**The role of new PET tracers for lung cancer**

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**Abstract**

18F-fluorodeoxyglucose (18F-FDG) positron emission tomography – computed tomography (PET/CT) is established for characterising indeterminate pulmonary nodules and staging lung cancer where there is curative intent. Whilst a sensitive technique, specificity for characterising lung cancer is limited. There is also recognition that evaluation of other aspects of abnormal cancer biology in addition to glucose metabolism may be more helpful in characterising tumours and predicting response to novel targeted cancer therapeutics. Therefore, efforts have been made to develop and evaluate new radiopharmaceuticals in order to improve the sensitivity and specificity of PET imaging in lung cancer with regards to characterisation, treatment stratification and therapeutic monitoring. 18F-fluorothymidine (18F-FLT) is a marker of cellular proliferation. It shows a lower accumulation in tumours than 18F-FDG as it only accumulates in the cells that are in the S phase of growth and demonstrates a low sensitivity for nodal staging. Its main role is in evaluating treatment response. Methionine is an essential amino acid. 11C-methionine is more specific and sensitive when compared with 18F-FDG in differentiating benign and malignant thoracic nodules. 18F-fluoromisonidazole (18F-FMISO) is used for imaging tumour oxygenation. Tumour response to treatment is significantly related to the level of tumour oxygenation. Angiogenesis is the process by which new blood vessels are formed and is involved in various physiological as well as pathological processes including response to ischaemia, solid tumour growth and metastatic tumour spread. Most clinical studies have focused on targeted integrin PET imaging of which αvβ3 integrin is the most extensively investigated. It is upregulated on activated endothelial cells in association with tumour angiogenesis.These tracers have predominantly been used in the research environment with limited clinical usage thus far. Neuroendocrine tumour tracers, particularly 68Ga-DOTA-peptides do have an established role in PET imaging, including imaging of carcinoid tumours, but these are not specific to lung lesions.

**Introduction**

18F-fluorodeoxyglucose (18F-FDG) positron emission tomography – computed tomography (PET/CT) is now established for characterising indeterminate pulmonary nodules and staging lung cancer where there is curative intent [1-3]. Whilst a sensitive technique, specificity for characterising lung cancer is limited [4]. There is also recognition that evaluation of other aspects of abnormal cancer biology in addition to glucose metabolism may be more helpful in characterising tumours and predicting response to novel targeted cancer therapeutics. Therefore, efforts have been made to develop and evaluate new radiopharmaceuticals in order to improve the sensitivity and specificity of PET imaging in lung cancer with regards to characterisation, treatment stratification and therapeutic monitoring.

**Glucose metabolism in lung cancer**

18F-FDG is the most commonly used tracer in PET imaging, especially within oncology and it has an established role in staging lung malignancy [5-7]. However, the main disadvantage of 18F-FDG is that it is not tumour specific and false positives occur due to inflammation [8], especially from uptake in macrophages [9]. Uptake of 18F-FDG is multifactorial and is influenced by a number of factors, e.g. upregulation of glucose transporter 1 receptors [10,11], the number of viable tumour cells [12], microvessel density and hexokinase expression [13], amongst others. For diagnosis of lung nodules larger than 1cm, the overall sensitivity, specificity, and positive and negative predictive values have been reported as 96%, 78%, 91%, and 92%, respectively [1]. False-negatives can occur in small or well-differentiated malignancies such as adenocarcinoma in situ, carcinoma or carcinoid [1]. 18F-FDG PET/CT is significantly more sensitive and specific than conventional imaging for the detection of mediastinal lymph nodes and distant metastases [2]; it is, therefore, routinely used for preoperative staging. 18F-FDG PET/CT performed at baseline also provides prognostic information and tumour standardised uptake value (SUV) is a predictor of outcome in non-small cell lung cancer (NSCLC) [14]. In multivariate analysis, a preoperative maximum SUV (SUVmax) of 5.5 or higher was found to be an independent predictor of relapse and death in 136 patients with stage 1 lung cancer [15]. 18F-FDG PET is also of value in predicting outcome of induction therapy and it probably also has a predictive value early in the course of first-line therapy in the case of advanced disease, non-specifically reflecting common downstream effects of many cytotoxic and targeted cancer therapeutics [16]. Weber et al. assessed 57 patients with advanced NSCLC before and after the first cycle of platinum-based chemotherapy. There was a close correlation between the change in SUV and the tumour response to chemotherapy using a reduction of 20% in tumour SUVmax as a criterion for metabolic response. In another study [17], 18F-FDG PET was performed before and after neoadjuvant chemotherapy followed by tumour resection. The change in the SUVmax has a near linear relationship to the percent of nonviable tumour cells in the resected tumours. 18F-FDG-PET's SUVmax is better correlated to pathology than the change in size on CT scan (r2 = 0.75, r2 = 0.03, respectively, p < 0.001). When the SUVmax decreased by 80% or more, a complete pathologic response could be predicted with a sensitivity of 90%, specificity of 100%, and accuracy of 96%. A decline in SUVmax of 50% or more was associated with improved survival [18].

