PET Imaging-Based Phenotyping as a Predictive Biomarker of Response to Tyrosine Kinase Inhibitor Therapy in Non-small Cell Lung Cancer: Are We There Yet?

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Abstract The increased understanding of the molecular pathology of different malignancies, especially lung cancer, has directed investigational efforts to center on the identification of different molecular targets and on the development of targeted therapies against these targets. A good representative is the epidermal growth factor receptor (EGFR); a major driver of non-small cell lung cancer tumorigenesis. Today, tumor growth inhibition is possible after treating lung tumors expressing somatic mutations of the EGFR gene with tyrosine kinase inhibitors (TKI). This opened the doors to biomarker-directed precision or personalized treatments for lung cancer patients. The success of these targeted anticancer therapies depends in part on being able to identify biomarkers and their patho-molecular make-up in order to select patients that could respond to specific therapeutic agents. While the identification of reliable biomarkers is crucial to predict response to treatment before it begins, it is also essential to be able to monitor treatment early during therapy to avoid the toxicity and morbidity of futile treatment in non-responding patients. In this context, we share our perspective on the role of PET imaging-based phenotyping in the personalized care of lung cancer patients to non-invasively direct and monitor the treatment efficacy of TKIs in clinical practice.

Keywords EGFR · Erlotinib · Lung cancer · Molecular targeted therapy · Precision medicine · Positron emission tomography

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In today's era of precision medicine the success of targeted anticancer therapies depends in part on being able to identify biomarkers and their patho-molecular make-up in order to select patients that could respond to specific therapeutic agents. While the identification of these biomarkers is crucial to predict response to treatment before it begins, it is also essential to be able to monitor treatment early during therapy in order to avoid the toxicity and morbidity of futile treatment in non-responding patients.

Clinical evidence and experience have confirmed that ¹⁸F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) imaging is a superior clinical tool for the diagnosis, staging, and restaging of lung cancer patients treated with cytotoxic therapy and radiotherapy. Preliminary data is now available on its promising clinical value to monitor the success of cytostatic therapies in the lung cancer patient.

In this context, we share our perspective on today's role and contribution of PET molecular imaging-based phenotyping to the personalized care of lung cancer patients to non-invasively predict and monitor treatment efficacy of tyrosine kinase inhibitors in daily clinical practice.

Biomarker-Directed Precision Medicine in Lung Cancer

Precision medicine has emerged as a novel approach to treatment and prevention of disease based on the recognition that when dealing with the pathobiology of malignant disease, the whole is certainly more than the sum of its parts. The clinical management of the cancer patient is shifting toward the use of targeted treatments directed to the molecular makeup of the malignant entity affecting the patient. This approach takes into consideration the morphological and functional heterogeneity

that exists in the molecular pathogenesis of lung cancer, not only at the level of the primary tumor but also in its systemic metastases [1]. In addition, as a function of time the malignant molecular phenotype may take control of its capacity to become resistant to cancer treatments [2, 3].

This is the reason why today the practice of clinical oncology relies on characterizing malignancies by studying and acting upon the intrinsic relationships that exist between cell biology and genomics, the processes that drive the ability of cancer cells to proliferate, their expression of oncogenes, gene mutations, and their metabolic state, all of which are responsible for the tumor's aggressive phenotype.

The increased understanding of the molecular pathology of different malignancies, especially lung cancer, has directed investigational efforts to center on the identification of different molecular targets and on the development of targeted therapies against these targets. A good representative is the epidermal growth factor receptor (EGFR); a major driver of non-small cell lung cancer (NSCLC) tumorigenesis.

