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Initial Experience of Monitoring Response of Breast Cancer to Bevacizumab-containing Chemotherapy using A New Integrin Specific PET Imaging Tracer [F-18]RGD-K5

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Abstract

This study investigates the use of [F-18]RGD-K5, an integrin αvβ3 targeting PET tracer, in breast cancer patients receiving chemotherapy with bevacizumab (Avastin®). Two patients were analyzed: Subject-1 had metastatic breast cancers and Subject-2 had a primary cancer in the breast. The therapy regimen was weekly paclitaxel and carboplatin combined with bi-weekly bevacizumab. Each subject received 5 PET-CT scans: pre-treatment [F-18]RGD-K5 and [F-18]FDG, one [F-18]RGD-K5 F/U scan after 2 doses of bevacizumab, and another [F-18]RGD-K5 and [F-18]FDG F/U after 4 doses of bevacizumab. Many lesions in Subject-1 showed a high [F-18]RGD-K5 baseline uptake. The two most [F-18]RGD-K5 avid lesions had SUVs of 10.8 and 10.1, and the corresponding [F-18]FDG uptakes were much lower (SUV of 1.0 and 3.5). The [F-18]RGD-K5 SUVs in all analyzed lesions decreased during treatment, showing a mean of 34% reduction after 2 doses, and 47% reduction after 4 doses of bevacizumab. The changes in the [F-18]FDG SUVs were much smaller, with a mean reduction of 24%. In contrast to the patient with metastatic cancer, the primary tumor in Subject-2 showed a low [F-18]RGD-K5 uptake (SUV=1.8), but a high [F-18]FDG uptake (SUV=8.7). The [F-18]FDG SUV decreased to 2.4 (72% reduction) after 4 doses of bevacizumab, while the [F-18]RGD-K5 uptake remained unchanged. The results that [F-18]RGD-K5 avid lesions show a great SUV reduction after bevacizumab treatment suggest that the [F-18]RGD-K5 tracer may be potentially used for selecting candidate patient for receiving bevacizumab, as well as in monitoring of the early treatment changes.

Keywords: Angiogenesis; Integrins; Bevacizumab; [F-18]RGD-K5; [F-18]FDG; Molecular imaging

Introduction

Tumor-induced angiogenesis is an important multi-step process in both tumor progression and metastasis serving as a conduit for tumor cell dissemination, nutrition and waste removal. The importance of these processes, foremost angiogenesis, has been shown in multiple studies over several decades. Gimbrone et al. showed that a tumor implanted on an avascular tissue attracts new capillaries, which feed the expanding mass. Further research proofed that lack of adequate vasculature leads to necrosis and apoptosis in a tumor. Further question of when a tumor requires to induce angiogenesis to sustain growth lead to the introduction of the "angiogenic switch" by Hanahan and Folkman who described that the interaction between angiogenic inducers and inhibitors regulates the endothelial cell proliferation and migration and that the balance between the inducers and inhibitors governs over the "angiogenic switch" [1-6].

Anti-angiogenic treatment strategies undermine tumor vasculature function resulting in a disruption of vascular permeability and neovascular survival [7-11]. The use of trastuzumab (Herceptin®) for treating HER2-positive breast cancer patients lowers both the risk of recurrence and mortality. However, the anti-angiogenic agent bevacizumab (Avastin®), a humanized monoclonal antibody that targets a specific isoform of the vascular endothelial growth factor (VEGF), has not been as successful. It was granted accelerated approval by the United States Food and Drug Administration (FDA) in 2008 for use in patients with metastatic HER-2 negative breast cancer based on the data of the E2100 trial showing a prolonged progression-free survival of approximately 5 months [11-13]. In December 2010, an advisory FDA panel reviewed the new data submitted by Genentech and determined that the treatment only increased progression-free survival by one month and was associated with potentially severe side effects. These findings resulted in a recommendation to withdraw the market approval of bevacizumab for treatment of metastatic breast cancer. The decision was strongly opposed by both advocate groups and cancer survivors, many of who personally experienced benefits of bevacizumab treatment well beyond the progression-free survival of one month. This debate exposed a fundamental gap in identifying patients who would receive the greatest therapeutic benefit from bevacizumab treatment.

While the concept of using biomarkers to pre-select patients most likely to respond to a particular therapy, e.g. identifying HER2/neu or EGFR positive patients prior to therapy, is widely utilized, no widely accepted biomarkers exist that can efficiently detect the key biological proteins to link those patients with beneficial bevacizumab therapy [14,15].

