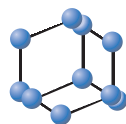
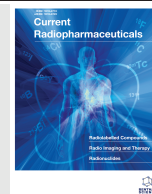


## REVIEW ARTICLE



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SCIENCE**

## Alternative and New Radiopharmaceutical Agents for Lung Cancer



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**Abstract: Background:** FDG PET/CT imaging has an established role in lung cancer (LC) management. Whilst it is a sensitive technique, FDG PET/CT has a limited specificity in the differentiation between LC and benign conditions and is not capable of defining LC heterogeneity since FDG uptake varies between histotypes.

**Objective:** To get an overview of new radiopharmaceuticals for the study of cancer biology features beyond glucose metabolism in LC.

**Methods:** A comprehensive literature review of PubMed/Medline was performed using a combination of the following keywords: “positron emission tomography”, “lung neoplasms”, “non-FDG”, “radiopharmaceuticals”, “tracers”.

**Results:** Evidences suggest that proliferation markers, such as <sup>18</sup>F-Fluorothymidine and <sup>11</sup>C-Methionine, improve LC staging and are useful in evaluating treatment response and progression free survival. <sup>68</sup>Ga-DOTA-peptides are already routinely used in pulmonary neuroendocrine neoplasms (NENs) management and should be firstly performed in suspected NENs. <sup>18</sup>F-Fluoromisonidazole and other radiopharmaceuticals show a promising impact on staging, prognosis assessment and therapy response in LC patients, by visualizing hypoxia and perfusion. Radiolabeled RGD-peptides, targeting angiogenesis, may have a role in LC staging, treatment outcome and therapy. PET radiopharmaceuticals tracing a specific oncogene/signal pathway, such as EGFR or ALK, are gaining interest especially for therapeutic implications. Other PET tracers, like <sup>68</sup>Ga-PSMA-peptides or radiolabeled FAPIs, need more development in LC, though, they are promising for therapy purposes.

**Conclusion:** To date, the employment of most of the described tracers is limited to the experimental field, however, research development may offer innovative opportunities to improve LC staging, characterization, stratification and response assessment in an era of increased personalized therapy.

**Keywords:** Lung cancer, PET/CT, radiopharmaceuticals, non-FDG tracers, tomoscintigraphy, alternative tracers, new radiopharmaceuticals.

### 1. INTRODUCTION

Lung cancer (LC) is the leading cause of cancer-related death worldwide, accounting for nearly 17% of all cancer-related deaths [1]. LC is histologically classified into small-cell lung cancer (SCLC), non-small-cell lung cancer (NSCLC), pulmonary neuroendocrine neoplasms (NENs), and others [2]. Among NSCLC, which is the most common type [3], squamous cell carcinoma (SCC), adenocarcinoma and large-cell carcinoma are included [4].

Positron emission tomography/computed-tomography (PET/CT), as well as conventional chest radiography and

computed tomography (CT), plays an important role in staging, restaging, evaluation of treatment response and prognosis assessment in LC [5]. <sup>18</sup>F-Fluorodeoxyglucose (FDG) is nowadays the most commonly used radiotracer for pulmonary malignancies evaluation. FDG is internalized in the cell by glucose transporters (GLUT-1 and GLUT-3) and phosphorylated by a hexokinase but does not undergo further metabolism in the glucose pathway. FDG is therefore trapped within cells [6]. This uptake is nonspecific for malignancies, which is indeed observed in various conditions, such as infective/inflammatory processes (e.g. pneumonias, abscesses and aspergillosis or granulomatous conditions like sarcoidosis or tuberculosis). Therefore, FDG PET/CT has a high false-positive rate in the staging of pulmonary nodules, especially in those geographic areas with a high prevalence of infectious lung diseases [7]. Furthermore, FDG uptake is

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variable among different LC histotypes: adenocarcinomas are generally less FDG-avid than SCC, while pulmonary NENs, mucinous neoplasms and lepidic predominant adenocarcinomas show low FDG uptake [8, 9]. To investigate other aspects of the pathological lung cancer biology, in addition to glucose metabolism, could be useful in characterizing different tumor histotypes and predicting the response to new targeted therapies against cancer [10]. Recent developments of new radiopharmaceuticals are gaining interest in order to improve the sensitivity and specificity of PET/CT imaging in LC in terms of characterization, treatment stratification and therapeutic monitoring [11]. The main purpose of this article is to review non-FDG PET tracers in LC. A comprehensive literature review of PubMed/Medline was performed using a combination of the following keywords: “positron emission tomography”, “lung neoplasms”, “non-FDG”, “radiopharmaceuticals”, “tracers”. No date limit or language restrictions were applied, and the research included articles published online up through September 2018. A total of 194 records including 18 review articles were identified and the most pertinent articles are discussed herein.

