

# Image-derived biomarkers and multimodal imaging strategies for lung cancer management

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**Abstract** Non-small-cell lung cancer is the most common type of lung cancer and one of the leading causes of cancer-related death worldwide. For this reason, advances in diagnosis and treatment are urgently needed. With the introduction of new, highly innovative hybrid imaging technologies such as PET/CT, staging and therapy response monitoring in lung cancer patients have substantially evolved. In this review, we discuss the role of FDG PET/CT in the management of lung cancer patients and the importance of new emerging imaging technologies and radiotracer developments on the path to personalized medicine.

**Keywords** Lung cancer · Non-small-cell lung cancer · NSCLC · FDG PET/CT · CT perfusion · VPCT · Hybrid imaging · MRI · PET/MRI

## Introduction

Lung cancer is still the most frequent cancer with an estimated number of cancer-related deaths worldwide of 1.5 million, representing 19 % of all cancer deaths in 2011 [1]. About 80 % of lung cancers are classified as non-small-cell lung cancers (NSCLC) [2] and more than 65 % of these patients present with locally advanced or metastatic disease [3]. The 5-

year survival rate in patients with NSCLC is 17 % [4]. The most prevalent histological type of lung cancer in smokers and nonsmokers is adenocarcinoma at 38.5 %, while the prevalence of squamous cell carcinoma is 23.8 % [5]. Until the turn of the century, advanced lung cancer was treated with platinum-based combination therapy, regardless of the underlying histological subtype [6]. Overall survival has since improved to a median survival of 12 months and longer [7] due to the development of new targeted drugs, consideration of different histological subtypes and driver mutations [8]. Multimodal therapy strategies have further decreased morbidity and mortality with adjuvant and neoadjuvant chemotherapy protocols for patients with resectable tumours [9], and the combination of chemotherapy and radiation instead of radiation alone [10].

In patients with NSCLC and epidermal growth factor receptor (EGFR) mutations, the response rate to the EGFR tyrosine kinase inhibitor erlotinib is 58 %, a dramatic improvement over results achieved with chemotherapy [11]. Mutational profiling in Korean patients with adenocarcinoma revealed mutations of EGFR in 60.5 % [12]. Interestingly, genetic modifications such as EGFR mutations and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) rearrangements are more common in patients who have never smoked [6]. Additionally, new imaging strategies such as endoscopic ultrasonography have improved the accuracy of mediastinal staging [13] and the combination of PET and CT has refined the detection rate of distant metastases and therefore lowered the rate of unnecessary thoracotomies [14, 15]. Thus, multimodal imaging constitutes a key element in the process of staging and therapy response assessment of lung cancer, and additionally, in the era of genome-based specific therapies, the role of image-derived biomarkers and novel tracers has become increasingly important.

In this review, we discuss the role of [<sup>18</sup>F]FDG PET/CT and other advanced imaging technologies such as diffusion-

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weighted MRI, CT perfusion and hybrid PET/MRI in the management of lung cancer patients. Emerging molecular imaging techniques utilizing novel target-specific radiotracers, which bring us one step closer to personalized medicine, are also described.

## FDG PET/CT

### Staging

More than 40 % of patients with NSCLC have metastases at the time of presentation [16]. An accurate staging of the disease with confident detection of distant metastases is therefore of the utmost importance for selection of the most effective therapy [6]. Even though most patients are diagnosed initially by chest radiography or low-dose CT, which might become of importance in lung cancer screening [17], FDG PET/CT plays an important role in the staging of lung cancer. While CT provides high anatomic resolution, the CT criteria for abnormal lymph nodes, such as axial short-axis diameter of  $\geq 1$  cm, abnormal shape and low attenuation, yield a limited sensitivity (51 – 64 %) and specificity (74 – 86 %) [18]. Although PET has a lower spatial resolution than CT, the metabolic information derived from FDG PET allows more accurate detection of lymph node metastases than CT, with a sensitivity of 85 % and a specificity of 90 % [19].

