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Molecular imaging biomarkers of resistance to radiation therapy for spontaneous nasal tumors in canines

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Abstract

Purpose/Objective(s)—Imaging biomarkers of resistance to radiation therapy can inform and guide treatment management. Most studies so far have focused on assessing a single imaging biomarker. The goal of this study was to explore a number of different molecular imaging biomarkers as surrogates of resistance to radiation therapy.

Methods and Materials—Twenty-two canine patients with spontaneous sinonasal tumors were treated with accelerated hypofractionated radiation therapy, receiving either 10 fractions of 4.2 Gy or 10 fractions of 5.0 Gy to the GTV. Patients underwent FDG, FLT, and Cu-ATSM PET/CT imaging before therapy, and FLT and Cu-ATSM PET/CT imaging during therapy. In addition to traditional SUV measures (eg, maximum SUV), imaging metrics providing response and spatiotemporal information were extracted for each patient. Progression-free survival was assessed

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Conflicts of Interest: None

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according to RECIST criteria. The prognostic value of each imaging biomarker was evaluated using univariable Cox proportional hazards regression. Multivariable analysis was also performed, but was restricted to two predictor variables due to the limited patient number. The best bivariable model was selected according to Pseudo R^2 .

Results—The following variables were significantly associated with poor clinical outcome following radiation therapy according to univariable analysis: tumor volume ($P=0.011$), midtreatment FLT SUV_{mean} ($P=0.018$), and midtreatment FLT SUV_{max} ($P=0.006$). Large decreases in FLT SUV_{mean} from pretreatment to midtreatment were associated with worse clinical outcome ($P=0.013$). In the bivariable model, the best two-variable combination for predicting poor outcome was high midtreatment FLT SUV_{max} ($P=0.022$) in combination with large FLT response from pretreatment to midtreatment ($P=0.041$).

Conclusions—In addition to tumor volume, pronounced tumor proliferative response quantified using FLT PET, especially when associated with high residual FLT PET at midtreatment, is a negative prognostic biomarker of outcome in canine tumors following radiation therapy. Neither FDG PET nor Cu-ATSM PET were predictive of outcome.

Keywords

PET; radiotherapy; biomarkers

Introduction

Outcome following radiation therapy can be highly variable across different patients, even in tumors with similar clinical presentation [1]. Due to the biological complexity of tumor resistance and its multiple underlying sources, treatment outcome remains difficult to predict. Better methods of predicting outcome following radiation therapy could greatly improve patient management by helping physicians better tailor treatments to patient-specific biology.

There is great interest in identifying biomarkers of tumor resistance to radiation therapy. Numerous studies have investigated genetic, molecular, and anatomical biomarkers of radiation resistance in different tumor types [2–3]. Many of these biomarkers are biopsy-based and therefore limited by sampling, invasiveness, and intratumor heterogeneity. Positron emission tomography (PET) imaging, however, non-invasively provides spatially-resolved quantitative measurements of tumor biological processes. Therefore, there is great promise for molecular imaging biomarkers to improve treatment outcomes in radiation oncology [4].

Several different biological properties are of particular interest as imaging biomarkers. The best established biomarker of tumor resistance to radiation therapy is tumor oxygenation. Highly hypoxic tumors have been shown to respond poorly to radiation therapy [5–7]. PET imaging of tumor hypoxia may also identify patients who will respond poorly to radiation therapy; this has been demonstrated in head-and-neck tumors using the radiotracers ^{18}F -fluoromisonidazole (FMISO) [8] and ^{18}F -fluoroazomycin arabinoside (FAZA) [9], and in

cervical [10–11], lung [12], rectal [13], and head-and-neck [14] tumors using the radiotracer copper(II)-diacetyl-bis(N4-methylthiosemicarbazone) (Cu-ATSM).

Measurements of tumor proliferation may also be useful in predicting tumor outcome following radiation therapy. Tumor types with faster proliferation rates and higher growth fractions are generally regarded as more radiosensitive than slow-growing tumors [15]. On the other hand, radiation damage can dramatically increase tumor proliferation rates during the course of therapy, which has been shown to adversely affect patient outcome [16]. Studies have investigated using 3'-deoxy-3'-¹⁸F-fluorothymidine (FLT) PET imaging, a marker of proliferative index, at multiple time points over the course of treatment for early treatment response assessment [17–22]. These studies demonstrated that changes in FLT uptake generally precede anatomical response for both radiation therapy and chemotherapy, although the studies found variable relationships between FLT response and clinical outcome.

