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Modern radiopharmaceuticals for lung cancer imaging with positron emission tomography/computed tomography scan: A systematic review

Athanasios S Theodoropoulos[1,2], Ioannis Gkiozos[1], Georgios Kontopyrgias[1], Adrianni Charpidou[1], Elias Kotteas[1], George Kyrgias[3] and Maria Tolia[3]

Abstract

Introduction: In this study, we evaluated the use and the contribution of radiopharmaceuticals to the field of lung neoplasms imaging using positron emission tomography/computed tomography.

Methods: We conducted review of the current literature at PubMed/MEDLINE until February 2020. The search language was English.

Results: The most widely used radiopharmaceuticals are the following:

Experimental/pre-clinical approaches: (18)F-Misonidazole (18F-MISO) under clinical development, D(18)F-Fluoro-Methyl-Tyrosine (18F-FMT), 18F-FAMT (L-[3-18F] (18)F-Fluorothymidine (18F-FLT)), (18)F-Fluoro-Azomycin-Arabinoside (18F-FAZA), (68)Ga-Neomannosylated-Human-Serum-Albumin (68Ga-MSA) (23), (68)Ga-Tetraazacyclododecane (68Ga-DOTA) (as theranostic agent), (11)C-Methionine (11C-MET), 18F-FPDOPA, $\alpha v\beta_3$ integrin, ^{68}Ga-RGD$_2$, ^{64}Cu-DOTA-RGD, ^{18}F-Alfatide, Folate Radio tracers, and immuno-positron emission tomography radiopharmaceutical agents.

Clinically approved procedures/radiopharmaceuticals agents: (18)F-Fluoro-Deoxy-Glucose (18F-FDG), (18)F-sodium fluoride (18F-NaF) (bone metastases), and (68)Ga-Tetraazacyclododecane (68Ga-DOTA). The quantitative determination and the change in radiopharmaceutical uptake parameters such as standard uptake value, metabolic tumor volume, total lesion glycolysis, FAZA tumor to muscle ratio, standard uptake value tumor to liver ratio, standard uptake value tumor to spleen ratio, standard uptake value maximum ratio, and the degree of hypoxia have prognostic and predictive (concerning the therapeutic outcome) value. They have been associated with the assessment of overall survival and disease free survival. With the positron emission tomography/computed tomography radiopharmaceuticals, the sensitivity and the specificity of the method have increased.

Conclusion: In terms of lung cancer, positron emission tomography/computed tomography may have clinical application and utility (a) in personalizing treatment, (b) as a biomarker for the estimation of overall survival, disease free survival, and (c) apply a cost-effective patient approach because it reveals focuses of the disease, which are not found with the other imaging methods.

Keywords

Positron emission tomography/computed tomography, lung cancer, radiopharmaceuticals

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Introduction

Lung cancer is one of the world's most common and aggressive neoplasms. For this reason, it is important to have a timely diagnosis and then a proper treatment and follow-up. Positron emission tomography/computed tomography (PET/CT) is a useful tool for detecting, staging, taking therapeutic decisions, and assessing response to treatment (chemotherapy, radiotherapy, immunotherapy, etc.). Because of (lung cancer) high death rates and deficiency in investigation, preclinical and clinical introduction of novel radiopharmaceuticals in PET/CT domain is vital.[1] The approval of more new

[1]Third Department of Medicine, Oncology Unit, School of Medicine, Sotiria General Hospital, University of Athens, Athens, Greece
[2]Interventional Department of Cardiology-Cardiac Catheterization Laboratory, Thriassio General Hospital of Elefsina, Athens, Greece
[3]Department of Radiotherapy/Radiation Oncology, Faculty of Medicine, School of Health Sciences, University of Thessaly, University Hospital of Larissa, Biopolis, Larisa, Greece

Corresponding author:
Athanasios S Theodoropoulos, Third Department of Medicine, Oncology Unit, School of Medicine, Sotiria General Hospital, University of Athens, Radiographer at Interventional Department of Cardiology-Cardiac Catheterization Laboratory at Thriassio General Hospital of Elefsina, 32 Digeni Street, Nea Philadelphia, Athens 14342, Greece.
Email: athanasios.theodoropoulos@gmail.com

radiopharmaceuticals at the lowest possible cost for patients is also material. PET/CT may be particularly important in the field of research and the clinical-laboratory approach of lung cancer. In addition to the field of research in lung cancer, it is increasingly gaining ground the combination of one therapeutic and one diagnostic agent (theranostics). PET/CT imaging in lung cancer with theranostics such as somatostatin receptor (SSR) (diagnostic) and ^{111}Indium or ^{68}Gallium (therapeutic) could be a potential target not only with the above agents but also with other agents.[1] The main idea is the finding of driver mutation, the suppression, and the killing of specific proteins in the mutations.[1] The purpose of this article is to review systematically the current literature on (a) use and (b) contribution of newer radiopharmaceuticals to PET/CT imaging.

Prognostic factors in lung cancer patients

Lung cancer is a prevalent disease with very high death rates globally.[2] Surgical treatment is the best option for early stage patients and chemotherapy or radiotherapy or the combination of these therapies is a choice for patients with advanced disease. Performance status and stage of disease are main prognostic factors, but there is no prognostic biomarker for the assessment of overall survival (OS) after therapeutic managements. There is evidence for different biomarkers which target in different pathways of cancer biology such as angiogenesis, cell proliferation, or metastases. There is needed further investigation for the establishment of a molecular biomarker for the evaluation of therapeutic outcomes in lung cancer.

Tumor-specific PET tracers beyond fluoro-deoxy-glucose

In general, 18F-FDG is the widely used radiotracer for oncologic diagnosis, but there is not confidence if it is tumor-specific, because it has high false-positive results rate in inflammatory and granulomatous diseases.[2] The investigation of tumor-specific PET tracers which will not show false-positive findings in PET benign lesions is necessary. There are tumor PET tracers beyond FDG which utilize amino-acid metabolism, hypoxia, and DNA synthesis.[2] The clinical significance of these new PET tracers is discussed as follows:

1. Amino-Acid Metabolism: for their growth and survival tumor cells need nutrients like glucose, amino-acids, fatty-acids, and vitamins. Vascular nutrients from formation and upregulation of specific transporters meet this need. Amino-acids are required for protein synthesis and as a source of nitrogen and carbon for purine and pyrimidine (nucleotides) synthesis, for synthesis of glutathione, and for synthesis of amino-sugars.[2] Transporters of amino-acid are regarded to have vital role in tumor development and cell proliferation. Several types of amino-acid transporters exist. L system is Na^+-independent large and neutral amino-acid transporter. L-Amino-acid-Transporter 1 (LAT1) transports large neutral amino-acids like leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan, methionine, and histidine. Apart from LAT1, LAT family has another three subtypes: LAT2, LAT3, and LAT4. 18F-FAMT, L-[3-^{18}F]-α-methyltyrosine is an amino-acid PET tracer useful for distinguishing malignant from benign lesions.[2] 18F-FAMT is transported into tumor cells although the LAT1. LAT1 is highly expressed in many human neoplasms. In normal tissue and benign lesions, there are no elements for LAT1 expression. 18F-FAMT uptake is strongly connected with the expression of LAT1. So, 18F-FAMT is regarded to be a specific PET tracer for malignant tumors. From these, it is obvious that 18F-FAMT-PET can be another technique of LAT1 molecular imaging. ^{11}C-labeled Methionine is another amino-acid PET tracer which has been used in several human tumor imaging tests. ^{11}C-MET has superior specificity than ^{18}F-FDG in the tracing of malignant tumors, a fact that makes the discrimination of malignant from benign lesions more feasible. The practicability of ^{18}F-FDG-PET and ^{11}C-MET-PET for the assessment of therapeutic response after stereotactic radiotherapy (SRT) in lung cancer was examined. ^{18}F-FDG-PET and ^{11}C-MET-PET were conducted 1 week before and up to 8 months after SRT in nine patients. Standard uptake value (SUV) of ^{18}F-FDG-PET and ^{11}C-MET-PET after SRT altered consistently, and the addition of ^{11}C-MET-PET did not confer any new information.[2] The usefulness of ^{11}C-MET-PET in the evaluation of prognosis and chemotherapy response is not enough examined in lung cancer patients. Moreover, PET tracers which are combined with tyrosine derivatives like 2-18F-fluoro-L-tyrosine (^{18}F-FET) and 3-123I-iodo-α-methyl-L-tyrosine (^{123}I-IMT) have been analyzed. ^{18}F-FET-PET has been tested for each diagnostic utility and performance in lung cancer patients. The level of ^{18}F-FET uptake was noticeably incompatible with histology.[2] Patients with squamous cell carcinoma (SCC) presented positive ^{18}F-FET results and patients with adeno-carcinoma (AC) had negative ^{18}F-FET (uptake) results. Nevertheless, ^{18}F-FET-PET is regarded to be practical in the discrimination between malignant and benign sites in SCC patients but not in AC patients. ^{123}I-IMT-SPECT (single photon emission tomography) reveals high sensitivity for the depiction of primary lesions in lung cancer at about 94%. In contrast for lesions less than 20 mm, the sensitivity is too low. ^{123}I-IMT as well as ^{18}F-FET was found to be transported selectively by human LAT1

which is expressed in normal cells. It is still vague in human malignant tumors if ^{11}C-MET, ^{18}F-FET, and ^{123}I-IMT are connected strongly with the amino-acid transporters like LAT1.[2] The uptake of the ^{18}F-FAMT is closely connected with the expression of LAT1 in lung cancer patients. Moreover, in amino-acid PET tracers, Gang Huang adds other specific radiotracers which have been used in clinical PET like BAY 94-9392, BAY 85-8050, and ^{18}F-(2S, 4R)4F-GLN.[3]