**Proliferation in lung cancer**

18F-fluorothymidine (18F-FLT) is a marker of cellular proliferation. 18F-FLT follows the thymidine salvage pathway and is trapped in cells during the S-phase. Its uptake correlates with the activity of thymidine kinase-1 (TK-1), an enzyme that is up-regulated during DNA synthesis and cellular growth [19,20]. 18F-FLT is phosphorylated to 3-fluorothymidine monophosphate by TK-1 but it is then trapped intracellularly and not incorporated into DNA [21].

11C-thymidine was used initially, however, the short half-life (carbon-11 has a half-life of 20 minutes and requires a cyclotron on site for production) and rapid metabolism made it less suitable for routine use. With thymidine tracers there is marked physiological uptake in bone marrow and liver, making these tissues difficult to investigate [22]. Compared with 18F-FDG uptake, 18F-FLT generally shows a lower accumulation in tumours as it only accumulates in the cells that are in the S phase [23]. Its uptake in tumour cells directly correlates with histopathological Ki-67 expression in NSCLC [24,25]. 18F-FLT is a more specific oncological tracer than 18F-FDG and can show a good sensitivity in the detection of primary tumours. However, its main role is in evaluating treatment response.

Buck et al. compared uptake in lung cancer (NSCLC, SCLC and metastases) using both 18F-FDG and 18F-FLT and showed that 18F-FLT uptake was related exclusively to malignant tumours; in contrast 18F-FDG uptake was seen in 4/8 benign lesions [4]. Buck also found that the sensitivity of 18F-FLT for nodal staging was unacceptably low (53%), but as there was no physiological tracer accumulation in the brain, it could be a suitable radiotracer for investigating brain metastases [25] and also suggested that 18F-FLT may be the superior tracer for assessment of therapy response and outcome. In a similar study in 31 patients with NSCLC, Yang et al. reported that the sensitivities of 18F-FLT and 18F-FDG for primary lesions were 74% and 94%, respectively (p=0.003) and 18F-FDG was more sensitive in regional nodal staging [26]. Tian et al. studied dual tracer imaging of pulmonary nodules with 18F-FLT and 18F-FDG in 55 patients and found this to be better than either tracer alone [27]. Each patient was imaged twice using 18F-FDG and 18F-FLT within 7 days. The order of 18F-FDG or 18F-FLT scanning of each patient was determined randomly by a binary code produced by a computer. Within 7 days, the whole procedure was repeated using the alternative radiopharmaceutical. The uptake of a lesion was also scored qualitatively ranging from no uptake to very high uptake. The sensitivity and specificity of 18F-FDG were 87.5% and 58.97% and for 18F-FLT 68.75% and 76.92%, respectively. The combination of dual-tracer PET/CT improved the sensitivity and specificity up to 100% and 89.74%. Sohn et al. studied gefitinib (an EGFR tyrosine kinase inhibitor) response in patients with advanced adenocarcinoma of the lung measuring changes in 18F-FLT uptake and found that activity on day 7 differed significantly between responders and non-responders [28]. Trigonis et al. found that in patients with NSCLC treated with radiotherapy and imaged with 18F-FLT PET, that radiotherapy induced an early significant decrease in tracer uptake, after 5-11 treatment fractions [29]. 18F-FDG has also been used to assess arginine deprivation in patients with ASS1 (Argininosuccinate synthetase 1)-deficient mesothelioma with metabolic responses noted in 46% of patients [30]. More recently, work with 18F-FLT to assess treatment response of NSCLC and mesothelioma with ADI-PEG20 in combination with cisplatin and pemetrexed is encouraging and has shown a significant decrease in tracer uptake at the end of treatment, consistent with human tumour xenograft studies of ADI-PEG20 and the known pharmacology of arginine depletion in ASS1-deficient tumours suggesting that measuring changes in proliferation with 18F-FLT are likely to be more specific than non-specific downstream effects on 18F-FDG [31].