The EGFR is a transmembrane tyrosine kinase glycoprotein receptor found in epithelial cells that belongs to the human epidermal growth factor family of receptors. It is expressed in a substantial percentage of NSCLCs, and its expression is correlated with poor prognosis [4]. The members of the EGFR tyrosine kinase family include EGFR or HER-1 or (ErbB-1); HER-2/neu or (ErbB-2); HER-3 or (ErbB-3), and HER-4 or (ErbB-4). Once the EGFR in the cancer cell comes in contact with its growth factor (EGF), the receptor becomes activated leading to the formation of homo- and heterodimers with other receptor subtypes. Activation triggers the autophosphorylation of the EGFR tyrosine kinase pathway and downstream signaling responsible for gene transcription, followed by cellular events that culminate on tumor growth and aggressiveness as a result of increased cell proliferation, inhibition of apoptosis, increased angiogenesis, and the acquisition of a higher ability to invade and metastasize.

Activating mutations of the EGFR gene kinase domain are not uncommon and are well known today [5]. In general, higher mutation frequency is observed in women, non-smokers, and in non-mucinous cell types [e.g., lepidic pattern adenocarcinoma in situ (former bronchioloalveolar carcinoma)]. Eighty-five percent of these mutations are found in the intracellular domain, and include those in exon 18 (G719X), the exon 19 deletion, which is more common in Europeans, the exon 21 point mutation (L858R), and less common is the insertion in exon 20. The prevalence of these mutations in adenocarcinomas is higher in Asians than in Caucasians. On the other hand, 2–7 deletions are more commonly found in the extracellular domain of tumors of the squamous cell type [5].

The EGFR gene can also be amplified. This amplification is associated with disease progression, and may be shared with mutation and be distributed heterogeneously in some tumors. Unfortunately, the interaction between EGFR mutations and

amplification in lung cancer remains unclear as of today. Sholl and colleagues demonstrated that EGFR-amplified adenocarcinomas have specific genetic alterations, clinico-pathologic features, and bad prognosis. These findings have important treatment efficacy implications when using tyrosine kinase inhibitors (TKI) to treat patients with EGFR-mutant lung adenocarcinomas [6].

In 2004, Paez and colleagues, as well as Lynch et al., showed that tumor growth inhibition was possible after treating lung tumors expressing somatic mutations of the EGFR gene with TKI [5, 7].

These discoveries opened the doors to biomarker-directed personalized treatments for lung cancer patients. Daily clinical management today leverages on the knowledge of the molecular biology of lung neoplasia that we have accrued in recent years. This is due to the availability of therapies that are directed toward specific molecular targets in the lung cancer cell. These targeted therapies block key biological tumoral pathways and are less toxic to normal tissues [8].

Amongst these molecular-targeted therapies are TKIs like erlotinib, gefitinib, and afatinib [9]. These TKIs bind to the adenosine triphosphate binding cassette of the mutated EGFR kinase domain and inhibit phosphor-transfer downstream blocking the signaling pathway.

Response rates to these drugs tend to be higher in never smokers, in females, in East Asians, and in patients with adenocarcinoma and bronchioloalveolar carcinoma. Favorable responses are mostly observed in tumors harboring mutations in the tyrosine kinase domain of the EGFR in the absence of K-RAS mutations. While there is a significant association between exon 19 and 21 mutations with favorable response to TKIs, exon 18 and 20 mutations are less responsive [9].

On the other hand, the presence of T790 mutations of the EGFR gene is associated with resistance and found to be present in approximately 50 % of patients with disease progression. T790 mutations inhibit the binding of TKIs which prevents receptor blockade. The occurrence of T790M is usually associated with previous TKI treatment, but can be present in the tumor cells before therapy. The use of the Afatinib has shown promising results in tumors harboring resistant mutations, and these exciting results definitely call for further confirmation in controlled, randomized trials [10].

The success of TKIs on their lung cancer targets opened the doors to additional investigations in search of other drivers of oncogenic mutations as therapeutic targets. This led to the identification of a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene, and the anaplastic lymphoma kinase (ALK) gene in NSCLC, highly responsive to treatment with crizotinib, a TKI that inhibits c-MET and ALK [11].