2. Hypoxic Imaging: tumor hypoxia is related with resistance to radiotherapy and chemotherapy and triggers angiogenesis, metastasis and tumor aggressiveness, leading to poor prognosis. Hypoxia has a major role in biology of several cancers and is a target for tumor imaging.[2] Several radiopharmaceuticals for hypoxia imaging have been investigated for the detection of malignant tumors and for the evaluation of therapeutic outcomes. ^{18}F-Fluoromisomidazole (FMISO) and ^{60}Cu or ^{64}Cu-diacetyl-bis (4-(*N*)-methylthiosemicarbazone) (ASTM) are available in clinical practice as PET tracers. ^{60}Cu-ASTM-PET and ^{18}F-FDG-PET were evaluated for their utility in monitoring of therapeutic response of 14 non-small cell lung cancer (NSCLC) patients. Responders had lower mean tumor to muscle ratio T/M of ^{60}Cu-ASTM than non-responders. However, the mean SUV of ^{60}Cu-ASTM had no difference (between responders and non-responders). ^{60}Cu-ASTM uptake did not correlate with ^{18}F-FDG uptake. ^{60}Cu-ASTM-PET seems to be an efficient radiotracer for non-responders to any treatment. FMISO is PET tracer of hypoxia with selected uptake from hypoxic cells. FMISO has slower washout from normoxic cells than ^{60}Cu-ASTM. FMISO-PET and ^{18}F-FDG-PET carried out in eight patients with advanced NSCLC before and after 2 weeks of chemotherapy. Alterations in FMISO accumulation within tumor cells calculate the early response to chemotherapy, and FMISO may have a role as a prognostic biomarker.[2] The uptake level of FMISO was found to be remarkably lower than ^{18}F-FDG uptake. FMISO uptake and ^{18}F-FDG uptake were not correlated with Micro-Vessel Density (MVD) and HIF-1α, VEGF or Glut1 expression. There was a small positive association between FMISO uptake, ^{18}F-FDG uptake, and Ki-67 proliferative marker. Nevertheless, these findings are still under further investigation. Hypoxia modification could have a positive outcome in local control and prognosis after treatment. The absence of correlation between FMISO and ^{18}F-FDG indicated a mismatch between increased hypoxia and glycolysis in NSCLC. It appears to be difficult the utilization of FMISO or ^{60}Cu-ASTM-PET for the evaluation of therapeutic outcomes and prognosis in NSCLC after chemotherapy.[2] One other promising tracer for NSCLC imaging with PET in hypoxic sites is the ^{18}F-FETNIM (Fluoro Erytrho Nitro Imidazole) according to Huang.[3] This tracer is favorable for prediction of therapeutic outcome and has higher selective uptake in hypoxic tumors than ^{18}F-MISO. However, there is limited evidence compared to ^{18}F-MISO.

3. DNA synthesis: one analogue of thymidine is the 3′-Deoxy-3′-[^{18}F] Fluorothymidine (^{18}F-FLT) which was investigated for the calculation of cell proliferation.[2] Phosphorylation of ^{18}F-FLT is performed by thymidine kinase. ^{18}F-FLT enters into the salvage-signaling pathway without embodiment in DNA molecules. The uptake of ^{18}F-FLT represents strongly the tumor cell proliferation depending on Ki67 (labeled index) expression. ^{18}F-FLT seems to be more specific PET tracer than ^{18}F-FDG for tumor imaging. Nevertheless, in the course of ^{18}F-FLT-PET, the ^{18}F-FLT presents intake in normal liver and bone marrow tissues; therefore, the differential diagnosis of malignant and benign lesions in these organs is unfeasible. There is close relation between ^{18}F-FLT and Ki67 in NSCLC. There is also strong correlation not only between ^{18}F-FLT uptake and Ki67 ($p < 0.0001$) but also between ^{18}F-FLT uptake and ^{18}F-FDG uptake. Despite the fact that in staging ^{18}F-FLT-PET may have less sensitivity than ^{18}F-FDG-PET, ^{18}F-FLT uptake is superior in the calculation of tumor proliferative activity than ^{18}F-FDG. ^{18}F-FLT-PET is useful for the evaluation of therapeutic response after radical chemo-radio therapy in NSCLC. ^{18}F-FLT-PET has higher sensitivity than ^{18}F-FDG-PET in the early therapeutic response.[2] 18F-FLT represents different responses of cell proliferation early after treatment in NSCLC; it is ambiguous if it can forecast the whole therapeutic outcome. One early ^{18}F-FLT response, especially 1 week after treatment, has the ability to predict longer PFS (progression free survival) after therapy with erlotinib. In contrast, ^{18}F-FLT cannot be predictive after 6 weeks therapy for the evaluation of response.[2] On this basis, ^{18}F-FLT-PET appears to be more efficient monitoring biomarker in the prediction of early response after therapy. For validation of the above, further investigation is needed. Huang[3] concluded that apart from ^{18}F-FLT, PET tracers may have significance as potential biomarkers of DNA synthesis like: 18F-(fluoroarabinofuranosyl) cytosine, ^{11}C-labeled nucleosides, such as ^{11}C-methionine, ^{11}C-flumazenil, and ^{11}C-4DST.

Folate radiotracers for nuclear medicine imaging

Folate is required in high levels for rapid-proliferated cells like cancer cells.[3] FRs (folate receptors) are proved to be overexpressed on the tumor cell surface under low folate

conditions and regarded us tumor-associated antigen. The FRs have the ability of selective folate binding. Folate is bound with high affinity and via an endocytic mechanism folate bonds are transported into cells. Several tumors are folate dependent and this is challenge for investigation and application of anti-FR-α antibodies, high-affinity anti-folates, folate conjugated drugs and toxins and folate-based imaging tracers in order to improve tumor detection and therapy. Four FR proteins are known as follows: FR-α, FR-β, FR-γ, and FR-δ. FR-α isoform has a significant importance for folate-based radiotracers in nuclear medicine tumor imaging because FR-α reveals high expression in several solid tumors. Investigators concentrate their attention to folate bonds in order to label the above with a radiotracer like ^{99m}Tc, ^{111}In, ^{18}F and ^{68}Ga for nuclear medicine imaging (SPECT and PET). Thus, folate-based imaging agents become practical for selection of patients with aim to be examined in new therapies and for the evaluation of therapeutic response.

^{18}F-Alfatide a novel molecular probe

Angiogenesis is a principal process for the tumor growth and metastasis. An appealing method that demonstrates a novel non-invasive approach for visualization of angiogenesis and evaluation of effectiveness from different anti-angiogenic therapies is the targeted imaging of angiogenesis in vivo. $\alpha v\beta_3$ Integrins are heterodimeric transmembrane glycoproteins with significant contribution in the regulation of cellular activation, survival, and migration. Non-interventional depiction of $\alpha v\beta_3$ expression will be favorable in the assessment of tumor neovascularization and useful for the detection and therapy of several cancers. A sequence of three peptides especially the arginine–glycine–aspartic acid (RGD) is an appropriate vehicle for its selective targeting to integrin $\alpha v\beta_3$. Different ^{18}F-labeled RGD peptides have been examined. Nevertheless, low yield and multi-step processes limited the broad use in clinical practice. For the solution of this problem, Min Yang, from the Jiangsu Institute of Nuclear Medicine, and Xiaoyuan Chen, from the National Institute of Health, collaborated on using ALF-labeling technique.[3] First, they developed a lyophilized kit for labeling $PRGD_2$ peptide (18F-ALF-NOTA $PRGD_2$ or 18F-Alfatide). The first PET/CT with ^{18}F-Alfatide was conducted in a patient with lung cancer. ^{18}F-Alfatide-PET detected all tumors with mean SUVs of 2.90 ± 0.10. T/M (tumor to muscle) ratio and T/B (tumor to blood ratio) were 5.87 ± 2.02 and 2.71 ± 0.92 correspondingly. The first in-human experience implies that ^{18}F-Alfatide is suitable for use in vivo. Additional studies can be conducted due to the simple technique. ^{18}F-Alfatide was regarded an alternative of 18F-$FPPRGD_2$ which could be used for the evaluation of angiogenesis, for treatment planning, and for the assessment of therapeutic response in several cancer therapies. Additional examination was conducted in 26 patients with suspected lung cancer. ^{18}F-Alfatide PET/CT detected 17 patients with lung cancer, four patients had true-negative results (hamartoma), and five patients had false-positive results (four chronic inflammations, one inflammatory pseudo-tumor). The sensitivity was 100%, the specificity was 44.44%, PPV (positive predictive value) was 77.27%, and NPV (negative predictive value) was 100%. Furthermore, 16 patients successfully underwent surgical resection and histopathology validated 14 of 152 lymph node positive for metastasis. The evaluation of lymph nodes with PET/CT demonstrated sensitivity 92.86%, specificity 95.65%, PPV 61.90%, and NPV 99.25%. On this basis, the ^{18}F-Alfatide PET/CT seems to be an effective and safe option for the diagnosis of suspected lung cancer.

Targeting $\alpha v\beta_3$ integrin with ^{68}Ga-RGD_2

The $\alpha v\beta_3$ integrin plays a crucial role in the pathophysiological pathways of lung cancer. Tripeptide of Arg-Gly-Asp (RGD) in combination with a radionuclide can selectively bind to integrin $\alpha v\beta_3$ receptor. This process has been considered to be a non-interventional technique for early detection of tumor angiogenesis. Kang Fei from Xijing Hospital made a comparison of $\alpha v\beta_3$ levels in NSCLC and small cell lung cancer (SCLC) patients via the ^{68}Ga-RGD_2 PET/CT.[3] The findings proved that the ^{68}Ga-RGD_2 uptake in SCLC patients is remarkably lower than that in NSCLC patients. From these, it was confirmed the eligibility of ^{68}Ga-RGD_2 PET/CT in lung cancer.