In agreement with others, Lardinois et al. showed that staging is more accurate with integrated PET/CT than with CT alone, PET alone, or visual correlation of PET and CT [20]. Valuable, additional information can be derived from the radiological appearance and location of the primary tumour on the CT part of PET/CT. For example, an adenocarcinoma may present as a solitary, lobulated or irregular pulmonary mass that can invade the pleura or grow circumferentially around the lungs [21]. Furthermore, squamous cell carcinoma is highly associated with smoking and chronic inflammation, therefore two-thirds of these tumours are located in the central to mid-lung zones [21]. The appearance of these endoluminal lesions is often associated with airway obstruction (postobstructive atelectasis or pneumonia) [5]. Moreover, the maximal standardized uptake value ( $SUV_{max}$ ) of FDG in adenocarcinoma with a bronchioloalveolar carcinoma is significantly lower than that of other subtypes of NSCLC [22].

International guidelines for staging and therapy management of lung cancer recommend the PET/CT scan in the routine diagnostic work-up of lung neoplasms. The interdisciplinary guidelines of the German Respiratory Society and the German Cancer Society strongly recommend a whole-body PET/CT scan and head MRI scan in clinical stage IB/IIIB with the intention of curative treatment, even in patients negative on clinical evaluation [23, 24]. The high negative predictive value for distant metastasis has changed the clinical

algorithms to proceed towards surgery without further histological verification. Currently, there is a trend to follow up PET-positive mediastinal lesions using new endoscopic ultrasonography techniques and less-invasive mediastinoscopy [6]. Endoscopic ultrasonography (EUS) and endobronchial ultrasonography (EBUS) have high positive predictive values and are therefore the methods of choice for tissue verification with the advantage of real-time biopsy [25].

### Response monitoring and prediction of prognosis

Traditional tumour response assessment in lung cancer is based on measurements of changes in tumour size using the conventional Response Evaluation Criteria in Solid Tumors (RECIST). These anatomically based methods have significant limitations in response monitoring and prediction, especially in the case of molecular target therapies. There are numerous clinical trials that have shown promising results for therapy response assessment and evaluation of prognosis using FDG PET/CT. Several studies have demonstrated that a metabolic response on PET (documented as a decrease in SUV) is a significant predictor of histopathological response and survival. In addition, the SUV of the primary tumour has been identified as an independent prognostic factor [26–28]. Recently, Machtay et al. showed that higher posttreatment tumour SUVs ( $SUV_{peak}$  or  $SUV_{max}$ ), measured approximately 14 weeks after conventional concurrent platinum-based chemoradiotherapy, are associated with worse survival in stage III NSCLC [29]. Usmanij et al. found that the degree of change in total lesion glycolysis (TLG) is predictive of response to concomitant chemoradiotherapy as early as the end of the second week in patients with locally advanced NSCLC [30].

Early identification of nonresponders could avoid drug side effects and reduce costs associated with unsuccessful therapy. There is some evidence that even after 2 days of erlotinib, assessment of FDG uptake could be useful to identify early resistance in patients [31, 32]. Interestingly, in patients with early-stage NSCLC under neoadjuvant therapy with erlotinib, PET evaluation revealed a metabolic response in 27 %, while CT evaluation using RECIST criteria confirmed a response in only 5 % [33]. Pathological examination following surgery disclosed more than 50 % necrosis in 23 % of these patients and more than 95 % necrosis in 5 % of these patients [34]. These results are in the line with the findings of a current study showing the predictive value of FDG uptake in locally advanced NSCLC, independent of tumour size [34]. In a recently published prospective multicentre study Vera et al. found that assessment of curative-intent radiotherapy or chemoradiotherapy after the 5th week using  $SUV_{max}$  was predictive of disease-free survival after 1 year [35]. The biological basis for the use of FDG uptake for prediction of postsurgical outcome is not yet fully understood. Therefore, Nair et al. analysed FDG uptake and gene expression signatures in

NSCLC [36]. They found four single genes (*LY6E*, *RNF149*, *MCM6*, and *FAP*) that are associated with FDG uptake and survival [36]. In addition, analysis of immunohistochemistry revealed that FDG uptake is significantly associated with glucose transporter 1 (GLUT1), hexokinase I, hypoxia-inducible factor-1 alpha (HIF-1 $\alpha$ ), vascular endothelial growth factor (VEGF), microvessels (CD34), PI3K/Akt/mTOR signalling pathways (p-Akt, p-mTOR) and EGFR, but PTEN expression showed an inverse correlation [37]. Vesselle et al. described an additional, significant positive correlation between FDG uptake and Ki-67 proliferation index [38]. However, tumour size is still the determining factor in FDG uptake rather than overexpression of GLUT1 and GLUT3 [39].