## 2. PET IMAGING OF CELLULAR PROLIFERATION

### 2.1. $^{18}\text{F}$ -Fluorothymidine

$^{18}\text{F}$ -fluorothymidine (FLT) is a thymidine analog in which the 3'-hydroxy group is replaced by  $^{18}\text{F}$ -fluorine. FLT is a marker of cellular proliferation and follows the salvage pathway of thymidine being phosphorylated by thymidine kinase 1 and trapped inside the cell during the S-phase, but not incorporated into DNA [12]. Uncontrolled cell proliferation is a key feature of malignant processes, and FLT uptake in tumor cells correlates with Ki-67 expression in many neoplasms, including NSCLC [13]. Buck *et al.* [14], Tian *et al.* [15], Halter *et al.* [16] and Li *et al.* [17] compared FLT to FDG PET/CT and found that the first is more specific and equally or more accurate in the detection of primitive LC. Furthermore, according to Yang *et al.* [18], FLT is more specific than FDG PET/CT in detecting lung cancer lymph node metastasis. Data from about all these studies show, however, that sensitivity and accuracy in detecting primitive LC and pathologic lymph nodes are lower for FLT than for FDG PET/CT. Trigonis *et al.* [19] found that, across a group of NSCLC patients, radiation therapy induces an early significant lesion FLT uptake decrease, exceeding test-retest variability. Therefore, FLT PET/CT seems to be useful in evaluating treatment response in patients with NSCLC. This was confirmed by Everitt *et al.* [20] who evaluated proliferation during radical chemotherapy in 20 NSCLC patients with both FDG and FLT PET/CT and found that FLT uptake correlates with treatment response better than FDG uptake.

FLT PET/CT has also a prognostic role in NSCLC patients: Kobe and colleagues [21] found that residual FDG uptake measured at different times has a prognostic role in NSCLC patients treated with Erlotinib. Additionally, lower residual FDG and FLT uptake during therapy with Erlotinib is associated with improved progression-free survival.

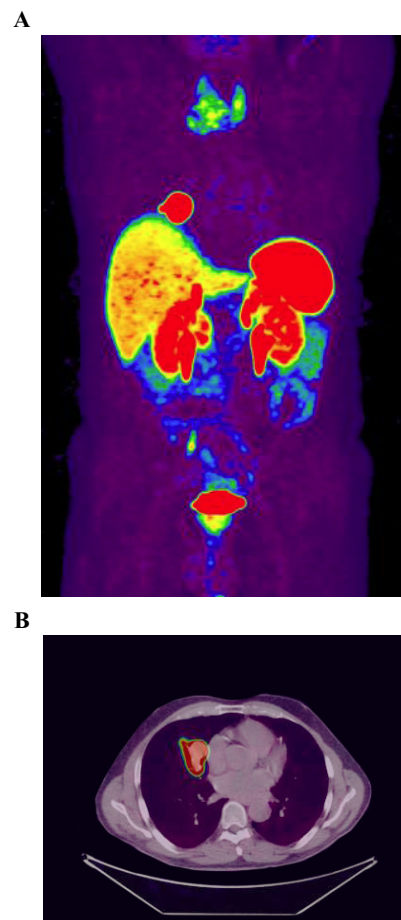
### 2.2. $^{11}\text{C}$ -Methionine

Tumor proliferation leads to an up-regulated protein metabolism.  $^{11}\text{C}$ -Methionine (MET) directly reflects amino acid

transport, being methionine an essential amino acid and an intermediate in phospholipidic biosynthesis. MET doesn't have physiological uptake in the brain, for this reason, it has been used mostly for detecting brain tumors and could be a suitable tracer for investigating brain metastases [22, 23]. MET has a role in differentiating benign and malignant thoracic nodules. Hsieh *et al.* [24] and Sasaki *et al.* [25] found that sensitivity, specificity and accuracy in detecting lung malignancies are higher with MET PET/CT than with FDG PET/CT. Instead Kanegae and colleagues [26], comparing the two radiopharmaceuticals and analyzing their capability of differentiation between LC and benign conditions, concluded that sensitivity is higher for MET PET/CT and accuracy is the same.