Targeting $\alpha v\beta_3$ integrin with ^{64}Cu-DOTA-RGD

^{64}Cu-DOTA-RGD has been confirmed for its efficacy in the monitoring of $\alpha v\beta_3$ at a very low integrin levels. Cai et al.[4] examined a sequence of ^{64}Cu-labeled multimeric RGD peptides for imaging integrin $\alpha v\beta_3$ expression with PET like RGD tetramer and RGD octamer. In a micro-PET experimental base, preclinical findings indicated favorable effects of ^{64}Cu-DOTA-RGD tetramers and octamers in U87MG tumor bearing nude mice. More specifically, U87MG tumors could be depicted with high contrast with ^{64}Cu-DOTA-RGD. ^{64}Cu-DOTA-RGD tetramer and octamer specificity was validated with receptor blocking tests. RGD octamers had noticeably higher affinity and specificity than tetramers. The accumulation of ^{64}Cu-DOTA-RGD octamers in the tumor was $11.7 \pm 0.7\%$, $10.6 \pm 0.7\%$, $10.6 \pm 0.3\%$, $10.5 \pm 0.7\%$, and $10.3 \pm 1.0\%$ injection dose per gram at 0.5, 1, 2, 6, and 20 h after administration, significantly higher than those of ^{64}Cu-DOTA-RGD tetramers. Further development and progress of ^{64}Cu-DOTA-RGD peptides may direct into a potential integrin-based imaging and radiotherapy (with targeting integrin $\alpha v\beta_3$) for many human cancers.

Neuroendocrine tumors and Amino-Acid PET tracers

Neuroendocrine tumors (NETs) are a group of neoplasms with heterogeneity from well differentiated to slowly growing

tumors.[3] 18F-FDG is the widely used radiopharmaceutical, but shows low uptake in most NETs. Serotonin pathway demonstrates high activity in many NETs. Thus, the investigation of a PET tracer for NETs serotonin pathway is crucial. ^{11}C-5-HTP is a carbon-11-labeled tracer which has been developed for the signaling of this pathway. ^{11}C-HTP is helpful for the depiction of small-sized tumors and early recurrences detection. Nevertheless, the half-life of 20 min and the difficult synthesis are drawbacks for broad clinical practice. Aromatic amino-acid decarboxylase (AADC) demonstrates high activity in NETs. ^{18}F-DOPA is a promising tracer with appealing imaging properties and high uptake in the AADC expression. Moreover, ^{18}F-DOPA has high accuracy in the detection of pheochromocytomas, pancreatic pheochromocytomas, and insulinomas and in staging of carcinoids which cannot be displayed by CT, magnetic resonance imaging (MRI), or other imaging tracers. In addition, ^{18}F-DOPA has high sensitivity in patients with functional carcinoids, but has low sensitivity for malignant NETs like medullary thyroid cancer and pancreatic islet cell tumors.

Clinical value of 18F-FAMT-PET in lung cancer

Patients with NSCLC and high uptake of ^{18}F-FAMT are strongly connected with worse prognosis after therapy. ^{18}F-FAMT intake is a major marker which forecasts poor survival results in adenocarcinoma patients; the same is not true for adenocarcinoma patients. The accumulation of ^{18}F-FAMT in tumor cells is remarkably higher is SCC patients in comparison with AC patients although its prognostication appears to be more efficient in AC patients than non-AC patients. There is no strong evidence about the relation of ^{18}F-FAMT uptake and the tumor aggressiveness of AC patients. ^{18}F-FAMT-PET demonstrates sensitivity 57.8%, specificity 100%, and accuracy 92.5% in malignant lymph nodes. ^{18}F-FDG-PET reveals 65.7% sensitivity, 91% specificity, and 86.5% accuracy. The tumor specificity of ^{18}F-FAMT-PET is noticeably higher than that of ^{18}F-FDG-PET. However, the sensitivity of ^{18}F-FAMT-PET is inferior to that of ^{18}F-FDG-PET. It becomes obvious that the uptake of ^{18}F-FAMT with the use of lymph node to primary tumor ratio after therapy has the ability to predict the therapeutic outcome ($p = 0.014$). The ^{18}F-FDG lymph node to primary tumor ratio does not have considerable results. Tumor metabolic response is considered to be more precise on ^{18}F-FAMT-PET than 18F-FDG-PET. ^{18}F-FDG can lead to under or overestimation of the therapeutic response. ^{18}F-FAMT is a tumor specific PET tracer which can distinguish lung cancer from sarcoidosis, which is an entity with false-positive results on ^{18}F-FDG-PET. More research is needed for the increase of sensitivity in diagnosis of malignant tumors.

Prognostic value of LAT1

LAT1 is expressed in high levels in several human cancers and is the transporter of ^{18}F-FAMT in tumor cells. Thus, it is connected strongly with the ^{18}F-FAMT uptake. In malignant tumor sites, LAT1 is in close relation with tumor cell proliferation, angiogenesis, and metastasis. High expression of LAT1 is a crucial marker for poor prognosis prediction for several human neoplasms such as lung cancer, gastrointestinal cancer, breast cancer, head and neck cancer, hematological malignancies, and malignant melanoma. High uptake of ^{18}F-FAMT and high expression of LAT1 are crucial predictors for poor outcome. LAT1 expression is more prognostic than ^{18}F-FAMT uptake in NSCLC; nevertheless, ^{18}F-FAMT-PET is regarded to be a novel molecular imaging technique of LAT1 expression in lung cancer patients.

Imaging of fatty acid metabolism

The predominant alteration in malignant tumor metabolism is the high rate of glycolysis. Apart from metabolism of glucose, lipid metabolism is also vital for tumor proliferation, energy storage, and the generation of signaling molecules. Metabolic activity imaging of fatty acid can be displayed with PET/CT scanning in malignant tumors (in vivo) for the visualization of lipid metabolism. This process has a crucial role in the detection and staging of malignancies. Such PET tracers are ^{11}C-Choline, ^{18}F-Choline, and ^{11}C-Acetate. Huang[3] supported that the application of Lipid PET probes in the detection of malignant tumors can have significance. More specifically, ^{11}C-Choline and ^{18}F-Choline could be used in a PET/CT scanning for the detection of intracranial tumors, nasopharyngeal carcinoma, lung cancer, esophageal cancer, and carcinomas of soft tissues.[3] For the clinical practicability of ^{11}C-Acetate PET/CT in the detection of malignant tumors, Huang[3] made clear that the above tracer can also have a role in the diagnosis of: renal carcinoma, bladder urothelial carcinoma, glioma, lung bronchioloalveolar carcinoma, and multiple myeloma. When it is compared with ^{18}F-FDG PET/CT, ^{11}C-Acetate PET/CT seems to have some advantages in the assessment of aforementioned malignancies. As yet, it is not widely used in daily clinical practice.

PET/CT staging in lung cancer with TNM system, advantages and limitations

TNM is a system which has a basic purpose to classify tumors concerning the primary tumor (T), loco-regional involvement of lymph nodes (N), and the existence of metastases (M) local or distant. TNM constitutes the major instrument in order to be determined the expansion of several tumor entities and especially for lung cancer. The stages result from different combinations of T, N, and M descriptors. The applications of TNM are the clinical (preoperative) staging (c); pathological (p) staging, after therapeutic modalities staging or staging after recurrent disease. TNM is an essential axis for the management and the assessment of therapeutic outcomes, assists the multi-center communication and has significant role as an index of OS of patients. On

a regular basis, TNM is revised by the UICC (Union for International Cancer Control) and AJCC (American Joint Committee on Cancer). According to Kandathil et al.[5] IASLC (International Association for the Study of Lung Cancer) created a new database with aim to update the seventh edition of TNM staging. Data have collected from 1999 to 2010 and for 77.156 patients with lung cancer diagnosis on a global basis. The eighth edition has changes in staging of NSCLC (non-small cell lung cancer) because of different prognosis in diagnosis (clinical stage) and surgical (pathological stage) intervention for patients with disparate T and M. From 2017 and then, the eighth edition is considered the main tool of NSCLC staging. Many improvements have happened in the diagnostic and therapeutic algorithms. The use of contrast-enhanced CT and FDG-PET/CT (clinical stage) and the histopathological results (pathological stage) are included in the NSCLC staging routine. Other progressions including endoscopic biopsy with minimally invasive technique, radiotherapy with high precision, surgical minimally invasive techniques, immunotherapy, and targeted therapies have an utmost importance in the whole management of NSCLC and taken into consideration in eighth edition. Eighth edition includes the reclassification of WHO (World Health Organization), IASLC, ATS (American Thoracic Society), and ERS (European Respiratory Society) in 2011 about the lung adenocarcinoma with aim to highlight the growth and the invasiveness (adenocarcinoma in situ, minimally invasive adenocarcinoma, invasive adenocarcinoma).