**Amino acid metabolism in lung cancer**

### Methionine is an essential amino acid. Uptake of the tracer 11C-methionine directly reflects amino acid transport (carrier mediated transport processes) and protein metabolism. These processes are known to be upregulated in malignant cells as a consequence of the increased cellular proliferation activity [32]. System L is a Na+-independent amino acid transport agency mediating the cellular uptake of large neutral amino acids. So far, 4 isoforms of system L transporters have been identified: LAT1, LAT2, LAT3, and LAT4. LAT1 is widely expressed in primary human tumours of various tissue origins, including lung cancer [33]. LAT1 is upregulated in malignant tumours, and its expression is associated with tumour proliferation. 11C-methionine has been used as an oncological PET tracer predominantly in brain tumours, as it has an advantage over 18F-FDG in that there is almost no tracer uptake in normal brain tissue allowing good lesion to background contrast. 11C methionine may reduce the number of false-positive findings in inflammatory lung disorders being more specific for malignancy than 18F-FDG. Several papers (from China and Japan, countries where inflammatory lung disorders are prevalent) have looked at the possible diagnostic contribution of 11C-methioinine PET in differentiating benign and malignant thoracic nodules [34]. Kubota et al. [35] and Hsieh et al. [36] reported that 11C-methionine is more specific and sensitive when compared with 18F-FDG. l-3-18F-α-methyl tyrosine (18F-FAMT) has also been developed as a PET radiotracer for tumour amino acid imaging. Clinical studies have demonstrated that 18F-FAMT exhibits higher cancer specificity in peripheral organs than other amino acid PET tracers and 18F-FDG. The accumulation of 18F-FAMT is strongly correlated with the expression of L-type amino acid transporter 1 (LAT1) [33].

### Hypoxia in lung cancer

Tumour hypoxia and oxygen metabolism are important factors in oncology. Tumour response to treatment is significantly related to the level of tumour oxygenation. Intratumoural hypoxia increases radioresistance and chemoresistance, requiring an increase of 2.5 – 3 times the radiotherapy dose to achieve the same biological effect [37,38]. It is also associated with poor clinical outcomes in solid tumours, including lung cancer [39-42].

18F-fluoromisonidazole (18F-FMISO) [43] was the first PET tracer used for imaging tumour oxygenation. It was initially a tracer used in nuclear cardiology for imaging myocardial ischaemia, then subsequently introduced into oncology for imaging several malignancies, such as lung cancer, sarcomas, brain tumours and head and neck cancers [44,45]. 18F-FMISO enters cells by passive diffusion and is thought to undergo metabolism similar to MISO, being reduced by nitroreductase enzymes to form reduction products that bind to intracellular macromolecules when the oxygen tension is less than 10 mmHg and is then trapped intracellularly [46]. It is lipophilic and excreted via the hepatobiliary route with pronounced liver and gut uptake. It does not accumulate in necrotic tissues, as the trapping process requires viable cells with functional nitroreductase enzymes [47]. Limitations include slow tracer accumulation and low tumour-to-background contrast requiring delayed scans to allow background activity to decrease [48]. Parameters used to quantify tumour hypoxia include tumour-to-blood uptake ratio (TBR) at 2 hours after injection using a cut off of 1.2 or 1.4 [49] (although TBR continues to increase up to 6 hours) [50]; standardised uptake value and hypoxic fraction (HF, the fraction of pixels within the imaged tumour volume ) [48].