### 2.3. $^{11}\text{C}$ -Choline and $^{18}\text{F}$ -Fluorocholine

Choline, as a quaternary ammonium base, is a precursor of cell membrane phospholipids. Cellular membrane construction requires choline transport and acetylcholine production. Choline is phosphorylated and is further incorporated into phosphatidylcholine and metabolized through acetylation [27]. Increased choline metabolism is typical of oncogenesis and tumor growth processes [28].  $^{11}\text{C}$ -Choline (Fig. 1) and  $^{18}\text{F}$ -Fluorocholine are radiopharmaceuticals used



**Fig. (1).** Coronal (A) and axial (B) scans of a  $^{11}\text{C}$ -Choline PET/CT in a patient with biochemical recurrent prostate cancer which highlights the presence of LC. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

to identify neoplastic tissue since an increase in cell proliferation is associated with an increase in choline cellular component. Apart from prostate adenocarcinoma imaging, where it is mostly employed,  $^{11}\text{C}$ -Choline is known to have good performances in other malignancies, such as hepatocellular-carcinoma, glioma, bone tumor, soft-tissue tumors, and lung cancer [29]. Furthermore,  $^{11}\text{C}$ -Choline PET/CT has several advantages over FDG PET/CT: first, fasting is not required before examination, radiation exposure from  $^{11}\text{C}$ -Choline is less than that from  $^{18}\text{F}$ -FDG because the half-life is much shorter, and less time is required for the examination (in Table 1 physical features of the different isotopes). By contrast,  $^{11}\text{C}$ -Choline is not a specific tracer for cancer cells as well as FDG. Granulation processes cells need plenty of choline for cell membrane synthesis. Highly differentiated and low malignant degree neoplasms, such as alveolar cancer, have a low choline metabolism and usually appear as false negatives at  $^{11}\text{C}$ -Choline PET/CT [30, 31]. In addition, some authors demonstrate the advantage of FDG PET/CT over  $^{11}\text{C}$ -Choline PET/CT in the diagnosis of metastatic lymph nodes [32]. On the contrary, according to Hara *et al* [33],  $^{11}\text{C}$ -Choline PET/CT may be superior to FDG PET/CT in the diagnosis of lymph node metastasis. Especially for granulomatous lymph nodes, uptake of choline is increased, due to the exuberant macrophages metabolism.

### 3. PET IMAGING IN PULMONARY NENS

#### 3.1. $^{68}\text{Ga}$ -DOTA Peptides

NENs are a heterogeneous group of malignancies that develop from neuroendocrine cells in different organs, such as lungs. One of the classifications of gastro-enteropancreatic NENs is based on their mitotic count or Ki-67 index, associated with cellular proliferation; while grade refers to the proliferative activity of these malignancies, measured by Ki-67 index or mitotic activity, differentiation refers to the extent of resemblance between tumor cells and their normal counterparts. Well differentiated (grade 1) and moderately differentiated (grade 2) NENs express, respectively a high and moderated density of surface somatostatin receptors (SSTRs), while low differentiated NENs (grade 3) express low densities of SSTRs. Classification of pulmonary NENs, representing 1%-2% of all lung malignancies, include typical carcinoids, well differentiated and with a better prognosis, and atypical carcinoids, low differentiated and with a worst prognosis. The binding mechanism between soma-

tostatin analogs and SSTRs is the base for the theranostic approach that characterizes NENs. In high density SSTRs-NENs  $^{68}\text{Ga}$ -DOTA peptides, (obtained from labeling a synthetic and stable somatostatin analog with a  $\beta$ -emitting radioisotope) bind the SSTRs allowing imaging. Therapy can be performed using a synthetic and stable somatostatin analog linked to a higher  $\beta$ -emitting radioisotope allowing peptide radionuclide receptor therapy (PRRT) [34, 35].