T

Several descriptors exist in T category: size of primary tumor, main bronchus involvement, obstructive pneumonitis, or peripheral structures involvement (hilum, visceral pleura, chest wall, phrenic nerve, parietal pericardium, diaphragm, carina, trachea, heart, great vessels, recurrent laryngeal nerve, esophagus, vertebral body) nodule in the same or different ipsilateral located relative to the primary tumor. In case that one tumor fulfills many criteria in multiple T descriptors, the highest T-stage defines the category. The measurements are performed concerning the long axis in centimeters (with millimeter conversions). Because of different 5-year prognosis, there are new T descriptors, new size cut-offs, and new categories. 3 and 5 cm still distinguish the T1 from T2 and T2 from T3 tumors, respectively. From T1 to T2, every cm has significant difference in OS. T3 descriptor about diaphragm invasion changed and is regarded as T4 due to worse prognosis than other descriptors. On the grounds that mediastinal pleural invasion is hard to be defined from clinical staging and affiliated with mediastinal invasion in pathologic staging tissues, it is not counted as T descriptor. Carcinoma in situ (Tis) is the tumor with 3 cm or less measurement without component of invasion at histopathological tests. T1a Minimally Invasive Adenocarcinoma (mi) is defined as tumor 3 cm or less with invasive component 5 mm or less at histopathological tests. T1: T1a are tumors with 1 cm or less measurement. T1b are tumors more than 1 cm and equal or less than 2 cm. Tumors with measure more than 2 cm and equal or less than 3 cm are categorized as T1c. Irrespective of location, tumor with superficial spreading in the central airways is T1a. T2: T2 are tumors with measure more than 3 cm and equal or less than 5 cm. T2a are tumors more than 3 cm and equal or less than 4 cm. T2b are tumors more than 4 cm and equal or less than 5 cm. Tumor involvement of main bronchus without the carina or the visceral pleura invasion or tumor which causes atelectasis or post-obstructive pneumonitis with extension to the hilum is a T2a tumor. The eighth edition does not take into consideration the differentiation between partial and complete atelectasis and the distance from the carina.[5] T3: tumors more than 5 cm and equal or less than 7 cm are T3. Nodule in the same lobe with the primary tumor, invasion of chest wall, phrenic nerve or parietal pericardium invasion is T3 descriptor. Also as T3 is categorized a Pancoast tumor with only T1 or T2 nerve roots invasion. T4: tumors more than 7 cm or with separate tumor nodule or nodules in an ipsilateral separate lobe are classified as T4. Involvement of diaphragm, mediastinum, carina, trachea, heart, grade vessels, recurrent laryngeal nerve, esophagus, vertebral body is T4 descriptor. Pancoast tumor with C8 or higher nerve roots involvement, cords of the brachial plexus, subclavian vessels, vertebral bodies, or spinal canal invasion are all T4 descriptors.

N

There are no changes about N descriptor in the eighth edition of TNM. According to a basis of IASLC lymph node map N0, N1, N2, and N3, nodal involvement categories were proved to have the same consistent prognostic distinguishment in different groups.[5] N1: N1 descriptor includes metastasis in ipsilateral peribronchial or hilar nodes or intra-pulmonary nodes. N2: N2 descriptor includes metastasis in ipsilateral mediastinal or sub-carinal nodes. N3: N3 descriptor includes metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular nodes. The involvement of lymph nodes—N descriptor—is not an uncommon intrathoracic site of nodal metastasis like the internal thoracic and cardio-phrenic chains. The number of N1 and N2 involved nodes in combination with the absence or presence of skip-metastases is a superior staging tool for the prognosis than the location. IASLC performed histopathological assessment for the N descriptors classification in eighth edition of TNM recommending also clinical evaluation and testing for more additional parameters. Nodal categories are based on the number of lymph nodes involved and on the existence of skip-metastases. N1a: single N1 group involvement; N1b: multiple N1 group involvement; N2a1: single N2 group without N1 involvement (skip); N2a2: single N2 group with N1 involvement; and N2b: multiple N2 group involvement.

M

Eighth edition of TNM staging has three M descriptors.[5] Extra-thoracic metastases from M1b in seventh edition became M1b and M1c. An extra-thoracic metastasis in one distant organ (M1b) has better prognosis than multiple extra-thoracic lesions (M1c) and can be resected surgically or with ablation localized therapy. M1a includes tumor nodule or nodules in a contralateral lobe from the primary tumor, or one tumor with malignant pericardial or pleural nodules, or malignant pericardial or pleural effusion. M1b includes single extra-thoracic metastasis in one organ (brain, liver, distant lymph node, bone, skin, peritoneum, or adrenal gland). Patients with a solitary atypical lesion must be histopathological validated in order to proceed in surgical resection. M1c includes multiple extra-thoracic metastases in one organ or multiple extra-thoracic metastases in multiple organs. Organs with more reference for invasion are as follows: bone 34.3%, lung 32.1%, brain 28.4%, adrenal glands 16.7%, and liver 13.4%. The M descriptor does not take into consideration the metastatic burden or the specific site. The metastatic site has no importance for survival either for solitary or for multiple lesions in a single organ. Eighth edition includes new stages due to modifications of T and M descriptors and changes of old stages in order to mark the important differences in patient prognosis. Stage I is classified as IA1, IA2, and IA3 depending on the cut-off of 1 cm in T1 tumors with distant metastases or lymph node involvement evidence. IIIC is a new stage which contains T3 and T4 locally advanced disease lesions with N3 involvement and without distant metastases. IVA stage embraces M1a and M1b tumors, and IVB stage embraces M1c tumors.

Advantages and drawbacks of FDG-PET/CT for lung cancer TNM staging

PET/CT with the use of FDG merges anatomical information with functional and metabolic data. Size of tumor and regional aggressiveness are the anatomical information from CT which is combined with the metabolic data of PET/CT remains the basic staging tool of NSCLC for nodal involvement evaluation but this use has limitations.

Kandathil et al.[5] quoted that the integration of FDG-PET with a conventional diagnostic procedure had as a result a 51% reduction of pointless thoracotomies (patients with benign disease, stages IIIA-N2/IIIB in histopathological specimens, postoperative relapse, death in 12-month period, explorative thoracotomies) contrary to conventional workup only. Furthermore, they reported that when FDG-PET/CT imaging test were carried out, there were a 72% change in the whole management of lung cancer cases.[5] They also mentioned that the diagnostic efficacy of FDG-PET/CT in NSCLC was 72% and 91% for the sensitivity and specificity, respectively, in mediastinal nodal staging assessment.[5] For the detection of all extra-thoracic metastases, FDG-PET/CT had 77% sensitivity and 95% specificity. National Comprehensive Cancer Network (NCCN) criteria[6] for imaging appropriateness are as follows: FDG-PET/CT from the skull base to the knees or FDG-PET/CT of whole body for the assessment of I to IV stage in NSCLC. In respect to NCCN, PET/CT positive for distant disease must be confirmed in histopathological specimens or in other radiological tests. Histopathological validation is also needed for FDG uptake in mediastinal lymph nodes. Incidental finding more than 8 mm lung nodule must be tested with FDG-PET/CT according to NCCN. Standardized uptake value (SUV) greater than mediastinal blood pool baseline SUV is considered to be positive PET result.

Assessment of T descriptor with FDG-PET/CT

A big spectrum of carcinomas with heterogeneity in biology and prognosis is included in NSCLC. Kandathil et al.[5] highlighted the connection between the FDG uptake, semi-quantitative measurements as the SUV, size of tumor, subtype in terms of histology, and aggressiveness in terms of biology and prognosis. Small nodules, less than 8–10 mm (T1a), adenocarcinomas with mucin and few cells, carcinoma in citu (Tis), and minimally invasive adenocarcinoma T1a (mi), which are low grade malignancies, can be PET false-negative findings. Tis and T1a (mi) on CT can be detected as ground-glass opacities or part solid ground-glass opacities. Invasive adenocarcinomas with predominant lepidic pattern can manifested as solid and ground-glass mixed nodules. The union for international cancer control recommends that the sub-solid tumors must be measured in the solid invasive component with aim to determine the T descriptor. In a sub-solid ground-glass nodule, PET/CT with FDG is performed only if the solid component is more than 8 mm. Lung cancer with solid lesions less than 8–10 mm, lepidic carcinoma, and adenocarcinoma with well differentiation have been connected with false-negative findings on PET/CT. The main diagnostic option for the assessment of invasion and tumor size is the chest CT with or without contrast enhancement. In clinical routine during PET/CT scan, the CT modality uses free breathing and low-dose techniques with thick intervals of reconstruction which is not the superior option for the morphological analysis of a nodule. The distinguishment between tumor and post-obstructive atelectasis is one aspect of FDG-PET/CT superior to CT and has a major role in staging, biopsy, radiotherapy planning, and evaluation of therapeutic response. Higher FDG uptake is detected in atelectatic areas in contrast to normal lung tissue and lower FDG uptake is seen in atelectatic areas in comparison with neoplastic tissue. The GTV (gross tumor volume) on PET has been demonstrated to be smaller than measured volume on CT in approximately 13%–17% of cases. As a result of blooming artifact, chest wall invasion evaluation is not preferential with PET/CT. Chest wall or diaphragm involvement can be

better assessed with MRI or CT with contrast enhancement. A poor survival index, such as the lymphangitic carcinomatosis, is not a T descriptor. In addition to CT results, PET/CT with FDG may provide more specificity with high uptake in nodular inter-lobar septal thickening. PET/CT provides 86% and 100% sensitivity and specificity, respectively, in lymphangitic carcinomatosis entity.

Assessment of N descriptor with FDG-PET/CT

Lymph nodes more than 1 cm in short axis on MRI or CT are thought to be metastatic involvement in NSCLC patients. CT imaging for the depiction of involved nodes ranges from 51% to 64% and 74% to 86% for the sensitivity and specificity correspondingly. The sensitivity and specificity of FDG-PET/CT are estimated to 58%–94% and 76%–96%, respectively, for the mediastinal lymph node metastasis imaging. Low volume malignancies or malignant tumors with low metabolic rate have low FDG uptake. This fact suggests low sensitivity because of high percentage of false-negative findings. Granulomatous infections (tuberculosis) and inflammatory lesions (sarcoidosis) have nodal involvement and can lead to false-positive PET results. Kandathil et al.[5] marked that NPV for mediastinal lymph node metastasis was 94% in T1 and 89% in T2 tumors. FDG uptake may be manifested on FDG-PET/CT modality in involved nodes less than 10 mm or may have as a result false-negative findings in involved lymph nodes more than 10 mm. Primary tumors with high FDG uptake are strongly connected with higher risk of occult nodal metastasis. NCCN suggests histopathological assessment of mediastinal lymph nodes for stage II tumors before surgical resection and the same optional technique for solid tumors less than 1 cm or purely non-solid (tumors) less than 3 cm without lymph node involvement on CT and PET.

