

Tumor heterogeneity on ^{18}F -FDG-PET/CT for response monitoring in non-small cell lung cancer treated with erlotinib

Matthijs H. van Gool¹, Tjeerd S. Aukema², Michiel Sinaasappel³, Renato A. Valdés Olmos², Houke M. Klomp¹

¹Department of Surgical Oncology, ²Department of Nuclear Medicine, ³Department of Physics, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Correspondence to: Houke M. Klomp, MD, PhD. Department of Surgical Oncology, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Plesmanlaan 1211066 CX Amsterdam, The Netherlands. Email: h.klomp@nki.nl.

Abstract: Response monitoring using fluorodeoxyglucose positron emission tomography acquired together with low dose computed tomography (FDG-PET/CT) textural features has potential in targeted treatment with erlotinib in non-small cell lung cancer (NSCLC) patients. Patients with substantial decrease of metabolic activity during erlotinib treatment will probably benefit from continued treatment. However, various aspects of the method (quantification tools, cut-off values, etc.) need to be standardized before the software becomes widely available in a similar manner as standardized uptake value (SUV) measurements. Heterogeneity on FDG-PET/CT opened an additional window for innovation but simultaneously a new challenge for molecular hybrid imaging.

Keywords: Fluorodeoxyglucose positron emission tomography acquired together with low dose computed tomography (FDG-PET/CT); epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI); non-small cell lung cancer (NSCLC)

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With advances in molecular research, molecular-targeted agents such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) have emerged for the treatment of (advanced) non-small cell lung cancer (NSCLC). In NSCLC the EGFR is over-expressed or harbours sensitizing mutations (1). Inhibition of this receptor with TKI therapy such as erlotinib blocks the tyrosine kinase domain of the EGFR, thereby inhibiting downstream signaling pathways involved in cell proliferation, angiogenesis, invasion and metastasis and prevention of apoptosis. They can be orally administered and have a relatively favorable toxicity profile and are registered for the treatment of patients with advanced (chemotherapy-refractory) NSCLC (2). Molecular biologic testing of the tumour has become paramount to consider these (often expensive) targeted treatment options.

The probability of response to EGFR-TKIs is considerably higher in patients with EGFR-mutated tumors (3). However, prediction of response is suboptimal by mutation

analysis only (4). In addition, EGFR mutation positive NSCLC represents only 10–15% of all NSCLC (3). Thus, the vast majority of NSCLC are so-called “wild-type” for EGFR. For these patients more controversy arises. It is known that several patients without apparent sensitizing EGFR mutations do benefit from erlotinib therapy (5). Biopsy quality, tissue availability, and heterogeneity within the tumor are factors that may hamper molecular analysis for relevant genetic alterations (6).

Efforts have been made to identify patients most likely to respond to EGFR-TKIs, despite the presence of activating mutations. ^{18}F -fluorodeoxyglucose positron emission tomography acquired together with low dose computed tomography (FDG-PET/CT) has proven its role as a staging modality (7). In addition, several studies demonstrated that FDG-PET/CT is able to predict response to chemotherapy (8,9).

The initial results in response monitoring of EGR-TKI with FDG-PET/CT using SUV_{max} are promising (10).

Early response measured with FDG-PET/CT seems to correlate to histopathological response (11). However, there is an ongoing search for reliable parameters to measure response with FDG-PET/CT (12). There are several methods for measuring the rate and/or total amount of FDG-accumulation in tumors. PET scanners are designed to measure the *in vivo* radioactivity concentration [kBq/mL], which is directly linked to the FDG-concentration. Typically, however, it is the relative tissue uptake of FDG that is of interest. The two most significant sources of variation that occur in practice are the amount of injected FDG and the patient size. To compensate for these variations, at least to first order, SUV is commonly used as a relative measure of FDG-uptake. However, there is increasing interest in assessing the global and local-regional heterogeneity of FDG-distribution with feature analysis by using a variety of mathematical methods that describe the relationships between the gray-level intensity of pixels or voxels and their position within an image. Initial validation of the measurement of intratumoral heterogeneity on FDG-PET images appears to provide predictive information at pretherapy imaging in a number of solid tumors.

