with [^{188}Re] have promising theragnostic applications in cancer care. This approach was undertaken in 2014 by Lin et al. [64], who embedded [^{188}Re] particles in PEGylated liposomes and investigated the biodistribution, pharmacokinetics, and therapeutic efficacy of this radiopharmaceutical in a xenograft tumor model using the NCI-H292 cell line. First, the authors checked two combinations of radioliposomes: [^{188}Re] bound to N,N-bis(2-mercaptoethyl)-N′, N′-diethylethylenediamine (BMEDA) chelator ([^{188}Re]Re–BMEDA) and ^{188}Re alone (^{188}Re-liposomes). [^{188}Re]Re-liposomes exhibited longer retention and better tumorous accumulation than [^{188}Re]Re-BMEDA in LC-bearing mice. The therapeutic efficacy of the two kinds of structures was evaluated using a multiple-reporter-gene-integrated orthotopic tumor-bearing animal model, where [^{188}Re]Re-liposomes successfully suppressed tumor growth. The authors noted that the circulation period of PEGylated [^{188}Re]Re-liposomes is longer than that of [^{188}Re]Re-BMEDA *in vivo,* making the therapeutic efficacy higher, but at the same time, the accumulation of [^{188}Re] in organs such as the liver and spleen is higher, which can cause potential side effects [64].

In addition to the mentioned therapeutic strategies, there are interesting works focusing on pain alleviation. Recently, Chen et al. [65] published the results of effectiveness in pain alleviation and improvement of global quality of life in 54 LC patients with painful bone metastases using [^{188}Re]Re-hydroxyethylidine diphosphonate. According to the authors' results, the radiopharmaceutical was safe and well tolerated at doses of 40–50 MBq/kg. In 2003, a similar concept of work was published by Zhang et al. [66], showing the results of a group of 30 patients with osseous metastases from LC. Intravenously, the same radiopharmaceutical was injected, but with a mean activity of 1158 ± 240 MBq for a single injection. Twenty-four patients received one injection, three of them were injected twice, two of them received three treatments, and one patient received four therapies. The authors reported that significant relief of bone pain was observed in 80% of patients with no significant side effects or hematopoietic toxicity. Moreover, 46% of patients decided to stop using analgesics [66].

In the case of NETs, radionuclide therapy is a form of systemic irradiation for tumors with high SSTR expression [67]. Strong expression of SSTR present in the majority of pulmonary NETs (except carcinoid atypical tumors) allows for radiolabelled somatostatin analog use. For this purpose, an isotope (e.g. ^{90}Y, ^{177}Lu) was bound to a carrier molecule derived from octreotide and a chelating agent (e.g. DOTA, DTPA) stabilizing this complex. Zidan et al. [68] published the assessment of the efficacy and safety of [^{177}Lu]Lu-DOTA-TATE in 48 patients (13F, 35M) with SSTR-positive lung NETs. The authors showed that [^{177}Lu]Lu DOTA-TATE is effective and safe with a high disease control rate and encouraging PFS and OS. In 2016, Mariniello et al. [69] reported a comparison of three different PRRT protocol outcomes, namely, [^{90}Y]Y-DOTA-TOC, [^{177}Lu]Lu-DOTA-TATE, and [^{90}Y]Y-DOTA-TOC + [^{177}Lu]Lu-DOTA-TATE, with regard to their efficacy and tolerability in a single center and in a group of 114 patients with pulmonary NETs. According to the authors and considering the risk-benefit ratio, monotherapy using [^{177}Lu]Lu-DOTA-TATE is the best option for PRRT. The combined therapy caused myelotoxicity that negatively affected survival, and treatment with [^{90}Y]Y-DOTA-TOC more often resulted in a mild/moderate disturbance of renal function. Notably, [^{177}Lu]Lu-DOTA-TATE was approved by the US Food and Drug Administration in 2018 and the European Medicines Agency in 2017 for the treatment of gastroenteropancreatic NETs. On the basis of the results mentioned above, it seems reasonable to expect the approval of this radiopharmaceutical for the treatment of selected patients with pulmonary NETs soon. Other approaches are presented in the literature, e.g. the use of octreotide, a biologically stable and naturally occurring peptide that targets SSTRs present on a majority of gastroenteropancreatic NETs, for pulmonary NET purposes. Kim et al. [70] published the results of a phase I study of ^{177}Lu-DOTA-Tyr3-octreotate (Lutathera®) in combination with nivolumab. Although the group of patients was small and diversified (nine patients: six with extensive-stage-SCLC, two with pulmonary atypical carcinoid, and one with high-grade pulmonary neuroendocrine carcinoma), the results showed that such a combination of therapy is well tolerated and antitumor activity is present in advanced NETs of the lung.

Conclusions

Nuclear medicine is a medical specialty that focuses on both diagnosis and therapy. This article provides current information about the participation of nuclear medicine in lung cancer diagnosis and treatment. In both cases, one has to use a ligand that is responsible for targeting and a bond radionuclide that has to undergo a specific radioactive decay to be imaged by PET or SPECT or to kill the tumor cells. It is also possible that radionuclide does both at the same time without the need to expose the patient to an additional dose of radiation. At the same time, there are fewer side effects, especially in the case of LC patients, where the lungs, as a targeted organ, are located so close to organs at risk. Since the most popular current trends in medical science are focused on theragnostics and targeted therapy, nuclear medicine meets both requirements and has shown very interesting and promising results.

Conflict of interest

Authors declare no conflict of interest.

Funding

None declare.

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