Assessment of M descriptor with FDG-PET/CT

In cases of assessment of extra-encephalic metastasis in patients with NSCLC, FDG-PET/CT is the best option technique. 11%–36% of patients with NSCLC have distant metastases. Most common sites are adrenal glands, liver, brain, bones, and abdominal lymph nodes. Kandathil et al.[5] cited 93% sensitivity and 96% specificity as well as 28.4% positive likelihood ratio and 0.08% negative likelihood ratio for the distant metastases depiction with FDG-PET/CT. NCCN recommend biopsy or further cross-sectional imaging workup (MRI and CT) for the validation of highest stage in sites with high FDG uptake suspect for metastasis. NCCN also suggests PET imaging in tumors with clinical aggressiveness which seems to be in advanced stage. In this instance, prebiopsy PET will be useful in the optimal sampling of abnormal areas that would confirm the highest stage (after biopsy). Solitary extra-thoracic metastasis in one organ such as brain, liver, bone, distant lymph node, skin, peritoneum, and adrenal gland has better prognosis than multiple extra-thoracic metastases and may be surgically resected or can be confronted with local ablation therapy. Candidates for surgical resection with solitary atypical lesion must have histopathological confirmation. FDG-PET/CT may be performed for the detection of unsuspected metastases in locally advanced NSCLC patients which are candidates for curative intent treatments in order to limit futile thoracotomies. PFS and OS are worse in PET/CT upstaged cases with a level of statistical significance p-value < 0.001. There is no recommendation from NCCN for bone scintigraphy in every day clinical practice for NSCLC patients staging. In pleural metastases, it is detected that FDG accumulation may be found in malignant tumor cells. FDG-PET/CT has high-diagnostic accuracy in malignant pleural effusion.[5] Pleural nodules with small size when there is no pleural effusion may have low FDG avidity and may represent dry pleural dissemination in NSCLC cases. High incidence of brain metastases is present in NSCLC patients. MRI with contrast enhancement shows higher sensitivity in the evaluation of brain metastases in NSCLC than FDG-PET/CT. Kandathil et al.[5] reported 21% and 77% sensitivities for PET and MRI. Specificities were 100% and 99% for PET and MRI, respectively. For patients with NSCLC and stage II–IV, NCCN suggests MRI for the exclusion of brain metastases. FDG-PET/CT is not preferential because of intensive accumulation of FDG in brain parenchyma, a fact that can lead to distinguishable FDG-avid sites.[5] FDG-PET/CT presents higher sensitivity and specificity in the detection of bone marrow metastases than bone scintigraphy. If the results from PET and CT are consistent, PPV rises to 98%. FDG-PET/CT is the modality of choice for the detection of bone metastases because of higher diagnostic value than other modalities (MRI and bone scan). Extra-thoracic lymph node metastases can be detected in unsuspected sites with FDG-PET/CT. FDG-PET/CT can depict metastases in normal sized lymph nodes <1 cm and lymph nodes with fatty hilum. FDG uptake in a lymph node higher than the blood pool FDG uptake is susceptible for lymph node metastasis. Also FDG uptake in lymph node higher than the liver uptake (of FDG) is strongly associated with lymph node metastasis. The proper validation for the diagnosis of an FDG-avid lesion (lymph node) must have a biopsy report which will direct the whole therapeutic management. In 20% of NSCLC cases, incidental adrenal nodules are found. Most are benign adenomas. Kandathil et al.[5] mentioned that in patients with lung cancer or with the suspicion of having lung cancer mean CT attenuation higher than 10 HU (Hounsfield units) and SUVmax (maximum standardized uptake value) higher than 3.1 showed 97% and 86% sensitivity and specificity, respectively, for metastatic disease detection. SUVmax of adrenal

nodule about 2.5 with reference value the liver's average SUV had 100% NPV for malignancy. Lesions less than 1 cm, metastasis with hemorrhage or necrosis can have false-negative results in FDG-PET/CT findings. False-positive findings may be detected due to adrenal adenoma, tuberculosis, or adrenal hyperplasia. If the metastatic site is located only in the adrenal gland, then histopathologic examination must be performed.

Second primary malignancy

Incidental FDG-avid areas may be depicted in whole-body FDG-PET/CT, which are suspicious in 4% of NSCLC patients for secondary primary malignancy. 25% of these results are estimated to be owed to second malignancy. Common sites of uptake are mainly located at: colon, thyroid, proximal aero-digestive tract, and ovaries. Depending on the site, the risk becomes greater for malignancy if there is loco-regional FDG avidity in breast, colon, thyroid or prostate. About 30% of local FDG uptake can represent malignancy. In contrast a diffuse pattern of uptake represents benign lesion. FDG-PET/CT detects second primary tumor or pre-malignant lesion in about 3% of NSCLC cases, a result that changes the therapeutic intent from curative to palliative.

Limitations in the TNM staging of NSCLC with PET/CT

False-positive results: infection and inflammation are two processes that can imitate malignancies and have as a result false-positive results in FDG-PET/CT. PET/CT has a 7% false-positive rate. Inflammatory pseudo-tumor (43%), tuberculoma (37%), and organizing pneumonia (6%) are the main reasons of false-positive results. Higher levels of interleukin-6, positive results on interferon-γ assays for tuberculosis, age less than 50 years, and non-diabetic are associated with higher false-positive rates. Age older than 65 years and non-adenocarcinoma histologic subtype are independent factors connected with false-positive hilar and mediastinal lymph nodes in PET/CT for NSCLC patient evaluation. Other pathologic entities such as emphysema, silicosis, previous tuberculosis, and interstitial pneumonitis can be linked with false-positive lymph nodes. False-negative results: small nodule, low cellularity in lesions like carcinoma in situ and low FDG avidity in several tumors can have as a result false-negative lesions in PET. The radiologic factor with crucial importance for risk evaluation is the change or the stability in comparison to successive previous imaging studies. For patients with low pretest likelihood of malignancy, who have solitary pulmonary module, that indicates negative finding at PET, consecutive CT follow-up may be contacted. For high pretest likelihood of malignancy patients, histopathological examination with biopsy or surgery should be taken into account.

SCLC staging

Over time, SCLC was counted as a systemic disease and stratified as limited or extensive disease in consistent with the modified version of the Veterans Administration Lung Cancer Study Group (VALSG) staging system and that is because at the initial diagnosis, about 60%–70% of cases with SCLC have metastases.[7] Limited stage (LS) is defined as disease confined to one hemi-thorax, includes involvement of mediastinal, contralateral hilar and/or supraclavicular and scalene lymph nodes. Extensive disease is defined as disease with spread beyond the definition of LS or the existence of malignant pleural effusion. The above are definitions of eighth edition for the lung cancer stage classification. In this edition, a change in the therapeutic management of patients with SCLC with more emphasis in curative intent has been taken into consideration, which is now a preferential choice.[7]

SCLC investigation

SCLC is characterized by high aggressiveness with rapid doubling time and dissemination at the time of the initial diagnosis.[7] It is estimated at around 15%–20% of all lung cancers. The discrimination of LS and extensive stage (ES) is crucial on the basis of whether the disease is limited to one hemi-thorax or is disseminated. The cure intent is different in both cases, palliative care in the extensive disease and chemo-radio therapy in limited disease. For the depiction of the disseminated disease, PET/CT has 89% sensitivity and specificity. PET/CT also changes the stage and the therapeutic management in 12%–26% of SCLC patients.[7] The global scientific literature does not provide enough data for SCLC and PET/CT.

Diagnosis

Lung cancer can be diagnosed from the symptoms of primary tumor, local spread, metastases from inappropriate, or ectopic hormone excretion.[7]

Radiological assessment

Chest X-rays are the usual initial radiographic test in persistent respiratory symptoms.[7] Chest X-rays have 70%–80% overall diagnostic accuracy for lung cancer imaging. CT with contrast enhancement may be useful for discrimination of benign and malignant lesions. An augmentation of 20 HU or more has 98% sensitivity and 73% specificity in lung cancer diagnosis.[7] In 90% of cases, peripheral nodules with irregular, ill-defined, and speculated borders are malignant. PET is more accurate than CT in distinguishment of 1 cm benign and malignant lesions.[7] MRI is regarded better choice than CT for the assessment of tumors which are located in superior sulcus or invade branchial plexus, subclavian vessels, and adjacent vertebral bodies.[7] Furthermore, MRI is the modality of choice for the detection of brain metastases.