In the United States TKIs are considered effective as front line therapy in patients with inoperable NSCLC harboring EGFR-activating mutations. Amongst them, Erlotinib is also

authorized after failure of previous chemotherapy. TKIs are also recommended as maintenance therapy in patients with metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

PET Imaging-Based Phenotyping to Predict and Monitor the Efficacy of Targeted Treatment for the Lung Cancer Patient

It is now common knowledge that the presence of alterations in gene expression and mutations in cancer driver genes can significantly affect response to treatment and clinical outcomes. One of the major challenges faced in the clinic today is the inability to non-invasively identify cancers that will respond to therapy, thus exposing patients to the risks of ineffective, futile treatments.

As we stated previously, the success of targeted anticancer therapy depends in part on the identification of biomarkers in order to select future responders to specific therapeutic agents. It would be ideal to be able to identify non-invasively EGFR gene amplifications and/or mutations within an individual's lung tumor in order to select the best targeted treatment regimen for a particular patient. The identification of these biomarkers is essential not only to predict response to treatment before it begins, but also to monitor treatment early during therapy to avoid futile therapy in non-responding patients.

PET imaging-based phenotyping refers to the ability of this imaging technique to portray the interface and relationship between molecular imaging and pathology in an attempt: 1) to identify correlations and understand their meaning between tumor pathobiology and in-vivo molecular imaging patterns; 2) to find and characterize the observed molecular imaging signatures that relate to the non-invasive diagnosis, prediction, and prognostication of human disease, and last but not least, 3) to study and understand the pathobiologic, anatomic-metabolic, prognostic, and therapeutic dimensions of these molecular imaging-based phenotypes. Thus, in the context of this perspective, the main goal of imaging-based phenotyping would be to elucidate the image signatures that represent the pathogenic, genetic, temporal, and compartmental heterogeneity of the lung cancer phenotype in an attempt to predict, direct, and assess the efficacy of its personalized treatment.

Molecular imaging techniques such as PET are capable of characterizing in-vivo many of the heterogeneous signatures of the cancer cell phenotype. PET-based molecular probes are available today to interrogate non-invasively tumoral glycolytic activity, hypoxia, cellular proliferation, amino acid transport, receptor expression, and apoptosis, amongst other pathomolecular processes [12].

Otto Warburg described abnormally high glucose consumption as a decisive driver of aggressiveness of the cancer cell [13, 14]. Cancer cells use glucose anaerobically under

aerobic conditions leading to the production of lactic acid, rather than relying on the efficiency of the tricarboxylic acid cycle of oxidative phosphorylation to produce ATP in the mitochondria [15]. Increased glucose consumption by cancer cells is also associated with overexpression and increased activity of glucose transporters, hexokinase and hypoxia selection and adaptation [16].

FDG is used in the clinic to evaluate glucose metabolism in many cancer types. The basis for the use of PET with FDG is the increased glucose consumption by cancer cells compared to normal tissues. In addition, pathologic changes in tissue metabolism that precede those in tumor size are well characterized by FDG-PET/CT. Today, FDG-PET and FDG-PET/CT are considered almost indispensable techniques for the management of lung cancer patients. Its success in clinical practice is based on the fact that information on lesion morphology provided by CT is related to its biological significance in the PET images. This leads to greater confidence during image interpretation when compared to either modality alone. Today the molecular imaging community agrees that FDG-PET/CT imaging is a superior clinical tool to accurately assess the tumor anatomic-metabolic phenotype during diagnosis, and initial and subsequent treatment strategy of the lung cancer patient treated with cytotoxic therapy.

Yet, what have we learned so far about the ability of PET imaging-based phenotyping to predict the success of targeted therapies in lung cancer patients? Can these molecular imaging-based phenotypes be used to identify non-invasively gene amplifications and/or mutations in lung tumors?