The use of 18F-FMISO as a hypoxia tracer is supported by several preclinical and clinical studies which have shown moderate correlations between tracer uptake and direct oxygen electrode measurements. Clinical studies have shown 18F-FMISO selectivity in NSCLC but the mechanism for how radiotherapy affects intratumoural oxygenation status remains uncertain and only very weak correlations have been shown between 18F-FMISO and 18F-FDG uptake and so further evaluation is required [51-55]. The feasibility of multi-tracer PET/CT scans performed in a short period of time prior to and during radiotherapy opens the way to a more sophisticated individualisation of NSCLC treatment. Further studies using larger sample sizes and relating findings to patient outcomes are necessary [56].

The presence of a suboptimal signal-to-background ratio led to the development of further hypoxic tracers. These include 18F-fluoroazomycin arabinozide (18F-FAZA). This has better tumour to background ratios and is excreted via the renal route [57,58]. The published clinical studies show that uptake of 18F-FAZA and 18F-FDG differ in NSCLC, confirming that these tracers assess different intratumoural biological processes [48]. Another hypoxia tracer is 18F-FETNIM which is a nitroimidazole and clinical studies have shown the feasibility of 18F-FETNIM PET and its potential as a prognostic marker in NSCLC [48]. 18F-HX4 (3-fluoro-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-1-ol) is a nitroimidazole analogue, however there is relatively little evidence of preclinical or clinical hypoxia specificity and it has not been assessed as a prognostic factor in the clinical setting [48].

The most commonly used hypoxia tracer after 18F-MISO is 64Cu-methylthiosemicarbazone (64Cu-ATSM). This has rapid uptake, an optimal biodistribution, good tumour-to-background image contrast and has demonstrated good prognostic values in different tumours, including lung and cervical cancers [59-62]. Copper has several positron-emitting radioisotopes which can be used. 64Cu is the most often used because its half-life of 12.7 hours is long enough for long-distance distribution. 60Cu (T1/2 24 mins and 62Cu (T1/2 9.7 mins) can also be used. Their short half-lives allow serial imaging sessions within a short time period to assess acute changes in hypoxia, e.g. due to therapeutic intervention. The question as to whether or not Cu-ATSM is a true hypoxic imaging agent remains unanswered as correlative evidence with invasive oxygen measurements is conflicting. The timing of image acquisition is important, as the initial phase of tracer uptake can be perfusion and hypoxia-driven, whereas at later time points uptake is probably more indicative of tumour hypoxia, but later still may reflect trafficking of released copper following metabolism of the tracer. Clinical studies have shown that Cu-ATSM PET is feasible in NSCLC and may play a role as a prognostic marker [48,63-65].

### Angiogenesis in lung cancer

### Angiogenesis is the process by which new blood vessels are formed. It is involved in various physiological as well as pathological processes including wound repair, response to ischaemia, solid tumour growth and metastatic tumour spread. Angiogenesis is a highly-controlled process that is dependent on the intricate balance of both promoting and inhibiting factors and is an important target for cancer therapeutics and hence imaging [66]. PET offers a number of methods to quantify the angiogenic process in tumours, including measurement of tumour blood flow with 15O-water (H215O) or associated macromolecular events, such as integrin expression [67].