Due to the small number of enrolled patients in most of the clinical trials using FDG PET for therapy assessment, the explanatory power of most of the studies is limited and more multicentre trials are needed. Moreover, exacerbating the problem of low statistical power, trials that utilize PET systems of different generations are not using protocol-optimized imaging for harmonization of SUV evaluation or other FDG uptake parameters (TLG, metabolic rate of glucose) in order to meet the criteria set out in the European Association of Nuclear Medicine (EANM) guidelines for harmonization of quantitative values [40]. It is essential for future prospective studies of high quality to standardize response criteria, imaging time-points, primary targets (primary tumour or lymph nodes) and clinical endpoints (histology, progression-free survival). Due to the increasing economic constraints on the health-care sector, diagnostic methods such as PET/CT have to show a proven clinical benefit to obtain financial reimbursement. Therefore, Vach et al. prepared some guidelines for the evaluation of direct and indirect clinical benefit covering the following six clinical scenarios: replacement of an invasive procedure, improved accuracy of initial diagnosis, improved accuracy of staging for curative versus palliative treatment, improved accuracy of staging for radiation versus chemotherapy, response evaluation, and acceleration of clinical decisions [41].

## Other advanced imaging technologies and biomarkers

### Diffusion-weighted MRI

Diffusion-weighted imaging (DWI) is based on the Brownian motion of water within tissue. In contrast to free diffusion, the diffusion of water within biological tissues is restricted by interactions with cell membranes, cell organelles, macromolecules, fibres etc. Thus, diffusion is limited in most parts of malignant tumours due to increased cellularity which decreases the value of the apparent diffusion coefficient

(ADC). Originally established in brain imaging, adapted DWI techniques allowing acquisition under free breathing paved the way for extracranial whole-body DWI applications [42]. Based on diffusion characteristics it is possible to distinguish malignant and benign lung nodules [43] and also small-cell lung cancer from NSCLC [44]. Besides tissue characterization in primary staging, DWI offers information of value in monitoring therapy response. Overall, therapy success is mainly indicated by increasing ADC values, in some studies only a few days after starting therapy [45]. In contrast, depending on drug and tumour type, an initial decrease in ADC can also be seen [46], and this might be induced by cellular swelling, reduction in blood flow or haemorrhage. These findings indicate that DWI might represent a complex interplay of several processes and strongly depends on treatment and histological tumour type. Moreover, changes over time have to be observed to draw the right conclusions for a dedicated therapy.

### Dynamic contrast-enhanced MRI

Dynamic contrast-enhanced (DCE) MRI is a promising method for tumour characterization and in therapy monitoring. However, several technical aspects have to be taken into account. Although the concentrations of contrast medium normally found in tissue show a linear correlation with the change in spin-lattice relaxation rate, several other factors influence the relationship between contrast medium concentration and signal change in commonly used spoiled gradient echo sequences, including T1 prior to contrast medium injection, flip angle, time of repetition and proton density [47]. Since standard sequences can be used, DCE can easily be integrated in a standard MR protocol. For perfusion quantification, different evaluation methods have been proposed that are mainly based on tracer kinetic models [48]. However, efforts are being made to investigate the role of MRI DCE in therapy monitoring of NSCLC. Chang et al. found distinct changes in perfusion parameters indicating early treatment response to a combined chemotherapy regimen (bevacizumab, gemcitabine, cisplatin) [49].