PET Imaging-Based Phenotyping as a Predictor of EGFR Amplification

FDG uptake in malignancies in general, and in lung cancer in particular, is a function of the number of cancer cells, their degree of differentiation, capacity to proliferate, and the cellular expression and activity of the rate limiting steps of FDG uptake, mainly GLUT receptors and hexokinase, all of which have been correlated with poor prognosis. The value of the intensity of FDG uptake in lung cancer as a biomarker of histologic grade and prognosis rests on the ability to stratify patients that are at high risk of fast disease progression and relapse, regardless of their clinical stage at diagnosis [17–21]. This information is quite helpful when attempting to personalize therapy in order to decide if post-surgical adjuvant chemotherapy could be of benefit in early stage lung cancer patients with highly FDG avid tumors.

Highly metabolic tumors are more aggressive and drivers of poor clinical outcomes. For the most part, this statement holds true across different stages and histologic types of lung cancer. While an optimal SUV cut off value remains to be

defined, investigators have used a wide range of primary tumor SUVmax values, as low as 2.5 to as high as 21, to stratify histologic grade and survival in lung cancer patients [17–21].

We have already discussed that the EGFR gene can be amplified in lung cancer. This amplification is associated with disease progression, and can be distributed heterogeneously in some tumors [22]. This brings us to our next question:

Is the Intensity of FDG Tumor Uptake a Reliable Predictor of Tumor EGFR Amplification?

Park and colleagues studied the relationship between PET imaging features and EGFR gene copy number in lung cancer [23]. The investigators retrospectively analyzed CT, FDG-PET, and histopathology data in 132 patients with surgically resected lung adenocarcinomas [23]. They evaluated and correlated different tumor characteristics in their patient cohort, to include tumor features on preoperative chest CT, such as the proportion of ground glass opacity (GGO), tumor diameters, and cavitation, tumor SUVmax from FDG-PET/CT images, and histologic type and degrees of cellular differentiation. The authors assessed EGFR gene copy number status using fluorescence in situ hybridization (FISH) and found EGFR gene amplification in the tumors of 53 patients (40.2 %). EGFR gene amplification was found to be more frequent in tumors with higher FDG uptake ($P = 0.0008$) and with lower proportion of GGO ($P = 0.01$). The significant difference in SUVmax between amplified and non-amplified tumors held steady even in Stage I cancers. A tumor SUVmax higher than 7 was found to be an independent predictor of lung cancer EGFR gene amplification status (odds ratio, 3.941; 95 % CI, 1.691–9.182; $P = 0.01$). When correlated with CT and pathologic findings, non-amplified EGFR was more frequent in tumors with a GGO proportion higher than 50 % ($P = 0.023$), a tumor diameter smaller than 15.5 mm on CT ($P = 0.006$), and well-differentiated histopathology ($P = 0.002$). The investigators clarified that no specific histologic subtype was found to have a significantly higher prevalence of EGFR gene amplification ($P > 0.05$). While the proportion of GGO increased, the frequency of gene amplification decreased ($P = 0.01$), and the presence of cavitation showed no statistical difference between the gene amplification and non-amplification groups.

More imaging studies are definitely needed to corroborate the findings reported by Park and co-investigators, and the endpoint of these studies should be expanded to include the value of PET imaging-based phenotyping of receptor amplification to stratify progression-free and overall survival of lung cancer patients.

PET Imaging-Based Phenotyping as a Predictor of EGFR Mutation Status

Is the Intensity of FDG Tumor Uptake a Predictor of Tumor EGFR Mutation Status?