Up to 10% of NSCLC show neuroendocrine differentiation. Compared to FDG,  $^{68}\text{Ga}$ -DOTA-peptides (Fig. 2) are easy to label and synthesize and offer the possibility to image somatostatin receptor expression with direct therapeutic implications [36]. Venkitaraman *et al.* [37] found that  $^{68}\text{Ga}$ -DOTA-TOC PET/CT shows better specificity, sensitivity and accuracy than FDG PET/CT in patients with the suspect of pulmonary NENs. Walker *et al.* [38] confirmed that specificity is higher in  $^{68}\text{Ga}$ -DOTA PET/CT than in FDG PET/CT in the evaluation of indeterminate pulmonary nodules. Li *et al.* [39] found that in a group of NSCLC patients  $^{68}\text{Ga}$ -DOTA-TATE is more specific than FDG and accuracy between the two radiopharmaceuticals does not show significant differences.

$^{68}\text{Ga}$ -somatostatin analogs should be the first choice in the initial evaluation of patients with suspected pulmonary NENs and, in case of negative result, FDG PET/CT could be performed [40]. However, FDG PET/CT is more sensitive for undifferentiated pulmonary NENs. In some cases, performing a dual tracer PET/CT can provide useful information in the management of patients with pulmonary NENs [41].

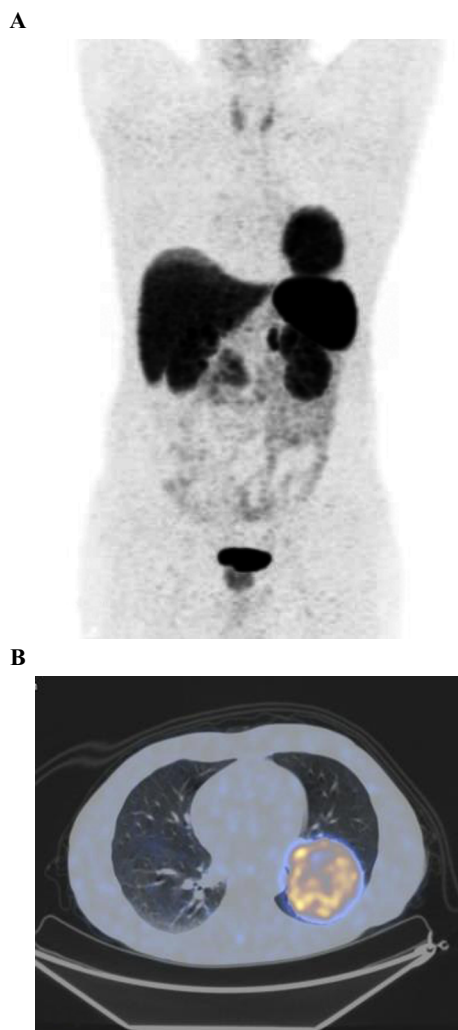
### 4. PET IMAGING OF HYPOXIA

#### 4.1. $^{18}\text{F}$ -Fluoromisonidazole

In malignancies, including NSCLC, hypoxia is associated with resistance to treatment and a poor outcome [42].  $^{18}\text{F}$ -Fluoromisonidazole (FMISO), the most studied hypoxia tracer, enters the cell with low oxygen level by passive diffusion and is trapped after a reduction reaction [43]. Gagel *et al.* [44] found that FMISO PET/CT provides qualitative and quantitative information about hypoxic areas, which may correspond to local recurrences, in NSCLC patients. Furthermore, changes in FMISO PET/CT, in addition to FDG PET/CT, give information about early response to therapy

**Table 1. Physical features of Isotopes discussed in this review [94].**

Isotope	$^{11}\text{C}$	$^{18}\text{F}$	$^{68}\text{Ga}$	$^{64}\text{Cu}$
Half-life	20.4 min	110 min	67.8 min	12.7 h
Branching ( $\beta^+$ ) in %	99.8	96.9	89.1	17.5
E max (MeV)	0.96	0.634	1.899	0.653
E mean (MeV)	0.386	0.25	0.89	0.278
Range mean (mm)	1.2	0.6	2.9	0.7
Pure/non-pure	pure	pure	$\gamma$ 1.077 MeV	$\beta^-$ 34%
Production method	Cyclotron (gas target)	Cyclotron (liquid target)	$^{68}\text{Ge}/^{68}\text{Ga}$ Generator	Cyclotron (solid target)



