RGD PET: From Lesion Detection to Therapy Response Monitoring

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In the past 20 years or so, molecular imaging has been well recognized and numerous imaging probes have been developed along with the advancement and emergence of novel imaging techniques. With exquisite sensitivity and specificity, positron emission tomography (PET) became the workhorse in the field, especially for oncological applications. Almost every cancer hallmark summerized by Hanahan and Weinberg (1) can be visualized and evaluated with PET using the corresponding imaging probes.

Angiogenesis has been well recognized as an essential hallmark for tumor growth, invasion and metastasis (2). Integrin $\alpha_v\beta_3$ represents a potential molecular marker for angiogenesis due to its significant upregulation on activated endothelial cells but not on quiescent endothelial cells (3). Most of the currently available integrin-targeted imaging probes are based on Arg-Gly-Asp (RGD) tripeptide sequence because of its high affinity and specificity for integrin $\alpha_v\beta_3$. [$^{18}$F]Galacto-RGD was the first reported RGD peptide tracer in human subjects (4). Since then, quite a few RGD containing PET tracers have been developed and tested in the clinic. Although being structurally different, all of the clinically investigated RGD peptides, including both monomers and dimers, depict very similar in vivo pharmacokinetic properties (5).

So far, most of the clinical studies only focused on the evaluation of safety and dosimetry, or preliminary observation of tracer accumulation in solid tumors, including glioblastoma multiforme (GBM), squamous cell carcinoma of the head and neck (SCCHN), non-small cell lung cancer (NSCLC), breast cancer, melanoma, sarcoma, renal cancer, and rectal cancer. Based on the currently available data for lesion detection, the
sensitivity of $[^{18}\text{F}]$Galacto-RGD PET for all lesions falls in the range of 59-94% ($6, 7$), which is not superior to that of $[^{18}\text{F}]$FDG PET ($8$). With higher binding affinity and tumor retention from the possible multivalency effect, dimeric RGD peptide tracers such as $[^{18}\text{F}]$FPPRGD2 and Alfatide showed comparable results as FDG for lesion detection in a small scale clinical studies ($9-11$). Especially for brain metastases, RGD based tracers demonstrated much higher tumor/background ratio than $[^{18}\text{F}]$FDG due to its low background uptake in normal brain tissue ($12$).

However, the application of a molecular imaging probe such as RGD should not be stopped at the level of lesion detection. Instead, the two most commonly suggested uses are the selection of patients for treatments involving angiogenesis and the monitoring of patients receiving such therapies ($13$). As integrin $\alpha_\text{v} \beta_3$ is a key player in angiogenesis, it therefore can act as a predictive biomarker to select patients who will most likely benefit from a specific angiogenesis inhibitor, to evaluate treatment response, and to detect emerging resistance. This is particularly important as antiangiogenic therapy usually leads to a delay of tumor growth, rather than tumor shrinkage. Indeed, quite a few preclinical studies reported the use of RGD-based PET tracers for antiangiogenic therapy response monitoring ($14, 15$). Some studies suggested that RGD PET could represent the changes of neovascular density and integrin expression during antiangiogenic therapy ($16, 17$), while other studies concluded that the tumor uptake of RGD peptide does not necessarily reflect the change of integrin $\alpha_\text{v} \beta_3$ expression upon treatment ($18$). The change of ligand binding affinity of integrin $\alpha_\text{v} \beta_3$ at non-activated or activated state further
increases the complexity of image interpretation (3). Consequently, the real potential of RGD PET in therapy response monitoring needs to be confirmed with well-designed clinical investigations.

In this issue of Journal of Nuclear Medicine, we are glad to see that Zhang et al. (19) performed a pilot clinical study to evaluate the predictive value of PET using Alfatide II in patients with glioma. They found that the residual lesions can be visualized clearly with decent contrast to surrounding normal brain tissue. More importantly, Alfatide II PET/CT parameters, especially intra-treatment SUV\textsubscript{max}, predicted the tumor sensitivity to concurrent chemoradiotherapy (CCRT). Using this parameter, the effectiveness of CCRT can be predicted as early as three weeks after treatment was initiated. This is the first clinical investigation to apply RGD PET for patient screening and therapy response monitoring. Both baseline SUV\textsubscript{max} and intra-treatment SUV\textsubscript{max} showed correlation with response to CCRT, with the lesion volume change determined by MRI as the “gold” standard. Compared with baseline SUV\textsubscript{max}, intra-treatment SUV\textsubscript{max} showed higher sensitivity and specificity. With baseline SUV\textsubscript{max}, patient screening can be performed to avoid unnecessary therapy. With intra-treatment parameter, the patients with resistant lesions can be switched to other more sensitive treatment plans. These findings substantiate the value of RGD PET in guiding treatment plan.

In most preclinical studies, the tracer uptake difference between the intra-treatment scan and baseline scan was used as the parameter to reflect tumor response to various therapeutic interventions (14-17). However, in this study (19), the change of SUV
showed no correlation with the responsiveness of the tumor. As the authors stated, this may be due to the irregular tumor margin and intra-tumor cavity caused by surgery. In fact, using one single PET scan to make the decision without baseline subtraction will save the patients from extra radiation exposure. This also reveals the fundamental differences between preclinical studies and clinical trials. The heterogeneity of the target expression in different patients with the same tumor type can be used as a biomarker for patient stratification. In preclinical models, however, it is almost impossible to do so as the variance of imaging target expression in tumor xenografts developed from cancer cell lines is rather limited.

Expression of integrin $\alpha_v\beta_3$ has been reported to be associated with tumor aggressiveness and metastatic potential in malignant tumors (3). For sarcoma and glioma, RGD uptake was positively correlated with the grade of tumor differentiation (20, 21). The responsiveness of tumor to CCRT may be partially due to the low malignancy indicated by the low $SUV_{\text{max}}$ value of RGD PET. Compared with $SUV_{\text{mean}}$, $SUV_{\text{max}}$ is more straightforward and no accurate tumor contour is needed. However, it is questionable whether $SUV_{\text{max}}$ can reflect the overall integrin expression on tumor cells or tumor vasculature.

Besides, we also need to address the following questions. Will this strategy be applicable to other cancer types with other treatment plans? Is there any inflammatory reaction at the intra-treatment phase and will this affect the tracer uptake? What is the relationship between tumor blood perfusion and tracer uptake? Will the local BBB
disruption affect the tracer uptake? Is there any change of integrin αvβ3 induced by CCRT?

All these questions warrant further exploration.

In addition to the oncological applications, RGD based tracers have been investigated in other clinical settings, when angiogenesis is related, including myocardial infarction (MI) (22), stroke (23), atherosclerosis (24) and rheumatoid arthritis (RA) (25). Hopefully, we will see more clinical studies to reveal the value of RGD PET in therapy decision and therapy response monitoring in these diseases.

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References