A promising biomarker for angiogenesis is integrin $\alpha_v\beta_3$, a protein

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expressed by newly formed blood vessels in neoplastic tissues making it vital to the angiogenic cascade [16,17]. The *in vivo* method of detecting aberrant integrin $\alpha_v\beta_3$ in tumors has been studied using positron emission tomography (PET). A well-studied PET-based integrin tracer is [F-18]Galacto-RGD, a cyclic peptide which is reported to non-invasively determine both $\alpha_v\beta_3$ expression and tumor vasculature in humans [18-20]. In a study by Beer et al. in 19 patients with solid tumor, the uptake measured by [18F]Galacto-RGD was shown to be highly correlated with immunohistochemical staining expression using $\alpha_v\beta_3$ -specific antibody LM609, and the uptake was also highly correlated with microvessel density [20]. A structurally related analog, [F-18]RGD-K5, was identified as a promising PET imaging agent for detecting integrin $\alpha_v\beta_3$ expression in vivo [21]. This tracer contains the well-established integrin $\alpha_v\beta_3$-binding motif (an "R-G-D" cyclic peptide) with the addition of a polar, yet metabolically stable, 1,2,3-antitriazole moiety, which biases excretion through the kidneys and into the bladder. The preparation of [F-18]RGD-K5 is simple, utilizing Click Chemistry [22,23], which is both straightforward and tolerant of a diverse array of functional groups, resulting in a radiosynthetic production method, which can readily be automated.

Given that bevacizumab disrupts the VEGF signaling pathway, blocking vascular growth and later perturbing integrin $\alpha_v\beta_3$ function, there was interest in determining if [F-18]RGD-K5 could identify and track changes in integrin $\alpha_v\beta_3$ expression as a function of bevacizumab treatment. While preclinical reports exist demonstrating a successful tracking of tracer uptake as a function of anti-angiogenic treatment [24-26], no such clinical data is available. Therefore, the aim of this study was to examine the utility of [F-18]RGD-K5 for monitoring treatment responses in breast cancer patients undergoing bevacizumab treatment plus standard chemotherapy. The pre-treatment uptake SUVs of both [F-18]RGD-K5 and [F-18]FDG were measured and compared. The changes in the post-treatment uptake after the patient received two and four doses of bevacizumab were also measured and compared.

Materials and Methods

Subjects

The institutional review board approved this study and all subjects provided their written informed consent. Two breast cancer patients who completed all study related procedures were reported in this study. Subject-1 was a 73-year-old female patient with metastatic breast cancer. The initial diagnosis of invasive ductal carcinoma was made 9 years ago. Subject-2 was a 56-year-old female patient with a mass-type, 2.5 cm invasive ductal carcinoma in the breast. She was a newly diagnosed patient, and all standard of care imaging studies suggested that she did not have other lesions or suspicious metastatic lymph nodes elsewhere. Because the tumor was greater than 2 cm, she opted to receive neoadjuvant chemotherapy prior to surgery. The chemotherapeutic regimen for these two patients was the same, including weekly paclitaxel and carboplatin, combined with bi-weekly bevacizumab treatments for a total of 5 doses over a period of 12 weeks.

PET/CT imaging studies and evaluation

Each subject received five PET/CT scans during this bevacizumab-chemotherapy regimen: 2 pre-treatment scans (1 x [F-18]RGD-K5 and 1 x [F-18]FDG), a follow-up scan after 4 weeks of treatment with 2 doses of bevacizumab (1 x [F-18]RGD-K5), and 2 additional follow-up scans after 8 weeks of treatment with 4 doses of bevacizumab (1 x [F-18]RGD-K5 and 1 x [F-18]FDG). The PET-CT scans were performed in accordance to our institution's clinical guidelines. Images were acquired on a GE Discovery VCT scanner (General Electric, Milwaukee, WI, USA). The PET imaging acquisition was performed using a 3D acquisition with a pixel size of 5.47 mm and a slice thickness of 3.27 mm. The CT portion of the scanner is a 64-slice scanner, and the CT images were acquired for both attenuation correction of the PET images and anatomical registration.

The SUV(max) (g/ml) of lesions seen on both [F-18]FDG and [F-18]RGD-K5 images were measured on a GE AW 4.4 Workstation. For lesions that showed a clear boundary on the CT images (e.g. the primary lesion and additional lymph nodes), the sizes were measured based on the CT images.