Baseline levels of glucose metabolism, as measured by 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG) PET, have been shown to predict outcome following radiation therapy in some tumor sites [23–26]. However, the relationship between FDG uptake and tumor resistance is complex and not well understood, as FDG uptake is influenced by a myriad of biological processes, including hypoxia, inflammation, tumor cell density, and proliferation [27]. On the other hand, the wide availability of FDG PET makes FDG uptake an appealing imaging biomarker for radiation oncology.

Given the multiple factors affecting resistance to radiation therapy, a direct comparison of multiple imaging biomarkers may shed further light on the characteristics of tumor resistance. This study aimed to concurrently evaluate the predictive value of numerous quantitative imaging biomarkers derived from multi-tracer PET imaging in tumors before and during radiation therapy. Canines with spontaneous sinonasal tumors were used as research subjects, wherein patient motion and positioning could be carefully controlled during imaging. In addition to traditional quantitative PET imaging metrics (ie, standardized uptake values), advanced imaging metrics containing spatiotemporal and response information were also tested for their predictive value.

Methods and Materials

Patients

This study included 22 canine patients referred to the XXX. The research protocol was approved by the Animal Care and Use Committee of the XXX, and all canine owners signed a written informed consent. Patients were diagnosed using CT and biopsied for histopathologic verification. All dogs had treatment-naïve nasal or paranasal sinus tumors with no evidence of distant metastases or intracranial invasion. Histopathology results were 13 adenocarcinoma, 7 chondrosarcoma, 1 squamous cell carcinoma, and 1 osteosarcoma tumor.

Treatment and imaging

Patients received intensity-modulated radiation therapy (IMRT) delivered by helical tomotherapy with curative intent. Patients were split into two treatment groups as part of a study investigating dose escalation. The first group received the veterinary standard-of-care prescription at our institution: 10 fractions of 4.2 Gy to the planning target volume (PTV) for a total of 42 Gy. The second group was prescribed 10 fractions of 4.2 Gy to the PTV with an integrated boost of 0.8 Gy per fraction to the gross tumor volume (GTV), for a total of 50 Gy to the GTV.

The imaging and treatment schedules for patients are illustrated in Figure 1. Dogs fasted for at least 12 hours before each imaging and treatment session. Patients had pretreatment [^{18}F]FDG, [^{18}F]FLT, and [^{61}Cu]Cu-ATSM PET/CT scans on consecutive days beginning 3 days before the onset of therapy. Patients received a second FLT PET/CT scan after two fractions of IMRT (8.4 or 10 Gy) and a weekend break. Patients received a second Cu-ATSM PET/CT scan following the third fraction of IMRT (12.6 or 15 Gy). One patient missed the midtreatment FLT scan due to equipment failure. Patients were injected with 150–370 MBq of tracer. After injection, patients were kept in a kennel to limit physical activity. PET/CT scans were acquired on a Discovery VCT (GE Healthcare, Waukesha, WI) scanner. FDG and Cu-ATSM PET scans were acquired 60 minutes and 180 minutes post-injection, respectively; both were 20-minute 3D static acquisitions over a single 15 cm bed position. A 180 minute uptake period was used for Cu-ATSM based on preliminary analysis showing greater spatial stability of Cu-ATSM uptake at 180 minutes than at 60 minutes, as described in [28]. FLT scans were 90-minute 3D dynamic acquisitions over a single 15 cm bed position. Patients were anesthetized during imaging and treatment with an initial propofol bolus injection, and then maintained on isoflurane inhalation plus 100% oxygen. Emission data were attenuation corrected and reconstructed using ordered subset expectation maximization (2 iterations, 35 subsets, and 3 mm postfiltering). The image grid was $256 \times 256 \times 47$ with $2.0 \times 2.0 \times 3.3 \text{ mm}^3$ voxel sizes. Voxel activity measurements were converted to standardized uptake values (SUVs) for analysis. For FLT scans, SUVs were calculated by averaging frames from 60–90 minutes; we have previously shown FLT SUV to have high correlations to FLT influx (K_i) from kinetic analysis [29]. To achieve reproducible positioning across PET/CT scans and IMRT treatment sessions, patients' maxillae were positioned into custom dental molds that were affixed to the scanner and treatment couches, and patients' bodies were immobilized with vacuum mattresses [30].