### Quantitative CT perfusion

Currently, efforts are being made to analyse the benefit of measuring tumour perfusion with functional CT. This technique is based on the exchange of iodinated contrast agents between the intravascular space and the extravascular interstitial space. Other possible technologies for measurement of tumour vascularization include  $^{15}\text{O}$ -labelled water PET and DCE MRI discussed above. In contrast to iodine-containing contrast agents,  $[^{15}\text{O}]\text{H}_2\text{O}$  is an ideal perfusion tracer that is freely diffusible and metabolically inert [50]. In spite of different physical backgrounds a good correlation between CT

perfusion and [ $^{15}\text{O}$ ]H $_2\text{O}$  PET has been demonstrated [51]. CT-based techniques can be easily integrated into a clinical routine setting [52], due to short-duration scans and independence from an on-site cyclotron. To further increase perfusion coverage without increasing detector width, repeated spiral scanning and continuous table movement have been combined [53].

The parameters derived from CT perfusion imaging correlate with tumour angiogenesis as reflected by microvessel density (MVD) and VEGF expression [54]. Results from our own group show that higher MVD is associated with higher blood flow and blood volume values [55]. Regarding the assessment of therapy response, some interesting studies have been performed. Tacelli et al. determined whether CT perfusion can depict early perfusion changes in lung cancer treated with antiangiogenic drugs [56]. They found that patients treated with conventional chemotherapy with bevacizumab had a significant perfusion reduction, in contrast to patients without antiangiogenic treatment [56]. Finally, NSCLC with high perfusion values seems to be more sensitive to chemoradiotherapy than tumours with low values, and CT perfusion parameters are significant predictors of early tumour response and overall survival [57].

### New radiotracers

Tumour cells are usually highly metabolically active and favour a more inefficient anaerobic pathway, a phenomenon called the Warburg effect. To adjust for the increased glucose demands, glucose transporters and hexokinases are often up-regulated, as shown previously. These combined mechanisms allow tumour cells to take up and retain higher levels of FDG than healthy tissues [58]. Because FDG is not cancer-specific and will accumulate in regions with high levels of glucose metabolism and glycolysis, more specific radiotracers are of interest. Besides energy metabolism, there are numerous targets that are specifically upregulated in lung cancer and that could be further elucidated using dedicated radiotracers, including: sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, genome instability, inflammation, evading immune destruction and the tumour microenvironment [59–61]. Blood tests that measure cell-free DNA [62] or anticancer antibodies [63] can be used to diagnose the presence of lung cancer and the cancer subtype, but lack the key benefits of novel radiotracers which provide both spatial and temporal information that is important for guiding further interventional strategies.

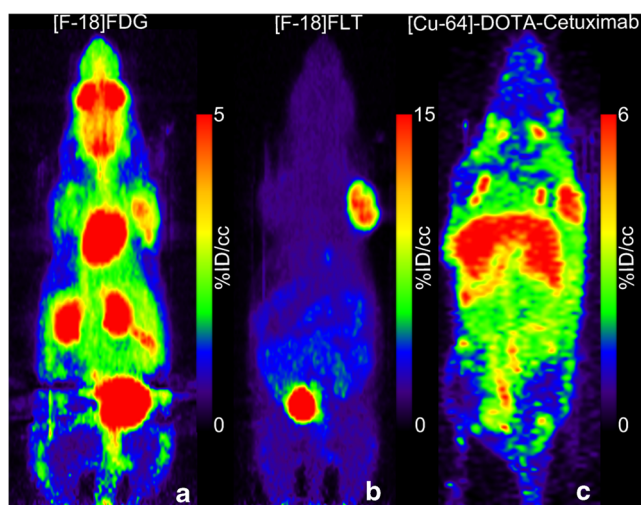
There is some evidence that changes in 3'-deoxy-3'-[ $^{18}\text{F}$ ]fluorothymidine (FLT) uptake during radiotherapy exceed test–retest variability and are predictive of early therapy