**Fig. (2).** MIP (A) and axial PET/CT scan (B) of a patient with Typical Pulmonary NEN (Ki67=4%) undergoing  $^{68}\text{Ga}$ -DOTANOC PET/CT for staging. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

and may predict progression free disease, as well as overall survival. Vera *et al.* [45] investigated NSCLC patients with PET/CT using three tracers: FLT, FDG and FMISO performed simultaneously before and during radiotherapy (RT). A significant correlation was observed between FLT and FDG uptake before and during RT, while FDG and FMISO uptake were significantly correlated during RT. A fast decrease in tumor proliferation exists during RT with differences in metabolism and hypoxia. Arvold *et al.* found that FMISO PET/CT detects variations in tumor hypoxia after hypoxia target therapy (with EGFR-tyrosine kinase inhibitors) in EGFR-mutant NSCLC both preclinically and clinically. Whether FMISO PET/CT could be used in imaging for the early evaluation of treatment response after hypoxia-reducing therapies in EGFR-mutant NSCLC remains to be tested in a larger cohort [46].

#### 4.2. $^{64}\text{Cu}$ -Diacetyl-Bis(N4-Methylthiosemicarbazone)

$^{64}\text{Cu}$ -Diacetyl-Bis(N4-methylthiosemicarbazone) (Cu-ATSM) is a promising PET radiopharmaceutical for tumor imaging of hypoxia. Copper has several positron-emitting

radioisotopes, including  $^{64}\text{Cu}$ , which is the most commonly used for its long half-life that allows distant distribution. There are clinical evidences that Cu-ATSM PET/CT is feasible in NSCLC and may play a role as a prognostic marker. One of the advantages of this compound, compared with other hypoxia-avid tracers, is the high tumor-to-background signal offered, which guarantees facilitated tumor delineation [47]. Lopci *et al.* [48] evaluated optimal semi-quantitative and quantitative parameters obtained by Cu-ATSM PET/CT in patients with locally advanced NSCLC and neck cancer and observed that hypoxic tumor volume and hypoxic burden (=hypoxic tumor volume x mean SUV) has a significant correlation to progression free survival. In the study performed by Zhang *et al.* [49] Cu-ATSM PET/CT scans show that evaluating lung neoplasms by visualizing hypoxia and perfusion is a promising technique.

#### 4.3. $^{18}\text{F}$ -Fluoroazomycin Arabinoside

$^{18}\text{F}$ -Fluoroazomycin arabinoside (FAZA) is a nitroimidazole compound which is reduced and trapped within the cell under hypoxic conditions. Compared to FMISO, FAZA shows superior biokinetics and is, thus, a promising PET tracer for the visualization of tumor hypoxia [50]. Di Perri *et al.* [51] studied patients with non resectable LC with FDG and FAZA PET/CT prior and during RT and the radiopharmaceuticals uptake distributions displayed unexpectedly strong similarity. Saga *et al.* [52] demonstrated that in patients with advanced NSCLC, FAZA uptake in lymph nodes is predictive of treatment outcome.