Following treatment, patients were scheduled for follow-up CT scans every 3 months for the first 9 months or until patients had progressive disease. Patient response was classified according to the response evaluation criteria in solid tumor (RECIST) [31]. Patients without progressive disease within the first 9 months received an additional CT scan whenever they presented with clinical signs suspicious of recurrence (eg, epistaxis).

Imaging biomarkers

Numerous imaging biomarkers were extracted from each patient's imaging set. Table 1 describes the imaging biomarkers used for analysis. These included the conventional mean SUV (SUV_{mean}) and maximum SUV (SUV_{max}) measures at pretreatment and midtreatment,

as well as response and spatiotemporal variables. Response variables, quantifying the relative change from pretreatment to midtreatment, were calculated according to

$$R_x^T = \frac{X_{\text{mid}}^T - X_{\text{pre}}^T}{X_{\text{pre}}^T},$$

where X is either the SUV_{mean} or SUV_{max} of tracer T , evaluated at pretreatment and midtreatment. For spatiotemporal variables, voxel-based Spearman correlation coefficients (ρ) quantified the relative spatial agreement between two different tracer distributions, T_1 and T_2 , at baseline (ρ_{T_1, T_2}). Spearman correlation coefficients also quantified the relative spatial stability of a tracer T from pretreatment to midtreatment ($\rho_{\text{pre, mid}}^T$). The computation of ρ has been described previously [28,32].

Statistical analysis

Progression-free survival was assessed according to the RECIST criteria. Kaplan-Meier analysis with log-rank tests for significance were applied to the following categorical variables: dose level (42 Gy vs. 50 Gy), histologic tumor type (sarcoma vs. carcinoma), sex, and the tumor stage as defined by Adams *et al.* [33]. For continuous variables, such as patient age and the imaging biomarkers of Table 1, Cox proportional hazards (PH) regression was used to assess their impact on progression-free survival. Univariable Cox PH regression was performed for each continuous variable, and hazard ratios (HR) with their respective 95% confidence intervals (CI) were calculated.

A full multivariable regression model was not developed in this study due to the limited number of patients and the high number of predictor variables. However, we investigated bivariable Cox PH regression models that contained 2 predictor variables, thus following the recommended ratio of ~10 patients per explanatory variable [34–35]. This was done by creating regression models for all possible combinations of 2 explanatory variables, considering both categorical and continuous variables. Of the SUV measures, only SUV_{max} was used due to the strong correlations between SUV_{max} and SUV_{mean} . The best bivariable model was selected according to the Pseudo R^2 [36]. P values less than 0.05 were considered statistically significant.

Results

The average time to disease progression was 14.3 months, the median was 12.5 months, and the range was 3 months to 35 months. Four cases were censored: two due to death unrelated to disease, and two who were alive without progressive disease at the time of the analysis but had the longest progression-free intervals.

Figure 2 shows results from Kaplan-Meier analysis for categorical variables. Dose level, histologic tumor type, sex, and tumor stage were found not to be significant predictors of time to progression after radiation therapy. Table 2 summarizes the results of univariable Cox PH regression for continuous variables. Large tumor volume (HR [95% CI] = 1.01

[1.00, 1.02]; $P=0.011$), high midtreatment FLT SUV_{mean} (2.76 [1.19, 6.40]; $P=0.018$), and high midtreatment FLT SUV_{max} (1.36 [1.09, 1.68]; $P=0.006$) were found to be significant independent predictors of worse outcome. Positive $R_{SUV_{mean}}^{FLT}$ values (ie, increases in FLT SUV_{mean} from pretreatment to midtreatment) were significantly associated with better clinical outcome (0.11 [0.02, 0.64]; $P=0.013$). FDG and Cu-ATSM PET imaging biomarkers were not significant predictors of patient outcome, although FDG SUV_{max} was borderline significant ($P=0.08$). None of the spatial imaging biomarkers (ie, voxel correlation coefficients) were significant predictors of outcome. Figure 2 also shows Kaplan-Meier plots (for display purposes only) for the group of continuous variables found to be significant predictors according to univariable analysis.

Table 3 presents the two bivariable models with the highest Pseudo R^2 . Both models indicate that significantly worse outcome was associated with large reductions in FLT uptake (ie, negative response values) in combination with high midtreatment FLT SUV_{max}. The relationships between patients' clinical outcome and their various FLT measures are illustrated in the scatter plots of Figure 3.