response [64]. A direct comparison between FLT and FDG in NSCLC patients treated with erlotinib revealed that FLT uptake also predicted significantly longer progression-free survival, but not overall survival, and was not predictive of nonprogression after 6 weeks of therapy [65, 66]. A recent study has shown that thymidine phosphorylase, a key enzyme in the pyrimidine nucleoside salvage pathway, catalyses the reversible phosphorylation of thymidine [67]. By regulating the levels of endogenous thymidine, thymidine phosphorylase can influence FLT uptake in cancer cells and in patients with NSCLC. While Kaira et al. [37] described a positive correlation between FDG uptake and EGFR expression, Putora et al. [68] found no correlation between SUV and EGFR mutation status in lung adenocarcinomas. Therefore, methods that would enable in vivo monitoring of receptor drug binding and receptor occupancy, determination of the duration of EGFR inhibition and identification of a primary or secondary mutation in EGFR would be of interest [69]. EGFR comprises three regions as possible targets: an extracellular binding domain, a single hydrophobic transmembrane region, and an intracellular domain with tyrosine kinase activity. EGFR-labelled biomarkers are directed either at the external ligand binding domain using antibodies and Affibodies [70] or at the internal ATP binding domain using small reversible and irreversible inhibitors [69].

Recently, small-animal PET and biodistribution studies have shown that [ $^{11}\text{C}$ ]erlotinib shows high uptake in HCC827 tumour-bearing mice [71]. HCC827 lung cancer cells show high expression of EGFR and harbour an in-frame deletion mutation (delE746-A750), in contrast to A549 and NC1358 cells. Irreversible labelled bioprobes such as [ $^{18}\text{F}$ ]ML04 appear to provide clear and elevated signals in tumour tissue with low background activity levels [69]. Also the new tracer [ $^{18}\text{F}$ ]PEG $_6$ -IPQA binds irreversibly with high selectivity to the activated EGFR mutant L858R in NSCLC and might therefore provide additional information as to resistance to gefitinib or erlotinib treatment [72]. For targeting the external binding domain of the EGFR, labelled anti-EGFR monoclonal antibodies such as cetuximab using various radionuclides ( $^{64}\text{Cu}$ ,  $^{88}\text{Y}$ ,  $^{111}\text{In}$ ,  $^{125}\text{I}$ ) have been developed (Fig. 1). These labelled antibodies specifically detect tumours with EGFR overexpression, but often high liver accumulation is present. This limitation can be overcome either by acquiring late images or by adding PEG chains to the conjugating chelators [69]. Affibodies are antibody fragments with a low molecular weight and fast target binding. However, only low to moderate tumour uptake and high kidney uptake limit their range of application.

Overexpression of cell surface antigens in malignant tumours is not only of major interest for detection using immuno-SPECT or immuno-PET. The availability of matched imaging and therapeutic radionuclide pairs, such as  $^{124}\text{I}/^{131}\text{I}$ ,  $^{64}\text{Cu}/^{67}\text{Cu}$  and  $^{86}\text{Y}/^{90}\text{Y}$ , is a very interesting option for





**Fig. 1** Uptake patterns of PET tracers FDG (a), FLT (b) and [ $^{64}\text{Cu}$ ]DOTA-cetuximab (c) visualized as maximum intensity profiles in nude mice bearing EGFR overexpressing NSCLC xenograft tumours in the right shoulder. Increased glycolysis as measured with FDG and tumour cell proliferation measured with FLT have both been attributed to tumour aggressiveness. [ $^{64}\text{Cu}$ ]DOTA-cetuximab shows moderate uptake in the tumour, indicating the presence of EGFR overexpression. EGFR overexpression is linked specifically to hallmarks of cancer such as uncontrolled growth, invasion, angiogenic potential and metastasis development. Although the absolute uptake of [ $^{64}\text{Cu}$ ]DOTA-cetuximab in the tumour is similar to that of [ $^{18}\text{F}$ ]FDG and the specificity to the tumour can't compare to that of [ $^{18}\text{F}$ ]FLT, this radiolabeled anti-body not only reveals the presence of EGFR in the tumour, but can give an indication of drug penetration into the tumour