Results

Comparison of pre-treatment uptake on [F-18]FDG and [F-18]RGD-K5 scans

The baseline [F-18]RGD-K5 scan of Subject-1, having metastatic breast cancer, showed a relatively higher uptake in the nodal and bony lesions as compared to the baseline [F-18]FDG scan (Figure 1). The two most [F-18]RGD-K5 avid lesions had SUVs of 10.8 and 10.1, with the corresponding [F-18]FDG SUVs in the same lesions being much lower (1.0 and 3.5). The results of an axillary lymph node are shown in Figure 2. The two most [F-18]FDG avid lesions (SUVs of 6.3 and 4.0) also showed high [F-18]RGD-K5 SUVs (6.7 and 5.5). The results of an anterior mediastinal lymph node are shown in Figure 3. Subject-2 had a 2.5 cm primary breast cancer. In contrast to the metastatic lesions in Subject-1, this mass had a low [F-18]RGD-K5 uptake (SUV=1.8) and much higher [F-18]FDG uptake (SUV=8.7) (Figure 4).

Comparison of post-treatment uptake changes of [F-18]FDG and [F-18]RGD-K5 scans

Both patients received a total of three [F-18]RGD-K5 scans: a baseline scan prior to treatment followed by scanning after the second and fourth doses of bevacizumab. The changes in SUV(max) values

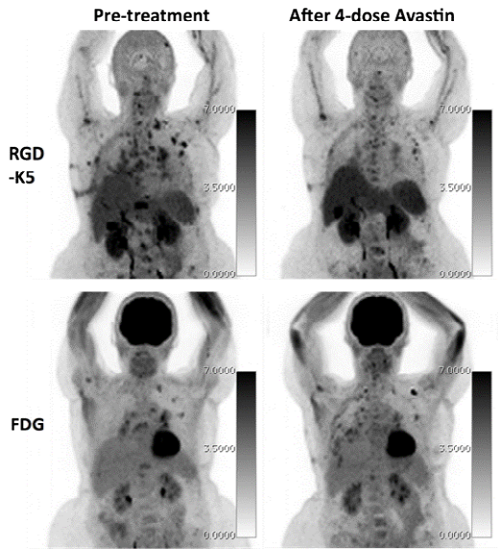

Figure 1: Maximum intensity projections of Subject-1. More lesions can be seen on the baseline RGD-K5 scan compared to the FDG scan. The uptake decreases after the patient receives 8 weeks of paclitaxel and carboplatin (given weekly) with 4 doses of bevacizumab (given bi-weekly). The pre-treatment FDG uptake is much lower than the RGD-K5 uptake. No new lesions were discovered during the course of treatment

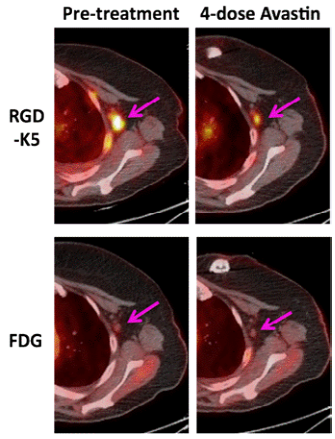

Figure 2: A low axillary lymph node is the most RGD-K5 avid lesion in Subject-1, shown on the top row. The baseline RGD-K5 SUVmax measured before treatment is 10.8, and the value is decreased to 3.5 after receiving 4 doses of bevacizumab. The size measured on CT is 1.5×1.1 cm on the baseline scan, and 1.0×0.6 cm on the follow-up scan. The FDG uptake is much lower. The pre-treatment FDG SUVmax is 1.03, and is decreased slightly to 0.9 after 4 doses of bevacizumab.

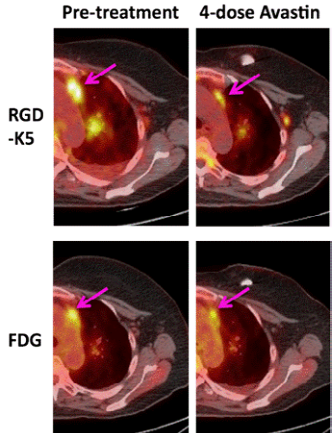

Figure 3: A pre-vascular lymph node in Subject-1. The baseline RGD-K5 SUVmax measured before treatment is 5.5, and the value is decreased to 3.7 after receiving 4 doses of bevacizumab. The FDG uptake is comparable. The size measured on CT is 1.8×1.1 cm on the baseline scan, and 1.1×0.7 on the follow-up scan. The pre-treatment FDG SUVmax is 4.0, and is decreased to 2.8 after 4 doses of bevacizumab

from five [F-18]RGD-K5 avid lesions (≥ 1.5 cm by CT), in Subject-1 pre- and post-dosing are summarized in Table 1. The [F-18]RGD-K5 uptake in all five analyzed lesions decreased after bevacizumab treatments, showing a mean of 34% reduction after 2 doses, and 47% reduction after 4 doses of bevacizumab when compared to the baseline values. In comparison, the [F-18]FDG SUVmax of the same lesions after 4 doses of bevacizumab treatment decreased in four of five lesions (Table 1), with a mean reduction of 24%.