### 5. PET IMAGING OF ANGIOGENESIS

#### 5.1. Radiolabeled Integrin Antagonists

Angiogenesis leads to the creation of new blood vessels and is involved in various pathological processes, including solid tumor growth and metastasis. Integrins are cell adhesion molecules upregulated on activated endothelial cells in association with tumor angiogenesis [53]. Integrin  $\alpha v \beta 3$  represents the most studied protein of the integrins group. The arginine-glycine-aspartic acid (RGD) sequence on ligands allows bindings between integrin  $\alpha v \beta 3$  and extra cellular matrix molecules [54]. PET imaging with radiolabeled RGD-peptides, because of their high affinity and selectivity for integrin  $\alpha v \beta 3$ , is a useful tool for the study of angiogenesis. It has been shown that RGD-peptides labeled with  $^{18}\text{F}$  have a good tumor specificity and are eliminated through urine in a short period [55]. Beer *et al.* [56] investigated  $^{18}\text{F}$ -Galacto-RGD and revealed no significant correlation between FDG SUVs and  $^{18}\text{F}$ -galacto-RGD SUVs in NSCLC patients with primary or metastatic lesions. Zheng and colleagues [57] investigated  $^{68}\text{Ga}$ -labelled RDG tracers in LC and found that  $^{68}\text{Ga}$ -NOTA-PRGD2 PET/CT has a similar diagnostic value for lung malignancies compared to FDG PET/CT and has higher specificity in the diagnosis of lymph node metastasis. A recent effort to label RDG peptides had led to the development of  $^{18}\text{F}$ -AIF-NOTA-PRGD2 ( $^{18}\text{F}$ -alfatide) which is produced with higher purity and with a simpler process than  $^{18}\text{F}$ -labeled RDG peptides.  $^{18}\text{F}$ -alfatide was used as a PET tracer by Luan *et al.* in patients with advanced NSCLC before therapy. They concluded that SUVmax, peakSUV and tumor to tissue ratios are higher in non-responders compared to responders [58].



## 5.2. VEGF Pathway

### 5.2.1. <sup>64</sup>Cu-NOTA-RamAb

The vascular endothelial growth factor (VEGF) is a homodimeric glycoprotein that binds to a VEGF tyrosine kinase receptor and initiates a signaling cascade that mediates endothelial cell migration and proliferation. VEGF pathway inhibitors showed improvements in response, progression free survival and overall survival in NSCLC patients and in patients with other neoplasms [59]. This pathway represents an interesting PET imaging target for angiogenesis [60]. A recent study made by Luo *et al.* gives initial evidence that <sup>64</sup>Cu-NOTA-RamAb can be useful as a PET tracer for imaging of VEGFR-2 expression *in vivo*, which may also find potential applications in monitoring the treatment response of VEGFR-2-targeted cancer therapy [61].

## 6. PET TRACERS FOR TARGETED THERAPIES

### 6.1. Immune Related Radiopharmaceuticals

#### 6.1.1. PDL-1 Checkpoint

Immunotherapy with checkpoint inhibitors, such as anti PDL-1 drugs, represents a new effective treatment option for many tumor types, such as NSCLC. Conventional criteria to assess response can fail in the correct evaluation of immune-related responses. Some patients may show pseudo-progression due to the apparent rise of tumor burden connected to inflammatory cells infiltrating the tumor, and this can lead to early or unnecessary interruption of immunotherapy. The activation of the immune system in responders might determine an early increase of FDG uptake in these patients. FDG is not specific as required in the evaluation of response during immunotherapy. For this reason, immuno-PET/CT can be useful to assess response and to select patients who will undergo immunotherapy [62]. This technique is based on monoclonal antibodies combined with radioactive elements. Most of these radiopharmaceuticals have been tested in preclinical studies and require clinical validation [63-65].

### 6.2. Radiopharmaceuticals for Targeted Molecular Therapy

#### 6.2.1. EGFR Pathway

Targeted biological therapy and molecular characterization are features of modern medicine. Molecular diagnostics are now a fundamental part in the clinical management of various malignancies including NSCLC. LC is categorized by histological subtypes and, in addition, by testing for EGFR mutation, recommended by the 2017 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology [66].

##### 6.2.1.1. <sup>11</sup>C-Erlotinib

The epidermal growth factor receptor (EGFR) is involved in the pathogenesis and progression of different types of carcinoma [67]. In patients with activated EGFR mutation target therapy with tyrosine-kinase inhibitors (TKIs) such as Erlotinib can be considered. Erlotinib inhibits signaling through the EGFR pathway and this kind of treatment

reached a great success [68, 69]. <sup>11</sup>C-Erlotinib is a novel PET tracer targeting the EGFR-TKI signaling pathway. Memon *et al.* showed evidence that this tracer accumulates in NSCLC and in lymph nodes not detected by FDG PET/CT in humans. Furthermore, <sup>11</sup>C-Erlotinib may be useful for the selection of patients suitable for Erlotinib treatment [70]. In literature, there are conflicting results about the correlation between FDG uptake and EGFR mutations [71-73].