Prognosis from different indexes

There are many equivocal studies concerning the contribution of SUVmax in the estimation of prognosis.[7] Few investigators considered that MTV (metabolic tumor volume) and TLG (total lesion glycolysis) are superior predictors than SUVmax. High SUVmax, MTV, and TLG volumes are connected with higher risk of recurrent disease and death in patients with resectable NSCLC.[7]

PET tracers

There is a variety of radiopharmaceuticals for PET imaging. 18F (Fluorine-18)-labeled compounds are the most common. In comparison to other PET tracers, 18F has a little longer half-life. This fact makes 18F easily transportable, and there is no need for on-site cyclotron. In addition, different radionuclides with several properties can have different effects on imaging parameters. Spatial resolution is an imaging parameter, which is affected from positron range, because the annihilation can be occurred away from the positron production. The number of positrons produced from any decay can also affect the sensitivity. Furthermore, the different radiochemical characteristics of radionuclides allow them to become desired radiopharmaceuticals after labeling process. Some PET isotopes are the following: ^{18}F, ^{11}C, ^{13}N, ^{15}O, ^{68}Ga, and ^{82}Rb.[7] Harisinghani and his colleagues reported a list of PET agents that are under clinical development and represent different molecular and biological pathways and processes not confined only in lung cancer.[8] These are:

- ^{18}FLT (fluorothymidine), ^{11}C-Thymidine: proliferation marker (lung cancer, glioma).
- ^{11}C-methionine: proliferation marker (cancer).
- ^{11}C-acetate: lipid synthesis; incorporation into cell membrane lipids (cancer).
- ^{18}F-annexin V: putative apoptosis marker.
- ^{64}Cu-ATSM: hypoxia agent.
- ^{18}F-MISO, 18F-fluoromisonidazole: hypoxia agent.
- ^{18}F-galacto-RGD: integrin marker.
- ^{18}FES: estrogen receptor.
- ^{18}F-DHT: dihydrotestosterone, androgen receptor.
- ^{11}C-acetate: oxidative metabolism, incorporated into membrane lipids.
- ^{11}C-tyrosine, ^{18}F-fluorotyrosine, ^{18}F-fluoroethyltyrosine: tyrosine amino-acid transport (cancer).
- ^{18}F-fluorodihydroxyphenylalanine: response of neuroendocrine and brain tumors.
- ^{18}F/^{11}C-labeled therapeutic drugs (“minidosing”), for example: ^{18}F-fluorouracil (5-FU).

Methods

A systematic review of the literature in the PubMed/Medline database was performed. We included articles up to February 2020. The search was done with the following keywords: PET/CT, lung cancer, and radiopharmaceuticals. The categories of medical studies evaluated were as follows: Clinical-Phase I, II, III, IV prospective studies, comparative studies, observational studies, multi-center studies, meta-analyses, and reviews. The search language was English.

Study selection

For the first submission, the search term in PubMed was “PET/CTLUNGCANCERRADIOPHARMACEUTICALS” with filter: customize, clinical trial, meta-analysis, multicenter study, and review, published in the last 5 years. From the results above, only articles from 2015 and then were selected. The research in PubMed revealed 40 results, from which only nine were selected. For the resubmission, the results were the following: with the search term “New radiopharmaceuticals PET/CT lung cancer,” the results were 71 items and six of them included in the review, with the search term “New tracers PET/CT lung cancer,” the results were eight items and one of them included in the review, and with the research term “Design and Challenges of Radiopharmaceuticals,” one item was included in the review. One data item was retrieved from the NCCN website. In the PubMed research, only the results from 2017 to February 2020 were taken into consideration. The research of the current scientific literature highlighted five titles of bibliography extracted from reading 24 titles of bibliography. The pooled sources were 143. The final data items that were used were 23. The process of inclusion of each study resulted from thorough analysis, reading, and critical appraisal. Each study’s estimation was qualitative. The main criteria across the whole reading process of all studies were the relevance and the significance with the basic question of systematic review (introduction and clinical significance and practicability of new PET/CT radiopharmaceuticals beyond 18F-FDG for diagnosis of lung cancer). Anything else not related with this main question was excluded. The final results of the whole research procedure are depicted in Figure 1.

Results

Tripathy and Kumar[10] in a case study examined data of ^{68}GA-DOTANOC PET/CT from a 48-year-old man with surgically rejected bronchial carcinoid (lobectomy). He developed multiple metastases after a 12-year event-free survival.

Laura, et al.[11] in their study conducted a literature search and resulted that FDG-PET/CT can predict the response to immunotherapy of lung cancer patients, but its usefulness for the response assessment is not clearly confirmed. They reported that the role of FDG-PET/CT in patients with lung cancer who underwent immunotherapy is preliminary and must be directed properly. They also studied novel agents for PET imaging that must be clinically confirmed about their utility.

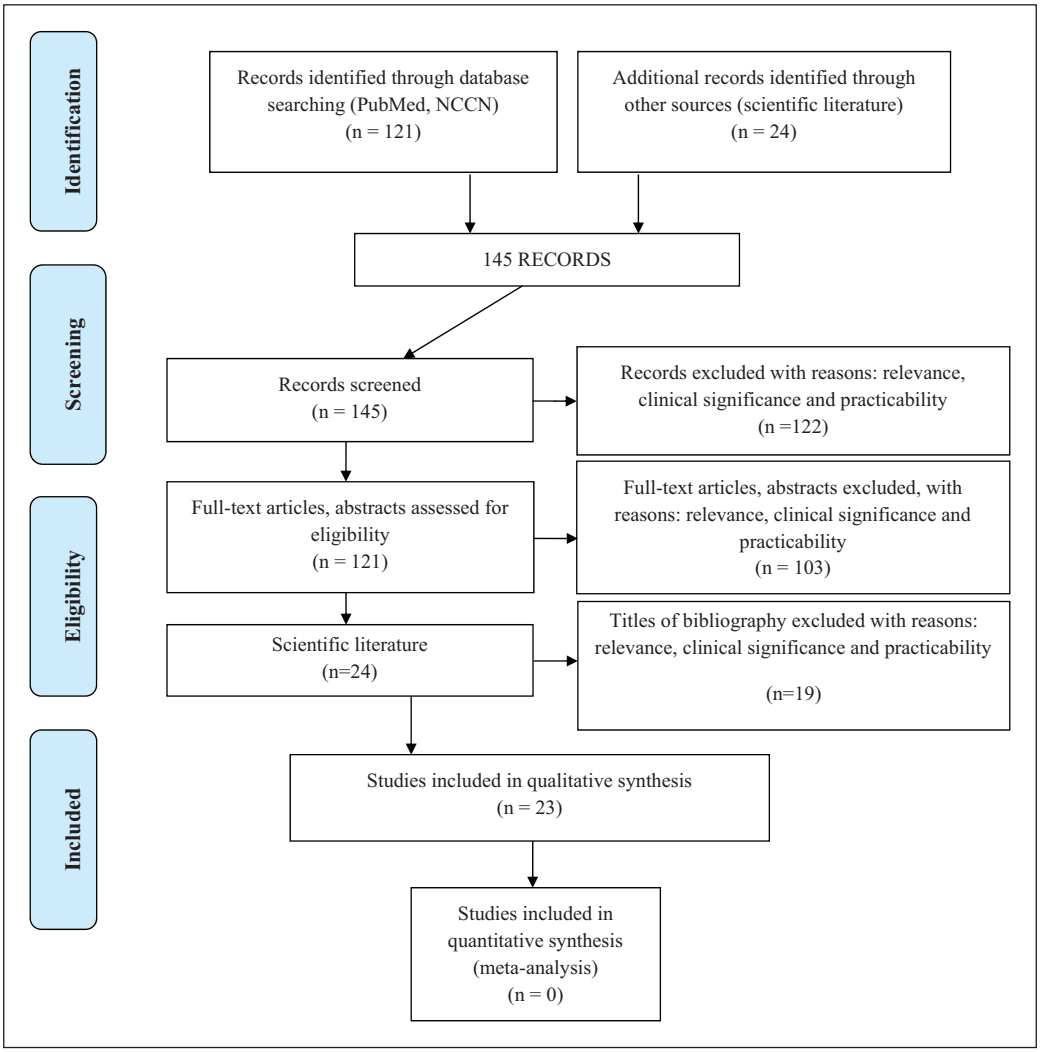

Figure 1. Prisma flow diagram.[9]

Telo et al.[12] in a review for alternative and new radiopharmaceutical agents for lung cancer considered that FDG-PET/CT has major contribution to lung cancer management. Although FDG-PET/CT has a satisfying sensitivity, its specificity is limited because of the weakness to distinguish benign conditions from lung cancer and its inability to define lung cancer heterogeneity between different subtypes according to FDG uptake. In addition, they mentioned that radio-labeled RGD peptides which have as target the angiogenesis may have an importance in lung cancer stratification, therapeutic results and management. They also marked that radiopharmaceutical agents, which target into a specific oncogene/signal pathway like anaplastic lymphoma kinase (ALK) or epidermal growth factor receptor (EGFR), gain ground for curative intents.[12] PET tracers such as ^{68}GA-PSMA or radio-labeled fibroblast-activation-protein-inhibitors (FAPIs) require further investigation but are promising for curative implications.

Kratochwil et al.[13] in their study examined several primary and metastatic tumors via quantification of uptake in FAPIs-PET/CT.[13] They noted that quinoline-based PET tracers that behave as FAPIs present promising preclinical and clinical results.[13] In a sample of patients with 28 different kinds of cancer (54 primary tumors and 299 metastases), it was observed that sarcoma, esophageal carcinoma, breast cancer, cholangiocarcinoma, and lung cancer had the highest SUVmax ($>$12). Authors ascertained that tumor entities with high prevalence displayed notable high image contrast and uptake in the FAPI PET/CT imaging. From this, FAPI PET/CT becomes potential candidate for new non-invasive tumor characterization techniques, radio-ligand therapies, and staging tests.[13]

Cai et al.[4] quoted that apart from FDG, other PET tracers like F-18, Fluoromisonidazole (FMISO) PET, copper-60-diacetylbis (*N*4-methylthiosemicarbazone; Cu-60 ATSM), and 18F-Fluoroazomycin arabinoside ((18)F-FAZA) PET have application in the non-invasive assessment of hypoxia levels in NSCLC patients.