Discussion

Using multi-tracer PET imaging in canines with spontaneous tumors, we were able to directly compare numerous imaging biomarkers as predictors of time-to-progression after radiation therapy. The precise immobilization of anesthetized canine patients during imaging sessions resulted in motionless image acquisition with repeatable positioning [30]. Furthermore, the bony anatomy surrounding the nasal cavity allowed for very accurate image registration. These conditions enabled us to extract non-conventional spatiotemporal imaging measures, which we compared against conventional SUV measures for their predictive value.

The best predictors of time to progression after radiation therapy were FLT-based biomarkers. FLT response and midtreatment FLT SUV were both found to be significant predictors of outcome in univariable and multivariable analysis. Whereas high midtreatment FLT SUV was found to be associated with worse clinical outcome, the relationship between FLT-response and patient outcome was counter to our expectations: tumors with large relative reductions in FLT uptake had worse outcomes than tumors with small relative changes. FLT response during radiation therapy has been previously investigated in humans [17,19–22]; unfortunately, several of these studies were small and no consistent picture is emerging at this point in time. In a small series of 12 lung cancer patients, Trigonis *et al.* found that higher midtreatment FLT SUV_{max}, but not baseline FLT SUV_{max}, was associated with worse local-regional control, which is consistent with our findings. However, FLT SUV response was not a significant predictor of outcome [17]. In another small study, Wieder *et al.* did not find significant relationships between histopathological tumor response and FLT SUV_{mean} at baseline or at midtreatment in 10 rectal cancer patients undergoing neoadjuvant chemoradiotherapy [19]. Hoeben *et al.* found that for 33 head-and-neck cancer patients, early FLT SUV response during radiation therapy was not predictive of patient outcome [21]. However, when they included 15 chemoradiotherapy patients in their analysis, large reductions in FLT SUV became associated with better 3-year disease-free

survival (but not overall survival). For tumors treated with chemotherapies, studies have generally found that large FLT reductions during treatment predict better clinical outcome [37–38]. The heterogeneity between the findings of these studies could be due to their limited statistical power compounded by differences in treatment schedules (hypofractionated vs. conventional), imaging time points (our patients were imaged after the second fraction, including a weekend break), treatment type (radiotherapy alone vs. chemoradiotherapy), tumor histology, and species.

It is unclear what radiobiological principles are driving the relationships between FLT biomarkers and patient outcome. It is not surprising that baseline FLT uptake was not significantly associated with clinical outcome in this study, as high baseline proliferation rates have been previously shown to be associated with both favorable and poor clinical outcome following radiation therapy [39]. However, we did find that high FLT uptake at midtreatment was associated with worse clinical outcome. It is tempting to speculate that these tumors could have contained a greater number of remaining viable cells after receiving ~10 Gy of radiation dose, or the population of surviving cells in these tumors were rapidly proliferating. We also found that tumors with large *reductions* in FLT uptake at midtreatment relative to baseline had a shorter time to progression than tumors with small changes or increases in FLT uptake, and this relationship was independent of pretreatment or midtreatment FLT uptake levels (see Figure 3). This is consistent with a hypothesis where tumors with pronounced responses at the beginning of treatment could be more likely to regrow rapidly following radiation therapy, resulting in shorter progression-free intervals. Indirect support for this hypothesis comes from the recent study by Brink *et al.*, who found that marked tumor regression during fractionated radiation therapy for non-small cell lung cancer was associated with worse clinical tumor outcome in a series of 99 patients [40].

In addition to FLT PET biomarkers, tumor volume was a predictor of adverse clinical outcome following radiation therapy. Dose level, histology, sex, age, and tumor stage were not significant predictors of outcome. Past veterinary studies have found conflicting results on the prognostic significance of tumor histology, patient age, and tumor stage in canine nasal tumors following radiation therapy [33,41–42]. It is possible that the low patient number, and thus the low statistical power, prevented us from detecting predictive relationships that would have been observed in a larger population. Interestingly, we did not find Cu-ATSM and FDG biomarkers to be significant predictors of outcome; although, FDG SUV_{max} was borderline significant ($P=0.08$). Even though Cu-ATSM uptake has been shown to have inconsistent correlations with hypoxia in rodent tumor models [43], several clinical studies have found Cu-ATSM uptake to be a prognostic biomarker of response to radiation therapy [10–14]. Therefore, it was surprising that Cu-ATSM uptake did not predict outcome in this study. It is possible that Cu-ATSM uptake in canines is not directly comparable to Cu-ATSM uptake in humans. For example, Cu-ATSM has lower binding affinity to serum albumin in canines than in humans [44]. Also, the use of anesthesia and oxygen during imaging may have reduced Cu-ATSM uptake levels, as has been demonstrated in rodents [45] (the dogs were awake and breathing air, however, for most of the 3-hour uptake period). On the other hand, Hansen *et al.* found that canine tumors with