At the time of this writing 12 studies had compared the intensity of FDG uptake in primary lung tumors with mutated versus wild-type EGFR genotypes, and the results are variable [24–35]. Nine of these studies found that lung cancers harboring the mutated EGFR tend to be less FDG avid than those in which the receptor is not mutated, regardless of whether the difference was found to be significant or not [24, 26–28, 30–32, 34, 35]. Two studies showed higher FDG uptake in mutated tumors; in one such difference was significant ($n = 77$ patients) [25], while in the other in which significance was not reached the sample size was small ($n = 14$ patients) [29]. Interestingly, there is also one study addressing the difference in FDG uptake between mutated and wild-type metastases [33]. Lee and colleagues reported a significant association between EGFR mutation status and FDG uptake in metastatic lesions of 71 patients with stage IV adenocarcinoma [33]. They observed lower FDG uptake in mutated lung cancer metastasis, and indicated that the metastatic SUVmax was an independent predictor of mutation status. On the other hand, the investigators could not find a statistical significant difference in primary tumors' SUVmax between EGFR-mutant and EGFR wild-type adenocarcinomas. It would be interesting to see whether their results can be reproduced in prospective studies that also attempt to explain the mechanisms responsible for the reported incongruence between metastatic and primary tumor uptake as a predictor of EGFR mutation status.

Why Do Tumors Harboring EGFR Mutations Tend to be Less FDG Avid?

As described previously, the EGFR receptor once activated homodimerizes or heterodimerizes with other members of the ErbB family of receptors giving place to downstream cell growth, proliferation, and survival signals. In parallel, EGFR also facilitates glucose transport independent of its kinase activity in order to prevent autophagic tumor cell death. Glucose transport in this case occurs after the activated EGFR binds to the sodium symporter receptor, SGLT1. This process stabilizes the SGLT1 expression in the tumor cell leading to glucose uptake irrespective of the extracellular glucose levels, thereby maintaining sufficient levels of intracellular ATP through glycolysis to prevent the tumor cells from dying [36]. FDG uptake in tumor cells on the other hand, mainly depends on the facilitated transport mediated by GLUT receptors as opposed to SGLT. This in part could explain the observation that some lung cancers with mutated EGFR tend to be

less FDG avid. It is important to keep in mind that EGFR receptor mutation (usually consistent with lower FDG avidity) and amplification (consistent with higher FDG avidity) may coexist in the cancer cell, phenomenon that may have an effect on the absolute degree of tumor FDG avidity at any time point. This could also contribute to the discrepancy in the results reported by different investigators studying the degree of FDG uptake in mutated tumors.

The reality is that what is actually relevant in the clinic is whether the intensity of tumor FDG uptake is in fact a non-invasive independent predictor of activated EGFR mutations in patients with lung cancer. The truth is that as of today, the evidence is scarce and variable, making it difficult to arrive at definite conclusions in this regard. While in the studies by Na et al. [24] ($n = 100$; 21 mutated) and Mak and colleagues [26] ($n = 100$; 24 mutated), a low SUV remained an independent predictor of tumoral EGFR mutations, Lee and co-investigators [32] who studied the largest cohort to date ($n = 206$; 47 mutated) did not find tumoral FDG uptake to be an independent predictor of mutation status in their cohort.

While in general lung cancers harboring the mutated EGFR tend to be less FDG avid, there still is significant overlap with the intensity of uptake observed in wild-type tumors. Thus, FDG-PET imaging-based phenotype of uptake cannot be used to replace tissue mutation analysis in the clinical setting. Therefore, genotyping for the presence or absence of relevant mutations still remains the gold standard for the overall clinical decision to use targeted therapy in lung cancer patients.

PET Imaging-Based Phenotyping of Targeted Treatment Efficacy in Lung Cancer

Is the Change in PET Probe Uptake During Therapy an Early Predictor of Response to TKIs?

Today FDG-PET/CT plays a decisive role in the subsequent treatment strategy of lung cancer patients. PET/CT is used clinically to assess the morphologic-metabolic phenotype of tumoral response to cytotoxic cancer therapies as well as to radiotherapy, and to characterize locoregional and systemic recurrent disease following treatment.

The stage and the histologic type of lung cancer dictate its treatment options. Depending on disease extent at presentation, treatment may include surgery, neoadjuvant and adjuvant chemotherapy, 3D conformal radiation therapy and stereotactic body radiation, or radiofrequency ablation. In advanced-stage disease, cytotoxic drugs may be combined with cytostatic agents such as erlotinib or gefitinib, bevacizumab, and crizotinib amongst others.