##### 6.2.1.2. <sup>11</sup>C-PD153035

Another promising imaging biomarker of EGFR pathway is <sup>11</sup>C-PD153035. It has been shown that this tracer predicts outcomes in chemotherapy refractory patients with advanced NSCLC treated with EGFR-TKIs and may be used to select this kind of patients. Meng *et al.* studied 21 patients with advanced NSCLC nonresponsive to chemotherapy and radiotherapy during and after Erlotinib treatment and concluded that higher baseline SUVmax correlates with longer overall survival and progression free survival. Despite these findings, this tracer was not good for monitoring treatment response [74].

#### 6.2.2. ALK Pathway and <sup>18</sup>F-Fluoroethyl-Ceritinib

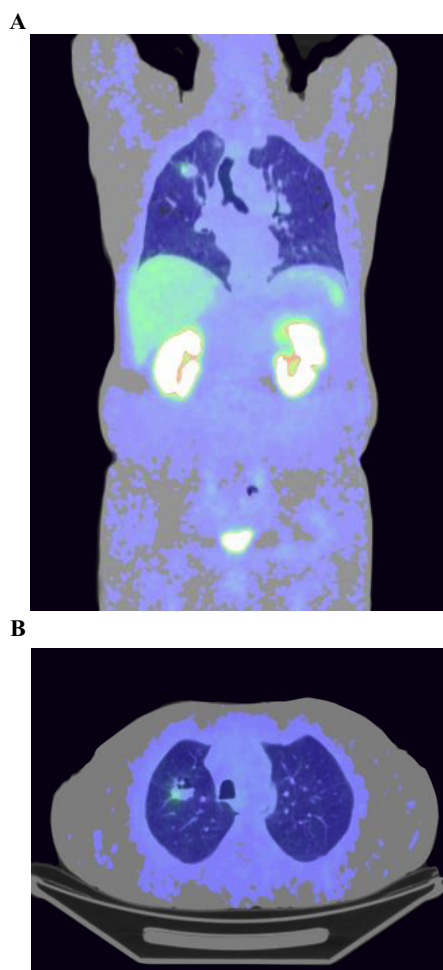
Anaplastic lymphoma kinase (ALK) is an oncogenic receptor tyrosine kinase which belongs to the insulin receptor superfamily. Mutated ALK proteins are involved in the development of various malignant processes like hematologic malignancies and NSCLC [75]. ALK is a therapeutic target in these malignancies. Some of the ALK mutations are linked to better response to ALK-inhibitors like Crizotinib, Ceritinib and Alectinib, whereas, some other mutations are connected to resistance to therapy [76, 77]. Perera *et al.* have synthesized a new tracer called <sup>18</sup>F-fluoroethyl-ceritinib for the study of solid malignancies that overexpress ALK although further *in vitro* and *in vivo* studies are needed to test this potential PET imaging agent. The current lack of diagnostic assays and markers predictive of disease sensitivity to ALK inhibition *in vivo* may limit the ability to properly select patients for clinical trials of drugs targeting the ALK kinase. ALK-specific-radiolabeled-agents-PET could provide enhanced assessment of the relative levels and heterogeneity of ALK protein in tumors and thus hone the selection criteria for the inclusion of patients in redesigned clinical trials [78, 79].

### 6.3. Radiopharmaceuticals for Theranostic Applications

#### 6.3.1. <sup>68</sup>Ga-PSMA Peptides

PSMA is a type II transmembrane protein with glutamate carboxypeptidase/folate hydrolase activity [80]. Human PSMA is composed of a big extracellular domain, a transmembrane part and an intracellular segment. Binding of the PSMA ligand to its anchored-cell membrane target mediates internalization [81]. This leads to enhanced retention of conjugated radionuclides into the cells even in small volume sites of disease, which enables high quality image acquisition for diagnostic procedures and high local dose for therapeutic applications [82]. <sup>68</sup>Ga-PSMA-11 (<sup>68</sup>Ga-PSMA-Glu-urea-Lys-(Ahx)-BED-CC) (GaPSMA) was introduced by the German Cancer Research Centre (Heidelberg, Germany) in May 2011 [83-85]. Since then GaPSMA has been widely