### Integrins (a family of cell adhesion molecules), including αvβ3, are upregulated on activated endothelial cells in association with tumour angiogenesis. Integrin αvβ3 binds to a variety of extracellular matrix (ECM) molecules such as fibronectin, fibrinogen, von Willebrand factor, vitronectin, collagen and laminin via the arginine-glycine-aspartic acid (RGD) sequence on ligands. To date, most clinical studies have focused on targeted integrin PET imaging [48] of which αvβ3 integrin is the most extensively investigated imaging target in the integrin family. The first generation RGD peptide tracers were associated with high hepatobiliary and intestinal uptake as these were mainly excreted by the hepatobiliary system. In addition, the aspartic acid residue of RGD was found to be susceptible to degradation. Cyclisation and glycosylation of these cyclic RGD peptides further improved their pharmacokinetics. Second generation peptides, such as RGD-K5, are predominantly excreted by the kidneys with increased uptake and retention in tumours improving their imaging characteristics [68-72].

### RGD peptides can be labelled with 18F, 68Ga or 64Cu for PET imaging. Pre-clinical studies have confirmed that 18F-labelled RGD has good tumour specificity and is rapidly cleared via renal excretion [73,74]. 18F-Galacto-RGD PET uptake correlates with immunohistological staining of αvβ3 integrin. Beer et al. conducted a study comparing the SUV of 18F-Galacto-RGD PET with 18F-FDG PET in NSCLC (n=10) but no correlation was found. (18)F-galacto-RGD PET warrants further evaluation for planning and response evaluation of targeted molecular therapies with antiangiogenic or αvβ3-targeted drugs [75]. Metz et al. performed a prospective study of the spatial relationship of αvβ3 expression, glucose metabolism and perfusion by PET and dynamic contrast-enhanced (DCE) MRI, focusing on tumour heterogeneity. This study included 13 patients with primary or metastasised cancer (NSCLC, n = 9; others, n = 4) [76] and found that simultaneous high uptake of 18F-Galacto-RGD and 18F-FDG also showed higher functional MRI perfusion parameters (initial area under the gadopentetate dimeglumine concentration time curve (IAUGC), as well as the regional blood volume (rBV) and regional blood flow (rBF)) compared to areas with low uptake of both radiotracers. There was higher correlation of 18F-Galacto-RGD uptake with tumour perfusion as determined by dynamic contrast enhanced (DCE)-MRI, compared to 18F-FDG. This is thought to be because glucose metabolism is upregulated in hypoxic cells (which may occur in poorly perfused tumours) [48].

### 18F-AH111585 (Fluciclatide), binds to αvβ3 and αvβ5 integrins with high affinity and in a preclinical study was found to bind to Lewis lung carcinoma and Calu-6 NSCLC xenografts in mice [77]. Attempts at optimising the strategies in labelling peptides with 18F led to the introduction of 18F aluminium fluoride [78] as 18F-Alfatide. In a pilot study including nine patients with lung cancer, 18F-Alfatide allowed identification of all tumours with SUVs of 2.9 ± 0.1 indicating a lower variance in tumour uptake as found by most other studies using RGD-derivatives in patients [66]. Due to increasing availability, in the last few years, 64Cu and 68Ga have become more interesting for labelling of peptides. Thus, a variety of tracers allowing labelling with these isotopes have been introduced. DOTA-conjugated RGD peptide (DOTA-RGDyK) has been labelled with 64Cu [79]. 68Ga NOTA-RGD is the first 68Ga-labeled integrin-targeting compound for which initial clinical data is available. A biodistribution and radiation dosimetry study with 10 patients with lung cancer or lymphoma confirmed the excretion route with the highest activity found in kidneys and urinary bladder [80].

### There is direct activation of the angiogenesis pathway by angiogenic factors, which include vascular endothelial growth factor (VEGF/VEGFR). Manipulation of angiogenesis has been used as a therapeutic strategy in NSCLC, for example, the addition of bevacizumab (Avastin), a humanised monoclonal antibody to VEGF (and hence inhibitor of the angiogenesis pathway) to first-line chemotherapy in advanced NSCLC, demonstrated a 2 month survival benefit compared to doublet chemotherapy alone [81] However, no clinical studies using targeted PET or imaging of VEGF/VEGFR in lung cancer were identified in the literature [48], although there is preclinical data showing the feasibility of VEGFR PET imaging using radiolabelled VEGF12118,63 and VEGF-A64-66 in glioma, breast, ovarian and colon tumour xenografts [82,83].