The use of these targeted therapies brings to the surface new clinical challenges when attempting to assess their efficacy in patients with lung cancer. Conventional imaging-based criteria such as WHO and the Response Evaluation

Criteria in Solid Tumors (RECIST), are well accepted today to assess response to cytotoxic chemotherapy, in which the hallmark of success is a tumor mass reduction in size. Targeted therapies are more cytostatic than cytolytic in nature, with the main outcome being disease stabilization rather than a reduction in tumor size. In fact, the regression in tumor mass is a slow process that occurs only when the tumor cell death rate outweighs arrested growth. Much remains to be learned about the relevance of morphologic criteria to assess response in patients treated with TKIs for example, because tumor shrinkage is not always consistent with treatment efficacy. It is clear that the follow up paradigm for lung cancer patients treated with targeted therapies needs to be adapted significantly.

The PET imaging-based phenotype of response is presently being studied to confirm if in fact it could provide relevant and useful treatment efficacy information in lung cancer patients treated with TKIs. As stated previously, effective treatment with these cytostatic agents halts tumor cell proliferation leading to disease stability, and does not induce fast and early tumor size reduction. Thus, the use of CT-based RECIST or WHO criteria to assess response may result in underestimation of the efficacy of these drugs.

There is emerging evidence that the FDG-PET imaging-based phenotype of response might be an effective early predictor of lung cancer response to TKIs such as erlotinib and gefitinib [35–45]. Recent studies showed that a reduction in FDG tumor uptake observed at 2 days [37, 38], 1 week [39], 2 weeks [40, 41], and 3 weeks [39, 41, 42] after treatment with erlotinib or gefitinib, predicts early tumor response as confirmed by CT 4 and 6 weeks later. In contrast, SUVmax has been reported to increase significantly in non-responding patients. So far, we have observed that when patients have been classified as non-responders by FDG-PET early during therapy, they remain as such on conventional imaging later on.

Beyond FDG

There is preliminary clinical evidence that early prediction of lung cancer response to TKIs can also be accomplished using 3'-deoxy-3'-[^{18}F]fluorothymidine (FLT)-PET imaging. Data from six recently published studies show that a reduction in FLT uptake after 2 days [43], 7 days [44–46], and 3 weeks [46, 47] post initiation of treatment with TKIs, predicts non-progression after 6 weeks of treatment [45, 46].

Reported changes in tumoral FDG and FLT uptake between baseline and post-treatment scans in responders range from 20 % to approximately 80 %, however, the magnitude of what should be considered a significant change in uptake as a function of successful treatment still remains to be defined. Therefore, randomized controlled trials are needed to reproduce these promising preliminary results, in order to

standardize the PET imaging-based phenotype of response criteria to cytostatic drugs.

While much remains to be learned, the following clinical take home messages should be kept in mind moving forward. First, it is important to remember that so far the data consistently shows that the main benefit resides in the fact that if PET-based response to TKIs is not evident early after the treatment has been initiated, patients may be spared the morbidity and toxicity of unnecessary treatment. Second, these studies also showed that FDG and FLT-PET patterns of response to cytostatic agents have better prognostic value in terms of progression-free and overall survival compared to conventional imaging modalities [37, 38, 40–46].

Similar results were found in a pilot study of 21 patients that investigated the correlation between ^{11}C -labeled 4-N-(3-bromoanilino)-6, 7-dimethoxyquinazoline (^{11}C -PD153035) - PET/CT imaging and survival in patients with advanced NSCLC treated with erlotinib. The patients underwent PET/CT imaging at baseline, at 1 to 2 weeks and at 6 weeks from the time therapy started. Tumor SUV at each imaging time point was correlated with progression free (PFS) and overall survival (OS). Based on their preliminary results the authors indicated that while this probe might not be very useful to monitor response to therapy, it may play a positive role as a non-invasive predictive biomarker of response to erlotinib treatment. A higher baseline tumor SUVmax was found to be an independent predictor of PFS and OS in their patient population. Patients with higher baseline tumor SUV had a median PFS of 4.4 months and a median OS of 11.4 months, compared to 1.8 months ($p < 0.001$) and 4.6 months ($p = 0.002$) respectively, in those with lower ^{11}C -PD153035 uptake [48].

