

RGD PET: From Lesion Detection to Therapy Response Monitoring

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In the past 20 y 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, PET became the workhorse in the field, especially for oncologic applications. Almost every cancer hallmark summarized 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 because of 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 the 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

much higher tumor-to-background ratio than ^{18}F -FDG because of 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 2 most commonly suggested uses are the selection of patients for treatments involving angiogenesis and the monitoring of patients receiving such therapies (13). Because integrin $\alpha_v\beta_3$ 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 because 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), whereas other studies concluded that the tumor uptake of RGD peptide did not necessarily reflect the change of integrin $\alpha_v\beta_3$ expression on treatment (18). The change of ligand binding affinity of integrin $\alpha_v\beta_3$ at nonactivated 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 *The 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 ^{18}F -AIF-NOTA-PRGD2 (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 intratreatment SUV_{max} , predicted the tumor sensitivity to concurrent chemoradiotherapy (CCRT). The effectiveness of CCRT can be predicted as early as 3 wk after treatment is initiated using this parameter. This is the first, to our knowledge, clinical investigation to apply RGD PET for patient screening and therapy response monitoring. Both baseline SUV_{max} and intratreatment SUV_{max} showed correlation with response to CCRT, with the lesion volume change determined by MRI as the gold standard. Compared with baseline SUV_{max} , intratreatment SUV_{max} showed higher sensitivity and specificity. With baseline SUV_{max} , patient screening can be performed to avoid unnecessary therapy. With an intratreatment 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 plans.

In most preclinical studies, the tracer uptake difference between the intratreatment scan and baseline scan was used as the parameter

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the clinic. Although they are structurally different, all of the clinically investigated RGD peptides, including both monomers and dimers, depict similar in vivo pharmacokinetic properties (5).

So far, most of the clinical studies focused only on the evaluation of safety and dosimetry or preliminary observation of tracer accumulation in solid tumors, including glioblastoma multiforme, squamous cell carcinoma of the head and neck, non-small cell lung cancer, breast cancer, melanoma, sarcoma, renal cancer, and rectal cancer. On the basis of the currently available data for lesion detection, the sensitivity of ^{18}F -galacto-RGD PET for all lesions falls in the range of 59%–94% (6,7), which is not superior to that of ^{18}F -FDG PET (8). With higher binding affinity and tumor retention from the possible multivalency effect, dimeric RGD peptide tracers such as ^{18}F -FPPRGD2 and alfatide showed results comparable to ^{18}F -FDG for lesion detection in small-scale clinical studies (9–11). Especially for brain metastases, RGD-based tracers demonstrated a

Received Nov. 1, 2015; revision accepted Nov. 3, 2015.

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Published online Nov. 25, 2015.

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DOI: 10.2967/jnumed.115.168278

to reflect tumor response to various therapeutic interventions (14–17). However, in the study by Zhang et al. (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 intratumor cavity caused by surgery. In fact, using 1 single PET scan to make the decision without baseline subtraction will save the patients from extra radiation exposure. These results also revealed 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 because 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_{max} of RGD PET. Compared with SUV_{mean} , SUV_{max} is more straightforward, and no accurate tumor contour is needed. However, it is questionable whether SUV_{max} can reflect the overall integrin expression on tumor cells or tumor vasculature.

Moreover, 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 intratreatment phase and will this affect the tracer uptake? What is the relationship between tumor blood perfusion and tracer uptake? Will the local blood–brain barrier disruption affect the tracer uptake? Is there any change of integrin $\alpha_v\beta_3$ induced by CCRT? All these questions warrant further exploration.

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

DISCLOSURE

This study was supported by the Intramural Research Program, National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health. No other potential conflict of interest relevant to this article was reported.

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