radioimmunotherapy [73]. One example is a radioimmunotherapy approach that uses the lupus-associated (La)-specific murine monoclonal antibody DAB4 radiolabelled with  $^{177}\text{Lu}$  [74]. Combining [ $^{177}\text{Lu}$ ]DAB4 with polymerase inhibitors and chemotherapy produced a substantial anti-tumour response in a murine Lewis lung (LL2) model. Immunotherapy that aims to stimulate the immune system is another interesting option for lung cancer treatment [75]. In 2011, the US Food and Drug Administration approved ipilimumab for the treatment of metastatic melanoma [76]. Recently, Neumann et al. identified HLA ligands and T-cell epitopes for potential immunotherapy of lung cancer [77]. It is well known that tumour growth often exceeds the vascular supply and this leads to hypoxia and upregulation of angiogenesis [78]. An interesting target for angiogenesis imaging is integrin  $\alpha_v\beta_3$  which has been reported to be a marker of activated, but not resting, vessels. Several markers that are based on the RGD motif, e.g. [ $^{18}\text{F}$ ]galacto-RGD, are under evaluation in NSCLC and other malignancies [79].

The variable blood flow through leaky, immature vessels in the heterogeneous tumour microenvironment in NSCLC causes hypoxia and acidosis [80]. These factors contribute to a reduced therapy response predisposing patients to metastasis [80]. Hypoxia imaging using PET in NSCLC has been assessed using various radiotracers such as 1H-1-(3- $^{18}\text{F}$ )fluoro-2-hydroxypropyl)-2-nitroimidazole ([ $^{18}\text{F}$ ]FMISO), [ $^{64}\text{Cu}$ ]diacetyl-

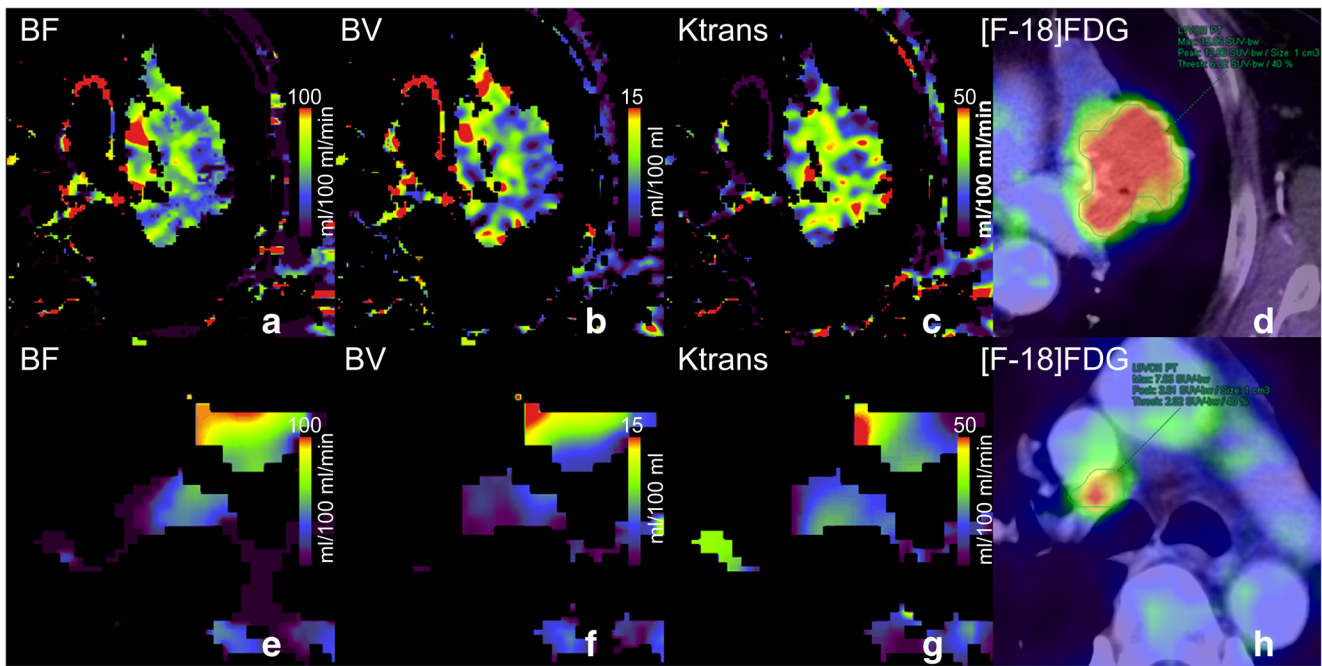
bis(*N*4-methylsemicarbazone ([ $^{64}\text{Cu}$ ]ATSM), 1- $\alpha$ -D-(5-deoxy-5- $^{18}\text{F}$ )fluoroarabinofuranosyl)-2-nitroimidazole ([ $^{18}\text{F}$ ]FAZA), 3- $^{18}\text{F}$ fluoro-2-(4-((2-nitro-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3,-triazol-1-yl)-propan-1-ol ([ $^{18}\text{F}$ ]HX4) and [ $^{18}\text{F}$ ]fluoroerythro-nitroimidazole ([ $^{18}\text{F}$ ]FETNIM) [81]. There is a large variation in the distribution of hypoxia across different lung tumours. Residual tumour hypoxia at the end of treatment seems to be a prognostic marker in regard to response after chemoradiotherapy, and therefore further studies that focus on hypoxia-based radiation dose escalation are needed [82].