The four lymph node sizes were measured on the corresponding CT images (Table 2) and all showed a gradual shrinkage in size, indicating a positive response to therapy. The size of the bony lesion could not be measured reliably. Subject-1 continued to receive chemotherapy and was shown to have stable disease in a follow-up [F-18]FDG scan 6 months after the start of therapy.

In Subject-2, the primary tumor did not have a high baseline [F-18]RGD-K5 uptake (SUVmax=1.8), the SUV(max) increased to 3.1 after two doses of bevacizumab, and then decreased to 1.9 after 4 doses of bevacizumab. Thus, little overall change was observed between the pretreatment scan and the third scan. The [F-18]FDG SUVmax of the tumor decreased from the baseline value of 8.7 to 2.4 after 4 doses of bevacizumab, showing 72% reduction (Table 3). The size of the primary tumor was measured on CT, decreasing from 2.5×1.5 cm (baseline scan) to 1.8×1.1 cm after 4 doses of bevacizumab, also indicating a positive response to therapy. This patient received surgery after completing 12 weeks of therapy, and the histopathological examination found no residual disease; thus achieved pathologic complete response (pCR).

Discussion

There is a keen interest in developing imaging techniques that provide an early indication of treatment effectiveness at either a functional or molecular level, as conventional response assessment techniques, such as RECIST (Response Evaluation Criteria In Solid Tumors), may not be appropriate for evaluating changes induced by anti-angiogenic therapies in a timely manner. For breast cancer patients receiving bevacizumab-containing chemotherapy, dynamic contrast enhanced MRI has been applied to study the early changes in vascular properties after one cycle of bevacizumab, but the early morphological vascular changes could not enable a differentiation between responders and non-responders [27]. Previously, the use of [F-18]FDG PET imaging to monitor a patient's response to bevacizumab therapy has generated mixed results. For example, it was shown to predict the response of colorectal liver metastases to bevacizumab therapy in 70% of the patient population after 4 treatment cycles [28]. Conversely, inconsistent [F-18]FDG uptake was observed in bone lesions in bevacizumab-treated patients having stable or responding non-small cell lung cancers [29].

In this study we report the initial treatment monitoring results of a new integrin PET tracer, [F-18]RGD-K5, for imaging of breast cancer patients undergoing bevacizumab-containing chemotherapy at three different time points in the treatment cycle. The chemical structure of [F-18]RGD-K5 was similar to that of another PET tracer,

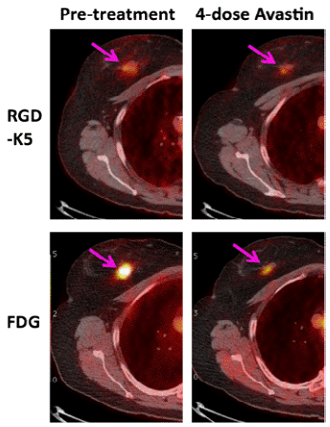

Figure 4: Subject-2 has a primary cancer in the breast. The baseline RGD-K5 SUVmax measured before treatment is 1.8, and the value is 1.9 after receiving 4 doses of bevacizumab. The size measured on CT is 2.5×1.5 cm on the baseline scan, and 1.8x1.1 on the follow-up scan. The FDG uptake is much higher. The pre-treatment FDG SUVmax is 8.7, and is decreased to 2.4 after 4 doses of bevacizumab

	RGD-K5			FDG	
	Pre-treatment	**Post 2-dose bevacizumab**	**Post 4-dose bevacizumab**	**Pre-treatment**	**Post 4-dose bevacizumab**
Axillary Node	10.8	4.7 (-56%)	3.5 (-68%)	1.0	0.9 (-13%)
Bone met	10.1	6.5 (-36%)	4.0 (-61%)	3.5	2.0 (-43%)
Hilar node L	6.7	4.8 (-29%)	3.6 (-46%)	6.3	3.9 (-38%)
Mediastinal Node	5.5	3.3 (-39%)	3.7 (-32%)	4.0	2.8 (-29%)
Hilar node R	4.8	4.4 (-8%)	3.4 (-29%)	3.8	4.0 (4%)

Table 1: The SUVmax of lesions that can be well identified on RGD-K5 scan of Subject-1, and the percentage reduction after treatment compared to the baseline value.