In their study, Tang et al.[14] examined radiosynthesis and biological evaluation of 18F-labeled l-DOPA analogue, *N*-(2-[18F] fluoropropionyl)-3,4-dihydroxy-l-phenylalanine ([18F]FPDOPA) for PET imaging in glioma (C6 glioma-bearing mice models), lung adenocarcinoma (SPC-A-1 cell lines), and large cell carcinoma (H460 large cell lung cancer mice models). [18F]FPDOPA had intense accumulation in PET for different heterografts, $8.50 \pm 0.40\%$ ID/g in glioma, $6.30 \pm 0.12\%$ ID/g in lung adenocarcinoma, and $6.50 \pm 0.10\%$ ID/g in large cell lung carcinoma. There were significant differences in terms of [18F]FPDOPA and [18F] FDG uptake after 1 h of injection in SPC-A-1 and H460 heterografts. Furthermore, there was higher tumor to background ratio of [18F]FPDOPA than [18F]FDG in 1-h post-injection for both SPC-A-1 and H460 heterografts ($p < 0.05$).[14]

In 70 patients with metastatic lymphadenopathy in thoracic CT who were subjected to whole-body PET/CT with 18F-FDG and 18F-FLT (within 1 week for each test), radiopharmaceutical uptake in the lymph node was determined by the calculation of SUV units for both tracers.[15] Then, the results of PET/CT were compared with the histopathological findings of the lymph nodes. The results of the histopathological findings were as follows: 37 patients with sarcoidosis, seven patients with tuberculosis, nine patients with NSCLC, five patients with Hodgkin's lymphoma, and 12 patients with non-Hodgkin's lymphoma. The mean FDG SUVmax of sarcoidosis, tuberculosis, Hodgkin's lymphoma, and non-Hodgkin's lymphoma was 12.7, 13.4, 8.2, and 8.8, respectively, while the mean SUV max of the FLT was 6.0, 5.4, 4.4, and 3.8, respectively. It was not possible to classify benign or malignant mediastinal lymphadenopathy only on the basis of SUVmax values for both FDG and FLT as the p-value was greater than 0.05 and therefore not statistically significant in both cases. There was no significant difference in the uptake of FDG ($p > 0.9$) or FLT ($p > 0.9$) between sarcoidosis and tuberculosis. In lung cancer patients, the SUVmax of FDG and FLT of the lymph nodes that were infiltrated in the biopsy was 6.7 and 3.9, respectively, and for those who were not filtered 6.4 and 3.7, respectively. Both tracers were not able to classify as benign or malignant lymph nodes ($p > 0.05$).[15]

38 patients with advanced NSCLC (23 stage III patients and 15 stage IV patients) underwent PET/CT with FAZA and FDG prior to treatment. The PET parameters (T/M at 1 and 2 h for FAZA and SUVmax for FDG) in primary lesion, lymph node metastases, and clinical parameters were compared with concerning their impact on free PFS and OS. In all patients, the clinical stage and the FAZA T/M in lymph node metastases at 1 and 2 h had prognostic value for PFS. In a multifactorial analysis, it also became apparent that the above parameters were independent prognostic factors for PFS. In an analysis of the subgroup of patients (stage III) receiving a combination chemotherapy-radiotherapy, it appeared that only the T/M of FAZA at 2 h had predictive value for PFS. The PET/CT parameters for FDG had no predictive value for the disease progression free survival. Regarding OS, no parameter was a significant predictor. In patients with advanced NSCLC, the uptake of FAZA not in primary lesions but in lymph node metastases was predictive of the therapeutic effect.[16]

Thirty-three patients with diagnosed pulmonary carcinoid were included in two centers. The semi-quantitative assessment included SUVmax, the SUV of the tumor relative to the maximal liver uptake for 18F-FDG (SUV T/L), or the maximal spleen uptake for ^{68}Ga-DOTA-peptides (SUV T/S) as well as the ratio of SUVmax for both ^{68}Ga-DOTA-peptide and 18F-FDG with PET/CT. Histopathology was used as a reference standard. The definitive diagnosis included 23 typical carcinoids and 10 atypical. PET/CT with 18F-FDG was positive in 18 cases and negative in 15 cases (55% detection rate). PET/CT with ^{68}Ga-DOTA-peptide was positive in 26 cases and negative in seven cases (79% detection rate). In subgroup analysis, the PET/CT with 68Ga-DOTA-peptide was superior in the detection of typical carcinoids (91% detection rate, $p < 0.001$) while 18F-FDG PET/CT was superior to atypical carcinoid detection (100% detection rate, $p = 0.04$). The SUVmax ratio was the most accurate semi-quantitative index in typical carcinoid identification.[17]

The effect impact of 18F-NaF-PET results on the monitoring of patients who received systemic therapies was evaluated.[18] Before and after imaging with NaF, they prospectively collected data from the referral and interpretation of results by doctors in patients from 65 years of age or older who received systemic therapy (using one or more categories including hormone therapy, chemotherapy, bisphosphonates, or immunotherapy). The analysis was based on a total of 2217 patients who received 2839 PET examinations (68% for prostate, 17% for breast, 6% for lung and 8% for other cancers) for treatment monitoring. Two or more systemic treatment categories were planned at 56% for prostate cancer patients and 43% for patients with breast cancer. Overall rates of prior radioisotope bone scans were 78%, 76%, and 66% for prostate, breast cancer, and other cancers, respectively.[18] 57% of patients were underwent prior PET with NaF. The overall change in PET-related management using 18F-NaF was 40%. In patients with previous NaF-PET scans for comparison, continuing current treatment was planned at 79% when the scans did not show any change, reduction, or absence of bone metastasis. Physicians planned to change treatment in 59% of patients when after the imaging tests there was evidence of new or existing aggressive bone metastasis. When an additional parameter such as the estimated prognosis worsened, the change in treatment was even more frequent (76%).[18]

Eighteen patients with biopsy proven NSCLC (10 patients) and head and neck squamous cell carcinoma (HNSCC eight patients). All patients were subjected to PET/CT with 18F-FDG over 3 weeks prior to PET/CT imaging using fluoro-methyl-tyrosine. For all patients, safety and

response data were evaluated. Adverse reactions associated with d-18F-FMT were not observed. Fifty-two lesions were positive with the FDG and 42 of them were malignant (34 histologically proven and eight reported clinically). Thirty-two of the 42 malignant lesions were also positive with the fluoro-methyl-tyrosine, and 10 lesions had no uptake of the radiotracer over the blood pool level. Altogether, there were 34 true-positive, eight true-negative, 10 false-negative, and two false-positive lesions for d-18F-FMT imaging, while in 18F-FDG imaging, there were 42 true-positive, 10 false-positive, and only two false-negative lesions resulting in a 77% detection rate for d-18F-FMT and 95% for 18F-FDG. Total accuracy for both probes was 78%. The high tumor-to-blood pool ratio for d-18F-FMT was negatively correlated with OS ($p = 0.050$) whereas for 18F-FDG, the same ratio was not associated with OS.[19]

Discussion

Tripathy and Kumar[10] concluded that neuroendocrine tumors are indolent and slow-growing tumors, detectable with metastatic burden in the initial diagnosis. They also confirmed this fact specifically for low/intermediate grade NETs. Clinical behavior is determined depending on excessive hormonal excretion from tumor cells. Follow-up of a long period of time is vital for the evaluation of toxicity and efficacy of several therapeutic managements. In their case, patient had metastatic dissemination from the very first ^{68}GA-DOTANOC PET/CT 12 years ago.[10] He overcame the mean survival period of 40–72 months, despite the fact that he did not continue the PRRT (Peptide Receptor Radionuclide Therapy). Phase III NETTER trial assesses the PFS (Progression Free Survival) at 65.2% in month 20 post ^{177}Lu DOTATATE therapy. Overall response rate amounts to 18%, and the administration of PRRT in a clinically stable and biochemically non-progressive disease is still under controversy. The balance between different toxicities (hepato-toxicity, nephro-toxicity, and hemato-toxicity) from radionuclide therapy and the survival benefit require further investigation. PRRT is presented as a tool which provides survival prolongation and progression disease delay in patients with metastatic bronchial carcinoids. In the field of clinical oncology, 12-year follow-up is a much extended period and event-free survival infrequent to find in the literature. Investigators with this study restate that PRRT had halted the disease for many years. ^{68}GA-DOTA peptides (NOC, TOC, and TATE) that target SSRs have given their credentials and are regarded as modality of choice in staging, restaging, and response evaluation to radionuclide or octreotide therapy in patients with low and intermediate grade NETs, something that seems to remain unambiguous in the near future.[10]

Laura et al.[11] quoted one list of promising agents for the prediction and evaluation of response to immunotherapy. Development of new radiopharmaceuticals is very important for the initially assessment of PD-L1 expression in metastatic sites of disease with aim to: (a) avoid multiple biopsies, (b) select more carefully the patients who will have benefit from immunotherapy, and (c) reduce the costs (with avoidance of unnecessary treatments). This list contains immuno-PET radiopharmaceutical agents which are in preclinical (experimental phase). Depending on the target, the following potential agents are:

- 89Zr-imgratuzumab → Target: EGFR.
- 64Cu-anti CD 146 → Target: CD 146.
- 64Cu-DOTA-ipilimumab → Target: Cytotoxic T lymphocyte associated protein (CTLA-4).
- 89Zr-nivolumab → Target: PD-L1.
- 89Zr-C4 → Target: Human IgG1.
- 89Zr-df-nivolumab → Target: PD-L1.

Huang[3] quoted the ^{89}Zr-Ibritumomab for assessment, prediction, and optimization of therapeutic dose in ^{90}Y-Ibritumomab patients with Non-Hodgkin Lymphoma (NHL). Telo et al.[12] concluded that the traces ^{68}GA-PSMA, radio-labeled FAPIs, specific oncogene/signal pathway, such as ALK or EGFR, and RGD peptides are in the experimental level, and more scientific research and development are needed in order to reach in the absolute personalized therapy through the proper lung cancer staging, characterization, and response evaluation.