### The ECM also plays a role in neovascularisation. Matrix metalloproteinases (MMP) are proteolytic enzymes that degrade basement membrane and ECM and enable sprouting of blood vessels. MMP inhibitors have also been investigated as a therapeutic strategy in lung cancer. Marimastat, a synthetic MMP inhibitor, has been investigated in randomised controlled trials in Stage III NSCLC and small cell lung cancer (SCLC), but failed to show any survival benefit with maintenance therapy. PET imaging using MMP-inhibitors has been investigated in the pre-clinical setting although results from in vivo animal studies have not been promising [84-86]

### Another pro-angiogenic factor in the ECM is fibronectin, which is involved in wound healing, cell migration and malignant transformation. The ED-B isoform of fibronectin localises to neovessels in proliferating animal tumour models including SCLC. ED-B has the identical 91 amino acid sequence in mouse, rat and human, thus making direct translation of pre-clinical imaging findings to clinical practice more straightforward .There are, however, no pre-clinical ED-B imaging studies in lung tumour models [48].

### Tracers in Pulmonary Neuroendocrine Tumours

18F-Dihydroxyphenylalanine (18F-DOPA) was first introduced as a marker for imaging dopamine uptake and metabolism in basal ganglia [87]. Afterwards, this tracer was applied for the detection of malignancies such as brain tumours [88] and neural crest derived (neuroendocrine) neoplasms [89] and has proved to be successful in imaging carcinoid tumours [90]. 18F-DOPA is an aromatic amino acid metabolised by the enzyme dihydroxyphenylalanine decarboxylase, which is overproduced in NETs and is therefore dependent on cellular metabolism [91]. 18F-DOPA PET may be used to characterise pulmonary nodules with neuroendocrine components and to evaluate treatment response, but the literature is sparse [92,93].

Neuroendocrine tumours express somatostatin receptors on their cell membrane and thus far, five somatostatin receptor subtypes have been described: SSTR1–5. The SSTR2, SSTR3 and SSTR5 subtypes, in particular, are often over-expressed on the cell membranes of neuroendocrine tumours (on average in 80–90% of cases) [94]. 68Ga-DOTA somatostatin analogues were developed for clinical purposes [95] and up to now several 68Ga-DOTA-peptides have been reported. The majority show a similar affinity for SSTR2 and 5, whereas 68Ga-DOTA-NOC has also demonstrated a high affinity for SSTR3 [96,97]. 68Ga also has a favourable half-life of 68 minutes and is obtained from a generator which can last a number of months rather than requiring a cyclotron. In the literature, 68Ga-DOTA-peptides are reported to be excellent candidates for imaging and staging patients with neuroendocrine tumours, including the localisation of primary tumours in patients with known NET metastasis (carcinoma of unknown primary origin) [98,99]. Sensitivity and specificity are documented as 97-100% and 96-100% in different papers [100,101] and in a large series the diagnostic accuracy was reported to be higher than that of CT. 68-DOTA peptides can be used to characterise pulmonary nodules suspected to have a neuroendocrine basis [91].