Finally, there are some promising new radiotracer developments based on amino acid compounds.  $x_C^-$  is a transporter involved in the cellular uptake of cystine in exchange for intracellular glutamate, and plays a role in growth and progression of cancer and glutathione-based drug resistance. Baek et al. developed a tracer called (4*S*)-4-(3- $^{18}\text{F}$ fluoropropyl)-L-glutamate (BAY 94-9392) that allows assessment of  $x_C^-$  transporter activity with a relatively high cancer detection rate in patients with NSCLC [83]. L-Type amino acid transporter 1 (LAT1) is associated with tumour growth as well as poor outcome, and can be detected using L-[3- $^{18}\text{F}$ ]- $\alpha$ -methyl tyrosine [84]. L-[3- $^{18}\text{F}$ ]- $\alpha$ -Methyl tyrosine seems to be an independent prognostic factor in patients with adenocarcinoma [85].

## Multiparametric imaging

### Hybrid PET/CT

Modern PET/CT scanners provide multifunctional parameters. This is due to the fact that the CT technology has evolved from yielding pure morphology towards more functional information, e.g. provided by CT perfusion as discussed above. Therefore, CT perfusion techniques can be fully integrated into conventional FDG PET/CT studies of lung cancer patients [86]. Results from our own group show that FDG uptake correlates with Ki67, whereas blood flow, blood volume and flow extraction product correlate with MVD [87]. Therefore, these image-derived parameters provide complementary information following noninvasive tumour profiling. This technology also offers the possibility to assess the blood flow–metabolism mismatch that is associated with a poor response to systemic therapy and early relapse or disease progression [88]. Miles et al. were pioneers in this field in NSCLC [89], and we have contributed with new results indicating that this mismatch is dependent on the histological subtype and is more pronounced in squamous cell carcinomas [87]. Possibly due to uncoupling of FDG uptake and perfusion parameters in primary tumours, there is no direct correlation between these two processes [90, 91]. However, in mediastinal lymph nodes in NSCLC patients there is a negative correlation between perfusion parameters and FDG uptake [90] (Fig. 2).



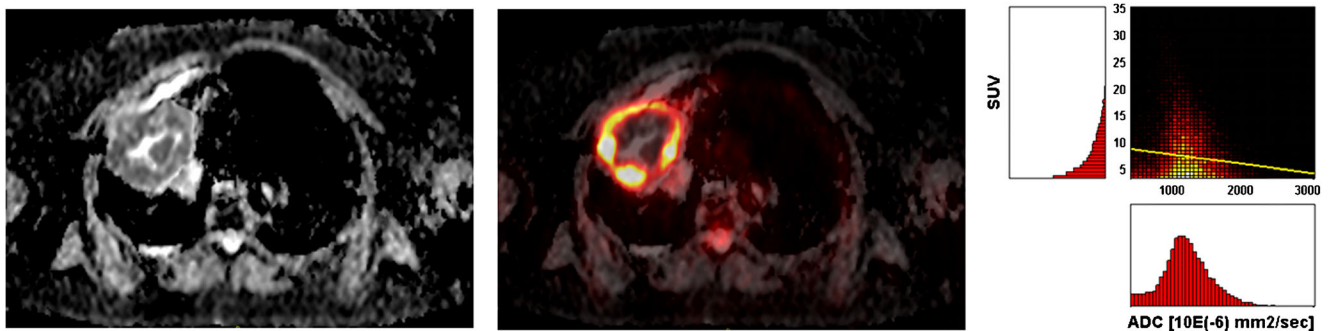
**Fig. 2** Perfusion maps (a–c, e–g) and FDG PET images (d, h) in a patient with a squamous cell carcinoma (a–d) and a patient with a lymph node metastasis of an adenocarcinoma (e–h). The perfusion maps of blood flow (BF a, e), blood volume (BV b, f) and flow extraction product ( $K^{trans}$  c, g) allow noninvasive elucidation of tumour angiogenesis. Compared