used for prostate cancer imaging. Biodistribution studies on dynamic GaPSMA PET imaging demonstrated sufficiently high radiotracer uptake in tumor lesions as early as five minutes post injection. Lesion-to-background ratios and SUVmax values of primary tumors, lymph nodes and bone malignancies significantly increase over time, mediated by GaPSMA internalization [86, 87]. GaPSMA uptake is high not only in prostate cancer lesions, but also in several other benign and malignant conditions (Fig. 3). Schmidt *et al.* analyzed 275 samples of NSCLC tissue specimens and reported that PSMA tumor cell expression in NSCLC was about 6% and was predominantly found in squamous cell carcinoma, while neovascular PSMA expression was found in 49% of NSCLC [88].



**Fig. (3).** Coronal (A) and axial (B) scans of a biochemical recurrent prostate cancer patient undergoing  $^{68}\text{Ga}$ -PSMA-11 PET/CT with a finding consistent with NSCLC. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Some case reports demonstrated the incidental detection of synchronous primary and metastatic lesions from other malignancies such as LC on imaging being performed for prostate cancer management. However, it is not possible to discriminate prostate cancer lung metastases from primary lung cancers and from inflammatory conditions, neither from a qualitative nor from a semiquantitative point of view [89, 90].

Jochumsen *et al.* reported a case of a man recently diagnosed with prostate cancer who underwent GaPSMA PET/CT which revealed an intense uptake in a lung nodule characterized by no significant uptake to FDG [91].

PSMA overexpression in other malignancies could pave the way potentially to expand the already promising therapeutic application of PSMA-targeted radioligands [92].

### 6.3.2. Radiolabeled FAPIs

Loktev *et al.* developed a DOTA-coupled radiotracer based on a fibroblast activation protein inhibitor (FAPI). Cancer-associated fibroblasts overexpressing FAP and extracellular fibrosis can contribute up to 90% of the gross tumor mass. FAP is overexpressed by cancer-associated fibroblasts of several tumor entities including LC. Biodistribution studies on the first patients demonstrated high uptake of the tracer in malignant tissues and fast body clearance, resulting in promising images and exposure of healthy tissue to radiation similar to other routinely used radiopharmaceuticals.

A comparison with  $^{18}\text{F}$ -FDG in a patient with locally advanced lung adenocarcinoma revealed that FAP ligand was clearly superior. Furthermore, coupling of these molecules to DOTA or other chelators, allows labeling not only with  $^{68}\text{Ga}$  but also with therapeutic isotopes [93].

## CONCLUSION

FDG PET/CT imaging has an established role in staging, restaging, treatment planning and prognosis assessment in LC. Pitfalls may be encountered in cases of infectious/inflammatory diseases, due to the high glucose uptake of inflammatory cells, in the visualization of brain metastasis for the physiologic FDG uptake in brain tissue and in some low FDG-avid LC histotypes, such as NENs, mucinous neoplasms and lepidic predominant adenocarcinoma. New and alternative radiopharmaceutical agents, targeting different aspects of tumor biology, such as proliferation, hypoxia, angiogenesis and a specific oncogene/signal pathway, are gaining interest. On the other hand, some non-FDG tracers (DOTA peptides) are already routinely used in pulmonary NENs management. Concerning the other radiopharmaceuticals described in this review, more development is still needed. Further research and clinical studies are mandatory to improve non-invasive LC management.

## LIST OF ABBREVIATIONS

$^{11}\text{C}$	=	Carbon-11
$^{11}\text{C}$ -PD153035	=	$^{11}\text{C}$ -labeled 4-N-(3-bromoanilino)-6,7-dimethoxyquinazoline
$^{64}\text{Cu}$	=	Curium-64
DOTATATE	=	(DOTA <sup>0</sup> -Tyr <sup>3</sup> ) octreotate
DOTATOC	=	(DOTA <sup>0</sup> -Tyr <sup>3</sup> ) octreotide
$^{18}\text{F}$	=	Fluorodeoxyglucose
$^{68}\text{Ga}$	=	Gallium-68
MIP	=	Maximum Intensity Projection
SUV	=	Standardized Uptake Value

## CONSENT FOR PUBLICATION

Not applicable.

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None.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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