	Pre-treatment	**Post 2-dose bevacizumab**	**Post 4-dose bevacizumab**	**Post 6-month chemotherapy**
Axillary Node	1.5 x 1.1	1.0 x 0.8	1.0 x 0.6	0.6 x 0.5
Hilar Node	2.5 x 1.7	2.3 x 1.4	1.6 x 0.8	1.5 x 0.6
Pre-vascular Node	1.8 x 1.1	1.3 x 0.8	1.1 x 0.7	1.0 x 0.6
Hilar Node	1.9 x 1.0	1.7 x 1.3	1.3 x 0.7	1.1 x 0.6

Table 2: The size (cm) of lymph nodes listed in Table 1, measured on corresponding CT images.

	RGD-K5			FDG	
	Pre-treatment	**Post 2-dose bevacizumab**	**Post 4-dose bevacizumab**	**Pre-treatment**	**Post 4-dose bevacizumab**
Primary tumor	1.8	3.1 (72%)	1.9 (5%)	8.7	2.4 (-72%)

Table 3: The SUVmax of the primary tumor of Subject-2, and the FDG percentage reduction after treatment compared to the baseline value.

[18F]Galacto-RGD, which was studied more extensively in humans [19,20,30,31]. Also the [18F]Galacto-RGD uptake was shown to be highly correlated with $\alpha_v\beta_3$ expression and the microvessel density measured by immunohistochemistry [20]. Although there were many studies reporting RGD-based labeling for imaging of animal models, to date the only feasible approach for human imaging is to use radio-labeling. Three studies have specifically reported imaging in breast cancer patients using RGD-labeled radioligands: [18F]Galacto-RGD [31], 99mTc-NC100692 [32] and 18F-AH111585 [33]. For [F-18] RGD-K5, it has been used in an earlier *in vivo* human imaging study to measure radiation dosimetry, test safety, and evaluate the uptake in patients with different types of cancers; also for proof-of-principle, the PET imaging findings in a sarcoma and a breast cancer patients were correlated with the immune histochemical staining results analyzed from the surgical specimens and showed a positive association. These results are submitted and pending for publication.

In the present study, Subject-1 having metastatic breast cancer, showed a high baseline uptake of [F-18]RGD-K5 in several lesions prior to treatment (SUVmax ≥ 4.8), and a continual SUV decrease with subsequent treatment doses. The reduction of [F-18]RGD-K5 and [F-18]FDG SUVs mirrored the continuing shrinkage of lesion size measured on CT. Given that the uptake of [F-18]RGD-K5 is purportedly sensitive to $\alpha_v\beta_3$ integrin expression density in tumors, our results suggest that [F-18]RGD-K5 avid tumors treated with at least 2 cycles of bevacizumab and chemotherapy treatment might result in a reduction of [F-18]RGD-K5 uptake, preceding tumor shrinkage. There was also a reduction of [F-18]FDG uptake in 4 out of the 5 lesions after treatment, although the reduction of tracer uptake was less pronounced than that of [F-18]RGD-K5. Given that the uptake of [F-18]FDG in treated lesions can be influenced by a multitude of factors, including enhanced glycolysis, inflammation and treatment flares, the response to therapy tracked reasonably well against [F-18]RGD-K5.