Recently Cook *et al.* evaluated this issue (13). The aim of their study was to determine if first-order and high-order textural features on FDG-PET images of NSCLC (I) at baseline; (II) at 6 weeks; or (III) the percentage change between baseline and 6 weeks can predict response or survival in patients treated with erlotinib. They assumed that textural features reflecting heterogeneity on FDG-PET images in patients with NSCLC who are being treated with erlotinib are associated with treatment response and survival. To verify this hypothesis they analyzed a population of 47 patients measuring: (I) First-order textural features included standard deviation, skewness, kurtosis, first-order entropy, and first-order uniformity; (II) high-order features, including coarseness, contrast, busyness, and complexity, derived from three-dimensional matrices describing differences between each PET image voxel and its neighbor, were calculated, taking into consideration for each voxel the neighboring voxels in the two adjacent planes. The median OS was 14.1 months. According to CT RECIST at 12 weeks, there were 21 non-responders and 11 responders. Response to erlotinib was associated with reduced heterogeneity (first-order standard deviation, $P=0.01$; entropy, $P=0.001$; uniformity, $P=0.001$). At multivariable analysis, high-order contrast at 6 weeks ($P=0.002$) and percentage change in first-order entropy ($P=0.03$) were independently associated with survival. Percentage change

in first-order entropy was also independently associated with treatment response ($P=0.01$). However, in this analysis the texture parameters appeared to be as predictive as the SUV parameters.

Although the evaluation of Cook *et al.* was limited to a small series of patients the results are promising and it is possible to consider applicability of the methodology in other clinical studies provided that the calculation software of the textural features becomes available after standardization. Reproducibility for ^{18}F -FDG textural features has been reported to be as good as or even better than the one used for SUV (14). In the work of Cook *et al.* measurement of all texture parameters showed a good interobserver variability.

However, other aspects must be elucidated. For instance, the clinical resolution of current PET scanners is still in the order of 4 to 5 mm, which means that for relatively small lung tumors the partial volume effect will make it challenging to accurately measure the volume for tumors with a diameter less than 3 cm with low FDG-uptake (15). Assessment of the heterogeneity within the tumor may suffer from this same lack of resolution. Despite the limitation in spatial resolution the measured SUV distribution inside the tumor still (although blurred) contains information about the heterogeneity of the tumor. Statistical methods are therefore necessary for the evaluation of this distribution.

A disadvantage of this approach is that it is not clear what type of heterogeneity is correlating with the tumor response. Information would be vital for future development towards prospective use. Relatively small tumors, like NSCLC, which are evaluated in this study, show a strong correlation between total uptake and the size of the tumor. For instance in a perfectly spherical tumor where the uptake decreases as function of the distance to the center the standard deviation of the distribution of the FDG-values will scale with the size of the tumor. In this case both total (or peak) SUV and standard deviation of the measured SUV will decrease when the tumor shrinks in size. In addition, the noise within the voxels follows a Poisson distribution, which results in noise, scales with the square root of the counts per voxel. Here a pitfall of using SUV emerges. In SUV calculation, the measured counts per voxel are normalized to the injected dose and body weight. This potentially results in comparable SUV values but different counts per voxel. So when statistics are used to characterize the tumor, SUV values can be misleading.

The approach chosen by Cook *et al.* to evaluate the

statistics of the distribution without modeling the change in this distribution inflicted by the therapy appears suboptimal for gaining more insight in this potential interesting technique for evaluation of tumor response.

An important feature of metabolic response monitoring is the possibility to identify patients who will potentially benefit from therapy. In contrast, patients who do not benefit from therapy are only exposed to potential toxicity for a short period of time (16). In addition, the successes of new therapeutic agents have led to increases in health care costs to a level that is now causing a serious financial burden to patients, hospitals and society (17). With early assessment futile use of medication can be avoided, and patients who do not respond to EGFR-TKI's may switch to other, more effective treatment.

Several limitations may occur with metabolic treatment monitoring and here we can underline two important features. First, FDG-uptake on PET may reflect various tissue reactions, as tumor progression or regression but also senescence, fibrosis formation, and inflammatory reactions as macrophage infiltration (18). The second consideration concerns the response to erlotinib. It can be expected to develop within several weeks, but apoptosis, transition of necrosis into fibrosis, and inflammatory and granulomatous reactions are difficult to quantify (19). Since some spontaneous necrosis exists in most NSCLCs, therapy response can be a combination of a decrease in the total amount of viable tumor cells and/or a decrease of FDG metabolism at cellular level. FDG-PET cannot differentiate between these two types of responses. Moreover FDG-uptake by the tumor is also dependent on perfusion and the rate of clearance by for instance the kidney (20). These factors make that tumor response assessment with absolute uptake of the tumor in total (expressed as SUV max or mean) is difficult to interpret. Other aspects of tumor response like volume or heterogeneity can also be measured using FDG-uptake. A big advantage is that these measured values are not solely dependent on the absolute uptake but take changes within the tumor into account.

In conclusion, Cook *et al.* have shown that response monitoring using FDG-PET/CT textural features has potential in targeted treatment with erlotinib in NSCLC patients. Patients with substantial decrease of metabolic activity during erlotinib treatment will probably benefit from continued treatment. However, various aspects of the method (quantification tools, cut-off values, etc.) need to be standardized before the software becomes widely available in a similar manner as SUV-measurements. They opened an

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Footnote

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