with FDG uptake, the tumour perfusion parameters are much more heterogeneously distributed across the tumour and the adjacent atelectasis. The negative correlation between perfusion and FDG uptake in a mediastinal lymph node metastasis is reflected by low BF and BV, while FDG uptake is high

Hybrid PET/MRI

Combined PET/MRI is a new imaging technology that integrates the superior tissue contrast and the functional information derived from MRI with the molecular parameters provided by PET [58]. At the moment, several approaches for the technical integration of the two systems exist, with simultaneous approaches being the most promising [92]. Comparison of whole-body hybrid PET/MRI and PET/CT in pulmonary lesion assessment has revealed similar tumour stages with both imaging systems [93]. However, such a system allows a more dedicated imaging-based tumour characterization, e.g. using DWI and FDG PET [94]. Data from our own group

comparing the  $ADC_{min}$  and  $SUV_{max}$  as measures of cell density and glucose metabolism showed a significant negative correlation ( $r=-0.80, P=0.0006$ ; Fig. 3). There is most probably an association between the measurements of the two methods because of increased cellularity and glucose metabolism of FDG-avid pulmonary lesions. Ohno et al. investigated the role of DWI and FDG PET in predicting tumour response in patients with NSCLC under chemotherapy, and found that ADC is superior to FDG PET [95]. These findings underline the complementary nature of DWI and FDG PET. It is not clear which parameters are complementary and which parameters can be omitted due to redundant information when dealing with multiparametric imaging.



**Fig. 3** PET/MR scan of ADC map (left) and superimposed ADC map and FDG PET image (middle) in a 60-year-old female patient with a necrotic bronchial carcinoma of the right lung (squamous cell carcinoma). Right Two-dimensional histogrammed voxel-wise scatterplot of SUV (y

axis) and ADC (x axis). The yellow line is the linear regression line. Note the discrepant behaviour of ADC and SUV at the inner rim of the tumour with low ADC and SUV. This example indicates the complementary nature of diffusivity and glycolysis

## Radiogenomics

One forward-looking approach for the identification of new prognostic imaging biomarkers is the integration of medical images with high-throughput molecular technologies such as metabolomics and genomics, as well as survival data in public gene expression datasets. This technology is summarized under the term radiogenomics. Gevaert et al. have described a special multistep strategy that may identify new biomarkers when long-term clinical outcomes are not immediately available [96]. This strategy involves integration of CT and PET images and gene microarray data from the study cohort, mapping of the metagenes to publicly available microarray data with survival, and linking of image features expressed in terms of metagenes to public gene expression data. The authors found several interesting associations, e.g. the presence of an internal air bronchogram is related to the overexpression of KRAS and its targets, but only in adenocarcinoma. The image features predicted all 56 metagenes with a mean accuracy of 72 %.

## Outlook

The development and use of new imaging biomarkers is still limited because of issues involving insurance coverage, health regulation aspects, and health-care policies. Given the fact that the cost of imaging procedures are only a fraction of the cost of therapy, new concepts need to be implemented. As shown in this review, imaging is an integral part of staging and therapy response assessment in lung cancer as it can document and objectify treatment strategies. New personalized therapy concepts will therefore profit from more refined imaging techniques offering noninvasive biomarkers.

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**Conflicts of interest** None.

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