high levels of pimonidazole staining generally had high uptake of Cu-ATSM as well, supporting its use as a surrogate marker of hypoxia in canines [46].

None of the spatial imaging biomarkers were significantly associated with patient outcome. The baseline voxel correlation coefficients ($\rho_{\text{FDG,FLT}}$, $\rho_{\text{FDG,Cu-ATSM}}$, and $\rho_{\text{FLT,Cu-ATSM}}$) represent how similar the spatial distributions of the three tracers were, so that a low correlation coefficient indicates spatial heterogeneity of phenotypes within a tumor [32]. We hypothesized that higher PET heterogeneity would predict worse response to therapy; however, this was not supported by our analysis. The voxel correlations from pretreatment to midtreatment ($\rho_{\text{pre,mid}}^{\text{Cu-ATSM}}$ and $\rho_{\text{pre,mid}}^{\text{FLT}}$) represent the spatial stability of Cu-ATSM and FLT uptake distributions during treatment. XXX [28]. We hypothesized that larger spatial stability of a tumor's Cu-ATSM or FLT maps during treatment might be associated with tumor resistance to radiation. However, we did not find PET spatial stability to be significantly associated with clinical outcome.

The cost and logistics of conducting multiple scans restricted the total sample size in this exploratory study. This in turn limited our ability to investigate biomarkers in subpopulations of tumors (eg, sarcomas), and to create a complex multivariable model. Multivariable models can become unstable when there are less than 10 observations per explanatory variable [34–35]. Therefore, we tested bivariable models, selected according to a goodness of fit statistic. Another caveat of the study is the large number of hypotheses tested in this study, which increases the likelihood of type I error. Consequently, these results should be considered as hypothesis-generating, and need to be tested in a larger cohort. It is also uncertain how these results will translate to humans, as canine and human tumors can differ substantially in biology. However, canine tumors are more similar in growth rate, vascularity, and treatment response to human tumors than are murine tumors, and represent a valuable model for cancer research [47].

Conclusions

Using extensive imaging of spontaneous tumors in canines, we explored a number of molecular imaging biomarkers as potential predictors of resistance to radiation therapy. In addition to tumor volume, pronounced tumor proliferative response measured with FLT PET, especially when associated with high residual FLT PET at midtreatment, was a predictive biomarker of poor outcome following radiation therapy. Neither FDG PET nor Cu-ATSM PET were significant predictors of outcome.

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Summary

Imaging biomarkers of resistance to radiation therapy can help guide treatment decisions and improve patient outcome. This study tested multiple quantitative imaging biomarkers derived from FDG, FLT, and Cu-ATSM PET imaging as predictors of resistance to radiation therapy in canines with spontaneous sinonasal tumors. We found FLT PET biomarkers, especially those acquired during treatment, to be the most predictive of patient outcome following radiation therapy.

Figure 1. Patients underwent pretreatment FDG, FLT, and Cu-ATSM PET/CT imaging (in no particular order). Midtreatment FLT and Cu-ATSM PET/CT scans were acquired before fractions 3 and 4, respectively. Following therapy, CT scans were acquired at 3, 6, and 9 months, and at time of recurrence (up until progressive disease was detected). Sagittal slices of a canine patient's PET/CT images are shown above.

Figure 2.

Top: Results of Kaplan-Meier analyses with log-rank tests for categorical variables. Categorical variables were not predictive of outcome. *Bottom:* For display purposes only, variables that were significant predictors of outcome according to Cox proportional hazards (PH) regression were dichotomized using an optimal cut point, and plotted according to Kaplan-Meier method. *P* values are from Cox PH regression.

Figure 3. Scatter plot matrix illustrating the relationships between patients' treatment outcome (*top row*) and various FLT measures. Each column and row corresponds to a different measure, as indicated by the labels in the diagonals. Crosses (+) indicate censored patients.