## Evolving technology: PET-MR

## PET/MR is an emerging technique in the assessment of lung malignancy. To date, the published literature relates to 18F-FDG PET/MR imaging. A comparison of PET/MR with PET/CT in NSCLC revealed that PET/MR did not provide any additional information compared with PET/CT in a study of 52 patients with proven or suspected NSCLC. Using a fast MR protocol (axial whole body T1 3D dual echo; coronal whole body STIR without breath hold and axial T2 lung during free breathing, using respiratory triggering) with a total acquisition time of 16 minutes, thus keeping the MR acquisition the same length as the PET acquisition does not improve the diagnostic accuracy [102] and does not provide any advantage in thoracic staging in NSCLC patients [103]. Heush et al. found that PET-MR agreed with PET/CT on T stage in all patients. PET/MR and PET/CT were concordant on N stage in 91% with PET/MR correct in 91% whereas PET/-CT was correct in 82%. Hueller et al. found that in T staging, PET/MR missed main bronchus involvement, misjudged size and misinterpreted pleural dissemination as lung metastases. However, MR was particularly helpful for assessing tumour growth into pulmonary veins. In N stage, PET/MR was found to underestimate disease to a greater extent than PET/CT and MR has not gained clinical acceptance for N staging in lung cancer. In terms of M disease, PET/MR missed a sclerotic metastasis, although other studies have indicated that PET/MR detects slightly more bone and liver lesions [104]. PET/CT misses small lesions and those close to regions with high background 18F-FDG uptake. ROC curve analysis showed that PET/MR has a specificity of 92% and a sensitivity of 97% in the determination of resectability with an area under the curve of 0.95 [104]. Hence the role of PET/MR in NSCLC is yet to be established.

**Conclusion**

Whilst 18F-FDG has high sensitivity and an established role in the staging of NSCLC and characterisation of lung nodules, there are a number of other tracers available to investigate different aspects of lung cancer biology that may enable better phenotypic characterisation and treatment response assessment. These include tracers of proliferation, amino acid metabolism, hypoxia and angiogenesis However, these tracers have predominantly been used in the research environment with limited clinical usage thus far. Neuroendocrine tumour tracers do have an established role in PET imaging and these are not specific to lung lesions. New technology with PET/MR has thus far not showed any advantage over conventional PETCT in the imaging of lung malignancy with 18F-FDG but its full potential has not yet been fully tested with other tracers and functional MRI sequences.

In the era of targeted biological therapy and molecular characterisation, more specific non-invasive tumour characterisation and therapy response assessment is evolving with the use of newer non 18F-FDG PET tracers.

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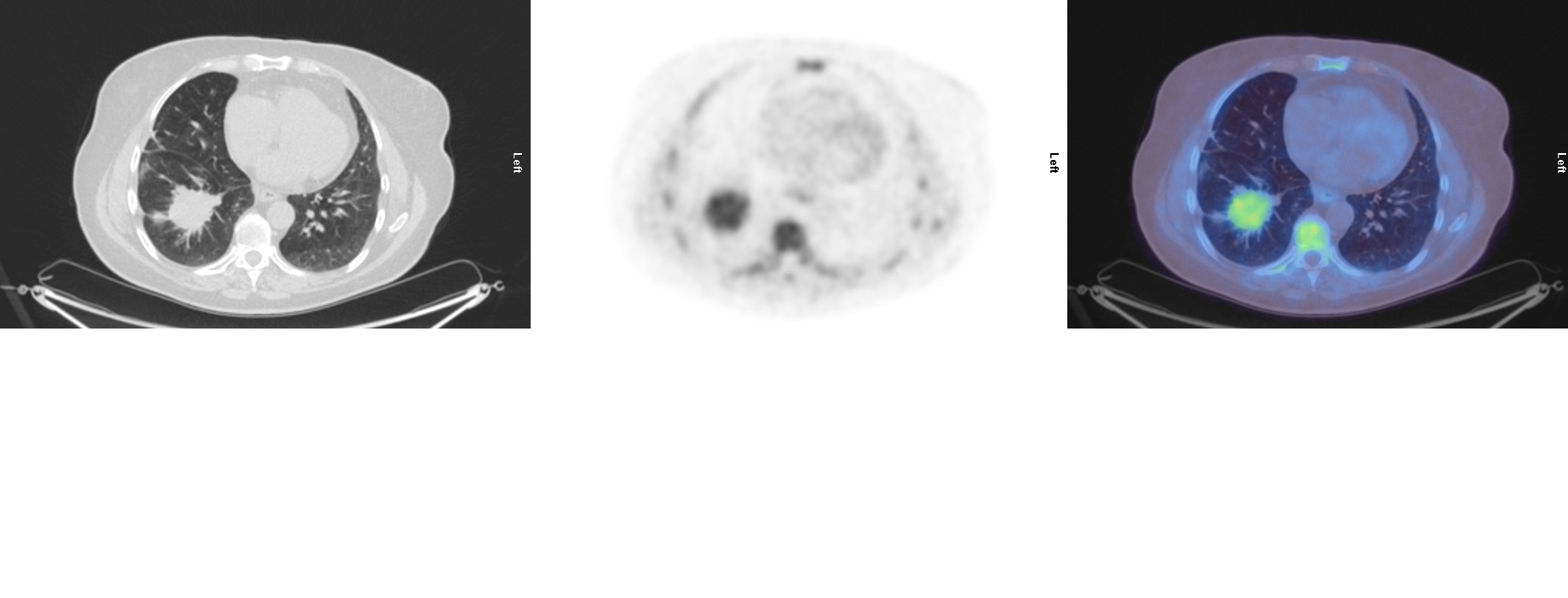
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**Figure Legends**