For Subject-2, having a primary breast cancer, the SUVmax for [F-18]RGD-K5 remained essentially unchanged after 4 doses of bevacizumab. However, a transient increase in the uptake of [F-18] RGD-K5 was observed after 2 doses of bevacizumab. While reason for the transient increase was not clear, it might be related to treatment induced flare or compensatory mechanisms by the tumor to resist the effects of anti-angiogenic treatment. Similar cases have been reported in patients treated with bevacizumab for non-small cell lung cancer [29]. In comparing the uptake with [F-18]FDG, the same mass had a high baseline uptake (SUVmax=8.7) which decreased substantially to 2.4 (72% reduction) after 4 doses of bevacizumab. The finding is consistent with literature reports demonstrating that metabolically active cancers are more likely to achieve a good response to chemotherapy regimens [34-37], albeit not bevacizumab plus chemotherapy. In a multi-center trial study of 104 patients, it was shown that patients with a baseline SUV less than 3.0 did not achieve a histopathologic response [36]. A recent study of 30 patients found that good responders (tumors showing greater than 40% reduction in SUVmax) had a baseline SUVmax of 10.2 ± 6.4 compared to 6.7 ± 3.1 in the poor responders [37]. In this instance, it is not unreasonable to assume that the decrease in [F-18] FDG SUV is a reflection of the tumor's response to both paclitaxel and carboplatin or a combination of all three rather than bevacizumab alone. However, since bevacizumab is typically given with chemotherapy, it was not possible in this study to separate the effects of bevacizumab treatment on the tumor with respect to both [F-18]RGD-K5 and [F-18] FDG imaging. Further research with larger numbers of patients using bevacizumab as monotherapy in conjunction with imaging is needed to verify the true potential of this drug.

We also observed that a high pre-treatment baseline uptake of [F-18]RGD-K5 in lesions, possibly in conjunction with a high [F-18] FDG uptake, may be predictive of a tumor's response to bevacizumab and chemotherapy. In Subject-1, the three highest [F-18]RGD-K5 avid lesions had the largest percent decrease after 4 doses of bevacizumab, which was not observed for [F-18]FDG. Given the questions surrounding bevacizumab's effectiveness in treating metastatic breast cancer, a key biomarker for selecting potential responders still remains elusive though many attempts have been reported. For example, in a gynecologic oncology phase II trial, bevacizumab was given as a single agent to patients with recurrent and persistent ovarian or peritoneal cancer. While this study provided a great database for evaluating the

predictive biomarker, the authors unfortunately discovered that neither investigated microvessel density nor VEGF markers were predictive of treatment response [38]. Although bevacizumab is categorized as a VEGF-targeted cancer therapy, it is important to note that neither VEGF nor the VEGF receptor have been validated as biomarkers suitable for selecting candidates for anti-angiogenic therapies. Integrin $\alpha_v\beta_3$ has the potential to serve as a useful biomarker for angiogenesis, but it is important to mention that it is also expressed on many different cancer cells including breast cancer and not exclusively on their vasculature [31]. Thus, it is not fully clear if the decrease in [F-18] RGD-K5 uptake is solely due to a diminishing tumor vasculature or a general decrease of tumor load.

We also noted a high range of SUV's measured by both [F-18] RGD-K5 and [F-18]FDG in these analyzed lesions. This was consistent with results of three previous studies using [F-18]Galacto-RGD, in 19 patients with solid tumor (SUV varying from 1.2 to 10.0 and no uptake in 2 lesions) [20]; in 11 patients with squamous cell carcinoma of the head and neck (SUV varying from 2.2 to 5.8 and missing two lesions) [30]; and in 16 patients with primary or metastasized breast cancer (SUV varying from 1.4 to 8.7 in invasive cancer) [31]. The angiogenic activity and metabolic activity may vary substantially depending on many factors. For Subject-2, a 2.5 cm primary breast lesion is likely to show central necrosis; and on the other hand for Subject-1, it is unlikely for metastatic lymph nodes to show necrosis. The different sizes of tumor mass burden and the difference between primary cancer vs. metastatic node may contribute to the wide range of SUV reported in our study, and more studies are needed to further understand the clinical application of [F-18]RGD-K5. Unfortunately the FDA's decision of withdrawing the market approval of bevacizumab for metastatic breast cancer patients interfered directly with our recruitment efforts for this study, not allowing us to enroll a larger number of patients who would receive bevacizumab in addition to their chemotherapy regimen. Future studies with a larger cohort of patients are needed to further investigate the clinical role of RGD-K5.

Conclusion

There is an urgent need to identify predictive biomarkers for selecting patients who are more likely to benefit from an anti-angiogenic treatment. The conventional methods used to assess for treatment response, such as RECIST, may not reflect changes induced by anti-angiogenic therapies in a timely manner to allow for therapy adjustments suitable for a certain cohort of patients. The results herein suggest that the *in vivo* imaging of $\alpha_v\beta_3$ integrins, using a tracer such as [F-18]RGD-K5, might help to both stratify patients based on a high pre-treatment SUV threshold, and in addition serve as a tool to monitor the effectiveness of the therapy, preceding changes in tumor volume. The [F-18]RGD-K5 PET scan can also be applied to other cancers treated with bevacizumab to investigate its role in selecting suitable patients and monitoring the early treatment changes to predict outcomes.

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