Table 1

Imaging biomarker definitions.

Variable	Description
Volume	Gross tumor volume (cm ³)
SUV _{mean}	Mean SUV in the GTV
SUV _{max}	Maximum voxel SUV in the GTV
$R_{SUVmean}^{FLT}$	Fractional change in FLT SUV _{mean} from pretreatment to midtreatment
R_{SUVmax}^{FLT}	Fractional change in FLT SUV _{max} from pretreatment to midtreatment
$R_{SUVmean}^{Cu-ATSM}$	Fractional change in Cu-ATSM SUV _{mean} from pretreatment to midtreatment
$R_{SUVmax}^{Cu-ATSM}$	Fractional change in Cu-ATSM SUV _{max} from pretreatment to midtreatment
$\rho_{FDG,FLT}$	Spatial (voxel) correlation between pretreatment FDG and FLT uptake distributions
$\rho_{FDG,Cu-ATSM}$	Spatial (voxel) correlation between pretreatment FDG and Cu-ATSM uptake distributions
$\rho_{FLT,Cu-ATSM}$	Spatial (voxel) correlation between pretreatment FLT and Cu-ATSM uptake distributions
$\rho_{pre,mid}^{FLT}$	Spatial (voxel) correlation between pretreatment and midtreatment FLT uptake distributions
$\rho_{pre,mid}^{Cu-ATSM}$	Spatial (voxel) correlation between pretreatment and midtreatment Cu-ATSM uptake distributions

Abbreviations: SUV = standardized uptake value; GTV = gross tumor volume; FLT = 3'-deoxy-3'-¹⁸F-fluorothymidine; Cu-ATSM = copper(II)-diacetyl-bis(N4-methylthiosemicarbazone); FDG = 2-deoxy-2-[¹⁸F]fluoro-D-glucose

Table 2

Results of univariable Cox proportional hazard regression for continuous variables.

Variable	Hazard Ratio	95% Confidence Interval	P
Volume (cm ³)	1.01	[1.00, 1.02]	0.011
Age	1.01	[0.87, 1.17]	0.911
Pre FDG*			
SUV _{mean}	1.12	[0.91, 1.40]	0.287
SUV _{max}	1.09	[0.99, 1.20]	0.080
Pre FLT			
SUV _{mean}	1.07	[0.86, 1.35]	0.543
SUV _{max}	1.02	[0.95, 1.01]	0.565
Pre Cu-ATSM			
SUV _{mean}	1.28	[0.84, 1.94]	0.245
SUV _{max}	1.08	[0.95, 1.23]	0.226
Mid FLT			
SUV _{mean}	2.76	[1.19, 6.40]	0.018
SUV _{max}	1.36	[1.09, 1.68]	0.006
Mid Cu-ATSM			
SUV _{mean}	1.63	[0.88, 3.02]	0.124
SUV _{max}	1.06	[0.96, 1.17]	0.288
$R_{SUV_{mean}}^{FLT}$	0.11	[0.02, 0.64]	0.013
$R_{SUV_{max}}^{FLT}$	0.15	[0.02, 1.11]	0.064
$R_{SUV_{mean}}^{Cu-ATSM}$	0.63	[0.10, 3.97]	0.620
$R_{SUV_{max}}^{Cu-ATSM}$	0.94	[0.19, 4.58]	0.941
$\rho_{FDG,FLT}$	5.08	[0.41, 62.2]	0.204
$\rho_{FDG,Cu-ATSM}$	0.99	[0.04, 25.8]	0.997
$\rho_{FLT,Cu-ATSM}$	3.82	[0.62, 23.7]	0.150
$\rho_{pre,mid}^{FLT}$	3.28	[0.17, 61.6]	0.428
$\rho_{pre,mid}^{Cu-ATSM}$	2.36	[0.02, 275]	0.724

* see Table 1 for variable definitions

Table 3

The two bivariable models with the highest Pseudo R^2 .

Variable	Hazard Ratio	<i>P</i>	Pseudo R^2
<i>Model 1</i>			0.44
Mid FLT SUV _{max} [*]	1.28	0.022	
$R_{\text{SUVmean}}^{\text{FLT}}$	0.17	0.041	
<i>Model 2</i>			0.43
Mid FLT SUV _{max}	1.38	0.002	
$R_{\text{SUVmax}}^{\text{FLT}}$	0.11	0.042	

*
see Table 1 for variable definitions