Bahce and colleagues [49] recently published their results of an interesting pilot study in ten NSCLC patients, looking at ^{11}C -erlotinib tumor uptake during therapeutic concentrations of non-labeled erlotinib, and while patients were off erlotinib therapy. They also investigated the effect of treatment on tumor blood flow with ^{15}O -H₂O and its correlation with ^{11}C -erlotinib tumor uptake. The authors found that tumor perfusion did not change after erlotinib treatment, and that there was no correlation between perfusion and ^{11}C -erlotinib volume of distribution in patients off and on therapy. On the other hand, ^{11}C -erlotinib tumor uptake decreased in patients with therapeutic concentrations of erlotinib, probably due to EGF receptors being occupied by non-labeled erlotinib. Another important finding was that because arterial and venous tumor-to-blood ratios (TBR) correlated better than SUV with the arterial volume of distribution at 40 to 60 min post injection, the authors recommended that TBR parameters should be used to quantify tumor uptake in whole body static PET imaging protocols. The results

of this pilot investigation definitely call for larger studies to further understand the clinical benefits of ^{11}C -erlotinib during TKI therapy [49].

Patterns of Tumoral Metabolic Heterogeneity as Early Predictors of Response to TKIs

PET-derived measures of tumor heterogeneity estimated using texture analysis have been proposed as prognostic indicators in NSCLC patients. Different image texture parameters of tumoral heterogeneity have been described, such as intensity, uniformity, correlation, contrast, energy, entropy, homogeneity, and dissimilarity [50, 51].

Intratumoral heterogeneity has been shown to be consistent with poor response to therapy and poor patient outcomes. Therefore, the thorough understanding of these textural patterns should prove very useful to personalize the selection of more aggressive therapy. In fact, first-order and high-order textural features on FDG-PET images of NSCLC patients have been proposed as predictors of response and survival in patients treated with TKIs [52]. Forty-seven lung cancer patients underwent FDG-PET/CT imaging before and 6 weeks after erlotinib therapy. CT-based RECIST criteria were used to assess tumor response 12 weeks after treatment. Interestingly, favorable response to erlotinib always correlated with a reduction in heterogeneity in texture analysis. These promising results call for further investigations to validate the use of these imaging-based textural phenotypes as biomarkers of response to cytostatic treatments.

In summary, while both PET and CT-based responses to therapy are associated with longer survival, the PET imaging-based phenotype of response tends to be a superior prognosticator. Larger and earlier reductions in tumor FDG and FLT uptake, as well as reduction in tumor heterogeneity, have been shown to be consistent with better patient outcomes.

Conclusion

While there is some evidence in the literature suggesting that FDG-PET imaging may play a role as a predictor of EGFR amplification, the role of FDG-PET to predict EGFR mutation status is at best controversial. Apart from that, we believe that at the time of this writing PET imaging-based phenotyping plays an important role in the personalized care of lung cancer patients. This patho-molecular imaging technique, in conjunction with CT, provides in-vivo anatomic-biological and functional insight into the inherent metabolic heterogeneity and behavior of lung neoplasia. Its clinical contribution spans from diagnosis, to the early monitoring of response to cytotoxic and most recently to cytostatic cancer therapies, and from the characterization of tumor relapse to the accurate prognostication of outcomes in patients with lung cancer.

Compliance with Ethical Standards

Conflict of Interest Victor H. Gerbaudo and Chun K Kim declare that they have no conflict of interest.

Ethical Approval This perspective type article does not contain any studies with human participants or animals performed by the authors.

Informed Consent Not required.

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