**Figure 1**

18F-FLT PET/CT: CT (lung windows), PET and fused PET/CT axial images (a) pre and (b) 24 hours post ADI-PEG20 in a 64 year old female patient with NSCLC.

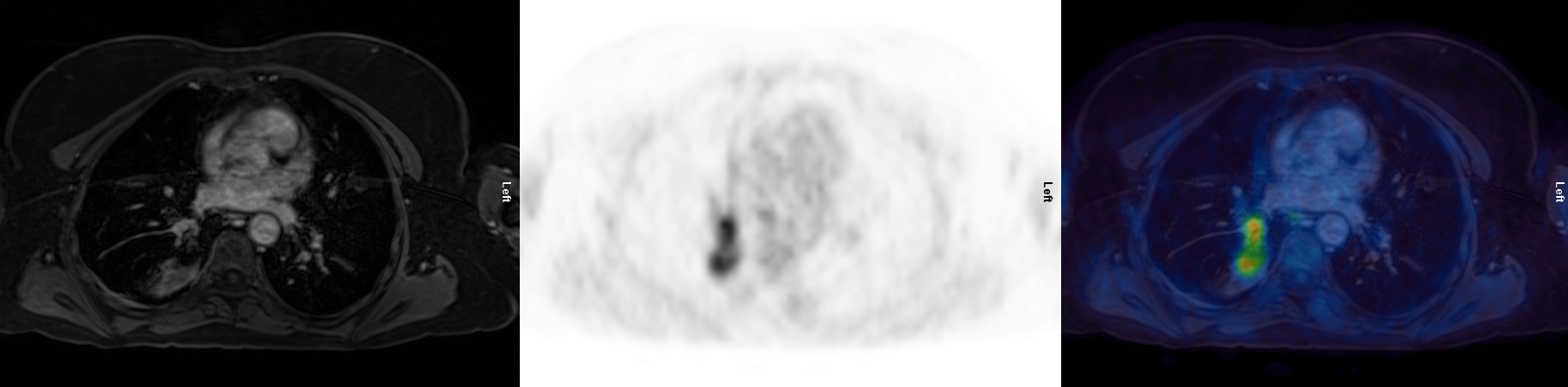
There is a 25% reduction in SUV max (6.4 to 4.8) on the post treatment images in keeping with a partial metabolic response.





**Figure 2**

FDG PET/MR: MR (T1 Caipirinha Vibe Dixon axial sequence), PET and fused axial images of a 62 year old female patient with NSCLC showing increased tracer uptake in the primary tumour in the right lower lobe of the lung.



**Figure 3**

1. 18F FDG axial CT, PET, fused and MIP images of a patient with a lung carcinoid tumour demonstrating only low grade FDG uptake (max SUV=2.4)



1. 68 Gallium dotatate axial CT, PET, fused and MIP images of the same lesion on the same patient demonstrating avid uptake