The major purpose of the retrospective study of Kratochwil et al.[13] was the role of FAPI ligand in several types of tumors. The high maximum SUV which was presented in lung cancer, breast cancer, esophageal carcinoma, and cholangiocellular carcinoma and sarcoma indicates that FAPI PET/CT may be superior in cases where FDG-PET/CT encounters imaging and molecular obstacles.[13] One main limitation of FDG-PET/CT in lung cancer is the high cerebral background owing to high brain parenchyma uptake. In this situation, brain MRI is needed for complete staging. FAPI PET/CT may also have an imaging benefit in these cases. For the confirmation of FAPI PET/CT role in subgroup analysis of histological subtypes and differentiation grades, larger studies with larger samples of patients are required. In addition, researchers found inconsistent results in terms of FAPI uptake and neuroendocrine or lung cancer tumor differentiation.[13] Intermediate group in FAPI PET was weak in histology for neuroendocrine tumors and high uptake in FAPI PET for lung cancer was intermediate in histology. Investigators concluded that the combination of FAPI with a DOTA-chelator and a therapeutic radionuclide (after radio-labeling process) can be a promising theranostic approach.[13] More elements and results will be deduced after completion of greater studies with higher number of samples for different tumor entities, more compact-patient groups, and more prospective assessments.

The results from the study of Tang et al.[14] were encouraging and showed that 18F-FPDOPA could be useful for several oncological applications in PET imaging. For glioma

imaging, 18F-FPDOPA showed better characteristics than 18F-FDG. For extracranial tumors like lung adenocarcinoma and large cell lung carcinoma, there was a basic drawback of 18F-FPDOPA about the high tumor to muscle ratio uptake which was similar to 18F-FDG. In the future, the 18F-FPDOPA may be a superior option than 18F-FDG in tumor imaging if the problems of high T/M (tumor to muscle ratio) overcome for lung cancer imaging (adenocarcinoma, large cell carcinoma).

Three systematic reviews (Sauter et al.,[20] Khiewvan et al.,[21] Szyszko et al.[22]) were identified which refer to the important role that modern imaging methods play in lung cancer, with particular emphasis on the PET/CT hybrid imaging.

More precisely, in the review of Khiewvan et al.,[20] PET/CT is presented as a useful tool for managing lung cancer patient. Diagnosis, staging, restaging, the designation of treatment plan, and the therapeutic response assessment are areas in which PET/CT proves to be beneficial. The same review also illustrates the contribution of PET to prognosis and therapeutic outcome. The results of PET before (baseline) and after treatment, the SUV who is the radiotracer absorption index, the MTV, the TLG as well as delayed PET/CT imaging can be used to predict prognosis and therapeutic effect. Indicators of hypoxia and cell proliferation can be used for prognosis. Khiewvan et al.[20] point out that using all these prognostic and predictive factors of PET/CT makes possible personalized treatment strategies, and this in turn results in a more cost-effective, more rational, and optimized management of each patient.

The review of Szyszko et al.[21] refers to the new PET radiopharmaceuticals on lung cancer. In addition to the standard in unspecified nodules use of 18F-Fluoro-deoxy-glucose, efforts are being made to develop new drugs that are not just about glucose metabolism. This effort is being done to increase the specificity and consequently the most reliable diagnosis of a pulmonary nodule which in the current literature has limitations. Apart from glucose metabolism, other signs of abnormal cancer biology are also controlled. 18F-FLT is an indicator of cell proliferation.[21] It shows less tumor concentration than 18F-FDG as it accumulates only in cells that are in Phase S of the cell division of cancer cell DNA. 18F-FLT has a low sensitivity to lymph node staging, and its main role is in assessing the response to treatment. Methionine is a basic amino-acid labeled with 11C, which is more specific and more sensitive than 18F-FDG in the differential diagnosis of benign and malignant thoracic nodules. 18F-FMISO belongs to the nitroimidazoles and is used to illustrate tumor hypoxia. The response of the tumor to the treatment is directly related to its level of oxygenation. Another area of the biological behavior of the tumor in which Szyszko T and his team focus on is angiogenesis.[21] The process of forming new blood vessels from the tumor helps in its development and metastatic dispersion. Angiogenesis is a major goal of a therapeutic approach, and therefore more and more clinical studies focus on Integrins targeting in PET imaging. From the Integrins team, $\alpha_v\beta_3$ has been extensively explored. This particular integrin is overexpressed in activated endothelial cells notably during angiogenesis. In conclusion, reference is made to neuroendocrine tumor markers, especially to the DOTA-labeled 68Ga (DOTA-TOC, DOTA-TATE, DOTA-NOC) peptides which have a prominent role in carcinoids imaging.[21] These specific radiopharmaceuticals are mostly in the research phase but may in the future be interesting choices for optimal staging, identification, categorization-stratification, and assessment of response to treatment at a time of complete individualization in the treatment of lung cancer.[21]

In another review of Sauter et al.,[22] the need for emerging new imaging technologies—such as PET/CT—and radiopharmaceuticals was highlighted in order to be the pathway for optimal management of lung cancer patients.

In the clinical prospective study of Rayamajhi et al.,[15] both 18F-FDG (PET/CT) and 18F-FLT (PET/CT) are being examined for the role they have in diagnosing mediastinal lymph nodes as benign or malignant. The results of the above research make it clear that the separation of the mediastinal lymph nodes into benign and malignant only on the basis of the maximum uptake of the two radiopharmaceuticals is not feasible specifically in cases where tuberculosis and sarcoidosis may coexist. Although both FDG and FLT markers represent different cellular biology, metabolism and proliferation functions, respectively, none of them provide satisfactory information for classification in benign and malignant lymph nodes.[15]

Saga et al.[16] in a clinical prospective study assessed the prognostic value of PET/CT using 18F-FAZA in patients with advanced NSCLC and compared it with 18F-FDG. The results of this study require confirmation with more and greater in the number (of patients) clinical studies, but indicate how important is the characterization of lymph node metastases, particularly in stage III patients who are candidates for combination chemotherapy and radiotherapy as the uptake of FAZA 2 h after administration can predict the therapeutic outcome.

In their clinical phase I study, Eo et al.[23] present a promising radiotracer (68) Ga-MSA for the detection-mapping of sentinel lymph node with PET/CT. The results of this test appear to be encouraging in the management of patients with NSCLC, but the sample is small (34 patients candidates for lobectomy and mediastinal lymph node surgery—clinical stage I) and larger clinical studies are required to show the effectiveness of (68) Ga-MSA.[23]

Lococo et al.[17] in a comparative multi-center study retrospectively assess and compare the detection rate of PET/CT with (68) Ga-DOTA-peptide and 18F-FDG in preoperative control of patients with pulmonary carcinoid. They also evaluate the usefulness of various functional markers for the diagnosis of histological type of pulmonary carcinoid (typical and atypical). From the above work, it was concluded

that the overall diagnostic performance of PET/CT in pulmonary carcinoid detection is optimal when integrating the results of both tracers (fusion images). SUVmax seems to be the most accurate index for the detection of typical carcinoids while both methods (68Ga-DOTA-peptide PET/CT, 18F-FDG PET/CT) should be performed when there is suspected pulmonary carcinoid or when the histological subtype is undefined.

Hilner et al.[18] evaluated the utility of 18F-NaF-PET in the predicted management of patients with bone metastases. The clinical value of NaF-PET in monitoring the response to systemic therapies in these patients is unknown. From the results of the above study, the authors concluded that the value of PET using 18F-NaF to monitor treatment was high in patients with progressively worsening bone metastasis. Most of these patients were planning to change their cancer-related treatment. A better treatment of patients was observed in total.[18]

Burger et al.[19] in a prospective multi-center study examined the ability of d-18F-FMT to detect tumors in patients with NSCLC or in patients with HNSCC. The ability to detect d-18F-FMT was evaluated in both inflammatory and normal tissues in direct comparison to 18F-FDG. D-18F-FMT is a novel fluorine-labeled tyrosine derivative which is transported directly via the (LAT1) L-amino-acid transporter and shows a faster clearance from the blood pool relative to the corresponding L-isomer. The investigators concluded that PET/CT imaging with the use of d-18F-FMT in patients with NSCLC and HNSCC was feasible and safe.[19] The preliminary results presented in this study suggest a lower sensitivity, but a higher specificity for d-18F-FMT compared to 18F-FDG as there was no uptake of d-18F-FMT in cases of inflammation. This high specificity may prove notably beneficial in areas with endemic granulomatous disease and may improve clinical management. However, more clinical investigations are required to determine the clinical value and the relevance that d-18F-FMT may have with the prediction of prognosis.[19]

Limitations

The small sample number of patients was the main limitation. In addition, there were radiopharmaceuticals that were under investigation or in experimental phase. One other limitation was that the study selection concerned the most significant and relevant results about the topic (the least significant and relevant results were rejected).

Conclusion

Molecular imaging is significant for the early diagnosis, personalized therapy direction, and the investigation of new drugs. Nuclear imaging with the use of PET and the integration of CT is broadly used in daily clinical routine. For the goal of functional monitoring, specific probes are essential. Independently of which radiotracer is examined and which is the molecular target (small molecule, amino-acid, peptide, antibody, aptamer, nanomaterial), the main components for nuclear probes are the radionuclides and the targeting ligands. The development of various radiotracers that were mentioned from preclinical (experimental) phase to clinical use in order to become radiopharmaceuticals encounters a lot of regulatory barriers that must be surpassed. After a comprehensive review of current medical literature, it appears that with the discovery and use of new radiotracers in PET/CT imaging, we have greatly increased the choices we have in overall clinical management of patients with lung cancer. However, in order to prove the above assertion correct, more clinical investigations involving larger patient samples are required.

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ORCID iD

Athanasios S Theodoropoulos https://orcid.org/0000-0002-2036-7462

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